Physical activity in patients with Chronic Obstructive Pulmonary Disease

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J.E. Hartman

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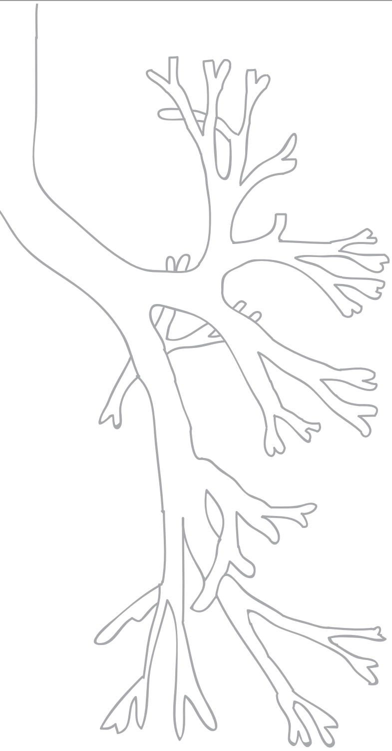
General introduction

CHAPTER 1



GENERAL INTRODUCTION

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease, that is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1] The prevalence of COPD in adults aged ≥ 40 years is estimated at 9-10%.[2] COPD is an important cause of morbidity and mortality. In 2002, COPD was the fifth leading cause of death world-wide and it is estimated to become the fourth leading cause of death in 2030.[3] The main symptoms of the disease are chronic and progressive breathlessness (dyspnea), cough and sputum production. However, COPD is not only a disease in the lung, often extra pulmonary manifestations are present and the prevalence of comorbid conditions is high.[4] Common extra pulmonary manifestation and comorbidities are skeletal muscle dysfunction, pulmonary hypertension, osteoporosis, depression and anxiety.[4] Therapeutic interventions for COPD include smoking cessation, pharmacologic therapy, rehabilitation, oxygen therapy, ventilatory support and surgical treatments.[1,5] Furthermore, the latest guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) underline the importance of regular physical activity for all patients with COPD in the management of stable COPD.[1,5,6]

Physical activity

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure.[7] Physical activity reflects what a patient actually does and is thereby different from functional capacity which indicates what a patient is capable of doing. Therefore, physical activity also has a behavioural component. Physical exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposeful, the objective being to improve or maintain one or more components of physical fitness.[7] Regular physical activity has important health benefits. There is strong evidence that regular physical activity leads to reduced rates of all-cause mortality and reduced rates of various diseases like coronary heart disease, stroke, type 2 diabetes and depression.[8] Furthermore, it can lead to increased cardio-respiratory and muscular fitness, healthier body mass and composition, improved bone health, increased functional health and improved cognitive function.[8] However, worldwide approximately a third of the adults are physically inactive.[9] Partly due to the development of new technologies, that caused a decrease in the need of occupational physical activity.[9] Physical inactivity was identified by the World Health Organization as the fourth leading risk factor for death in 2004, leading to 3.2 million preventable deaths.[10]

Physical activity and COPD

The prevalence of physical inactivity in COPD patients is even higher than in healthy individuals. Lower levels of physical activity compared to healthy controls have been reported already in the earlier stages of the disease and furthermore also compared to other patient groups like diabetes mellitus and rheumatoid arthritis.[11,12] COPD patients frequently report dyspnea induced by everyday tasks and consequently reduce or avoid physical activities and therefore may enter a downward spiral of symptom-induced immobility leading to deconditioning which in turn aggravates dyspnea even more.[13] Besides the earlier mentioned general health benefits, especially in COPD increasing physical activity has shown to decrease dyspnea severity and improve muscle function and quality of life.[14,15] Furthermore, physical activity was found to be the strongest predictor of all-cause mortality in COPD patients.[16] As physical activity is modifiable it is an important treatment target in this patient group. Until now, most evidence of the effects of increasing physical activity in COPD is based on structured exercise programs embedded in pulmonary rehabilitation settings. However, it is shown that these programs do not guarantee an improvement in physical activity levels.[17,18] Furthermore, little is known about the effects of these programs on physical activity in daily life some time after they have been completed. Understanding why COPD patients are physically active or sedentary could contribute to the development and optimizing of physical activity enhancement programs with long lasting effects. These programs could target the factors that are associated with physical activity or inactivity.

Predictors of physical activity

In general adult populations, female gender, higher age, higher body weight, lower level of education, health problems, lower self-efficacy, history of low physical activity and weather conditions were shown to be associated with low physical activity.[19-21] In COPD patients the potential predictors of physical activity are hardly investigated systematically so far. Furthermore, the literature is in general limited and inconsistent and only few studies have investigated both potential physical as well as psychosocial predictors. It would be helpful to identify and investigate the potential physical and psychosocial predictors of physical activity especially in COPD patients. The majority of studies on physical activity in COPD are based on a quantitative research approach. In contrast, the patient's own perceptions and thoughts on physical activity are hardly investigated. Exploring the reasons why COPD patients are physically active or sedentary and the opportunities and barriers they experience, could provide additional information and starting points to stimulate physical activity in these patients.

Physical activity recommendations

As regular physical activity has many health benefits the question arises how much physical activity is 'regular' and should consequently be advised to a COPD patient. Approximately 40 years ago the first physical activity recommendation was published reporting the recommended minimal amount of physical activity to promote or maintain health.[22] The currently often utilized physical activity recommendation are the guidelines of the American College of Sports Medicine (ACSM). Those guidelines recommend that adults should engage in moderate-intensity aerobic physical activity for a minimum of 30 minutes for 5 days each week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes for 3 days each week, or an equivalent combination of both.[23,24] Besides aerobic exercises, adults should also perform resistance, neuromotor and flexibility exercises. In general, the physical activity recommendations are mainly based on healthy adults, while the recommendations for adults with a chronic illness like COPD are less clear. For elderly adults the ACSM recommends to adjust the intensity to the adult's aerobic fitness level[25] that might be appropriate for COPD patients. The physical activity recommendations are hardly investigated in COPD patients and the suitability of the recommendations in this patient group is therefore still unclear.

Physical activity and lung hyperinflation

An important predictor of physical activity in COPD patients is lung hyperinflation.[26] Lung hyperinflation is an important clinical feature in COPD patients with emphysema and is a result of increased airway resistance, reduced lung recoil and shortened available expiratory time.[27] Lung hyperinflation is more strongly related to patient-centered outcomes like dyspnea or health related quality of life than forced expiratory volume in 1 second (FEV_1).[27] In the past decade, lung volume reduction techniques by bronchoscope are increasingly investigated. Endobronchial devices are implanted in emphysematous parts of the lung to reduce hyperinflation. These techniques are less invasive compared to lung volume reduction surgery, and show promising results in improving lung hyperinflation, quality of life and exercise capacity.[28-31] This treatment may improve the mechanical properties of the remaining lung and the efficiency of the inspiratory muscles. Consequently, this may lead to a reduction of dyspnea during exertion and improve functional capacity of the body. Theoretically, after lung volume reduction a COPD patient's physical activity level could improve, however, so far daily physical activity was never measured before and after lung volume reduction. Furthermore, it is not known what size of improvement in lung hyperinflation can be regarded as being clinically important for the patient.

Aims of the thesis

In summary, physical activity has many health benefits and is an important treatment target in COPD patients. Unfortunately, the physical activity level has shown to be low in this patient group, even in the earlier stages of the disease. It is unclear what determines whether a patient is physically active or sedentary. The first aim of this thesis is to gain more insight in all aspects of physical activity and its predictors in COPD patients in all severity stages of the disease, investigating both potential physical and psychosocial factors. A second aim is to investigate whether the current general guidelines for the recommended minimum amount of physical activity for adults to promote and maintain health are suitable for COPD patients. A final aim is to investigate more in depth lung hyperinflation, an important determinant of physical activity in COPD patients, and to study whether a decrease in lung hyperinflation is associated with an increase in physical activity.

Outline of the thesis

In *chapter 2* a review of the literature on potential physical and psychosocial factors that affect the physical activity level in COPD patients is presented. The role of these potential physical and psychosocial predictors of physical activity is investigated in a study that is presented in *chapter 3*. In *chapter 4* the results of a study on the predictors of physical activity, investigated with a qualitative approach, are presented. This study focuses on the patient's own perceptions on physical activity. The results of a study on the use of current physical activity recommendations in COPD patients are presented in *chapter 5*.

In *chapter 6* the results of a pilot study aimed at investigating the potential beneficial effects of bronchoscopic lung volume reduction on the physical activity level in patients with severe emphysema are presented. *Chapter 7* describes the results of a study on the determination of the minimal important difference (MID) of Residual Volume. The established MID could be useful when interpreting the significance of the results of clinical trials or power calculations. The established MID was used in the study presented in *chapter 6*. *Chapter 8* consists of a summary and a general discussion.

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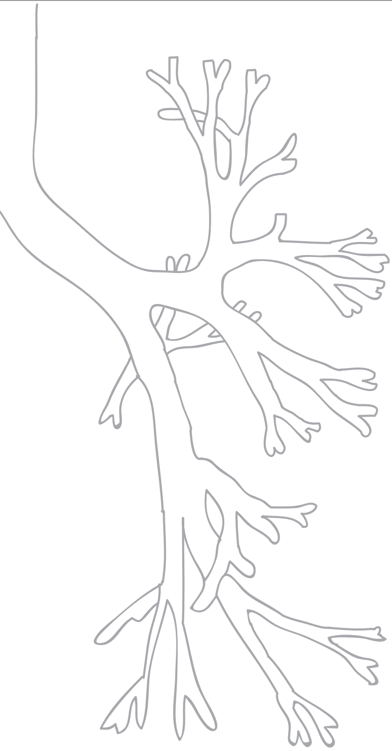
CHAPTER 2

Consequences of physical inactivity in Chronic Obstructive Pulmonary Disease



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ABSTRACT

The many health benefits of regular physical activity underline the importance of this topic, especially in this period of time when the prevalence of a sedentary lifestyle in the population is increasing. Physical activity levels are especially low in patients with chronic obstructive pulmonary disease (COPD). Regular physical activity and an active lifestyle has shown to be positively associated with outcomes such as exercise capacity and health-related quality of life, and therefore could be beneficial for the individual COPD patient. An adequate level of physical activity needs to be integrated into daily life, and stimulation of physical activity when absent is important. This article aims to discuss into more detail the possible role of regular physical activity for a number of well-known outcome parameters in COPD.

Keywords: COPD • health benefits • physical activity • physical activity stimulation

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by a usually progressive airflow limitation that is not fully reversible, and has potential significant extrapulmonary effects.[1] The symptoms of this debilitating disease may have huge impact on a patient's daily life.

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Exercise, on the other hand, is physical activity done on purpose, and carried out in a more structured manner with the aim of improving cardiorespiratory or muscular fitness.[2] It is important to distinguish physical activity from physical fitness, functional or exercise capacity. The latter three indicate what a person is capable of doing while physical activity reflects what someone actually does. The measurement of physical activity is therefore different from the measurement of physical fitness, functional or exercise capacity. Physical activity can be measured by direct observation, assessment of energy expenditure (*e.g.*, doubly labeled water technique), diaries, questionnaires and performance-based motion sensors (*e.g.*, pedometers and accelerometers).[3] The first two are time consuming and expensive and are therefore used less frequently. Performance-based motion sensors objectively quantify the amount of daily physical activity performed and is therefore more accurate as compared with questionnaires and diaries, which depend on a person's memory and interpretation.

Regular physical activity improves body composition, autonomic tone, coronary blood flow, psychological wellbeing, glucose homeostasis and insulin sensitivity, enhances lipid lipoprotein profiles and endothelial function, reduces blood pressure and systemic inflammation, decreases blood coagulation and augment cardiac function.[4] Physical inactivity is therefore a modifiable risk factor for cardiovascular disease and a variety of other diseases such as diabetes mellitus, cancer, hypertension and dementia.[4,5] The recommended minimum amount of physical activity for adults to promote and maintain physical health is 30 minutes of moderately intense aerobic physical activity at least 5 days a week or 20 minutes of vigorously intense aerobic physical activity at least 3 days a week, or an equivalent combination. Every adult should also perform muscular strength and endurance exercises at least 2 days each week.[6] For elderly adults (age ≥65 or ≥50 with clinically significant chronic conditions and/or functional limitations) it is necessary to adjust the recommended intensity of aerobic activity to the elderly adult's aerobic fitness. Moreover, activities that maintain or increase flexibility are recommended next to balance exercises for elderly adults at risk to fall.[7] The latter would be adequate for the majority of COPD patients. To our knowledge, there are no COPD-specific recommendations for an adequate physical activity level. Most guidelines on the management of COPD mention the importance of increasing the level of physical activity, however, this is often related to treatment with pulmonary rehabilitation. The American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation provides practice guidelines for exercise training during pulmonary rehabilitation and emphasizes the need for the transference of exercise adherence to the home setting.[8] Unfortunately, the recommended amount of physical activity in daily life is not specified in these guidelines.

Several studies have shown that the level of physical activity in COPD patients is low, especially compared with that of healthy controls. A selection of these studies is shown in table 1. Moreover, a recent study from Sweden[9] has reported that the number of COPD patients who do not reach the recommended amount of physical activity according to the earlier stated guidelines[7] was significantly higher than in patients with rheumatoid arthritis (RA), diabetes mellitus (DM) and healthy subjects (COPD 84%, RA 74%, DM 72% and healthy 60%, respectively). This indicates that the level of physical activity in COPD patients is also lower than in other diseases.

From the literature we can conclude that being physically active has many health benefits in general, and that many COPD patients lack an adequate level of physical activity. Consequently, a reduced level of physical activity may contribute to a lower physical fitness and wellbeing. The aim of this article is to discuss in more detail the possible role of regular physical activity in a number of well-known outcome parameters in COPD.

TABLE 1. Daily physical activity level in chronic obstructive pulmonary disease.

Study (year)	**Population**	**n**	**Mean FEV_1 %pred**	**Outcomes**		**Ref.**
Accelerometer (DynaPort) 12-h day*				Walking time (min per day)	Sitting time (min per day)	
Pitta et al. (2005)	Controls	25	111	81	306	[16]
	COPD patients	50	43	44	374	
Pitta et al. (2009)	COPD patients (Brazil)	40	46	56	296	[77]
	COPD patients (Austria)	40	48	40	388	
Camillo et al. (2008)	COPD patients	31	46	57		[45]
Pitta et al. (2006)	COPD patients	23	39	57	338	[25]
Accelerometer (SenseWear) ± 24-h day				Steps per day	PAL	
Troosters et al. (2010)	Controls	30	114	9372		[14]
	COPD patients	70	54	5584		
Watz et al. (2008)	COPD patients	170	56	5882	1.50	[42]
Watz et al. (2009)	Chronic bronchitis	29	99	± 9000	± 1.70	[36]
Accelerometer (SenseWear) 12-h day*				Daytime steps		
Pitta et al. (2008)	COPD patients	40	41	4178		[22]
Camillo et al. (2008)	COPD patients	31	46	4603		[45]
Pedometer (type)				Steps per day		
Schonhofer et al. (1997) (Fitty 3)	Controls	25	NA	8590		[11]
	COPD patients	25	47	3781		
McGlone et al. (2006) (Omron HJ003)	COPD patients	124	46	3716		[10]

**Duration measurement included 12 consecutive hours starting at waking up time.*
FEV_1: forced expiratory volume in 1 s; n: number of patients or controls; %pred: percentage predicted; NA: not available; PAL: physical activity level score (total energy expenditure/basal metabolic rate-24 h).

The role of physical activity in specific COPD characteristics

Lung function

Several cross-sectional studies have shown a significant relationship between physical activity and the forced expiratory volume in 1 second (FEV_1; correlation coefficients [r] ranges between 0.20 and 0.63),[10-20] while others did not.[21-24] Different studies categorized the lifestyle of COPD patients as 'active' or 'inactive' based on their level of physical activity. Higher FEV_1 values were found in patients who reached the recommended amount of physical activity[7] (a minimum of 30 minutes of walking every day) compared with those who did not[25] and in patients who reported moderate or high levels of physical activity compared with patients who reported low levels of physical activity, defined as time spent walking during leisure time.[26] By contrast, when patients were divided into groups based on their median physical activity level[27] or based on the level of energy expenditure in physical activity,[28] no difference in FEV_1 between groups was observed. However, these contradictory results may be explained by the differences in categorization used in these studies.

Surprisingly, one longitudinal study in the general population demonstrated that lower physical activity (among other variables) increased the 10-year decline in FEV_1 in active smokers. However, physical activity was not associated with lung function decline in young adults (<40 years of age) nor in subjects with mild COPD.[29] The same study showed that subjects who decreased their level of physical activity during follow-up had an accelerated lung function decline and were more likely to develop COPD, while subjects who increased their level of physical activity showed a reduction in lung function decline and COPD risk compared with subjects with unchanged physical activity levels. In addition, people with moderate-to-high levels of physical activity had a reduced risk of COPD compared with the group that reported low physical activity (odds ratio [OR]:0.8).[29] In line with these results, another study with a mean follow-up duration of 3.7 years showed that performing activities with a metabolic equivalent of task (MET) score of five or more (equal to, for example, riding on a bicycle at average speed), or more stair climbing was associated with a lower percent reduction in FEV_1 in both men and women.[30] MET expresses the intensity of physical activities and is based on the ratio of a person's working metabolic rate relative to their resting metabolic rate.[2]
In conclusion, cross-sectional data suggest that a lower level of physical activity is associated with a lower FEV_1. Furthermore, longitudinal studies suggest that physical activity reduces FEV_1 decline and thus disease progression.

Exacerbations and hospital admissions due to COPD

Worsening of respiratory symptoms can be indicative of a COPD exacerbation, which is the main cause of hospital admissions due to COPD. Exacerbations can lead to poorer health-related quality of life,[31] and severe exacerbations requiring hospitalization have shown to be associated with all-cause mortality in COPD patients.[32] Physical activity seems to play a role in the risk of hospitalization due to an exacerbation. COPD patients with low energy expenditure in physical activity were more likely to have a COPD-related admission in the previous year.[28] Furthermore, patients reporting a very low level of physical activity had a higher risk of hospital admission due to COPD than those reporting low, moderate or high levels of physical activity, after adjusting for confounders.[33] A very low level of physical activity was defined as reporting mainly sitting during work, no activity during work and no jogging or cycling. Moreover, patients who reported a physical activity level which included minimal 2 hours per week of walking or cycling had a 30-40% reduced risk of a hospital admission because of COPD.[33] In line with those results, less than 2 hours of physical activity per week showed to be a significant predictor (OR: 0.60) of hospitalizations in patients with severe COPD.[34]

After an exacerbation, the level of physical activity in COPD patients appears to decrease. A measurement of physical activity by an accelerometer 1 month after discharge from hospitalization due to a COPD exacerbation, showed that the walking time increased significantly when compared with day 2 or 7 after hospitalization. However, the level of physical activity 1 month after discharge was still markedly low compared with earlier observed daily physical activity levels of stable COPD patients.[35] Also, patients who were more often readmitted to the hospital for a subsequent acute exacerbation in the year following discharge had a significantly lower walking time 1 month after discharge than patients who were not readmitted (median 12 min/day vs 30 min/day).[35]

Dyspnea

The most prevalent symptom in COPD patients is shortness of breath, or dyspnea. Dyspnea often occurs during exertion, which can cause a patient to avoid these activities and could result in a decrease in physical activity. For example, COPD patients who reported being too breathless to leave the house had a physical activity level (PAL) score of 1.26, which is just above the PAL score of a chair- or bed-bound patient.[36] The PAL score expresses the daily physical activity level of a person over a 24-hour period as a number, and is based on the ratio of total energy expenditure and basal metabolic rate. Until now, limited research has focused on the association between physical activity and dyspnea, and moreover these few studies show inconsistent results. Some studies have demonstrated a poor-to-moderate association (r ranges: 0.26-0.46),[12,17,19,21] while other studies did not.[15,23,27] When the lifestyle of COPD patients was categorized into inactive and active, patients with an active lifestyle usually reported less dyspnea than the patients with an inactive lifestyle. Patients who reached the minimum recommended amount of physical activity reported less shortness of breath than patients who did not.[25] In line with this, a higher proportion of subjects with a higher level of dyspnea were reported to be in the group with low energy expenditure,[28] and patients who reported lower levels of physical activity (based on walking time and distance) had more dyspnea than those with moderate or high levels of physical activity.[26] By contrast, in a study that divided two groups according to the median level of physical activity, the above median active group did not have a higher dyspnea score.[27] In addition, one study evaluated a 6-month pulmonary rehabilitation program, in which increases in walking time in daily life, measured by a triaxial accelerometer, were significantly related to reductions in the dyspnea score, as well as with a higher number of completed rehabilitation sessions.[37]

Exercise capacity

As stated earlier physical fitness or exercise capacity differs from physical activity, and is therefore measured in a different way. Exercise capacity can be measured by a maximum capacity test (*e.g.*, an incremental [cycle] ergometer test) or a submaximal test (*e.g.*, a 6-minute walk test [6MWT]). Several studies showed a moderate or strong correlation between physical activity and exercise capacity measured by the 6MWT (r ranges: 0.42-0.76).[12,15,16,19,21,23,38] Significant correlations between physical activity and maximum reached workload (W_{max}) and peak oxygen uptake (peak VO_2) were also found (r ranges: 0.33-0.63).[16,19-21] Only two studies did not find a significant correlation.[24,27] Apparently, there seems to be a strong association between physical activity and exercise capacity. However, one study showed that the 6MWD was predictive of walking time in daily life only in patients with a 6-minute walk distance (6MWD) below 400 meter.[16] This indicates that in COPD patients with a higher exercise capacity the physical activity level is more variable. Two studies categorized patients into groups based on their level of physical activity. A study that compared COPD patients who reached the recommended amount of physical activity with patients who did not reach this level, showed that the relative inactive group had a significantly worse distance on the 6MWT (76 vs 66 %predicted), a lower peak VO_2 (71 vs 49 %predicted) and lower W_{max} (69 vs. 40 %predicted).[25] By contrast, when patients were divided by the median number of pedometer counts, the groups did not differ in exercise capacity measured by the 6MWT.[27]

Muscle function

Maintaining adequate muscle function (force and endurance) in the larger musculoskeletal groups such as the quadriceps muscles is important in performing daily activities like walking and remaining independent. Quadriceps weakness is found to be a significant predictor of mortality in COPD patients.[39] Two studies have shown a moderate correlation between physical activity and quadriceps function (r: 0.45 and 0.60)[16,20] while two others did not.[40,41] In both pairs, one study measured muscle endurance and one maximal muscle force. A group of patients who reached the recommended amount of physical activity also did not show significant difference in quadriceps peak torque compared with inactive patients.[25] Little is known about the relationship between physical activity and handgrip force in COPD patients and the results published so far are inconsistent.[16,42]

Comorbidity

The prevalence of comorbidity in COPD is high and COPD patients have been shown to be at increased risk of various diseases compared with an age matched non-COPD cohort (healthy or patients with other diseases than COPD).[43] In 200 COPD patients, after reviewing their medical chart, an average of 3.7 chronic medical conditions (including COPD) were reported, and only 6% of these patients did not have another chronic medical condition apart from COPD.[44] Comorbidities in COPD that occur frequently include osteoporosis, myocardial infarction, angina, fractures and glaucoma.[43] Interestingly, COPD patients who reported lower levels of physical activity had comorbidities more often than those with moderate or high levels of physical activity.[26] Furthermore, in COPD patients, a reduced level of physical activity correlated with left cardiac dysfunction,[42] hearth rate variability reduction,[45] self-reported diabetes, cataracts,[28] comorbid joint problems and a history of joint problems.[23]

Highly prevalent in COPD patients is the metabolic syndrome, a cluster of metabolic risk factors such as hypertension, obesity and impaired glucose tolerance.[46,47] Metabolic syndrome is associated with an increased risk of both type 2 diabetes and cardiovascular disease.[48] Moreover, COPD and chronic bronchitis patients with metabolic syndrome showed significantly reduced levels of physical activity in comparison with those without metabolic syndrome.[46] One review showed that exercise training has mildly or moderately favorable effects on many metabolic and cardiovascular risk factors that constitute or are related to the metabolic syndrome and thus can play a role in its prevention and treatment, although more research has to be conducted with metabolic syndrome as the main outcome.[49]

COPD is associated with increased levels of systemic inflammatory markers.[50] Higher levels of systemic inflammation (high-sensitivity C-reactive protein [hs-CRP], IL-6 and fibrinogen) have been shown to be associated with reduced physical activity in patients with COPD.[46] Moreover, physical activity was an independent predictor of hs-CRP, IL-6 and fibrinogen level.[46] The authors of a review on the anti-inflammatory effect of exercise in general, suggest that myokines may be involved in mediating the health-beneficial effects of exercise and therefore may play an important role in the protection against diseases associated with a low-grade systemic inflammation.[51] Unfortunately, there are only a few studies that have focused on the effect of exercise training on inflammatory markers in COPD, and these studies did not show changes in inflammatory markers (*e.g.*, TNF-α and IL-6) due to exercise training.[52] These data suggested that although exercise training did not result in anti-inflammatory effects in COPD patients, it also did not have a pro-inflammatory effect.[52]

Obesity, assessed by a body mass index (BMI) of 30 or higher, is highly prevalent in patients with COPD, especially in those with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages I and II.[53] A study in a general population, aimed at examining determinants of sedentary lifestyles in the European Union, showed that obese people significantly more often had a sedentary lifestyle compared with people with normal weight (BMI: 20-25 kg/m^2).[54] However, this relation was not found in COPD patients. A few studies found no association between BMI and physical activity.[10,16,23,27] In line with these results, different studies that classified patients into groups based on their level of physical activity, found that BMI was not significantly different between active and inactive COPD patients.[25,26,28]

Mortality

A follow-up study with a mean duration of 12 years among 2386 COPD patients showed that after adjusting for all relevant confounders, subjects who reported low, moderate or high physical activity had a lower risk of all-cause mortality, and death from respiratory causes or cardiovascular causes, than the group with very low physical activity, defined as mainly sitting during work, no activity during work and no jogging or cycling.[33] The same was also found in the general population; minimal adherence to earlier stated guidelines of physical activity was associated with a significant 20-30% reduction in risk of all-cause mortality.[55]

Health-related quality of life

Health-related quality of life (HRQL) is increasingly recognized as an important patient-centered outcome, which may be affected by a chronic disease like COPD. A significant positive correlation between physical activity and (one domain of) HRQL was frequently reported (r ranges: 0.20-0.42),[10,17,19,21,23,56] although one study found different results for the different domains of HRQL,[15] and one study did not find an association.[57] Studies that classified patients into groups based on physical activity showed conflicting results. A study which divided the patients into low, moderate and high energy expenditure in physical activity showed that lower levels of HRQL (physical and mental components) were independently associated with a low energy expenditure (OR physical component: 0.93; OR mental component: 0.96).[28] By contrast, there were no significant differences in HRQL between patients who reached the recommended amount of physical activity and patients who did not,[25] nor between those with above compared with below median physical activity.[27] However, outcomes of these studies are incomparable since different questionnaires were used to measure HRQL. Frequently used HRQL questionnaires are St. Georges Respiratory Questionnaire, Short Form 36 Health Survey and Chronic Respiratory Questionnaire. A recent study with a 5-year follow-up showed that the COPD patients who maintained a low physical activity level or decreased their physical activity level during follow-up, showed a significant decline in HRQL, while those maintaining a high level of physical activity or increasing their physical activity level showed an improvement in HRQL.[26]

Psychological parameters

Psychological characteristics such as depressive symptoms and anxiety are highly prevalent in COPD patients. One review showed that the prevalence of depression ranges between 7% and 79%, and the prevalence of anxiety between 10% and 100%.[58] The large variations can be explained by the differences in samples of COPD patients or the measures used for assessing psychiatric morbidity (*e.g.*, different questionnaires and clinical interviews).[58] Furthermore, patients with severe airway obstruction (GOLD stages III and IV) were 2.5-times more likely to have depression than controls, while patients with mild or moderate COPD (GOLD stage II) showed no increased risk for depression.[59] Moreover, depressive symptoms in COPD patients is strongly associated with worse HRQL.[60] Two studies found no association between physical activity and the presence of depression.[23,42] To our knowledge, no studies investigated the association between physical activity and anxiety in COPD patients. Self-efficacy in physical activity, the belief that you are capable of performing a physical activity, has been shown to correlate positively with physical activity (r: 0.27 and 0.43).[12,15]

Can we improve physical activity in COPD?

Because regular physical activity has many health benefits in general but especially in COPD patients, it is important to improve the level of physical activity in COPD patients. Most evidence on effects of increasing physical activity in COPD is based on structured exercise programs embedded in pulmonary rehabilitation settings, which are most often offered to patients with more severe COPD. Pulmonary rehabilitation usually consists of multiple disciplines, of which exercise is an important component. Pulmonary rehabilitation programs with a short duration (until 12 weeks), have shown different results regarding its effects on physical activity. A 3-week pulmonary rehabilitation program showed that the increased level of physical activity was related to the increasing intensity of the training sessions and the authors suggested that there was no change in personal lifestyle toward longer periods of walking.[57] Two studies with a slightly longer rehabilitation program (6-12 weeks) also found that there was not a significant increase in level of physical activity after rehabilitation.[27,61] By contrast, 3 studies found a significant increase in physical activity after pulmonary rehabilitation with about the same duration.[18,62,63] A pulmonary rehabilitation program with a duration of 6 months showed that the mean walking time did not improve significantly after 3 months, but actually did after 6 months.[37] Unfortunately, to our knowledge, no study examined the level of physical activity some time after finishing the pulmonary rehabilitation program. Consequently, an indication whether the patients have incorporated a more active lifestyle afterwards is lacking.

The effects of a structured exercise intervention or pulmonary rehabilitation are significant[64-68] and emphasize the importance of exercise or regular physical activity in COPD. However, a structured after-care program is often lacking and, furthermore, the disadvantages of a structured exercise program are that they are often time-consuming, expensive and require a lot of organization and, therefore, patients often drop out. It is also important that patients integrate physical activity in daily life and adopt a physical active lifestyle. Therefore, another way to improve physical activity is by enhancing daily physical activities such as walking, bicycling, gardening, and thereby promoting an active lifestyle. The primary focus of such a lifestyle strategy is not to improve functional capacity like in pulmonary rehabilitation, but to establish new physical activity routines in daily life, which could give better maintenance of the results in the long term. One study in an older general population compared the long-term effects of a structured exercise group to a home-based lifestyle intervention. After 1 year following the intervention, the lifestyle intervention group maintained their increase in physical activity while the structured exercise group no longer had higher levels of physical activity compared with the control group (without intervention).[69] Obviously, education and/or counseling is an important component of lifestyle physical activity enhancement. A successful example in COPD patients is a counseling program that used pedometers to monitor and motivate COPD patients to increase their physical activity in daily life. A total of 12 weeks after this program, the outclinic COPD patients who received exercise counseling showed a significant increase in the number of steps per day as compared with those who received usual care.[70] Furthermore, after 12 weeks, the counseling group showed a significant improvement in arm and leg strength, HRQL and changes in intrinsic motivation score to be physically active.[70] The same counseling strategy was added to COPD patients who already followed a rehabilitation program. Both the experimental (pulmonary rehabilitation plus exercise counseling) and control group (only pulmonary rehabilitation program) showed an increase in the number of steps per day, with the experimental group showing the largest increase.[71] Comparable, another study looked at the effects of a daily self-monitored walking training at home after a 7-week supervised pulmonary rehabilitation program. The integration of the daily walking training at home already started during rehabilitation. The improvements in exercise capacity after rehabilitation were maintained at 6 months and although slightly declined, were still significantly better at 1-year follow-up compared with baseline.[72] These results show that a lifestyle physical activity strategy and pulmonary rehabilitation or structured exercise programs can be complementary.

In the reconvalescence phase of a COPD exacerbation it may also be worthwhile to enhance physical activity. For example, one interesting study looked at the positive effects of a specialized walking program for COPD patients admitted to the hospital for an exacerbation.[73] During their hospital admission, patients walked six times per day and during the 6 months afterwards patients were stimulated to walk three times per day. All patients kept a diary with walking distances and time spent on walking at home. In these 6 months the patients recorded a mean daily walking distance of 2308 meter, on an average of 157 walking days. The training group increased their exercise performance and quality of life while the control group, which did not receive any structured training, did not (directly after the hospitalization, after 6 and 18 months).[74] These results show that the stimulation of walking, an important component of daily physical activity, has benefits even in COPD patients shortly after a hospitalization due to an exacerbation.

CONCLUSION AND DISCUSSION

While physical activity has many health benefits in general, the level of physical activity in COPD patients appears to be low, compared with a healthy population but also with other patient groups, and is therefore an important modifiable risk factor in COPD patients. Although there are general guidelines for the recommended minimum amount of physical activity for adults to promote and maintain health, it seems worthwhile to investigate whether these guidelines are also suitable for COPD patients.

Significant correlations were found between physical activity and important disease outcomes of COPD like FEV_1, dyspnea, exercise capacity, muscle function, comorbidities, systemic inflammation and HRQL. However, it should be recognized that the literature is limited and inconsistent, and that most correlations are only moderate. Furthermore, a few other cross-sectional studies separated active COPD patients from inactive COPD patients, which could give interesting insight into the determinants and consequences of an inactive lifestyle. Although not consistent, an inactive lifestyle was associated with lower FEV_1, higher levels of dyspnea, higher number of COPD admissions, worse exercise capacity and worse domains of HRQL. These results are obtained from cross-sectional data and therefore definite conclusions regarding a possible cause-effect relationship are difficult to draw.

To our surprise, no significant associations were found between physical activity and BMI in contrast with findings in the general population. This could be explained by the lower prevalence of obesity that has been found in GOLD stage IV patients[75] and in patients with emphysema.[76] Apparently, the disease severity and phenotype of COPD are far more important than BMI in this perspective. An association between physical activity and psychological factors, such as depression was also not found. We anticipate that other factors like motivation to be physically active play an important role for the physical activity level of COPD patients, however studies on this relationship are lacking.

The prevalence of comorbidites in COPD is high and comorbidities might play a determining role in the reduced level of physical activity. For example, common conditions like arthrosis and osteoporotic fractures reduce the COPD patient's ability to be physically active. Physical activity also has favorable effects on many metabolic and cardiovascular risk factors, which might have important implications for the prevention as well as management of many common comorbidities in COPD. Therefore, the existence of comorbidities needs to be taken into account when investigating physical activity in COPD, but also when developing physical activity enhancement programs for COPD patients.

The different methods used to classify COPD patients into active versus inactive makes it difficult to compare the results. The methods used to measure (accelerometer, pedometer, questionnaire and interview) and to express the variations in physical activity (*e.g.*, minimal recommended physical activity level, energy expenditure and time spent walking during leisure time) are extremely different. Furthermore, the question arises which level of physical activity can be considered as an active lifestyle that could lead to health benefits.

Clearly, more research is necessary to investigate the determinants and consequences of an inactive lifestyle in COPD patients, as well as more insight into the best way to stimulate the physical activity level in this group of patients. Figure 1 shows a theoretical framework of the role and consequences of physical inactivity in COPD, embedded into background factors.

The effects of an increase in physical activity are often obtained from research on structured exercise or pulmonary rehabilitation programs. These programs have shown significant improvements for important patient-centered outcome parameters, and the effects of stimulating physical activity during the hospitalization and pulmonary rehabilitation after an acute exacerbation are promising. However, owing to the multidisciplinary structure of pulmonary rehabilitation programs, it is difficult to identify the isolated role of exercise, and it is well-known that the long-term effects of pulmonary rehabilitation in general are modest. Programs that focused particularly on the enhancement of physical activity in daily life, to change a patient's lifestyle, also show good results.

Both pulmonary rehabilitation and lifestyle physical activity enhancement seem to increase physical activity at least immediately after the program ends. Unfortunately, there are no long-term data regarding physical activity after pulmonary rehabilitation or lifestyle physical activity enhancement. In the authors' opinion, it is important that especially sedentary COPD patients incorporate the desired increase in physical activity into daily life and maintain this behavior. Because most physical activity and pulmonary rehabilitation programs do not have a structured aftercare program, much attention should be paid to this aspect already during the program. Education, counseling, preparing the patients towards the end of the program, transfer to first-line healthcare providers and involving family members and colleagues at work might all contribute to a successful maintenance of physical activity after discharge.

We conclude that regular physical activity is positively associated with important health outcome parameters of COPD and that it may successfully be improved by structured exercise and lifestyle physical activity enhancement programs. Exacerbations and dyspnea are probably important threats against maintaining an adequate physical activity level in more severe COPD patients. We believe that stimulation of embedding low- or moderate-intensity physical activity in daily life is important for the long-term effects of specialized physical activity programs. Finally, the stimulation of physical activity should already start in the early stages of COPD, if appropriate also using high-intensity physical activity to prevent a sedentary lifestyle later in life.

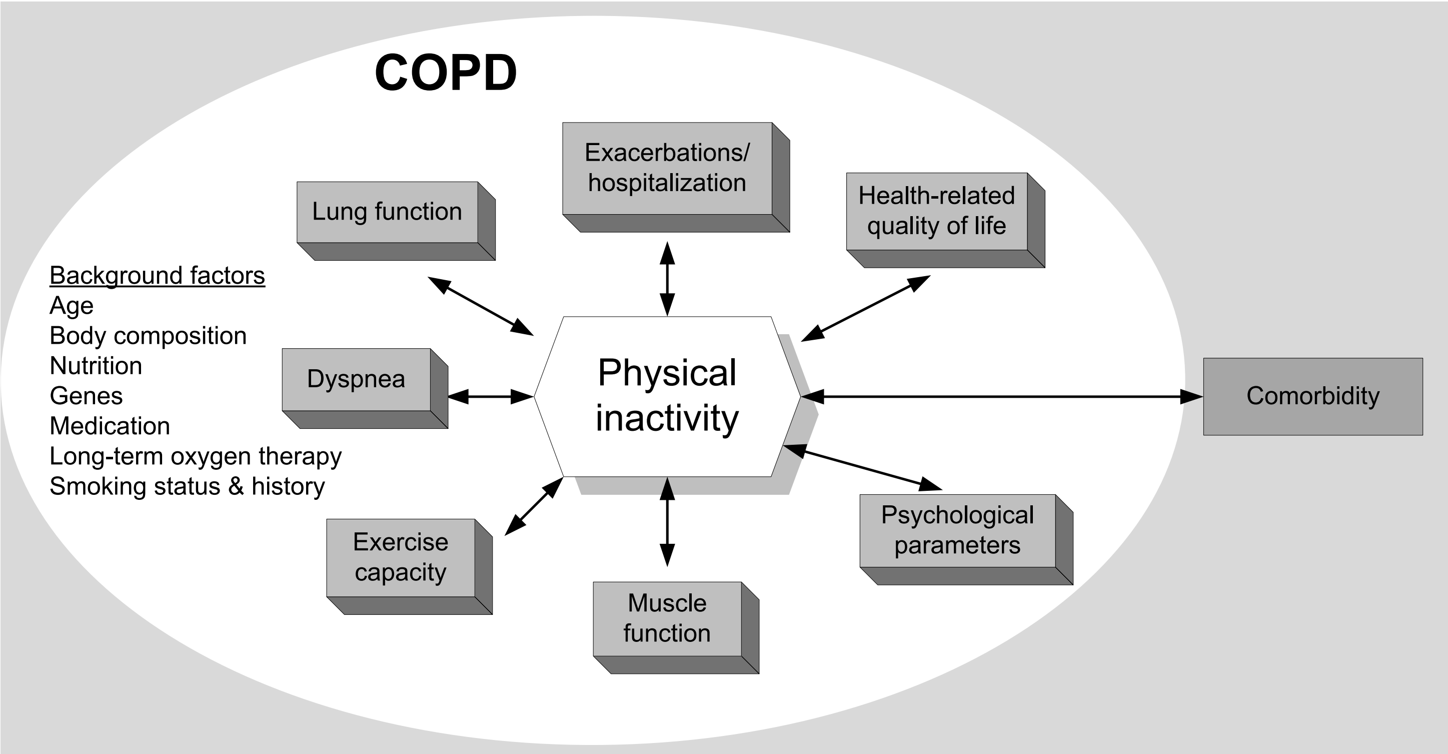

FIGURE 1. Theoretical framework of the role of physical activity in chronic obstructive pulmonary disease
The possible role and consequences of physical inactivity for important COPD outcomes are shown. These relationships are embedded in COPD-related background factors. Next to COPD-related factors, the presence of disease other than COPD (called comorbidity) may influence physical activity.

Authors' commentary

In the past decade, physical activity has increasingly been noticed as an important outcome variable in COPD and the literature on the role of physical activity in COPD patients is growing. The development of performance-based motion sensors (*e.g.,* pedometers and accelerometers) which are able to objectively measure the actual performed level of physical activity has given an important boost. Accelerometers are more technologically advanced devices, which detect body acceleration and are able to determine the quantity and intensity of movements. An extensive review on physical activity monitoring in COPD can be found in the reference list.[3] The results of this new research area are promising and indeed suggest that a higher physical activity level is healthy for most COPD patients. However, results are still inconsistent, which may be caused by small study samples or cross-sectional study designs. Moreover, a lot of different instruments are being used to measure physical activity, which complicates the comparison of results. Furthermore, the literature on the relationship between physical activity and psychological parameters is still limited.

The available literature shows that the physical activity level in COPD is generally low. Structured exercise programs show good results, but it is important that COPD patients integrate physical activity in their daily life and adopt an active lifestyle. More insight is necessary on the determinants of this physical activity level in order to develop more efficient programs to stimulate physical activity structurally in COPD patients. In our opinion, studies are needed that explore the strategies to enhance physical activity. Furthermore, the optimal embedment for these programs in the healthcare system needs to be established. Until now, much research has focused on the more severe COPD patients, however it is also useful to measure and already stimulate, if necessary, the level of physical activity of patients with mild and moderate COPD. This information can lead to the development of more structured physical activity enhancement programs that are suitable for COPD patients in all severity stages of their disease.

FIVE-YEAR VIEW

We are convinced that the interest in physical activity in COPD will persist and the knowledge about the role of physical activity in COPD will grow. We expect that the developments in ICT might have a huge influence on this field. The development and refinement of the performance-based motion sensors will continue. For example, accelerometers at this moment are mostly used in research settings but are becoming increasingly easier to use, and thus more applicable at home. Therefore, those instruments could be useful tools in the individually tailored stimulation of physical activity in COPD patients next to their measuring ability. This could also be useful in the fast developing field of home telemonitoring. The combination of these devices and computers/internet will provide the ability to give patients feedback on their physical activity level at their homes in a less time consuming and expensive manner. In 5 years, we expect that even more patients will be familiar with computer and internet use and therefore that these methods will become more easily applicable.

KEY ISSUES

- Regular physical activity has important health benefits in general.
- The level of physical activity in COPD is low compared with matched controls but also with other patient groups.
- Physical activity is positively associated with FEV_1, dyspnea, exercise capacity, muscle function, comorbidities, systemic inflammation, health-related quality of life and hospital admissions in COPD patients.
- Because of the many health benefits of physical activity in general and especially for COPD patients, it is important to improve the level of physical activity in COPD patients.
- More research is necessary on the modifiable predictors of a sedentary lifestyle in COPD patients.
- Structured exercise programs and pulmonary rehabilitation have shown important results for important outcome parameters in COPD, but the literature on the effect of the level of physical activity is limited and not convincing.
- Lifestyle physical activity enhancement should focus more on behavioral change in physical activity routines in daily life, and could result in better long-term outcomes. Such a strategy can exist next to but also complementary to structured exercise programs or pulmonary rehabilitation.

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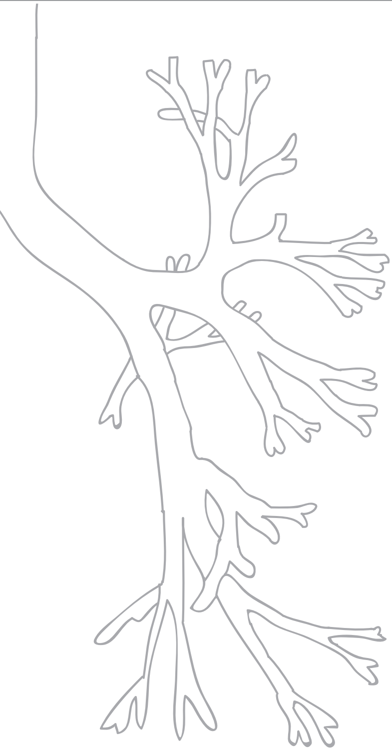
CHAPTER 3

Why are patients with Chronic Obstructive Pulmonary Disease physically active or sedentary?



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ABSTRACT

Background: The physical activity level in patients with Chronic Obstructive Pulmonary Disease (COPD) is low, and as a modifiable factor, physical activity is a potential treatment target. Clinical characteristics only incompletely reflect the physical activity level and potential psychosocial predictors are hardly investigated. Aim of this study was to assess physical activity and sitting time in COPD patients and to investigate their potential physical and psychosocial determinants.

Methods and results: We included 113 COPD patients. Physical activity, measured with an accelerometer (24hours/day), showed a mean locomotion and shuffling time per day of 6.8% (range:0.7-20.4). Reduced levels of physical activity were most prevalent in GOLD stage III-IV. Predictors of physical activity were higher self-efficacy, functional exercise capacity and lower lung hyperinflation. In GOLD stage I-II, higher self-efficacy and the spring/summer season were predictors, whereas in GOLD III-IV, worse lung hyperinflation, dyspnea severity, leg muscle function and oxygen use were. Predictors of sitting time in the total group were more positive perception on treatment control, less autonomous motivation to exercise, not using sleep medication and oxygen use.

Conclusion: In conclusion, both physical and psychosocial factors affected physical activity in COPD. The determinants of physical activity in the early stages of COPD were more generic, in contrast to the physical and disease-specific determinants in more severe stages. The determinants of sitting time were different from those of physical activity.

Keywords: COPD • lung hyperinflation • physical activity • sedentary lifestyle • self-efficacy

INTRODUCTION

Physical inactivity has shown to be a predictor of mortality in patients with Chronic Obstructive Pulmonary Disease (COPD).[1] Unfortunately, many COPD patients have a sedentary lifestyle.[2] Physical activity is a modifiable factor and is therefore an interesting and potential treatment goal in COPD. Increasing physical activity in these patients might be beneficial, since it may break the observed vicious circle of dyspnea-induced immobility, and subsequent deconditioning.[3] Furthermore, increasing physical activity has shown to decrease dyspnea severity and improve muscle function and quality of life.[4] The variation in physical activity between COPD patients is high[2] and to be able to reduce physical inactivity, it would be useful to explore the determinants of physical activity.

Physical inactivity could be caused by generic as well as COPD-specific factors. In general adult populations female gender, higher age, higher body weight, lower education, health problems and lower self-efficacy are shown to be associated with physical inactivity.[5,6] Furthermore, season and weather conditions are known to affect physical activity.[7]

COPD-specific factors that could affect the physical activity level are for example: lung function, lung hyperinflation, dyspnea severity, body composition, exercise capacity and muscle function. In several studies significant associations between these physical parameters and physical activity were observed, except for body composition, but results were inconsistent.[8,9] Since, COPD is a disease with high prevalence of comorbidity,[10] comorbidities could also affect physical activity. For example, joint problems and self-reported diabetes were shown to be related to reduced physical activity in COPD patients.[8] Additionally, the use of long term oxygen therapy (LTOT), and its subsequent limitation in mobility, could influence physical activity. However, the relation between LTOT and physical activity is not clear.[11,12]

Besides physical factors, psychosocial factors could explain the variation in physical activity in COPD patients. Unfortunately, psychosocial factors are less frequently investigated. Potential psychosocial determinants of physical activity could be social support, motivation to be physically active, depression, illness perception, self-efficacy and sleep quality. Studies found a significant association between physical activity and self-efficacy in physical activity and no association with depression.[8]

In the past decade, knowledge on the determinants of physical activity in COPD patients has importantly increased. However, a lot of studies underlying our knowledge had small sample sizes or specific COPD populations, and only a few studies investigated potential physical and psychosocial determinants. Therefore, it would be interesting to investigate whether the above described physical and psychosocial determinants contribute to physical activity in COPD patients with a broad range of disease severity.

The aims of this study are to assess 1) the level and variation of physical activity and sitting time in COPD patients; 2) the independent predictors of physical activity and sitting time, including physical and psychosocial variables; and 3) the association between physical activity and quality of life.

METHODS

Study population

Patients with mild to very severe COPD were recruited at outpatient clinics of general hospitals and from general practitioners. Patients were included if their FEV_1/FVC ratio post bronchodilator was below 0.7. Patients were excluded if they had a serious active disease that needed medical treatment (e.g. recent myocardial infarction, carcinoma) or treatment for a COPD exacerbation in the past 2 months. The study was approved by the local ethics committee and all patients provided informed consent.

Measurements

Physical activity

Physical activity was measured with a triaxial accelerometer, DynaPort (McRoberts, The Netherlands). Patients were instructed to wear the accelerometer day and night, for one week (24/7). The DynaPort has shown to be an accurate instrument for evaluating gait and postures in COPD patients.[13]

Biographical factors

Data on medication use, LTOT, number of exacerbations in the past year, smoking status, living situation and education level were reported. Seasons were split in two: spring and summer (April-September) versus autumn and winter (October-March). Comorbidity was assessed by the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).[14]

Physical determinants

Pulmonary function Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured using a spirometer (PFT, Masterscreen, Masterscope; Viasys) and residual volume (RV), total lung capacity and intrathoracic gas volume by body plethysmograpy (PFT; Viasys), both according to the ERS/ATS guidelines.[15,16]

Dyspnea severity was registered by the modified Medical Research Council dyspnea index (mMRC).[17]

Exercise capacity Maximal exercise capacity was measured by a symptom limited incremental cycle ergometer test (Bicycle ergometer: Jaeger ER 900L; Oxycon Pro, CareFusion) in line with the ATS/ACCP statement.[18] Functional exercise capacity by a 6-minute-walk-distance test (6MWD) according to the ATS guidelines.[19]

Leg muscle function was measured by a 30-seconds chair stand test.[20]

Body composition Fat free mass was measured by bioelectrical impedance (Bodystat-1500) and calculated with COPD and gender specific equations.[21] Body Mass Index (BMI) was calculated.
The BODE index, a multidimensional index combining BMI, FEV_1, mMRC and 6MWD was calculated.[22]

Psychosocial determinants

The influence of social support on physical activity was measured by the Dutch version of the social support for exercise behaviours scale questionnaire (SSQ).[23] Motivation to exercise by the Exercise Self-Regulation Questionnaire (SRQ-E).[24] Depression by the Beck Depression Inventory (BDI).[25] Illness perception by the revised version of the Illness Perception Questionnaire (IPQ-R).[26] Self-efficacy by the Dutch version of the Perceived Physical Ability Subscale questionnaire (LIVAS).[27] Sleep quality and disturbances by the Pittsburgh Sleep Quality Index (PSQI).[28]

Quality of life and health status

Quality of life was measured by a disease-specific questionnaire, the Saint Georges Respiratory Questionnaire (SGRQ)[29] and by a generic questionnaire, the RAND-36.[30] Health status by the Clinical COPD Questionnaire (CCQ).[31]

Statistical analyses

Patients were included in the analyses if they had worn the accelerometer for at least 4 full days, in accordance with literature.[32] A day was considered a valid measurement day if the device was worn for at least 94% of the day.[33] If patients did not wear the accelerometer during the night only, this time was recorded as lying. Physical activity outcomes were compared between GOLD stages and calculated quartiles of the BODE index using ANOVA or Kruskall-Wallis tests with Holm-Bonferroni adjustment. The sum of %locomotion and %shuffling during 24 hours was analyzed as outcome parameter for physical activity and %sitting during 24 hours for sitting time. Shuffling was defined as all movement from standing to standing that could not be classified as walking because of lower intensity or because the number of steps is less than 3. Pearson or Spearman correlation coefficients were calculated to test univariate associations between potential determinants and %locomotion&shuffling or %sitting, and between quality of life and physical activity. Differences between groups were tested using an independent sample T-test or a Mann-Whitney-U-test as appropriate for continuous variables. Stepwise backward linear regression analysis was performed to identify the independent predictors of %locomotion&shuffling or %sitting, with adjustment for age, gender and height. Variables were selected into the stepwise backward model if the p-value was <0.2 in univariate analysis. Table E1 shows the results of the univariate tests and variables that were included in the backward linear regression analyses. P-values <0.05 were considered statistically significant. Statistical analyses were performed using PASW statistics 18.

RESULTS

One hundred and fifteen COPD patients, that were on optimal medication, were included in the cross-sectional study and 113 patients (33% female, mean age 65 years and median FEV_1 52% predicted) wore the accelerometer for at least 4 full days and were included in the analyses. Patient characteristics per GOLD stage are shown in table 1.

TABLE 1. Patient characteristics per GOLD stage (n=113)

	GOLD I (n=30)	**GOLD II** (n=30)	**GOLD III** (n=32)	**GOLD IV** (n=21)	**p-value**
GOLD assessment, A/B/C/D¶	29/1/0/0	24/4/0/2	0/0/16/16	0/0/3/18	
Gender, female	8 (27%)	8 (27%)	10 (31%)	11 (52%)	0.174
Age, year	68.2 ± 8.9	64.4 ± 6.1	67.2 ± 8.2	57.8 ± 8.7	**<0.000**
Smoking status, current (%)	15 (50%)	9 (30%)	3 (9%)	3 (14%)	**0.001**
LTOT, yes	0 (0%)	0 (0%)	3 (9%)	11 (52%)	**<0.001**
BMI, kg/m^2	24.8 ± 2.1	26.3 ± 4.3	24.1 ± 3.3	25.3 ± 6.1	0.221
FFM, index	17.0 ± 1.9	17.5 ± 2.5	16.3 ± 1.7	16.2 ± 3.0	0.110
FEV_1*, % predicted	94 (82- 119)	64 (50- 79)	38 (30-49)	23 (14-29)	**<0.001**
RV, % predicted	122.6 ± 31.3	147.0 ± 36.4	190.7 ± 60.1	247.3 ± 61.6	**<0.001**
ITGV%TLC, %	59.1 ± 5.5	63.2 ± 6.9	73.1 ± 6.8	78.6 ± 4.5	**<0.001**
Peak VO_2, ml/min/kg	22.4 ± 4.8	19.7 ± 4.0	14.6 ± 3.7	12.0 ± 4.0	**<0.001**
Peak Workload, watt	135 ± 46	117 ± 34	63 ± 29	35 ± 22	**<0.001**
6MWD, meter	512 (358- 646)	521 (344- 641)	387 (60-600)	351 (175 - 576)	**<0.001**
mMRC dyspnea, score	1.0 (1-5)	2.0 (1-5)	2.5 (1-5)	4.0 (2-5)	**<0.001**
BODE index, score	0 (0-3)	1 (0-5)	3 (2-8)	6 (3-8)	**<0.001**
CIRS-G, total score	2.5 (0-10)	3.5 (0-6)	3.0 (0-9)	2.0 (0-8)	0.445
CCQ, total score	0.7 (0.2 - 4.6)	1.6 (0-4.6)	1.9 (0.1-4.4)	2.5 (0.6-4.4)	**<0.001**
Self-efficacy, LIVAS total score	33.5 ± 7.7	28.7 ± 8.4	26.8 ± 6.8	27.5 ± 5.6	**0.004**
SSQ, family positive score	12 (10-24)	14 (10-40)	12 (10-29)	18 (10-39)	**0.031**
SSQ, family negative score	3 (3-9)	3 (3-7)	3 (3-7)	3 (3-7)	0.456
SSQ, friends positive score	5 (5-16)	5 (5-20)	5 (5-13)	5 (5-16)	0.219
BDI, total score	3.0 (0-25)	5.5 (0-30)	6.0 (1-17)	9.0 (1-22)	0.071

*Data are presented as n, mean ± SD or median (range). Differences between groups were tested with ANOVA, Kruskal-wallis or Chi-Square. ¶Combined COPD assessment with use of the mMRC scale (GOLD 2011). *Post bronchodilator. LTOT: long term oxygen therapy, BMI: body mass index, FFM: fat free mass, FEV_1: forced expiratory volume in 1 second, RV: residual volume, ITGV: intra thoracic gas volume, TLC: total lung capacity, VO_2: oxygen uptake, 6MWD: 6-minute walk distance, mMRC: modified medical research council, CIRS-G: cumulative illness rating scale for geriatrics, CCQ: clinical COPD questionnaire, SSQ: social support for exercise behaviour scale questionnaire, BDI: Beck depression inventory.*

Figure 1 shows the physical activity variables per GOLD stage and BODE quartile. Locomotion and shuffling time and steps per day did not differ between GOLD stage I and II, all other GOLD stages significantly differed, with lower physical activity in more severe COPD (table 2). All BODE quartiles significantly differed in locomotion and shuffling time, and only BODE quartile I and II did not differ in steps per day (table E1). Furthermore, the ranges in physical activity outcomes were large within GOLD stage or BODE quartile. Sitting time during the day was not significantly different between GOLD stages or BODE quartiles.

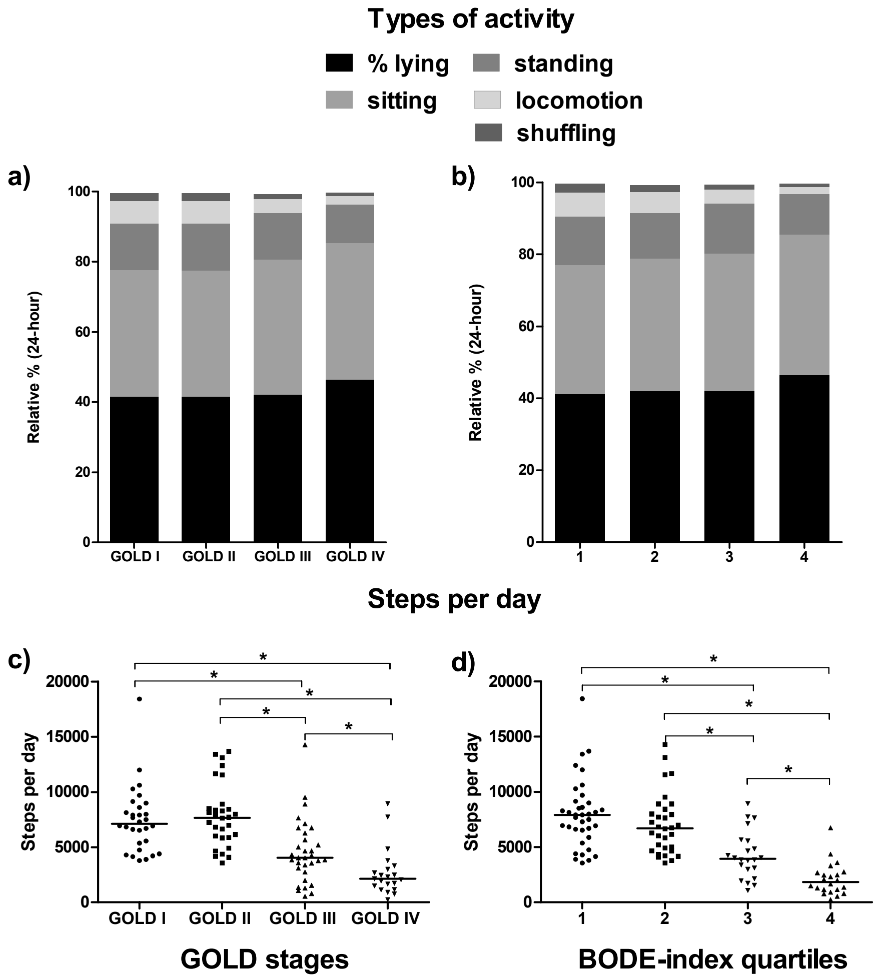

FIGURE 1. Distribution of types of activity and steps per GOLD stage or BODE-index quartile.
*a) distribution types of activity, mean percentage relative time per 24 hour per GOLD stage. b) distribution types of activity, mean percentage relative time per 24 hour per BODE-index quartile. c) steps per day per GOLD stage. d) steps per day per BODE-index quartile. BODE quartiles: 1= BODE score 0, 2= BODE score 1&2, 3=BODE score 3&4, 4=BODE score 5-8. *significant difference between groups; p<0.05.*

TABLE 2. Physical activity per GOLD stage (n=113)

	GOLD I (n=30)	**GOLD II** (n=30)	**GOLD III** (n=32)	**GOLD IV** (n=21)	**p-value**
Steps, per day	7117 (3796-18433)	7667 (3556-13680)	4034 (541-14281)	2136 (236-8944)	**<0.001**[#1]
Locomotion & shuffling time, % per day	8.3 (4.6-20.4)	8.3 (4.4-15.3)	5.1 (1.0-12.0)	2.9 (0.7-8.8)	**<0.001**[1]
Standing time, % per day	13.0 (5.5-24.2)	12.9 (7.4-19.6)	12.3 (3.7-30.8)	10.6 (4.4-21.7)	0.298
Sitting time, % per day	36.6 (22.6-49.1)	35.9 (21.0-50.6)	39.4 (13.3-64.4)	40.6 (19.8-53.4)	0.440
Lying time, % per day	40.7 (31.1-59.6)	39.8 (29.5-56.5)	40.1 (30.3-73.2)	43.7 (34.6-67.6)	0.378[#]
Physical Activity Level (PAL)	1.70 (1.51-2.04)	1.71 (1.45-1.98)	1.55 (1.38-1.85)	1.46 (1.32-1.84)	**<0.001**[1]
Movement intensity locomotion, g	0.188 (0.151-0.302)	0.207 (0.133-0.286)	0.175 (0.130-0.246)	0.173 (0.131-0.257)	**0.001**[#2]

Data are presented as median (range). g= average body acceleration. Differences between groups were tested with ANOVA or [#]Kruskal Wallis with Holm-Bonferroni adjustment. [1]There was no difference between GOLD stage I and II, all other GOLD stages were significantly different from each other. [2]GOLD stage II was significantly different compared to GOLD stage III and IV.

TABLE 3. Stepwise backward linear regression analyses with percentage locomotion & shuffling as dependent variable

a) Total population (R^2 0.56)			
Variable	**B**	**Std. Error**	**p-value**
Self-efficacy (LIVAS score)	0.096	0.034	**0.006**
6MWD (meter)	0.015	0.003	**<0.001**
RV (liter)	-0.612	0.200	**0.003**
b) GOLD I & II (R^2 0.25)			
Variable	**B**	**Std. Error**	**p-value**
Self-efficacy (LIVAS score)	0.161	0.051	**0.003**
Season (0=spring/summer)	-1.895	0.745	**0.014**
c) GOLD III & IV (R^2 0.66)			
Variable	**B**	**Std. Error**	**p-value**
RV (liter)	-0.538	0.170	**0.003**
Dyspnea (mMRC score)	-0.763	0.273	**0.008**
Chair stand test (number)	0.414	0.097	**<0.001**
LTOT (0=no)	-1.529	0.558	**0.009**

Analyses were adjusted for age, gender and height.
6MWD: 6-minute walk distance, RV: residual volume, mMRC: modified medical research council index, LTOT: long term oxygen therapy.

Determinants of physical activity (%locomotion and shuffling 24-hours)

Total group

Higher physical activity was significantly associated with higher functional and maximal exercise capacity, less airway obstruction, static lung hyperinflation and dyspnea severity, better leg muscle function, lower number of exacerbations, better illness perception scores (various IPQ-R subscales), lower depression score, higher self-efficacy in physical ability and more autonomous motivation to exercise. Physical activity was significantly lower in LTOT users and during autumn/winter (table E2).
Higher self-efficacy, higher 6MWD and lower RV were significant independent predictors of higher physical activity (R^2=0.56; table 3a). The number of steps per day was associated with the same independent predictors.

3

Mild to moderate COPD (GOLD I and II)

Higher physical activity was significantly associated with higher 6MWD, and physical activity was significantly lower in autumn/winter (table E1).
Higher self-efficacy and physical activity measured in spring or summer were significant independent predictors of higher physical activity (R^2=0.25; table 3b).

Severe to very severe COPD (GOLD III and IV)

Higher physical activity was significantly associated with higher functional and maximal exercise capacity, less airway obstruction, static lung hyperinflation and dyspnea severity, better leg muscle function, better subscale score 'consequences' of the Illness perception questionnaire and lower depression score. Additionally, physical activity was significantly lower in LTOT users (table E1).
Lower RV, less dyspnea severity, better leg muscle function and not using LTOT were significant independent predictors of higher physical activity (R^2=0.66; table 3c).

Physical activity and Quality of life and health status

Physical activity was significantly associated with all subscales and total score of the SGRQ and CCQ (table E3). All subscales of the RAND-36 except for the subscales mental health and bodily pain were significantly associated with physical activity.

Determinants of sitting time (%sitting 24-hours)

Total group

Higher sitting time was significantly associated with higher number of exacerbations in the past year, lower functional exercise capacity and less autonomous motivation for exercise (SRQ-E subscales; external regulation and introjected regulation). Sitting time was significantly higher in LTOT users, in patients who do not use sleep medication and in patients living together with others (table E1).
More positive perception on treatment control (IPQ-R), higher introjected regulation in exercise ('taking on other's values'-SRQ-E), not using sleep medication and use of LTOT were significant independent predictors of higher sitting time (R^2=0.26; table 4a).

Mild to moderate COPD (GOLD I and II)

Higher sitting time was significantly associated with higher fat free mass and more positive perception on treatment control (IPQ-R).
Higher introjected regulation and higher number of exacerbations in the past year were significant independent predictors of higher sitting time (R^2=0.23; table 4b).

Severe to very severe COPD (GOLD III and IV)

Higher sitting time was significantly associated with external regulation in exercise ('no choice others make me do it'-SRQ-E) and was significantly higher in LTOT users.
Using LTOT was a significant independent predictor of higher sitting time (R^2=0.16; table 4c).

TABLE 4. Stepwise backward linear regression with percentage sitting as dependent variable

a) Total population (R^2 0.26)			
Variable	**B**	**Std. Error**	**p-value**
LTOT (0=no)	8.143	2.360	**0.001**
Treatment control (IPQ-R score)	0.627	0.239	**0.010**
Introjected regulation (SRQ-E score)	1.381	0.560	**0.015**
Use sleep medication (0=no)	-4.511	2.264	**0.049**
b) GOLD I & II (R^2 0.230)			
Variable	**B**	**Std. Error**	**p-value**
Introjected regulation (SRQ-E score)	1.722	0.792	**0.035**
Number of exacerbations (number)	3.312	1.476	**0.030**
c) GOLD III & IV (R^2 0.164)			
Variable	**B**	**Std. Error**	**p-value**
LTOT (0=no)	8.449	3.120	**0.009**

Analyses were adjusted for age, gender and height.
LTOT: long term oxygen therapy, IPQ-R: illness perception questionnaire-revised, SRQ-E: exercise self-regulation questionnaire.

CONCLUSION AND DISCUSSION

Our study showed that reduced levels of physical activity were most prevalent in severe or very severe COPD patients, and that the variation in physical activity was high, even within GOLD stages or BODE quartiles. Physical activity was significantly associated with both physical and psychosocial factors. Self-efficacy, functional exercise capacity and static lung hyperinflation were identified as important determinants of physical activity. The determinants of physical activity in mild to moderate COPD were mainly generic, in contrast to the disease-specific determinants in (very) severe COPD. Physical activity was positively associated with almost all domains of quality of life and health status. Sitting time did not differ between GOLD stages or BODE quartiles and the determinants of sitting time differed from those of physical activity.

3

The largest difference in physical activity was present between GOLD stage II and III patients. This is in line with two studies, that furthermore demonstrated comparable number of steps/day in the GOLD stages.[33,34] The same studies also showed that the physical activity level of patients with GOLD stage I was not significantly different from matched controls, whereas patients with GOLD stage II did not differ in some physical activity outcomes.[33,34] This suggest that at approximate 50% of FEV_1 %predicted, patients start to become limited by their ventilator capacity. Furthermore, we found a high variation in physical activity within GOLD stages, which confirms that severity of airway obstruction alone does not explain the variation in physical activity. The BODE-index (containing besides lung function also exercise capacity, dyspnea and body mass index) was slightly stronger correlated with physical activity, however the variation was still high within quartiles, confirming that other factors also play a role.

Self-efficacy in physical ability, static lung hyperinflation and functional exercise capacity were determinants of physical activity. In line with our results, 2 studies found a positive association between self-efficacy and physical activity.[35,36] Self-efficacy has shown to be a strong predictor of exercise adherence,[37,38] and therefore might be an interesting treatment target for physical activity enhancement programs.
RV, contrary to FEV_1 was an independent predictor of physical activity. This is in line with the finding that lung hyperinflation is stronger associated with patient-centered outcomes than FEV_1,[39] suggesting that lung hyperinflation is importantly affecting physical activity. The finding that the 6MWD is a strong determinant of physical activity in COPD is consistent with results from many previous studies.[8] Interestingly, cycle ergometry outcomes in our study were significantly associated with physical activity but not identified as independent determinants. This supports the suggestion that the 6MWD gives a better reflection of the physical conditions needed to perform physical activity than a cycle ergometer test. Another study also found that 6MWD and lung hyperinflation were independent determinants of physical activity, while cycle ergometry outcomes were not.[9]

The determinants of physical activity were different between GOLD stages. In mild to moderate COPD patients, self-efficacy and season were identified as determinants. Probably, COPD patients in an early stage are less restricted by their disease and more influenced by general factors. These results suggest that improving self-efficacy in physical ability might be an attractive treatment target in an early stage of COPD. Furthermore, the influence of weather type on physical activity should be reduced, for example by discussing with the patient back-up activities in case of bad weather. Perhaps, COPD-specific physical activity enhancement is not necessary in the early disease stages, but to prevent physical inactivity in later stages, sedentary lifestyles should already be addressed. In (very) severe COPD patients, higher RV, higher dyspnea severity, worse leg muscle function and LTOT use were identified as determinants of low physical activity. These are more physical disease-specific factors. Apparently, symptoms are the main limiting factor for physical activity in more severe COPD.

A number of variables that we expected to be associated with physical activity were not, *e.g.* social support, sleep quality, comorbidity and body composition. Social support has been shown to improve exercise behaviour.[40] In our study, COPD patients reported low social support scores and therefore might hardly experience social support in that perspective. Involving significant others in the enhancement of physical activity could be important. Poor sleep quality could lead to fatigue during the day and consequently lower physical activity. However, although 29% of our patients were identified as poor sleepers (assessed by PSQI score> 5[28]) we found no association between sleep quality and physical activity. Contrary to other studies, we found no association between comorbidity and physical activity. An explanation could be that other studies used specific disease groups and not a composite index-score like we did. In our sample the numbers of patients in specific disease groups were too small to analyse separately. In line with previous studies in COPD we found no association between physical activity and fat free mass or BMI.[8] Apparently, in COPD patients body composition does not affect physical activity, in contrast to the general elderly population.[5]

Unexpectedly, sitting time during the day did not differ significantly between GOLD stages and BODE quartiles. However, patients with GOLD stage III-IV sat approximately 40 minutes per day longer than patients with GOLD stage I-II. This could be clinically relevant as sitting time has found to be associated with an increased risk of mortality, even independent of leisure time physical activity.[41] Our study demonstrated that the explained variances of the regression models with sitting time as dependent variable were much lower than those of physical activity models, indicating poorer predictive properties. This finding is consistent with one study in COPD patients and one in a general population.[42,43] The determinants of sitting time were more positive perception on treatment control, less autonomous motivation for physical activity, not using sleep medication and use of LTOT. The use of LTOT is clearly interfering with the mobility of the patients. Less autonomous motivation for physical activity could indicate a passive attitude towards the disease and physical activity, while the association between more positive perception on treatment control and higher sitting time is not clear. Opposite to what we expected, use of sleep medication was associated with lower sitting time. However, the patients that used sleep medications also had a higher lying time compared to the patients who did not use sleep medication. Apparently, this subset of patients might lay down rather than sit down during the day when feeling tired.

A strength of the study is that we investigated COPD patients from all severity stages of the disease, using an extensive list of both physical and psychosocial measurements. Unfortunately, we did not measure inflammation, which was also shown to affect physical activity.[44] Furthermore, our study lacked a control group and it would be interesting to investigate if determinants of physical activity differ between healthy subjects and COPD patients. Another strength of the study was measuring physical activity with a well-validated triaxial accelerometer.[13] However, this device is not able to measure non-ambulatory activities, like cycling or swimming. This may have led to underestimation of physical activity. We choose to use the percentage of activity or sitting during 24 hours, to include all physical activity and sitting time during the day. Unfortunately, there is no consensus yet on physical activity measurement duration of the day in COPD research, which makes it difficult to compare outcomes.

In conclusion, both physical and psychosocial factors affected physical activity in COPD patients. Decreased physical activity was strongest in more severe stages of the disease, in which the patients were mainly limited by physical disease-specific factors. In less severe COPD patients the determinants of physical activity were more generic and less COPD-specific. Our results could be useful for identifying starting points in the enhancement of physical activity in COPD patients with a sedentary lifestyle in all severity stages of the disease.

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SUPPLEMENTARY DATA

TABLE E1. Physical activity per BODE quartile (n=113)

	BODE I (n=37)	**BODE II** (n=32)	**BODE III** (n=22)	**BODE IV** (n=22)	**p-value**
Steps, per day	7906	6689	3940	1827	**<0.001**#1
	(3556-18433)	(3557-14281)	(1082-8944)	(236- 6737)	
Locomotion & shuffling time, % per day	9.1	7.6	5.1	2.6	**<0.001**2
	(4.9-20.4)	(4.4-15.3)	(1.2-8.8)	(0.7-8.1)	
Standing time, % per day	13.3	12.4	12.8	11.1	0.301
	(6.0-24.1)	(5.5-19.7)	(4.1-30.8)	(3.7-22.4)	
Sitting time, % per day	36.4	35.7	39.4	40.8	0.513
	(22.6-49.1)	(21.0-50.6)	(13.3-64.4)	(18.8-55.8)	
Lying time, % per day	40.3	39.3	40.9	45.9	0.183#
	(31.1-55.5)	(29.5-59.6)	(30.3-73.2)	(35.0-67.6)	
Physical Activity Level (PAL)	1.73	1.67	1.55	1.45	**<0.001**2
	(1.51-2.04)	(1.45-1.98)	(1.35-1.84)	(1.32-1.57)	
Movement intensity locomotion, g	0.202	0.191	0.178	0.169	**<0.001**#3
	(0.151-0.302)	(0.133-0.286)	(0.130-0.257)	(0.131-0.221)	

Data are presented as median (range). g= average body acceleration.
Differences between groups were tested with ANOVA or #Kruskal-wallis with Holm-Bonferroni adjustment.
[1]There was no difference between BODE quartile I and II, all other BODE quartiles were significantly different from each other. [2]All BODE quartiles were significantly different. [3]BODE quartile II was significantly different compared to BODE quartile III and IV.

Legend table 2a:
*All values are Spearman's rho, except for #Pearson correlation coefficient.*p<0.20, **p<0.05, ***p<0.001, the variables indicated with these symbols were included in the regression analyses. ¶post bronchodilator. FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; RV: residual volume, ITGV: intra thoracic gas volume; BMI: body mass index; FFM: fat free mass; VO_2: oxygen uptake; 6MWD: six-minute walk distance; CIRS-G: cumulative illness rating scale for geriatrics; mMRC: modified medical research ; IPQ-R: illness perception questionnaire-revised; BDI: beck depression inventory; LIVAS: dutch version of the perceived physical ability subscale questionnaire; SRQ-E: self-regulation questionnaire- exercise; PSQI: Pittsburgh sleep quality index.*

TABLE E2a. Univariate associations between potential predictor variables and percentage locomotion & shuffling or percentage sitting

		Total group (n=113)		**GOLD I + II (n= 60)**		**GOLD III + IV (n= 53)**	
		%locomotion & shuffling	%sitting	%locomotion & shuffling	%sitting	%locomotion & shuffling	%sitting
Physical factors		**Correlation coefficient**		**Correlation coefficient**		**Correlation coefficient**	
Age, year	#	0.183*	0.098	0.015	0.180*	0.209*	0.092
Height, cm	#	0.094	0.067	-0.004	0.146	-0.024	0.056
Packyears, year		0.023	-0.001	-0.146	-0.077	0.000	0.074
Exacerbations, number		**-0.312****	**0.261****	-0.038	0.227*	-0.245*	0.195*
FEV_1¶, liter		**0.621*****	-0.141*	0.029	0.130	**0.478*****	-0.057
FEV_1/FVC¶, %	#	**0.578*****	-0.156*	0.003	-0.063	**0.458****	-0.053
RV, liter	#	**-0.520*****	0.078	-0.090	-0.090	**-0.426****	0.024
ITGV/TLC, %	#	**-0.576*****	0.162*	-0.066	-0.054	**-0.456****	0.176
BMI, kg/m^2	#	0.026	0.086	-0.049	**0.263****	-0.077	0.013
FFM, index	#	0.156*	0.054	-0.007	**0.294****	0.071	-0.061
Peak VO_2max, ml/min/kg	#	**0.503*****	-0.047	0.046	0.084	**0.511*****	-0.073
Peak Workload, watt	#	**0.569*****	-0.098	0.056	0.124	**0.624*****	-0.134
6MWD, meter		**0.744*****	**-0.233****	**0.438*****	-0.123	**0.735*****	-0.219*
CIRS-G, total score		0.013	-0.097	0.115	-0.005	-0.053	-0.151
mMRC, score		**-0.609*****	0.105	-0.081	0.008	**-0.603*****	-0.076
Chair stand, number	#	**0.404*****	-0.173*	0.200*	-0.119	**0.528*****	-0.170
Psychosocial factors							
IPQ-R, consequences	#	**-0.464*****	0.067	-0.190*	0.166	**0.296****	-0.118
IPQ-R, Treatment control	#	0.153*	0.176*	0.005	**0.275****	0.139	0.154
IPQ-R, Illness coherence	#	-0.168*	-0.036	0.024	-0.103	0.003	-0.064
IPQ-R, emotional representations		**-0.233****	0.024	-0.076	0.198*	-0.226*	-0.156
Depression, BDI total score		**-0.229****	0.009	-0.076	0.059	**-0.278****	-0.090
Self-efficacy, LIVAS total score	#	**0.324*****	-0.082	0.202*	-0.021	0.237*	-0.071
SRQ-E, RAI index	#	**0.210****	-0.124*	0.130	-0.036	0.191*	-0.151
SRQ-E, external regulation		**-0.227****	**0.245****	-0.018	0.132	**-0.316****	**0.302****
SRQ-E, introjected regulation		**-0.197****	**0,198****	-0.043	0.207*	**-0.283****	0.219*
SRQ-E, identified regulation		0.046	0.109	**0.273****	0.061	-0.097	0.137
SRQ-E, intrinsic motivation		0.094	-0.046	0.163	-0.077	-0.023	0.022
Social support, family positive		-0.075	0.045	0.035	-0.072	-0.126	0.041
Social support, familiy negative		0.012	-0.030	0.040	-0.052	-0.044	-0.027
Social support, friends positive		0.070	-0.005	0.050	-0.008	-0.028	0.062
Sleep quality, PSQI total score		0.023	-0.047	-0.067	-0.072	0.034	0.002

TABLE E2b. Comparisons between groups in %locomotion & shuffling or %sitting with student t-test or ANOVA

		Total group (n=113)				GOLD I + II (n=60)				GOLD III + IV (N=53)			
		%locomotion & shuffling		%sitting		%locomotion & shuffling		%sitting		%locomotion & shuffling		%sitting	
		%	p-value	%	p-value	%	p-value	%	p-value	%	p-value	%	p-value
LTOT	user	3.04	**<0.001****	43.54	**0.002****		na		na	3.04	**0.008****	43.54	**0.025****
	non-user	7.33		36.37						5.12		36.86	
Gender	male	7.10	0.182*	37.72	0.403	8.85	0.726	37.26	**0.021****	4.70	0.646	38.34	0.795
	female	6.17		36.31		8.54		32.69		4.37		39.06	
Smoke status	current	7.13	0.541	36.03	0.352	7.99	0.093*	35.78	0.809	3.68	0.375	37.03	0.674
	not	6.68		37.70		9.28		36.22		4.68		38.83	
Work status	working	7.55	0.428	37.87	0.790	8.40	0.707	36.01	0.989	5.85	0.305	41.58	0.532
	non-working	6.71		37.18		8.82		36.05		4.47		38.38	
Sleep status[¶]	good sleeper	6.77	0.905	37.85	0.233	9.12	0.190*	36.16	0.859	4.49	0.672	39.50	0.230
	poor sleeper	6.86		35.76		8.07		35.82		4.85		35.65	
Use sleep medication	yes	6.90	0.906	32.58	**0.025****	9.25	0.617	31.89	0.065*	3.77	0.422	33.50	0.171*
	no	6.78		37.92		8.69		36.68		4.67		39.28	
Living situation	alone	7.66	0.113*	34.64	**0.046****	9.02	0.654	34.28	0.177*	5.31	0.289	35.27	0.201
	with others	6.49		38.20		8.65		36.86		4.38		39.50	
Season	April - September	7.45	**0.049****	36.05	0.137*	9.47	**0.030****	35.01	0.182*	4.19	0.384	37.74	0.595
	October - March	6.17		38.40		7.84		37.40		4.82		39.21	
Education level	low	6.68	0.879	36.69	0.635	8.51	0.423	35.50	0.566	4.56	0.298	38.07	0.872
	middle	6.89		38.48		9.66		37.78		3.90		39.24	
	high	7.14		37.60		8.40		35.60		5.71		39.85	

**p<0.20, **p<0.05, the variables indicated with these symbols were included in the regression analyses.*
[†]Sleep status was based on the Pittsburgh sleep quality index (PSQI), poor sleeper= PSQI total score > 5.

TABLE E3. Univariate association between quality of life or health status and percentage locomotion & shuffling in the total group (n=113)

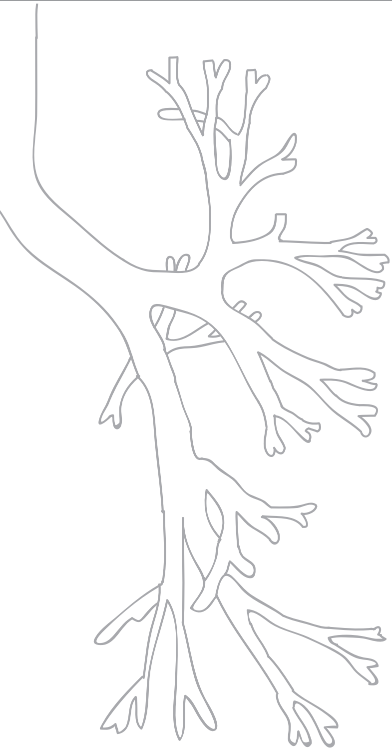
CCQ		**Correlation coefficient**	**p-value**
Symptom		-0.257	**0.006**
Functional state		-0.476	**<0.001**
Mental state		-0.298	**0.001**
Total score	#	-0.418	**<0.001**
SGRQ			
Symptoms	#	-0.255	**0.007**
Activity	#	-0.558	**<0.001**
Impacts		-0.479	**<0.001**
Total score	#	-0.503	**<0.001**
RAND-36			
Physical functioning		0.578	**<0.001**
Social functioning		0.281	**0.003**
Role physical		0.478	**<0.001**
Role emotional		0.235	**0.012**
Mental health		0.060	0.530
Vitality	#	0.247	**0.008**
Bodily pain		0.008	0.934
Health perceptions	#	0.285	**0.002**

All Spearman's rho, except for #Pearson correlation coefficient. CCQ: Clinical COPD Questionnaire, SGRQ: St. Georges Respiratory Questionnaire.

3

Self-reported barriers and facilitators to physical activity in patients with Chronic Obstructive Pulmonary Disease

4 CHAPTER



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ABSTRACT

Background: The level of physical activity in COPD patients is low, however qualitative data on why some patients are active and others are sedentary are scarce. Aim of this study was to investigate the personal reasons why COPD patients are physically active or sedentary using qualitative research methods, and to assess the relationship between those reasons and the actual measured level of physical activity.

Methods: We included 115 patients with mild to very severe COPD (68% male, mean age 65 years, FEV_1 57.5%predicted). Patients underwent a semi-structured interview.

Results: The most frequently reported reason to be physically active was health benefits, followed by enjoyment, continuous active lifestyle in the past and functional reasons. The most frequently reported reason to be sedentary was weather, followed by health problems and lack of intrinsic motivation. Mean steps per day ranged between 236 and 18433 steps (tri-axial accelerometer). A high physical activity level was related to enjoyment and self-efficacy in physical activity. A low physical activity level was related to weather influencing health, financial constraints, health and shame.

Conclusions: In conclusion, we identified important facilitators and barriers to be physically active, which is very useful for the enhancement of physical activity in sedentary COPD patients.

Keywords: COPD • interview • physical activity • sedentary lifestyle • self-efficacy

INTRODUCTION

Regular physical activity has many health benefits for the general population including patients with Chronic Obstructive Pulmonary Disease (COPD).[1] Although COPD is a chronic progressive disease, regular physical activity has shown to improve exercise capacity and muscle function, and to decrease feelings of fatigue and dyspnea.[2] These benefits increase the independence of the patients and improve their quality of life. Furthermore, physical activity has shown to be an independent predictor of mortality in COPD.[3,4] Despite the observed beneficial health effects of regular physical activity in COPD, the physical activity level appears to be low.[5]

As it is important to increase the physical activity level in COPD patients, it is necessary to unravel its determinants. Several studies found significant associations between physical activity and lung function, dyspnea severity, exercise capacity, muscle function, comorbid conditions, systemic inflammation, self-efficacy in physical activity and health-related quality of life.[6] We may conclude that the main focus is on physical determinants, leaving the potential large role of psychosocial or behavioural determinants neglected. Furthermore, it also has been shown that improving these features, *e.g.* by following a pulmonary rehabilitation program, does not automatically lead to a higher physical activity level.[7]

To be able to increase the physical activity level of COPD patients it would be very helpful to gain more insight in the patients' own thoughts and ideas on physical activity. Exploring the reasons why COPD patients are physically active or sedentary and the opportunities and barriers they experience, could provide additional information and starting points to stimulate physical activity in these patients. A good method to investigate the reasons to be physically active or sedentary is by performing qualitative research (*e.g.* by means of an interview), because this will provide detailed insight in behavioural aspects related to physical activity. Frequently reported reasons to be physically active in the general elderly population are: health concerns, socialization, facilities, physician encouragement and purposeful activity, whereas frequently reported reasons to be sedentary are: lack of time, fear of injury, tiredness, lack of discipline, inadequate motivation, boredom, intimidation (afraid to slow others down), poor health, physical environment, lack of knowledge and understanding the relationship between physical activity and health.[8-10] However, to be able to increase the physical activity level particularly in COPD patients we assume it is necessary to identify COPD-specific reasons to be physically active or sedentary. To our knowledge, the personal reasons to be physically active or sedentary are hardly studied yet using qualitative research methods in COPD patients. Furthermore, it would be interesting to investigate how these personal reasons relate to the patient's physical activity level. We suggest this could lead to a tailor made strategy to enhance daily physical activity in COPD patients.

The aim of this study is to gain insight in the personal reasons why COPD patients are physically active or sedentary using qualitative research methods. Additional aim is to assess the relationship between those reasons and the actual measured physical activity level of these patients.

METHODS

Patients with mild to very severe COPD were asked by their general practitioner or lung physician at outpatient clinics of general hospitals in the northern part of the Netherlands to participate in this study. Patients were included in this cross-sectional study if they had COPD according to the GOLD criteria.[11] Comorbidity was allowed but patients were excluded if they had serious active disease that needed medical treatment (*e.g.* recent myocardial infarct, carcinoma), or if they were treated for a COPD exacerbation in the past 2 months. All patients provided informed consent and the study was approved by the local ethics committee.

Interview

All patients were interviewed at home by one trained interviewer (JH) and the duration of the interview was approximately one hour. The interviews were semi-structured; a framework of themes related to physical activity guided the interviewer. The framework of themes was based on literature and finalised after discussion with medical experts and 2 COPD patients. The themes were: history of physical activity, experiences with physical activity, reasons to be physically active or sedentary, cognitions about physical activity and opportunities and barriers to become physically active. Interview questions were open and the framework guided the interviewer but unanticipated themes were allowed. During the interview the interviewer made notes and those were written down extensively directly after the interview.

Analyses

Answers to the questions raised during the interview were coded into categories using the inductive content analysis approach. The aim of this qualitative research technique is to attain a condensed and broad description of the phenomenon and the outcome of the analysis are categories describing the phenomenon.[12] The approach includes open coding, creating categories and abstraction.[12] Each interview transcript was red several times, and afterwards keywords in the text were labelled with codes and grouped into similar concepts, after that categories were formed. To increase consensus, the coding process was separately performed by 2 persons (JH and MG) and afterwards compared and discussed. Disagreements were resolved through discussion with the other authors.
We combined the qualitative analysis with a quantitative analysis to be able to assess the relationship between the personal reasons and the actual measured physical activity level.

To assess the relation between the obtained categories and the actual physical activity level, a k-means cluster analysis was performed using PASW statistics 18 (SPSS Inc., Chicago, IL, USA). Cluster analysis is a descriptive statistical method that attempts to identify relatively homogeneous groups of patients based on patient characteristics.

Physical activity

Physical activity was measured with a triaxial accelerometer: DynaPort (McRoberts, The Netherlands). The DynaPort is a small device that is worn around the waist. Patients were instructed to wear the DynaPort continuously for one week, except during showering and swimming. The DynaPort is able, int. al. to detect types of (in)activity and to measure steps. The DynaPort has shown to be an accurate instrument to measure postures and gait in older adults and COPD patients.[13,14]

Other measurements

Lung function (forced expiratory volume in 1 second and forced vital capacity) was measured by trained lung function technicians with a spirometer (PFT, Masterscreen, Masterscope; Viasys) according to the ERS/ATS guidelines.[15] Dyspnea severity was determined by the modified medical research council dyspnea index.[16] Exercise capacity was measured with the 6-minute-walk distance test.[17]

RESULTS

A total of 115 COPD patients were included and interviewed and performed all other measurements. Patient characteristics are shown in table 1. Patients were predominantly male (68%), with mild to very severe COPD and with a median number of steps per day of 5552. Twenty-eight percent of these patients claim they should be more physically active, 47% claim to be sufficiently active and 25% claim they are not able to be more physically active due to health problems.

TABLE 1. Patient characteristics (n=115)

Sex, male (%)	78 (68)
Age, years	65 ± 8.7
GOLD, I/II/III/IV	30/31/33/21
FEV_1, % predicted	57.5 ± 27.8
Employed, yes (%)	13 (11.3)
BMI, kg/m^2	25.1 ± 4.0
6MWD, meter	437 ± 118
mMRC, score	2.4 ± 1.2
Physical activity (n=113)	
Steps, per day	5552 (236-18433)
Lying & sitting, %	79.8 ± 7.2

Data are presented as n (%), mean ± SD or number/n/n/n. GOLD: Global Initiative for Chronic Obstructive Lung Disease, FEV_1: forced expiratory volume in 1 second, 6MWD: 6-minute walk distance, BMI: body mass index, mMRC: modified medical research council dyspnea index.

Reasons to be physically active	
Health benefits	65.2%
Enjoyment	43.5%
Continuous active lifestyle in the past	27.8%
Functional	26.1%
Number of reasons reported, (*n 1/2/3/4)*	47/57/5/6

Reasons to be sedentary	
Poor weather	47.8%
Health problems	42.6%
Lack of intrinsic motivation	11.3%
Miscellaneous answers	15.7%
None	20.0%
Number of reasons reported, *(n 0/1/2/3)*	23/54/35/3

History of physical activity	
Gymnastics at school	87.8%
Sports after age 30	48.7%
Physically active in lifestyle activities	47.8%

Barriers to become physically active	
Weather	74.8%
Health	67.8%
Weather health specific	53.0%
Financial constraints	32.2%
Not able to pay money	20.2%
Not willing to pay money	12.3%
Sleep	9.6%
Physical activity facilities in neighbourhood	7.0%
Fear of movement	6.1%
Shame	4.3%
Time	2.6%

Subjective experience on physical activity	
Pleasant	85.2%
Unpleasant	30.4%
None	9.6%
High self-efficacy in DPA	85.2%

Social support	
Positive	47.0%
Negative	2.6%
Positive and negative	3.5%
None, not applicable	46.9%
Influence of social support on physical activity	
Positive	19.1%
Negative	0.9%
None	80.0%

Stress	
Positive influence on physical activity	18.3%
Negative influence on physical activity	13.0%
None, not applicable	67.8%

FIGURE 1. Categories distinguished from the interview answers, using an inductive content analysis approach (n=115)
Data are presented as percentage patients that reported a specific reason. Or in case of 'number of reasons reported' as the number of patients that reported that number of reasons n/n/n/n.

Based on the coding analysis, several categories were distinguished (figure 1). Topics of the categories were: reasons to be physically active, reasons to be sedentary, history of physical activity, subjective experience on physical activity, barriers to become physically active and the influence of social support and stress on physical activity. The reasons to be physically active could be categorized into 4 categories. The most frequently reported reason to be physically active was health benefits (reported by 65% of the patients), followed by enjoyment (44%), continuous active lifestyle in the past (28%) and functional reasons (26%). An example of a reported functional reason is that physical activity is necessary for certain daily life activities, like transportation or gardening. The reasons to be sedentary could be categorized into 3 categories and there were 18 answers that did not fit into a category. The most frequently reported reason to be sedentary was poor weather (48%), followed by health problems (43%) and lack of intrinsic motivation (11% In addition 20% of the patients reported to have no reason to be sedentary.

On average, patients reported 1.7 (range 1-4) reasons to be physically active and 1.2 (range 0-3) reasons to be sedentary. Positive social support for physical activity was reported by almost 50% of the study population, this included social support from spouse, exercise group/partner, clinician, family and friends. Only a small group of patients (19%) feel that the experienced social support positively influences their physical activity level.

Figure 2 shows that there is a large variability in physical activity preferences. Approximately one-third of the patients prefer going to a health club or performing a sport activity, while 25% of the patients prefer lifestyle activities, like walking or gardening. Over 40% prefers a combination of both types of physical activity. Additionally, 40% of the patients prefer being physically active together with others, 30% alone and 30% prefer a combination of both. The patients who prefer sports or the health club prefer more often being physically active together and the patients who prefer lifestyle activities prefer more often to be physically active alone.

113 patients wore the accelerometer for at least 4 complete days and were included in the k-means cluster analysis. The cluster analysis formed 2 clusters, one cluster with a high physical activity level (n=52) and one cluster with a low physical activity level (n=61). Table 2 shows the results of the cluster analysis. A high physical activity level was related to being physically active because of enjoyment and high self-efficacy in physical activity. A low physical activity level was related to being sedentary because of poor weather influencing health, financial constraints, health problems and shame to be physically active. The cluster with a high physical activity level was characterized by higher lung function and exercise capacity and less dyspnea severity compared with the cluster with low physical activity level. Gender and age did not differ significantly between clusters.

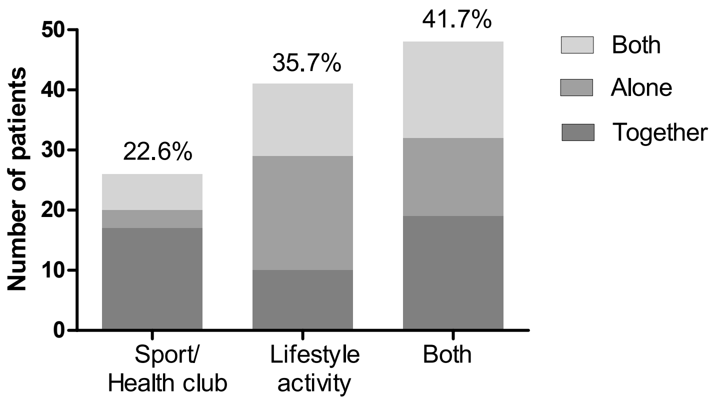

FIGURE 2. Physical activity type preferences

TABLE 2. K-means cluster analysis (n=113)

Variable	Cluster 1 (n=52) High physical activity	Cluster 2 (n=61) Low physical activity	p-value
Steps per day, steps	8807.4	3331.9	**<0.001**
Gender, (0=male)	0.27	0.38	0.227
Age, years	65.6	64.4	0.502
FEV_1, % predicted	71.6	45.5	**<0.001**
mMRC dyspnea, score (1-5)	1.8	2.9	**0.000**
6MWD, meter	511.5	373.9	**<0.001**
Answers on the interview			
Reasons to be physically active			
Enjoyment	0.56	0.33	**0.014**
Self-efficacy in physical activity (1= high self-efficacy)	0.94	0.79	**0.018**
Reasons to be sedentary			
Weather, health specific	0.38	0.66	**0.004**
Financial constraints	0.12	0.49	**<0.001**
Health	0.52	0.80	**0.001**
Shame	0.00	0.08	**0.035**

The cluster analysis shows the interview variables that were significantly different between the clusters. Reasons to be physically active or sedentary were coded as 0= not present, 1= present. Therefore, a higher score indicates that the specific reason was more present in that cluster. FEV_1= forced expiratory volume in 1 second; mMRC= modified medical research council dyspnea index; 6MWD= 6-minute walk distance.

DISCUSSION

The identification of personal perspectives about physical activity is important because it increases our knowledge on the facilitators and barriers of physical activity in COPD patients. Our results show that the most frequently reported reason to be physically active was health benefits, followed by enjoyment, continuous active lifestyle in the past and functional reasons. The most frequently reported reason to be sedentary was poor weather, followed by health problems and lack of intrinsic motivation.

Additionally, we could identify several factors that were related to the actual measured physical activity level. A high physical activity level was related to the following 2 facilitators: enjoyment and self-efficacy in physical activity. A low physical activity level was related to the following 4 barriers: weather influencing health, financial constraints, health problems and shame.

Facilitators

An identified facilitator of physical activity was enjoyment. This is in line with a review that also showed that perceived exercise enjoyment and satisfaction predict higher levels of physical activity and adherence to exercise in 2 general adult populations.[18] Another identified facilitator was high self-efficacy in physical activity. Self-efficacy is someone's belief in his/her capabilities to successfully execute a specific type of behaviour, in this case physical activity. High self-efficacy was found to be more present in mild to moderate COPD patients than (very) severe COPD patients and more in males than in females. It is known that self-efficacy is a strong and consistent predictor of exercise adherence and that it is essential for the process of behavioural change.[9,19,20] Furthermore, 2 studies in COPD patients showed that physical activity was positively associated with self-efficacy.[21,22] This emphasises the importance of enjoyment of physical activity and self-efficacy in physical activity for adherence to a physically active lifestyle.

Barriers

An identified barrier in being physically active was weather type, 75% of the patients reported poor weather as a barrier to become physically active. Mostly, patients reported disease-related complaints caused by different weather types, like more dyspnea with high humidity in the air. This is in line with studies in general but also COPD populations, showing that weather affects exercise adherence and physical activity levels.[23-25] A second barrier was health problems. Health as a barrier was mainly due to COPD-related complaints like dyspnea, but also other comorbidities were reported to affect physical activity, like joint problems. Health as a barrier was more frequently reported in (very) severe COPD patients. Health was also the most frequently reported reason to be physically active. Despite health-related limitations many patients also understand the benefits of regular physical activity for their health. These results are in line with those found in an elderly population.[8] A third barrier was financial constraints. Financial constraints were reported by almost a third of all patients. Financial constraints included patients that were not able to pay for physical activity or were not willing to. In general elderly populations, financial constraints are not among the most frequently reported reasons to be sedentary.[8-10] However, in our COPD population it appears to be an important factor. A last barrier was shame. The reasons to feel ashamed, limiting these patients in physical activity, were use of a walking aid with sometimes an oxygen cylinder or having to exercise with healthy people. Patients that reported this barrier all had very severe COPD and were mainly female. Partly, this is similar to a frequently mentioned reason in the general elderly population: intimidation; afraid to slow other people down during physical activities.[8]

Behavioural change theories

Several theories exist on behavioural change and may explain adherence to physical activity. Adherence to physical activity seems to be promoted by the presence of individual needs, personal level of fitness, readiness for behavioural change, self-efficacy and social support.[26] In line, we found that individual needs, personal level of fitness and self-efficacy were related to physical activity in COPD patients. Importance of individual needs was reflected by our finding that enjoyment in physical activity is important, as was the high variability in individual preferred type of activity. Readiness for change in behaviour was not a theme of the interview. In contrast with those theories, the influence of social support on physical activity was not clear in our population. Although a large group of patients report positive social support on physical activity, they do not feel that the experienced social support influences their actual physical activity level. Furthermore, we identified some disease specific barriers in physical activity in COPD patients that are not specifically present in the behavioural change theories; health, financial constraints, weather and shame. Additionally, lack of time, a frequently reported reason to be sedentary in the general elderly population, was only reported by 3 patients in our sample. Consequently, lack of time appears not to be an issue in our COPD patients. Remarkably, tiredness or poor sleep quality and fear of movement were not reported frequently as reasons to be sedentary.

Strengths and weaknesses of the study

This study is unique because of the large heterogeneous population of COPD patients we have studied and its qualitative design. Our population included 115 COPD patients in all severity stages of the disease and therefore allows conclusions about the full range of COPD patients. The use of qualitative research methods allows us to gain more insight in the personal thoughts and ideas on physical activity, especially when no suitable questionnaire is available. A disadvantage of the current study is that due to the relatively high number of patients, the interviews were not audio-taped and transcribed verbatim. Furthermore, we also measured physical activity in a performance based manner which gave us the possibility to compare the personal answers to the actual measured physical activity level.

Practical implications of the study

To be able to use our results in daily practice and to develop and optimize physical activity enhancement strategies in COPD, the practical implications of our results will be discussed in the next section. Three important implications useful for the enhancement of physical activity can be distinguished, namely reducing barriers and increasing insight in health benefits, tailoring type of activity and improvement of self-efficacy.

Reducing barriers and increasing insight in health benefits COPD patients pose a challenge, because they feel limited by their health problems to increase their physical activity level, but in the same time are aware of potential benefits of regular physical activity. Frequently, the balance is in favour of feelings of limitation because health as a barrier was related to low physical activity and because benefit awareness was not related to high physical activity. This implicates that we first should try to dissolve false perceptions on barriers for physical activity, and after that increase insight in the many potential health benefits of regular physical activity. In our opinion, removing barriers is not only an educational process, but should also be achieved with real-life physical activity experiences, for example with help of a physical therapist.

Tailoring type of activity The large variability in types of preferred physical activity between COPD patients suggests that one standardised physical activity program will not be suitable. Patients should not be forced to participate in one standard physical activity program, but programs should be discussed and chosen together with the patient. A clinician or physical therapist may discuss all options together with the patient, particular in those patients with a limited activity history, taking potential barriers in account like financial constraints and shame to exercise with healthy people or shame of using a walking aid. Additionally, the possible influences of weather on adherence to regular physical activity should be discussed with the patient. This could include talking about back-up activities in case of poor weather, *e.g.* the possibility of exercising at home.

Improvement of self-efficacy Increasing self-efficacy in physical activity means improving the patient's own judgment on the ability to perform certain physical activities. Factors that have shown to increase self-efficacy and that could be incorporated in physical activity programs are performance experience, vicarious experience (modelling), social persuasion and physiological and emotional arousal.[27] Improving physical activity performance experiences, could be accomplished during physical activity programs for example with help of a physical therapist. Starting with easy to perform physical exercises will be attractive because patients will first experience success instead of failure. During these programs social modelling and social persuasion is important, which could be achieved by group-orientated physical activity programs, physical activity with friends or family, or encouragement of a physician or physical therapist. The decrease of physiological and emotional arousal could be achieved by monitoring certain parameters during physical activity like blood oxygen saturation, blood pressure or Borg score, or, if warranted, teaching the patient stress management techniques.

In conclusion, this study using a qualitative approach, shows for the first time the personal reasons of COPD patients to be physically active or sedentary and the relation with the actual measured physical activity level. Furthermore, we identified 3 important recommendations for enhancing physical activity in COPD patients. The results increase our knowledge on the facilitators and barriers in physical activity, which could be very useful for enhancing physical activity in this patient group with a very high percentage of physical inactivity.

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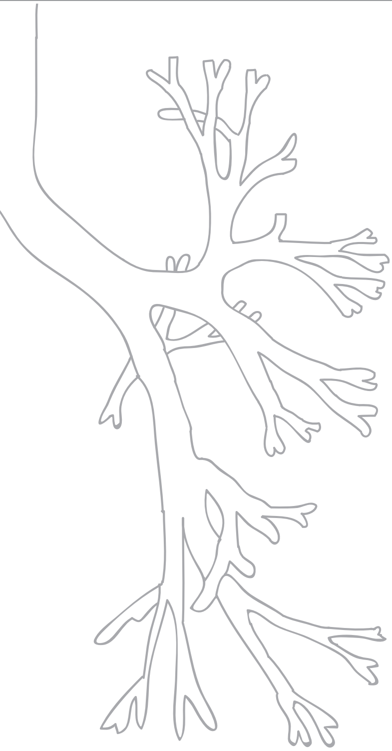
CHAPTER 5

Physical activity recommendations in patients with Chronic Obstructive Pulmonary Disease



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ABSTRACT

Background: Various physical activity recommendations exist, but those are hardly studied in COPD. This study compared different recommendations and investigated their suitability for COPD patients.

Methods: We compared 7 different physical activity recommendations. The recommendations differed in frequency, intensity and time and were measured with an accelerometer, pedometer or questionnaire in 115 mild to very severe COPD patients (68% male, mean age 65 years, mean FEV_1 57.5%predicted).

Results: The percentage of patients that met the different recommendations ranged from 22 to 86% and only 8 patients met all 7 recommendations. The agreement between the different recommendations was poor (ICC: 0.28). Individualizing the recommendations by adopting the intensity to a patient's aerobic fitness level resulted into a higher number of GOLD stage III and IV patients meeting the relative recommendations compared to the absolute recommendations. In contrast, GOLD stage I and II patients less frequently met the relative recommendations.

Conclusions: Our study showed that applying various physical activity recommendations with small differences in frequency, intensity or time led to large differences in the classification of COPD patients into sufficiently physically active or not. Consequently, the used recommendation will highly affect the proposed physical activity advice to the patient.

Keywords: COPD • health benefits • physical activity

INTRODUCTION

Regular physical activity is known to have important health benefits and may limit the development and progression of chronic disease.[1] As a sedentary lifestyle is frequently present in all severity stages of Chronic Obstructive Pulmonary Disease (COPD), increasing physical activity has become an important treatment target in these patients.[2] However, once adopting the fact that physical activity should be enhanced in sedentary COPD patients, the question rises how much physical activity is needed to obtain health benefits, in order to be able to give a tailored advice to the patient.

Approximately 40 years ago the first physical activity recommendation was published.[3] Currently, the physical activity recommendations of the American College of Sports Medicine (ACSM) for adults, which are in line with the recommendations of the World Health Organization (WHO), are often used.[4-6] The ACSM guidelines recommend that adults should engage in moderate-intensity aerobic physical activity for a minimum of 30 minutes on 5 days each week or vigorous-intensity aerobic physical activity for a minimum of 20 minutes on 3 days each week, or an equivalent combination of both.[4,5] Apart from aerobic exercises, resistance, neuromotor and flexibility exercises are also recommended. However, the focus of our current study is on aerobic physical activity.

The recommendations are hard to apply as it is difficult to discriminate light, moderate or vigorous-intensity physical activity from another. A frequently used measure in this perspective is metabolic equivalent of task (MET), of which 1 MET is the rate of energy expenditure while sitting at rest. An extensive compendium of physical activities has been created in which MET values are measured for various activities.[7] However, the intensity estimations in this compendium are absolute and do not take into account individual determinants of physical activity like body weight, gender and fitness level. The latest ACSM guidelines also describe several relative estimations of intensity, which can be used to discriminate between intensities for the individual. These individualized physical activity recommendations could be more appropriate, particularly for elderly and deconditioned persons.[8]

In general, physical activity recommendations are mainly based on healthy adults, while recommendations for adults with a chronic illness are less clear. The WHO states *e.g.* those adults who cannot reach the recommendations due to health problems, should be 'as physically active as their abilities and conditions allow'.[6] The ACSM advocates adjusting the recommended intensity of physical activity to the adult's aerobic fitness level and to use the relative estimations of intensity for elderly with a chronic illness.[8]

So far, physical activity recommendations are hardly studied in COPD patients. It would be interesting to know if the various recommendations using different instruments are applicable in COPD patients in all stages of the disease.

The aim of this study is to compare various physical activity recommendations, using both absolute and relative estimations of intensity, in mild to very severe COPD patients. Furthermore, to investigate whether these recommendations are associated with measures of functional capacity.

METHODS

Mild to very severe COPD patients were recruited from general practitioners and outpatient clinics of general hospitals. Patients were included if their post bronchodilator FEV_1/FVC ratio was below 0.7. Comorbidity was allowed, but patients were excluded if they had a serious active disease that needed medical treatment (*e.g.* carcinoma, recent myocardial infarction), or were treated for a COPD exacerbation in the past 2 months. All patients gave written informed consent, and the study was approved by the local ethics committee.

We compared 7 different forms of physical activity recommendations described in the literature. The recommendations differed in frequency, intensity and time of the recommended amount of physical activity and were measured with 3 different instruments (table 1). Three recommendations were based on absolute estimates of intensity and 4 on relative estimates of intensity.

TABLE 1. Overview of the different recommendations

	Recommendation	Frequency	Intensity		Time	Volume
Absolute	*1* **MET absolute**[1]	≥ 5 days	≥ 3 MET	moderate	≥ 30 minutes (in ≥10 min bouts*)	
		or ≥ 3 days	≥ 6 MET	vigorous	≥ 20 minutes (in ≥10 min bouts*)	
	2 **Questionnaire-based**[2]	≥ 5 days	≥ 3 MET	moderate	≥ 30 minutes	
	3 **Step-based**[3]	*no instructions on frequency, intensity or time*				mean ≥ 7000 step/ day
Relative	*4* **VO_2 reserve**[1]	≥ 5 days	≥ 40%	moderate	≥ 30 minutes (in ≥10 min bouts*)	
		or ≥ 3 days	≥ 60%	vigorous	≥ 20 minutes (in ≥10 min bouts*)	
	5 **VO_2 max**[1]	≥ 5 days	≥ 46%	moderate	≥ 30 minutes (in ≥10 min bouts*)	
		or ≥ 3 days	≥ 64%	vigorous	≥ 20 minutes (in ≥10 min bouts*)	
	6 **HR reserve**[1]	≥ 5 days	≥ 40%	moderate	≥ 30 minutes (in ≥10 min bouts*)	
		or ≥ 3 days	≥ 60%	vigorous	≥ 20 minutes (in ≥10 min bouts*)	
	7 **HR max**[1]	≥ 5 days	≥ 64%	moderate	≥ 30 minutes (in ≥10 min bouts*)	
		or ≥ 3 days	≥ 77%	vigorous	≥ 20 minutes (in ≥10 min bouts*)	

**2 minutes interruption duration was allowed in the 10 minute bout. [1]measured by an accelerometer; [2]measured by the SQUASH-questionnaire; [3]measured by a pedometer. VO_2: oxygen uptake; HR: heart rate.*

Recommendations based on absolute measures of intensity

1. MET-absolute

This recommendation described in the ACSM guideline, was met if patients engaged in at least 30 minutes of moderate-intensity physical activity (≥3 MET) on ≥5 days per week, or at least 20 minutes of vigorous-intensity physical activity (≥6 MET) ≥3 days per week, or a combination of both.[4] Resting energy expenditure was estimated with the Mifflin-St. Jeor equation.[9] Furthermore, physical activity had to be accumulated in bouts of at least 10 minutes, with maximal 2 minute interruption time within the bout.[10]

2. Step-based

The step-based recommendation was met if patients took on average at least 7000 steps per day during the week. Although the evidence for step-based recommendations is less extensive, a recent review and the ACSM have set this threshold measured with a pedometer for older adults.[4, 11]

3. Questionnaire-based

The recommendation according to the questionnaire was met if patients engaged in at least 30 minutes of moderate-intensity physical activity (≥3 MET) on ≥5 days per week. Intensity of activities was based on the physical activities compendium.[7]

Recommendations based on relative measures of intensity

These recommendations are described in the ACSM guideline and have the same instructions on frequency and time as the MET-absolute recommendation. To distinguish moderate and vigorous intensity we used the lowest thresholds described by the ACSM[4], based on:

4.Oxygen uptake (VO_2) reserve
5. VO_2 max
6. Heart rate (HR) reserve
7. HR max

The intensity thresholds are shown in table 1.

Patient perception

The questionnaire also determines how many days per week the patients themselves reported to be physically active for ≥30 minutes at moderate intensity, which we used as an indication of the patients' perception on meeting the recommendation.

Measurements

Meeting the recommendations was measured by an accelerometer (5x), pedometer (1x) and questionnaire (1x).

Physical activity

Accelerometer The Dynaport (McRoberts, The Netherlands) is a validated triaxial accelerometer, that is worn around the waist and detects postures, measures steps and estimates energy expenditure.[12-14] Patients were instructed to wear the accelerometer day and night for one week.
Pedometer The Yamax Digi-walker SW-200 is an accurate and reliable pedometer.[15,16] Patients were instructed to wear the pedometer for 2 weeks. The patients also reported in a diary if they performed other non-ambulatory activities, and these were translated into steps by using step equivalents based on the physical activities compendium.[7]
Questionnaire The short questionnaire to assess health enhancing physical activity (SQUASH) was administrated by an interviewer. The questionnaire has shown to be fairly reliable and reasonably valid.[17]

Cycle ergometry

Maximal and resting VO_2, HR, and energy expenditure (EE) were measured by a cycle ergometer test (bicycle ergometer: Jaeger ER900L: Oxygen Pro, CareFusion, Germany). A maximal incremental protocol was used with 3 minutes resting, 3 minutes unloaded cycling and approximately 10 minutes cycling with individualized incremental load of 5-25 Watt per minute, in line with the ATS/ACCP guidelines.[18] The cycle ergometry was used to derive the relative measures of intensity of physical activity (based on $VO_{2reserve}$, VO_{2max}, $HR_{reserve}$ and HR_{max}).

Functional capacity measures Functional exercise capacity was measured by a 6-minute walk distance test according to the ATS guidelines.[19] Leg muscle function was measured by a 30-second chair stand test.[20] Forced expiratory volume in 1 second was measured using a spirometer (PFT. Masterscope; Viasys) according to the ERS/ATS guidelines.[21]

Data analyses

Patients were included in the accelerometer-based analyses if they had worn the accelerometer for at least 5 full days. A day was considered a valid measurement day if the device was worn for ≥94% of the day.[22] If a patient had worn the accelerometer for 5 or 6 days the patients were only included if they already reached 5 days of enough physical activity or if they certainly would not. Resting and maximum values of VO_2, HR, and EE during the cycle ergometer test were obtained from the graphs in the ergometer software. The VO_2 and HR values were translated into EE measures by taking the corresponding EE value at that time point. Wilcoxon signed-rank test was used to test the difference between the absolute measure of intensity and relative measures of intensity (mean value). To assess agreement between the different recommendations we calculated intraclass correlation coefficients (ICC) with absolute agreement. Linear regression analyses were performed to assess if patients who met a specific recommendation had different scores on functional capacity tests than patients who failed the recommendation. Regression analyses were adjusted for FEV_1, age, gender, height and weight. P-values <0.05 (tested two-sided) were considered statistically significant. All statistical analyses were performed using IBM-SPSS statistics version 20.

TABLE 2. Patient characteristics

Variable	**Total group (n=115)**	**GOLD I+II (n=61)**	**GOLD III+IV (n=54)**
Gender, male (%)	78 (67.8)	45 (73.8)	33 (61.1)
Age, years	65 ± 8.7	66 ± 7.8	64 ± 9.5
COPD[¶], A/B/C/D	54/5/19/37	54/5/0/2	0/0/19/35
FEV_1, % predicted	52 (14-119)	79 (50-119)	34.5 (14-49)
BMI, kg/m^2	25.1 ± 4.0	25.5 ± 3.4	24.6 ± 4.6
6MWD, meter	447 (6-646)	518 (344-646)	367 (60-600)
mMRC, score	2 (1-5)	2 (1-5)	3 (1-5)
Chair stand test, number	10.9 ± 3.2	11.6 ± 3.3	10.1 ± 2.8
VO_2 max, ml/kg	18.2 (5.7-37.7)	20.2 (13.0-37.7)	13.4 (5.7-22.8)
HR rust, beat per minute	76 (56-121)	73 (56-97)	84 (58-121)
HR max, beat per minute	129 (89-166)	137 (93-166)	120 (89-161)
Steps, per day*	5552 (236-18433)	7388 (3556-18433)	3376 (236-14281)
Lying & sitting, %	79.8 ± 7.2	77.6 ± 6.3	82.3 ± 7.3
≥ 3MET, minutes per day	103 (15-298)	130 (19-298)	70 (15-177)

Data are presented as n(%), mean ± sd, median (range) or number/n/n/n.
*¶Combined assessment COPD with use of the mMRC scale (GOLD guidelines 2011[26]) *Steps measured by accelerometer FEV_1: forced expiratory volume in 1 second; 6MWD: 6-minute walk distance; BMI: body mass index, mMRC: modified Medical Research Council dyspnea index.*

5

RESULTS

One hundred and fifteen COPD patients participated in this study (68% male, mean age 65 years, mean FEV_1 58%predicted (table 2)). All patients wore the pedometer and completed the SQUASH-questionnaire, and 111 patients wore the accelerometer for at least 5 days. Patients were on average 103 minutes physically active per day at intensities above 3 MET (range 15-299).

Estimates of intensity

The calculated estimates of intensity, based on the absolute and relative estimates of intensities are shown in table 3. The mean value of the relative estimates of moderate-intensity was in GOLD stage I and II patients significantly higher than the absolute measure of moderate-intensity (p<0.001). In patients with GOLD stage III and IV the mean value of the relative estimates of moderate-intensity was significantly lower than the absolute measure of intensity (p<0.001).

Meeting the recommendation

Table 4 shows the minutes per day that patients met the lower threshold of the recommendations and the proportion of patients that met the different recommendations (also figure 1). The number of eligible patients per recommendation is presented in table E1 in the appendix. Remarkably, the recommendations based on HR_{max} were not

TABLE 3. Estimates of intensity based on the different physical activity recommendations

	Total group	GOLD I+II	GOLD III+IV
Moderate intensity			
3 MET absolute, kcal/minute	3.1 (2.0-4.1)	3.2 (2.0-3.9)	2.9 (2.1-4.1)
40% VO_2 reserve, kcal/minute	3.3 (1.2-7.6)	4.1 (2.0-7.6)	2.7 (1.2- 4.9)
46% VO_2 max, kcal/minute	3.0 (0.9-7.9)	3.8 (1.7-7.9)	2.2 (0.9-4.4)
40% HR reserve, kcal/minute	3.5 (0.5-7.4)	4.2 (1.8-7.4)	2.7 (0.5-6.0)
64% HR max, kcal/minute	3.0 (0.7-6.8)	3.1 (1.0-6.8)	1.9 (0.7-5.6)
Vigorous intensity			
6 MET absolute, kcal/minute	6.2 (4.1-8.3)	6.4 (4.1-7.9)	5.9 (4.3-8.3)
60% VO_2 reserve, kcal/minute	4.3 (1.5-10.8)	5.5 (2.6-10.8)	3.4 (1.5-6.4)
64% VO_2 max, kcal/minute	4.2 (1.2-11.0)	5.2 (2.3-11.0)	3.0 (1.2-6.1)
60% HR reserve, kcal/minute	4.9 (1.2-9.6)	5.8 (2.5-9.6)	3.2 (1.2-7.8)
77% HR max, kcal/minute	4.3 (1.6-9.8)	5.0 (1.6-9.8)	3.2 (1.6-7.7)

Data are presented as median (range). MET: metabolic equivalent of task, kcal/minute: kilocalorie per minute; VO_2: oxygen uptake; HR: heart rate.

applicable to a large proportion of the patients (49%), due to reaching very low HR_{max} values during the cycle ergometer test (table E1).

The proportion of patients that met the different recommendations ranged from 22 to 84% in the total group. In GOLD stage I and II patients from 36 to 90% and in GOLD stage III and IV from 6 to 78%. Only 8 patients (7%) met all 7 recommendations. The agreement between all recommendations in the total group was poor (ICC 0.28, HR_{max}-based recommendations left out).

The recommendations based on absolute measures of intensity showed poor agreement (ICC 0.17). Thirty-six percent of the patients met the MET-absolute recommendation, 22% the step-based recommendation and 84% the questionnaire-based recommendation.

By including step-equivalents 35% of the patients met the step-based recommendation. Although the step-based recommendation including step equivalents seems similar to the MET-absolute recommendation, the agreement between the two recommendations was moderate (ICC 0.49), indicating that different patients met the two different recommendations.

In patients with GOLD stage I and II, more patients met the absolute measure of intensity than the relative measures of intensity. In contrast, in GOLD stage III and IV, more patients met the relative measures of intensity than the absolute measure of intensity.

TABLE 4. Minutes per day of physical activity above the recommendation and the proportion of patients that met the different recommendations

			Total group		GOLD I+II		GOLD III+IV	
			Minutes/day	Number (%)	Minutes/day	Number (%)	Minutes/day	Number (%)
Absolute	**Step-based**			25 (21.7%)		22 (36.1%)		3 (5.6%)
	Step-based inc stepequivalents			40 (34.8%)		32 (52.5%)		8 (14.8%)
	Questionnaire-based			97 (84.3%)		55 (90.2%)		42 (77.8%)
	MET absolute	≥ 3	28.0 (0-201)	39 (35.1%)	51.7 (9-201)	33 (55.9%)	5.9 (0-144)	6 (11.5%)
		≥ 6	0.0 (0-50)	7 (6.3%)	0.0 (0-50)	6 (10.2%)	0.0 (0-12)	1 (1.9%)
		total		40 (36.0%)		33 (55.9%)		7 (13.5%)
Relative	**VO_2 reserve**	≥ 40%	26.5 (0-656)	26 (25.2%)	36.9 (0-198)	20 (34.55)	10.8 (0-656)	6 (13.3%)
		≥ 60%	5.4 (0-78)	25 (24.0%)	3.6 (0-78)	15 (25.4%)	7.2 (0-62)	10 (22.2%)
		total		36 (34.3%)		23 (39.0%)		13 (28.3%)
	VO_2 max	≥ 46%	35.2 (0-1380)	35 (34.3%)	42.0 (0-201)	22 (38.6%)	24.1 (0-1380)	13 (28.9%)
		≥ 64%	7.4 (0-643)	31 (30.1%)	7.4 (0-98)	17 (29.3%)	7.3 (0-643)	14 (31.1%)
		total		46 (45.1%)		26 (45.6%)		20 (44.4%)
	HR reserve	≥ 40%	26.8 (0-1440)	27 (30.3%)	30.9 (0-201)	15 (28.8%)	19.7 (0-1440)	12 (32.4%)
		≥ 60%	4.0 (0-643)	21 (23.9%)	1.7 (0-108)	10 (19.6%)	6.5 (0-643)	11 (29.7%)
		total		34 (38.2%)		17 (32.7%)		17 (45.9%)
	HR max	≥ 64%	50.4 (0-1343)	25 (51.0%)	52.6 (0-1343)	20 (50%)	46.3 (7-1250)	5 (55.6%)
		≥ 77%	10.4 (0-195)	24 (37.5%)	9.2 (0-195)	17 (34.7%)	13.5 (3-89)	7 (46.7%)
		total		34 (55.7%)		26 (55.3%)		8 (57.1%)
	Patient perception			81 (70.4%)		49 (80.3%)		32 (59.3%)

Data are presented as median minutes per day (range) or number of patients that met the recommendation (%).
'Total' represents the number of patients that met either the moderate or vigorous intensity recommendation.
MET: metabolic equivalent of task; VO_2: Oxygen uptake; HR: heart rate.

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Patient perception

Seventy percent of all patients reported that they were physically active for at least 30 minutes at moderate-intensity on at least 5 days per week and thus met the recommendation. In GOLD stage I and II this was reported by 80% of the patients and in GOLD stage III and IV by 59%.

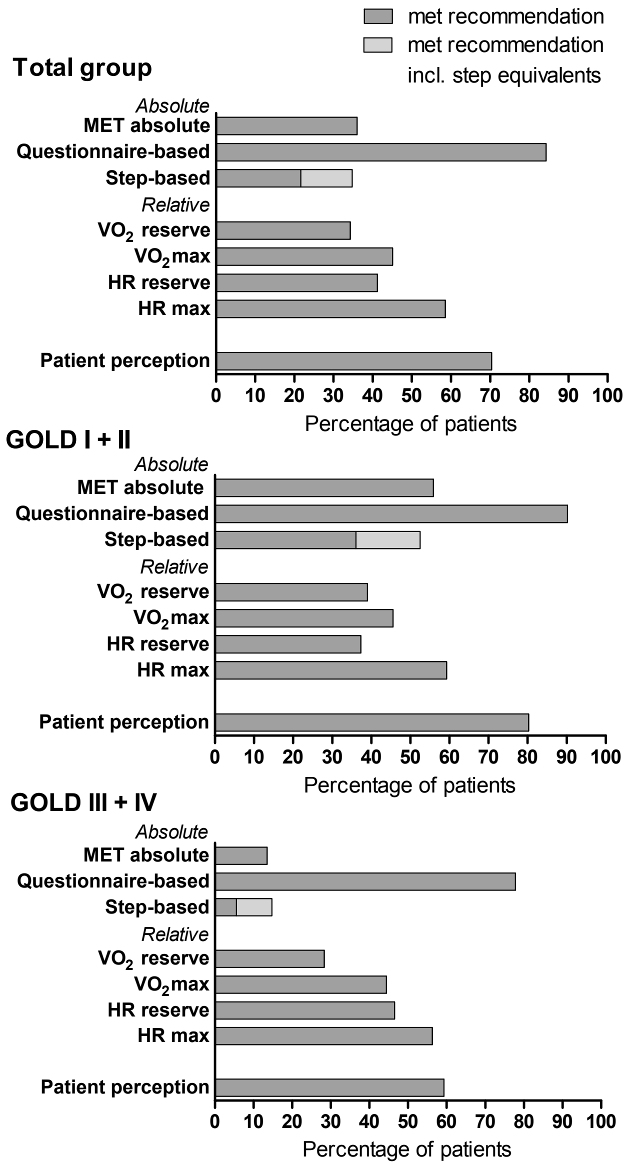

FIGURE 1. Proportion of patients that met the different recommendations

TABLE 5. Differences in functional capacity measures between patients that met or failed the different recommendations

		Chair stand test		6MWD		Wmax		VO_2 max	
		B	p-value	B	p-value	B	p-value	B	p-value
Absolute	**MET absolute**	-2.220	**0.001**	-82.799	**<0.001**	-21.257	**<0.001**	-185.255	**0.002**
	Questionnaire-based	-2.492	**0.002**	-97.234	**<0.001**	-19.741	**0.004**	-195.906	**0.009**
	Step-based	-3.155	**<0.001**	-79.884	**0.001**	-17.713	**0.005**	-144.321	**0.036**
Relative	**VO_2 reserve**	0.284	0.672	-37.309	0.061	-1.606	0.774	71.925	0.220
	VO_2 max	-0.583	0.383	-28.816	0.153	1.091	0.844	94.128	0.108
	HR reserve	-1.002	0.130	-35.778	0.066	0.657	0.904	78.714	0.174
	HR max	-0.038	0.966	-12.325	0.550	0.280	0.967	62.278	0.418

Analyses were adjusted for forced expiratory volume in 1 second, age, gender, height and weight. Recommendations were coded as 0= met recommendation, 1= failed recommendation. 6MWD: 6-minute walk distance test, Wmax: maximum workload, VO_2max/kg: maximum oxygen uptake/kilogram, MET: metabolic equivalent of task, VO_2: oxygen uptake, HR: heart rate.

Association with functional capacity measures

Table 5 shows the differences in functional capacity outcomes between patients that met or failed the different recommendations with adjustment for FEV_1, age, gender, height and weight. Patients who met the recommendations based on absolute estimates of intensity (MET-absolute, questionnaire-based and step-based) had significantly higher functional capacity scores than patients who failed the recommendations. Contrary, patients who met or failed the recommendations based on relative estimates of intensity did not differ in functional capacity outcomes. Absolute values without adjustment are shown in table E2 (appendix).

CONCLUSION AND DISCUSSION

Our results showed that the percentage of COPD patients that met the different physical activity recommendations ranged from 22 to 86%, and that the agreement between the recommendations was poor. It is important to acknowledge that adapting small differences in frequency, intensity or time lead to different conclusions and may have important consequences for the individual patient. Individualizing the recommendations by adopting the intensity to a patient's aerobic fitness level resulted into more patients with GOLD stage III and IV meting the relative recommendations than the absolute recommendations. In contrast, GOLD stage I and II patients less frequently met the relative recommendations. Seventy percent of all patients reported to be physically active at least 5 days per week for 30 minutes at moderate intensity.

Several factors might contribute to the low agreement between the different physical activity recommendations. Firstly, it is well known that subjective methods to measure physical activity are less accurate than performance-based methods[23]; usually patients overestimate their physical activity level.[24] Secondly, the pedometer and the accelerometer both mainly measure locomotion, and therefore could unjustly classify patients as inactive when they perform a lot of non-ambulatory activities like cycling. Thirdly, recommendations measured by an accelerometer include a threshold on 'bout duration', periods of physical activity only count when performed in bouts of at least 10 minutes. To illustrate the impact of bout duration, if we had allowed 1 minute interruption in the 10 minute bout instead 2 minutes, 23% of the patients would have met the recommendation instead of the current 36%. Contrary, in the step-based and questionnaire-based recommendation every step or minute counts. Our results are in line with a study in healthy men, which also showed huge differences between various recommendations.[25]

We investigated absolute and relative estimates of intensity in COPD patients with a broad range of disease severity. In GOLD stage I and II patients the relative estimates of moderate intensity were higher than the absolute estimate and fewer patients met these recommendations. As expected, the relative estimates of moderate intensity were lower in GOLD III and IV patients than the absolute estimates of intensity. Consequently, a larger number of these patients met the recommendation based on relative estimates of intensity compared to the absolute estimates of intensity. Furthermore, we found that patients who met the relative recommendations did not have better functional capacity scores than patients who failed the recommendation. Consequently, the question arises whether low recommended intensities due to adjusting the intensity of physical activity to the individual level of aerobic capacity still lead to health benefits. Unfortunately, due to the cross-sectional design, we cannot answer this question and physical activity patterns over time should be investigated to identify the optimal amount of physical activity to promote or maintain physical health.

Which physical activity recommendation should be used in COPD patients is quite speculative but we nevertheless comment on a few aspects. A recommendation based on an absolute measure of intensity like the ACSM is easy to understand and results in a clear advice to the patient. However, relying on subjective measures whether such a recommendation is met is not attractive, as patient-perception or filling in a questionnaire overestimates a patient's physical activity level. Additionally, recommendations based on absolute estimates of intensity could be discouraging for patients with severe COPD, because most patients are physically not able to achieve these high physical activity levels. In less severe COPD patients, who are less restricted by their pulmonary condition, the absolute estimates of intensity might be more appropriate. Another absolute recommendation, the step-based recommendation has the advantage that the goal is easy to understand and can be easily monitored by the patient. However, the evidence of the efficiency of the step-based recommendation is poor and dose-response studies in sedentary or old individuals are lacking.

We do agree with the ACSM guidelines that for older and deconditioned patients the relative estimates of intensity probably might be most suitable. An important advantage is that the dose of physical activity is individualized and patients do not get frustrated with too high targets. However, the use of relative estimations probably demands frequent monitoring of aerobic capacity and should therefore not be fixed at one time point. Aerobic capacity could increase because of exercise benefits but also decrease due to disease progression or aging. Using HR-based recommendations has the advantage that intensity goals are easy to measure by the patients, *e.g.* by a heart monitor watch. However, a problem with using HR is that it is not suitable for a lot of patients, because their HR goals are difficult to define because of very low exercise capacity, sometimes also partly due to medication like beta-blockers. A VO_2-based recommendation can only be applied in sophisticated exercise labs, but once a VO_{2max} has been measured it is possible to define individual advises for ergometer programs. As discussed earlier, another problem of the relative estimates of intensity is that the recommended physical activity may be too low to lead to health benefits in highly deconditioned patients.

A limitation of the present study is the cross-sectional design. Due to this design we could not investigate how much physical activity is sufficient to obtain health benefits. A next step would therefore be to investigate physical activity, dose-response relationships and its health benefits longitudinally. Another limitation of the study is the conversion of cycle ergometer data into energy expenditure and the transformation of accelerometer data into energy expenditure. As shown by others, the estimation of energy expenditure by accelerometers is still not perfect.[12] However, currently the accelerometer is the most practical and patient-friendly tool to use, in contrast to *e.g.* measuring energy expenditure by doubly labelled water or indirect calorimetry. Furthermore, we believe that the conclusions of this study would not change if we had used other instruments.

In conclusion, we found that applying various physical activity recommendations with small differences in frequency, intensity or time led to large differences in classifying if COPD patients are sufficiently physically active or not. This indicates the importance to precisely state the used recommendation and to be cautious with comparing results of recommendations. Future longitudinal studies on physical activity should determine how much physical activity should be recommended to patients to maintain or increase physical and mental health in the various stages of COPD.

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SUPPLEMENTARY DATA

TABLE E1. Number of eligible patients per recommendation

Recommendations	**Total group** n=115	**GOLD I** n=30	**GOLD II** n=31	**GOLD III** n=33	**GOLD IV** n=21
Step-based, n (%)	115 (100%)	30 (100%)	31 (100%)	33 (100%)	21 (100%)
Questionnaire-based, n (%)	115 (100%)	30 (100%)	31 (100%)	33 (100%)	21 (100%)
3 MET, n (%)	111 (97%)	30 (100%)	29 (94%)	32 (97%)	20 (95%)
40% VO_2 reserve, n (%)	105 (91%)	30 (100%)	29 (94%)	32 (97%)	14 (67%)
46% VO_2 max, n (%)	105 (91%)	30 (100%)	29 (94%)	32 (97%)	14 (67%)
40% HR reserve, n (%)	101 (88%)	30 (100%)	28 (90%)	31 (94%)	12 (57%)
64% HR max, n (%)	59 (51%)	24 (80%)	21 (68%)	8 (24%)	3 (14%)
6 MET, n (%)	111 (97%)	30 (100%)	29 (94%)	32 (97%)	20 (95%)
60% VO_2 reserve, n (%)	105 (91%)	30 (100%)	29 (94%)	32 (97%)	14 (67%)
64% VO_2 max, n (%)	105 (91%)	30 (100%)	29 (94%)	32 (97%)	14 (67%)
60% HR reserve, n (%)	101 (88%)	30 (100%)	28 (90%)	31 (94%)	12 (57%)
77% HR max, n (%)	73 (63%)	29 (97%)	27 (87%)	14 (42%)	3 (14%)

Causes for non eligibility

Recommendations based on accelerometer measurements: Four patients did not wear the accelerometer for at least 5 full days (1 patient wore the accelerometer for 5 full days and 12 for 6 full days).
Recommendations based on cycle ergometer measurements: Six patients did not perform a cycle ergometer test or did not wear the accelerometer for at least 5 full days.
Recommendations based on VO_2 values: Four patients received supplemental oxygen during the cycle ergometer test and therefore VO_2 values were not reliable.
Recommendations based on HR max: Due to low maximum HR values during the cycle ergometer test for some patients the estimated moderate-intensity HR value was lower than the HR at rest and therefore not usable.
Recommendations based on HR reserve: In a few patients HR reserve was not measurable due to minimal increase in HR. This also occurred in patients with a fluctuating HR.

TABLE E2. Differences in functional capacity measures between patients that met or failed the different recommendations

		Chair stand test			6MWD			Wmax			VO_2 max/kg		
		Failed	Met	p-value	Failed	Met	p-value	Failed	Met	p-value	Failed	Met	p-value
Absolute	**MET absolute**	10 (4-18)	13 (7-23)	**<0.001**	392 (60-646)	523 (352-645)	**<0.001**	60 (10-195)	120 (4-260)	**<0.001**	15.4 (5.7-33.6)	20.1 (13.3-37.7)	**<0.001**
	Questionnaire-based	8.5 (4-14)	11 (6-23)	**0.006**	342 (60-540)	465 (180-646)	**<0.001**	50 (10-140)	100 (20-260)	**0.004**	14.5 (5.7-23.7)	18.9 (7.5-37.7)	**0.003**
	Step-based	10 (4-17)	14 (9-23)	**<0.001**	410 (60-646)	540 (420-645)	**<0.001**	80 (10-195)	135 (60-260)	**<0.001**	15.7 (5.7-33.6)	21.6 (12.7-37.7)	**<0.001**
Relative	**VO_2 reserve**	10 (5-23)	10 (4-19)	0.773	437 (60-646)	497 (175-641)	0.166	90 (20-260)	103 (10-165)	0.808	18.7 (7.5-37.7)	18.1 (5.7-26.2)	0.685
	VO_2 max	10 (5-23)	11 (4-19)	0.572	456 (60-646)	454 (175-641)	0.912	95 (25-260)	90 (10-165)	0.107	19.1 (10.7-37.7)	17.0 (5.7-26.2)	**0.047**
	HR reserve	10 (5-23)	12 (4-19)	0.170	456 (60-646)	459 (175-641)	0.651	105 (20-260)	85 (10-165)	0.108	19.1 (7.7-37.7)	17.6 (5.7-26.8)	0.081
	HR max	11 (5-23)	12 (4-19)	0.995	505 (358-646)	507 (195-645)	0.853	120 (30-260)	110 (30-240)	0.268	22.5 (11.3-37.7)	19.0 (7.3-30.9)	**0.048**

Data are presented as median (range). Differences were tested with Mann-Whitney-U test.
Failed: patient group that failed the recommendation; Met: patient group that met the recommendation. 6MWD: 6-minute walk distance; Wmax: maximum workload; VO_2max/kg: Maximum oxygen uptake/kilogram; MET: metabolic equivalent of task; VO_2: Oxygen uptake; HR: heart rate.

5

CHAPTER 6

Daily physical activity after bronchoscopic lung volume reduction: a pilot study

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ABSTRACT

We performed a pilot study on the potential beneficial effects of bronchoscopic lung volume reduction on the daily physical activity level of patients with severe emphysema. This is the first study that has measured physical activity in a performance based manner after (bronchoscopic) lung volume reduction. We found that bronchoscopic lung volume reduction significantly improved lung hyperinflation and dyspnea severity, but that this was not followed by an increase in physical activity 6 months later. This implies that special attention on physical activity enhancement is necessary after lung volume reduction in order to increase the physical activity level of these patients.

Keywords: COPD • dyspnea • emphysema • lung hyperinflation

Daily physical activity is an important outcome variable in patients with chronic obstructive pulmonary disease (COPD) and has shown to be mainly associated with dynamic lung hyperinflation.[1] Physical inactivity is known to cause muscle deconditioning, which increases the ventilatory requirements during exercise, and in turn increases lung hyperinflation and worsens dyspnea, thus contributing to a downward spiral.[2] This is especially true in patients with emphysema, in which destruction of alveolar tissue can result in progressive static and dynamic lung hyperinflation. Moreover, physical inactivity is a strong predictor of mortality in COPD patients.[3] Notwithstanding the beneficial effects of regular physical activity, physical activity levels in COPD patients are low, especially in those with severe COPD.[4]

Lung volume reduction (LVR) by bronchoscopic techniques is an innovative and increasingly applied treatment method targeted at improving lung hyperinflation. Endobronchial devices are implanted in emphysematous parts of the lung to reduce hyperinflation. This may improve the mechanical properties of the remaining lung and the efficiency of the inspiratory muscles. Consequently, this may lead to reduction of dyspnea during exertion and improve functional capacity of the body. Theoretically, after LVR a COPD patient's physical activity level may improve, which would be beneficial for an independent lifestyle of the patient and for restoration of social participation. However, so far physical activity has never been measured before and after LVR. We therefore investigated the potential beneficial effects of bronchoscopic LVR on the physical activity level of these severely disabled COPD patients, and investigated whether decreased lung hyperinflation is associated with increased physical activity.

We performed a pilot study on 16 patients with severe emphysema who participated between July 2009 and August 2010 in bronchoscopic LVR with coils intervention studies (NCT01220908 and 01328899). The studies were approved by the local ethics committee and all patients provided informed consent. Prior to the bronchoscopic LVR treatment, physical activity was examined with a triaxial accelerometer together with lung function, lung volumes, exercise capacity, dyspnea severity and self-efficacy. Six months after the bronchoscopic LVR, all measurements were repeated.

Physical activity was measured in a performance-based manner with a triaxial accelerometer, using the DynaPort (McRoberts, the Hague, the Netherlands). The Dynaport is a small device which is worn around the waist. Patients were instructed to wear the DynaPort continuously for a period of 1 week. The DynaPort is able to detect physical activity (standing, locomotion, shuffling, lying and sitting), to measure steps and to estimate physical activity level (PAL) based on energy expenditure. PAL is calculated as total energy expenditure divided by basal metabolic rate. The DynaPort has proven to be an accurate tool to measure postures and gait in COPD patients.[5] Forced expiratory volume in 1 second (FEV_1) and lung volumes were measured according to European Respiratory Society/American Thoracic Society guidelines. Exercise capacity was determined using the 6-minute walk distance test (6MWD).[6] Dyspnea severity was determined using the modified Medical Research Council Dyspnea scale (mMRC).[7]

Self-efficacy in physical abilities was measured using the Dutch version of the Perceived Physical Activity Scale (LIVAS questionnaire).[8]

Of the 16 patients who were included at baseline, two were lost to follow up. Consequently, 14 patients were included in this analysis: four males (29%), median age 62.5 years, and median FEV_1 28% predicted. Physical activity was low at baseline: median number of steps per day was 2084, and median percentage activity (standing, locomotion and shuffling) was 17.6% (table 1).

After 6 months, no significant changes in physical activity, exercise capacity or self-efficacy were found (table 1). Static lung hyperinflation measurements improved significantly above the recently calculated minimal important difference,[9] and dyspnea severity decreased by 1 point on the mMRC scale (p=0.06).

In line with our hypothesis, decreased RV%TLC was significantly associated with decreased dyspnea severity (rho=0.65, p=0.01). However, in contrast with our hypothesis this was not associated with changes in physical activity outcomes. Although exercise capacity (6MWD) did not improve significantly after bronchoscopic LVR, this was positively associated with changes in physical activity as assessed by percentage activity (rho=0.55, p=0.04), number of steps per day (rho=0.57 and p=0.03), and borderline significant with dyspnea (rho= -0.48, p=0.09).

In summary, this pilot study showed that there was no improvement in physical activity 6 months after bronchoscopic LVR, despite significant improvements in static lung hyperinflation. Furthermore, decreased lung hyperinflation was not associated with

TABLE 1. Clinical characteristics at baseline and after 6 months

Variable	**Baseline**	**6-months follow up**	**p-value**
RV, % predicted	223 (184-267)	205 (134-223)	**0.001**
RV/TLC, %	61.4 (55.4-67.4)	56.7 (48.3-65.3)	**0.008**
FEV_1, % predicted	28 (22-42)	32 (15-58)	0.35
mMRC, score	3 (2-4)	2 (2-4)	0.06
6MWD, meter	336 (200-451)	348 (140-477)	0.22
Activity, %	17.6 (8.1-27.9)	15.0 (7.7-26.4)	0.29
Steps per day, steps	2084 (374-5800)	2426 (321-5721)	0.68
Physical activity Level (PAL)	1.51 (1.33-1.61)	1.50 (1.37-1.66)	0.55
Self-efficacy, LIVAS total score	29 (13-39)	30 (20-42)	0.28

Data are presented as median (range), unless otherwise stated. RV: residual volume; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnea index; 6MWD: 6-minute walk distance. Baseline and follow up measurements were compared with Wilcoxon signed-rank test (significant p-values are shown in bold).

improved physical activity or exercise capacity, in contrast to its significant association with reduced dyspnea severity.

This study indicates that a new treatment method in COPD, such as bronchoscopic LVR, can substantially improve lung hyperinflation and dyspnea severity. The improvement in dyspnea could indicate that patients might perform the same activities more comfortably than before the treatment. However, an increase in physical activity is not automatically warranted. Other treatment methods that increase functional capacity in COPD patients have shown similar results. For example, a recent review showed that participation in a pulmonary rehabilitation program does not automatically result in increased physical activity.[10] Furthermore, although lung transplantation improves lung function, physical activity remains below normal values and is significantly worse than in matched healthy controls.[11] Together, this suggests that although patients have larger pulmonary reserves to function at higher physical activity levels, other factors are apparently more important. These could be physical factors like chronic deconditioning or atrophic muscles, and/or psychological factors, such as motivation to be physically active, anxiety or anticipated breathlessness.

This study implies that it is important to provide a physical activity enhancement program after LVR. Such an intervention should include a structured exercise program with specific attention for atrophic muscles. Additionally, in our opinion, exercises should be combined with counselling consisting of promotion of physical activities in daily life in an attempt to achieve long term results.

We are aware that the number of patients is low and that our study lacked a control group. A large randomized controlled trial would be useful to confirm our results.

In conclusion, despite the low number of patients, this is the first study that shows data on physical activity in a performance-based manner after LVR. Unexpectedly, physical activity did not significantly improve after the intervention, while static lung hyperinflation and dyspnea severity did. This suggests that the improved pulmonary capacity is actually not used by the COPD patients for physical activities in daily life, probably also due to psychological reasons. Consequently, our study indicates that a short pulmonary rehabilitation program with counselling on the promotion of physical activity in daily life should be considered after such treatments.

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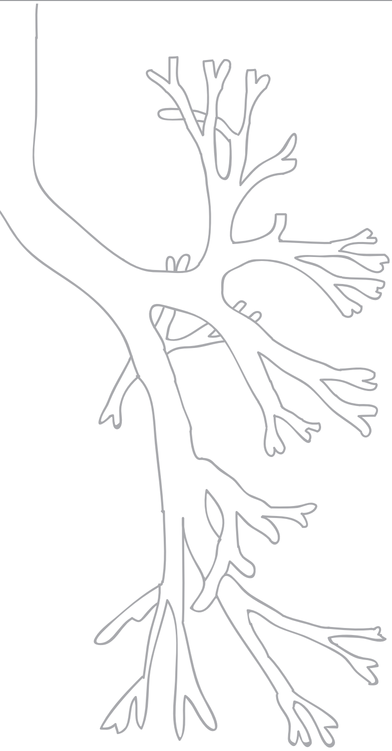
CHAPTER 7

The minimal important difference for residual volume in patients with severe emphysema



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ABSTRACT

Background: Residual volume (RV) measured by body plethysmography is a routine measurement in clinical pulmonary practice and is often an important outcome variable in clinical trials. However, it is not known what size of improvement can be regarded as being important in severe emphysema patients. Therefore, the aim of the study is to establish the minimal important difference (MID) for RV in severe emphysema patients undergoing bronchoscopic lung volume reduction.

Methods: Ninety-one severe emphysema patients were included. RV and total lung capacity (TLC) were measured by body plethysmography. MID estimates were calculated by anchor-based and distribution-based methods. Forced expiratory volume in 1 second, 6-minute walk distance and St George's Respiratory Questionnaire total score were used as anchors and Cohen's effect size was used as distribution-based method.

Results: The calculated MID estimates according to the different anchors and methods ranged between -0.31 and -0.43 L for RV, -6.1 and -8.6% for percentage change in RV (RV%) from baseline and -2.8 and -4.0% for RV%TLC.

Conclusions: These MID estimates are useful for sample size determination in new studies on interventions aimed at reducing RV and for interpreting the results from clinical trials in severe emphysema patients.

Keywords: COPD • hyperinflation • lung volume reduction

INTRODUCTION

Lung hyperinflation is an important feature in patients with chronic obstructive pulmonary disease (COPD) and is the result of increased airway resistance, reduced lung recoil and shortened available expiratory time.[1] Lung hyperinflation is strongly associated with important patient-centred outcomes, such as dyspnea, exercise tolerance and daily physical activity.[1,2] As a consequence, it negatively affects patients' daily functioning and their quality of life.

In the past decade, reducing lung hyperinflation has become an important treatment goal in the management of severe emphysema. Several treatment methods have been shown to improve lung hyperinflation temporarily, such as pursed-lip breathing, exercise training and oxygen use, while bronchodilators or lung volume reduction surgery have been shown to improve lung hyperinflation in patients with COPD more definitively.[1,3] Lung volume reduction surgery has been shown to improve lung function, quality of life and exercise capacity.[4] Lung volume reduction techniques by bronchoscope are less invasive, and show promising results in improving lung hyperinflation, quality of life and exercise capacity.[5-8]

Residual volume (RV) assessed by body plethysmography is commonly used to measure (changes in) lung hyperinflation. Body plethysmography is a routine measurement in clinical pulmonary practice based on Boyle's law, with reproducible measurements of absolute lung volumes. In studies on methods that aim to improve hyperinflation, increased RV constitutes an important inclusion criterion as well as outcome variable. Unfortunately, to date, it is not known what size of improvement can be regarded as being clinically important for the severe emphysema patient.

The concept of minimal important difference (MID) can be used to establish what size of effect in RV measurements after a treatment adequately reflects the perceived improvements by patients. MID can be defined as "a threshold value for a change that would be meaningful and worthwhile by the patients such that he/she would consider repeating the intervention if it were his/her choice to make again".[9] Any treatment effect above the MID is considered to be relevant. The MID for RV could, therefore, be useful when interpreting the significance of the results of clinical trials for patients, besides the statistical significance of the changes. Additionally, the MID could be used to establish the minimal numbers of subjects to be included in a study to be able to infer meaningful conclusions in future trials (*i.e.* power calculations). To our knowledge, the MID for RV in patients with severe emphysema has not yet been established.

The aim of this study was to establish the MID for RV in patients with severe emphysema who are being treated by bronchoscopic lung volume reduction.

METHODS

Study population

A total of 91 patients with severe emphysema were included in this study. All patients participated in one out of three different bronchoscopic lung volume reduction studies, performed in one hospital in the Netherlands (University Medical Center Groningen, Groningen). Patients were included in this study on MID if they had body plethsmography measurements both from baseline and 1 month after completing the specific bronchoscopic lung volume reduction treatment. Twenty-nine patients with severe homogeneous emphysema (10 controls) were included from a randomized, double-blind, sham-controlled trial on bronchoscopic transbronchial airway bypass treatment (www.clinicaltrials.gov identifier number NCT00391612),[10] 33 patients with severe upper- or lower-lobe heterogeneous emphysema (no controls) were included from a bronchoscopic lung volume reduction treatment study using self-expandable nitinol coils (NCT01220908),[6] and 29 patients with severe upper- or lower-lobe heterogeneous emphysema (9 controls) were included from a bronchoscopic lung volume reduction treatment study using one-way endobronchial valves (NCT01101958).[7] All studies were approved by the local medical ethics committee and all patients gave written informed consent.

Measurements

RV and total lung capacity (TLC) were measured by body plethysmography (Viasys, San Diego, CA, USA) according to the European Respiratory Society/American Thoracic Society guidelines.[11] Furthermore, all patients performed spirometry (Masterscreen, Viasys),[12] a 6-minute walk distance test (6MWD)[13] and completed the St George's Respiratory Questionnaire (SGRQ).[14] All measurements were performed at baseline and 1 month after the bronchoscopic lung volume reduction treatment.

MID calculation methods and statistical analysis

Selected outcome variables for the statistical analyses were RV, percentage change in RV (RV%) from baseline and the RV/TLC ratio (RV%TLC). Various methods for estimating MIDs have been described in the literature.[15,16] Because the combination of multiple methods is generally recommended, our current study included both anchor-based and distribution-based methods to calculate the MID.

Anchor-based methods compare the change in outcome measure with the change in another measure with an established MID ("the anchor").[9] The anchors chosen in this study were forced expiratory volume in 1 second (FEV_1) (MID 100 mL[17]), 6MWD (MID 26 meter[18]) and SGRQ total score (MID 4 units[19]). An anchor is suitable to use if there is an appreciable association between the outcome variable and the anchor. Therefore, first the correlation coefficient between the change in (Δ) RV, ΔRV% and ΔRV%TLC *versus* the change in the anchor were assessed. In general, there is no consensus on when a correlation coefficient is considered to be an appreciable association. One review recommends statistically significant ($p<0.05$) Pearson correlation coefficients of ≥0.3 as appreciable,[16] and 2 studies in COPD patients performed the analyses when correlation coefficients were 0.3 or 0.5.[18,20] Therefore, it is an arbitrary decision, and for the current study, Pearson correlation coefficients of ≥0.4 were accepted. Afterwards, linear regression analyses were performed with ΔRV, ΔRV% or ΔRV%TLC as dependent variables and one of the above-described anchors as the independent variable. Subsequently, the MID value of the anchor was entered into the equation derived from the linear regression analysis and the MID was calculated from the established equation.

Distribution-based methods compare the change in outcome measure with some measure of variability.[9] In this study, the Cohen's effect size was used. A moderate effect size was calculated of the change score of the outcome measure from baseline to 1 month after the bronchoscopic lung volume treatment. All statistical analyses were performed using PASW statistics 18 (SPSS Inc., Chicago, IL, USA).

RESULTS

Ninety-one patients with severe emphysema, who had undergone body plethysmography measurements at baseline and 1 month later, were included in this study (63% female; mean age 60 years). Population characteristics at baseline and the 1-month follow-up changes from baseline are shown in table 1.

TABLE 1. Baseline characteristics and change scores at 1-month follow-up (n=91)

	Baseline		**Change 1 month from baseline¶**		
Variable	**Absolute**	**% pred**	**Absolute**	**% change from baseline**	**% >MID**
Females/males	57/34	NA	NA	NA	NA
Age, year	60.1 ± 8.3	NA	NA	NA	NA
BMI, kg/m²	24.2 ± 3.3	NA	0.3 ± 0.8	1.2 ± 3.3	NA
FEV_1, L	0.73 ± 0.3	26.7 ± 9.8	0.10 ± 0.17	13.1 ± 21.2	35.2
6MWD, m	319.2 ± 97.5	48.8 ± 14.7	29.7 ± 58.6	11.3 ± 23.2	52.2
SGRQ, total score	62.5 ± 11.2	NA	-7.8 ± 12.9	-13.0 ± 21.5	64.0
RV, L	5.0 ± 1.1	241.0 ± 46.6	-0.43 ± 0.61	-8.7 ± 12.2	Unknown
TLC, L	7.8 ± 1.4	136.5 ± 14.2	-0.23 ± 0.43	-2.8 ± 5.5	Unknown
RV/TLC, %	64.3 ± 8.3	166.8 ± 23.5	-4.1 ± 5.7	-6.3 ± 8.8	Unknown

Data are presented as n or mean ± sd, unless otherwise stated. % pred: % predicted; MID: minimal important difference; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; 6MWD: 6-minute walk distance; SGRQ: St George's Respiratory Questionnaire; RV: residual volume; TLC: total lung capacity; NA: not applicable; ¶: placebo/control group included.

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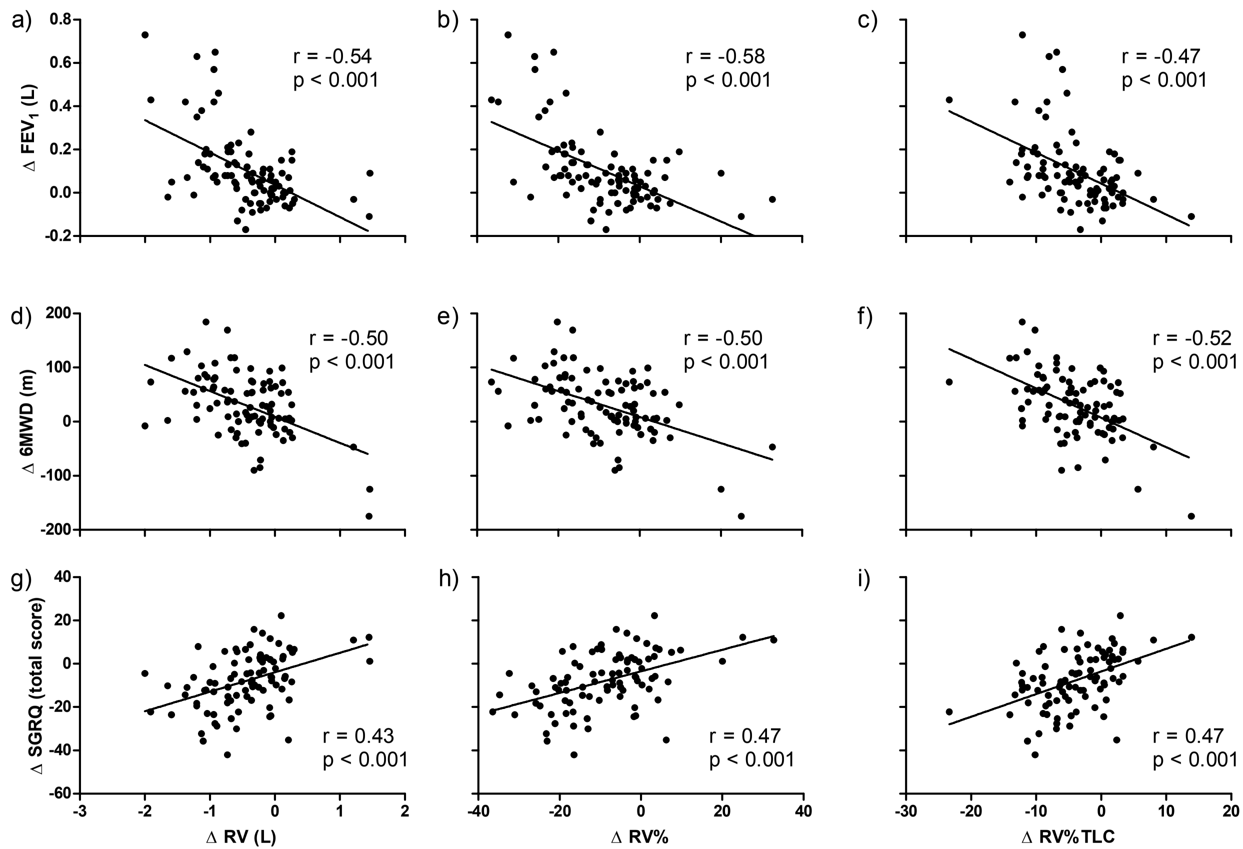

FIGURE 1. Scatter plots of change in lung hyperinflation measurement *versus* change in anchor variable. a-c) *change in (Δ) forced expiratory volume in 1 second (FEV_1)*; d-f) *Δ 6-minute walk distance (6MWD) and* g-i) *Δ St George's Respiratory Questionnaire (SGRQ) total score* versus a,d,g) *Δ residual volume (RV);* b,e,h) *Δ percentage change in RV (RV%) and* c,f,i) *Δ RV/total lung capacity ratio % (RV%TLC).*

MID estimates according to the anchor-based method

Scatter plots and Pearson correlation coefficients between ΔRV, ΔRV% from baseline, and ΔRV%TLC, *versus* ΔFEV_1, Δ6MWD and ΔSGRQ total score are presented in figure 1. Pearson correlation coefficients ranged from 0.43 to 0.58. The highest correlations were present with FEV_1 (range 0.47-0.58) and the lowest with SGRQ total score (range 0.43-0.47).

The MID estimates derived from the linear regression equations with use of the anchor MID showed that the MID estimates for the absolute change in RV according to the different anchors were: -0.43 L (FEV_1), -0.41 L (6MWD) and -0.35 L (SGRQ total score) (table 2). The MID estimates for RV% change from baseline according to the different anchors were: -8.6% (FEV_1), -8.4% (6MWD), and -6.9% (SGRQ total score). The MID estimates for RV%TLC according to the different anchors were: -4.0% (FEV_1), -3.9% (6MWD), and -3.2% (SGRQ total score).

MID estimates according to the distribution-based method

The MID estimates calculated with the distribution-based method (Cohen's effect size) were: -0.31 L for RV, -6.1% for RV% change from baseline and -2.8% for RV%TLC (table 2).

DISCUSSION

This is the first study describing MID estimates for lung hyperinflation measurements. Our results indicate MID estimates for RV of -0.31 - -0.43 L, for RV% from baseline of -6.1 - -8.6% and for RV%TLC of -2.8 - -4.0% in patients with severe emphysema undergoing bronchoscopic lung volume reduction. MID estimates were determined using both anchor-based and distribution-based methods. High correlations were found between changes in lung hyperinflation measurements and changes in patient-centred outcomes, such as exercise capacity and health-related quality of life, emphasising the importance of this clinical feature for patients with severe emphysema.

TABLE 2. Minimal important difference (MID) estimates for residual volume (RV)

	Δ RV (L)	Δ RV%	Δ RV/TLC (%)
Anchor-based method			
FEV_1	-0.43 (-0.62 - -0.24)	-8.6 (-9.5 - -5.7)	-4.0 (-5.9 - -2.2)
6MWD	-0.41 (-0.59 - -0.23)	-8.4 (-11.9 - -4.9)	-3.9 (-5.5 - -2.3)
SGRQ total score	-0.35 (-0.45 - -0.24)	-6.9 (-8.8 - -4.9)	-3.2 (-4.2 - -2.3)
Distribution-based method	-0.31	-6.1	-2.8

Data are presented as MID (95% CI). Δ:change; RV: Residual volume; RV%: percentage change in RV from baseline; TLC: total lung capacity; FEV_1: forced expiratory volume in 1 second; 6MWD: 6-minute walk distance; SGRQ: St George's Respiratory Questionnaire.

Anchor-based and distribution-based methods were used to determine the MID, and for the anchor-based method, three anchors were chosen. Therefore, four MID estimates of each outcome variable were generated. These ranges of MID estimates can be used for power calculations in future trials. Here, we critically evaluate the methods and anchors used for this specific intervention and study population.

For the anchor-based method, it is important that the anchor used is suitable for the analysis. A number of criteria can be used to establish the quality of the anchor. First, the MID of the anchor should be derived from multiple high-quality studies, including many well-characterized COPD patients, using multiple methods to establish the MID, and agreeing about the final MID estimate. Secondly, the anchor should be derived from a comparable COPD population; thus for the current study, patients with severe emphysema. Thirdly, the anchor should somehow reflect the perception of improved lung hyperinflation. Finally, the anchor should be highly correlated with changes in RV variables. The anchors used in the current study will be discussed here.

FEV_1 seems attractive, as it is a highly reproducible measurement that is strongly associated with RV outcomes. The MID calculation for FEV_1 is based on multiple studies, but establishing the MID was never the primary aim of these studies.[17] In addition, the MID of FEV_1 was based on a broad variety of COPD patients, including different treatment modalities and, therefore, might not be applicable to our population. Furthermore, the improvement in FEV_1 is largely dependent on improvement in vital capacity, which is mainly dependent on a change in RV, so RV and FEV_1 are indirectly related. However, the major disadvantage of this anchor is that it does not reflect the perceived improvement by patients[1] and is not a patient-reported outcome.

6MWD is highly correlated with RV measurements. Another advantage of this anchor is that the 6MWD MID estimate was calculated from a study investigating the effect of lung volume reduction surgery in severe COPD patients,[18] and, thus, is derived from a comparable COPD study population that underwent a comparable, although more invasive, intervention. Furthermore, another study investigated the 6MWD MID using another treatment method and demonstrated a similar MID estimate for pulmonary rehabilitation.[20] Also, the perceived improvement in 6MWD is thought to be a good reflection of the perceived improvement in lung hyperinflation after bronchoscopic lung volume reduction treatment.

SGRQ total score seems more attractive because this instrument is excellently validated for patient-reported outcomes in COPD. However, when using the SGRQ total score as an anchor, the Pearson correlation coefficients were of lowest of the three anchors in this study. Another disadvantage is that the MID estimate for SGRQ total score (4 units) is based on multiple studies, using different populations and different MID estimation techniques.[19]

A recent study showed that different interventions in different groups of COPD patients may produce different MID estimates.[21] The SGRQ total score from three different lung volume reduction treatment studies were plotted against the change in 6MWD and compared with the effects after pulmonary rehabilitation. A different response pattern for 6MWD and a larger result for health-related quality of life were found between the different treatment modalities. This could indicate that a higher MID estimate for the SGRQ total score for studies using lung volume reduction techniques would be more appropriate. Furthermore, it is important to acknowledge that unblinded interventions can lead to larger improvements in health-related quality of life, due to the fact that patients are aware that they have been treated. Therefore, we advocate that the MID of the SGRQ should subsequently be established in a similar COPD population after a similar treatment, preferably, with a placebo-controlled design before using it as an anchor.

Distribution-based methods do not comply with the primary aim of the MID concept, namely identifying an effect size that is meaningful in the perception of the patient. Therefore, we agree with the consensus that the distribution-based method should only be used to support estimates derived from anchor-based methods.[9,16]

In summary, out of the used methods and anchors in the current analyses, the anchor method is the best method to calculate the MID and the 6MWD appears to be the anchor with the highest quality for this specific patient group and intervention.

For the current study, RV% from baseline and RV%TLC were chosen as outcome variables besides absolute change in RV. RV% from baseline was chosen because this adjusts for baseline scores, *e.g.* it takes sex differences into account. RV%TLC was chosen because it takes individuals' lung capacity into account and has been shown to be an important determinant of improvement in forced vital capacity after lung volume reduction surgery.[22] Unfortunately, most MID estimates are only expressed in absolute numbers. One study that did measure the MID estimate of percentage change from baseline for 6MWD found a MID estimate of 14%.[20] However, this MID estimate was based on the effects after a rehabilitation program and, therefore, was not chosen as anchor in our current study. We recommend that in addition to MID estimates for absolute variables, the percentage change from baseline and percentage predicted should be calculated.

A first limitation of the current study is the relative small sample size. However, all study measurements were performed in one specialized research hospital in the Netherlands, always in the same setting, using the same equipment. This led to highly standardised measurements with low variation, possibly explaining the rather high correlations between changes in lung hyperinflation and the chosen anchors. A second limitation is the measurement of only static lung hyperinflation and not dynamic lung hyperinflation. We anticipate that improved dynamic lung hyperinflation is at least as important for perceived dyspnea and exercise tolerance as improved static lung volume. Future lung volume reduction studies might, therefore, also investigate correlations between improved dyspnea scores and improved inspiratory capacities during exercise. A final limitation of the current study is the potentially low generalisability of the MID estimates to other COPD populations or other treatment methods. Our study population is rather homogenous (predominantly female severe emphysema patients) and based on short-term results, which strengthens the MID estimate for this population, but might limit the usefulness for other COPD populations or treatment methods and long-term effects. It is indeed known, at least for SGRQ, that different interventions can lead to different MID estimates in different COPD populations.[21] Therefore, to be able to apply the MID estimates to a more heterogenic COPD population, further research in a larger, more sex-balanced population is needed to investigate whether other interventions that reduce lung hyperinflation, like treatment with bronchodilators, and other COPD populations provide the same MID estimates for RV measurements.

In conclusion, this is the first study that estimated the MID for change in emphysema-related static lung hyperinflation. The calculated MID estimates according to the different anchors and methods ranged between -0.31 and -0.43L for RV, -6.1 and -8.6% for RV% from baseline and -2.8 and -4.0% for RV%TLC. These MID estimates are useful for sample size determination of new studies on interventions aimed at reducing RV, and for interpreting the results from clinical trials in patients with severe emphysema.

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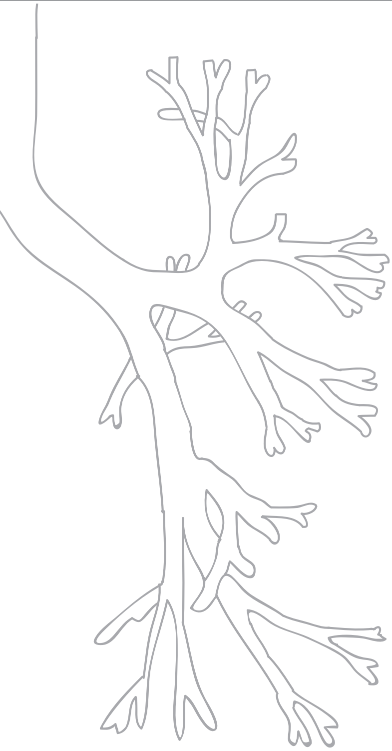
CHAPTER 8

Summary and General discussion



SUMMARY

Scope

The scope of this thesis was physical activity in patients with chronic obstructive pulmonary disease (COPD). *Chapter 1* provides an introduction to the subject. The many health benefits of regular physical activity underline the importance of this topic, especially in this period of time when the occurrence of a sedentary lifestyle is increasing. While physical activity has many health benefits in general, the physical activity level in COPD patients has shown to be low, compared with a healthy population but also with other patient groups. Physical activity is an important modifiable risk factor and therefore an important treatment target in this patient group. This thesis investigated physical activity and its potential predictors in COPD patients in all severity stages of the disease, the suitability of general physical activity recommendations in COPD patients and the association between decreased lung hyperinflation and physical activity.

Predictors of physical activity

In *Chapter 2* we identified the potential predictors of physical activity in COPD patients. Reviewing the literature, associations were found between physical activity and important disease outcomes of COPD like forced expiratory volume in 1 second (FEV_1), dyspnea, exercise capacity, muscle function, systemic inflammation, comorbidities and health-related quality of life (HRQL). No significant associations were described between physical activity and body mass index (BMI) in COPD patients, in contrast to findings in the general population. Furthermore, a few other cross-sectional studies separated physically active COPD patients from physically inactive COPD patients, giving interesting insights into the determinants and consequences of an inactive lifestyle. Although not consistent, an inactive lifestyle was associated with lower FEV_1, higher levels of dyspnea, higher number of COPD admissions, worse exercise capacity and worse HRQL. Furthermore, only a few studies investigated the relationship between physical activity and psychosocial factors like self-efficacy or depression. In general the literature was limited and inconsistent, and most associations were only moderate. Figure 1 shows a theoretical framework of the role of physical inactivity in COPD described in *chapter 2*.

Chapters 3, 4 and 5 were based on data from a cross-sectional study we performed that focussed on determining the predictors of physical activity in COPD. During 3 study visits, COPD patients performed various physical tests and completed psychosocial questionnaires. Physical activity was measured using a triaxial accelerometer, a pedometer and a questionnaire. Furthermore, patients were interviewed regarding physical activity. We included 115 patients with mild to very severe COPD (68% male, mean age 65 years, FEV_1 57.5 %predicted, Global initiative for Chronic Obstructive Lung Disease (GOLD) severity stages: 30 stage I, 31 stage II, 33 stage III and 21 stage IV). Mean steps per day ranged between 236 and 18433 steps (triaxial accelerometer).

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Chapter 3 presents a study that assessed physical activity and sitting time in COPD patients and investigated the potential physical and psychosocial determinants (that were identified in *chapter 2*). One hundred and thirteen COPD patients wore the accelerometer and were included in these analyses. Physical activity, measured by a triaxial accelerometer (24hours/day), showed a mean locomotion and shuffling time per day of 6.8% (range: 0.7-20.4). Reduced levels of physical activity were most prevalent in patients with GOLD stage III-IV. Predictors of physical activity were higher self-efficacy, sub-maximal exercise capacity and lower lung hyperinflation. In patients with GOLD stage I-II, higher self-efficacy and the spring/summer season were predictors, whereas in GOLD III-IV, worse lung hyperinflation, dyspnea severity, leg muscle function and oxygen use were. Predictors of sitting time in the total group were a more positive perception on treatment control, less autonomous motivation to exercise, not using sleep medication and oxygen use.

The conclusions were that both physical and psychosocial factors affected physical activity in COPD. The predictors of physical activity in the early stages of COPD were more generic, in contrast to the physical and disease-specific predictors in more severe stages. The predictors of sitting time were different from the predictors of physical activity.

When we compare the results of the univariate analyses in *chapter 3* with the potential predictors we identified in *chapter 2*, we found, <u>in line</u> with the literature, that HRQL and health status were positively associated with physical activity. Furthermore, we found significant associations between higher physical activity and better lung function, lung volumes and leg muscle function, higher (sub)maximal exercise capacity and self-efficacy, less dyspnea, lower number of exacerbations and not using long term oxygen therapy. Furthermore, <u>in line</u> with the literature we found no significant association between physical activity and body composition.

<u>In contrast</u> with the literature in *chapter 2,* we found a significant association between higher physical activity and lower depression, and no significant association between physical activity and comorbidities.

<u>In addition</u> to the literature in *chapter 2*, we found a significant association between better illness perception and motivation to exercise. Furthermore, physical activity level was lower in the autumn/winter season as compared to spring/summer season. Moreover, we did not find a significant association between physical activity and social support, sleep quality, use of sleep medication, work status, living status, education level, age, smoking status and smoking history.

In *Chapter 4* we investigated the personal reasons why COPD patients are physically active or sedentary using qualitative research methods, and assessed the relationship between those reasons and the actual measured level of physical activity. All 115 COPD patients underwent a semi-structured interview. The most frequently reported reason to be physically active was health benefits, followed by enjoyment, continuous active lifestyle in the past and functional reasons. The most frequently reported reason to be sedentary was weather, followed by health problems and lack of intrinsic motivation. Furthermore, a high physical activity level was related to enjoyment and self-efficacy in physical activity and a low physical activity level was related to weather (health specific), financial constraints, health and perceived shame. In conclusion, we identified important facilitators and barriers to be physically active, which could be very useful for the enhancement of physical activity in sedentary COPD patients.

Figure 2 shows the factors that were found to be related to physical activity in our study population of 115 COPD patients (*chapter 3 and 4*).

Physical activity recommendations

In *Chapter 5* we compared 7 different physical activity recommendations and investigated their suitability in COPD patients. The recommendations differed in frequency, intensity and time and were measured with an accelerometer, pedometer or questionnaire in our study population of 115 COPD patients. The recommendations were based on absolute measures of intensity or relative individualized measures of intensity based on the patient's aerobic fitness level. The proportion of patients classified as sufficient physically active by the different recommendations ranged from 22 to 86% and only 7% of the patients (n=8) met all 7 recommendations. The agreement between the different recommendations was poor (ICC: 0.28). Individualizing the recommendations resulted into a higher proportion of GOLD stage III and IV patients meeting the relative recommendations compared to the absolute recommendations. In contrast, GOLD stage I and II patients less frequently met the relative recommendations. The conclusion of this study was that applying various physical activity recommendations with small differences in frequency, intensity or time led to large differences in classifying whether COPD patients are sufficiently physically active or not. Consequently, the used recommendation will highly affect the proposed physical activity advice to the patient.

Lung hyperinflation and physical activity

Chapter 6 shows the results of a pilot study that investigated the potential beneficial effects of bronchoscopic lung volume reduction on the daily physical activity level of patients with severe emphysema and investigated whether decreased lung hyperinflation was associated with increased physical activity. Fourteen patients with severe emphysema who wore a triaxial accelerometer before and 6 months after the treatment were included in the analyses. We found that there was no improvement in physical activity 6 months after bronchoscopic lung volume reduction, despite significant improvements in static lung hyperinflation. Residual volume improved significantly above the calculated minimal importance difference *(chapter 7)*. Furthermore, decreased lung hyperinflation was not associated with improved physical activity or exercise capacity, in contrast to its significant association with reduced dyspnea severity. We concluded that special attention on physical activity enhancement is necessary after lung volume reduction in order to increase the physical activity level of these patients.

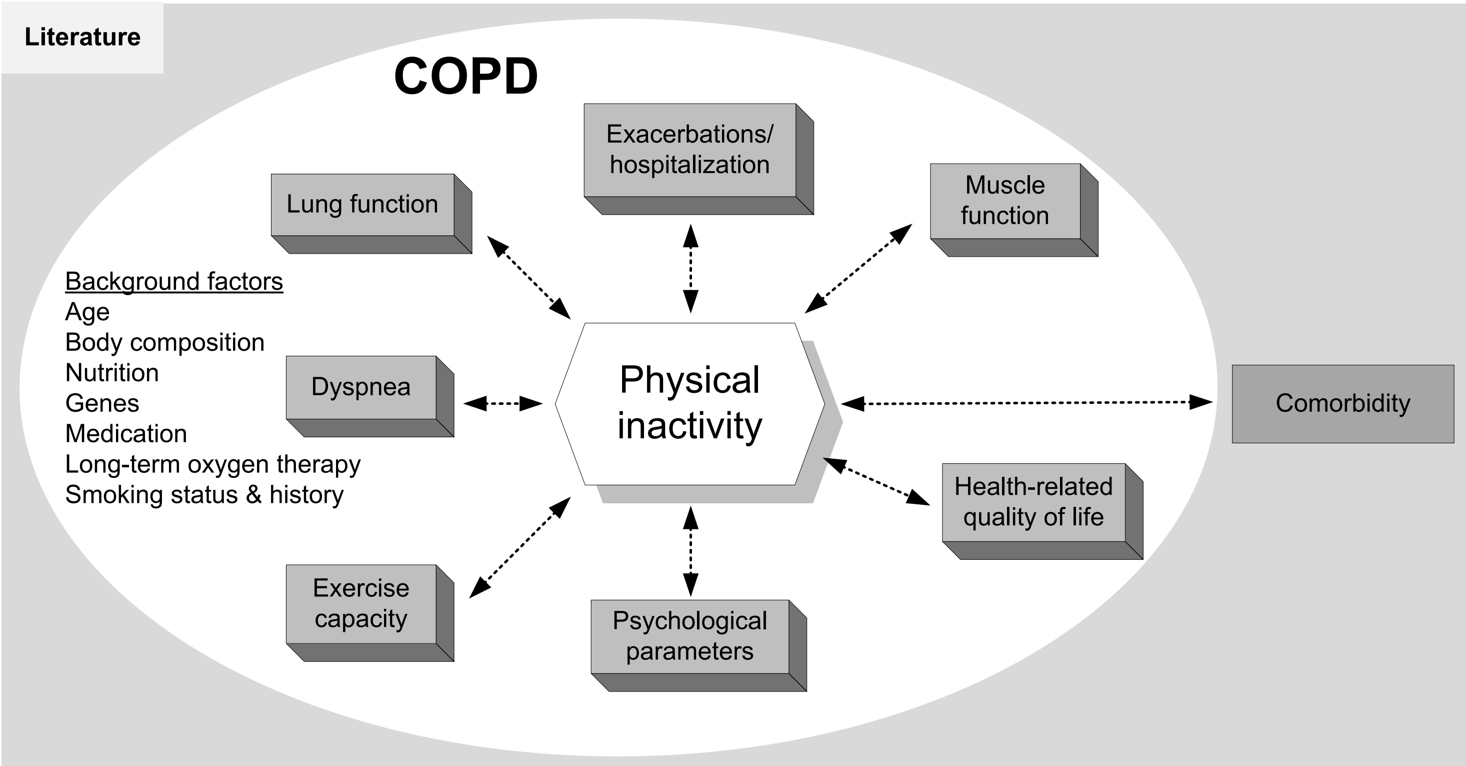

FIGURE 1. Theoretical framework of the role of physical inactivity in chronic obstructive pulmonary disease *(chapter 2).*
The posible role and consequences of physical inactivity for important COPD outcomes is shown. These relationships are embedded in COPD-related background factors. Next to COPD-related factors, the presence of disease other than COPD (comorbidity) may influence physical activity.

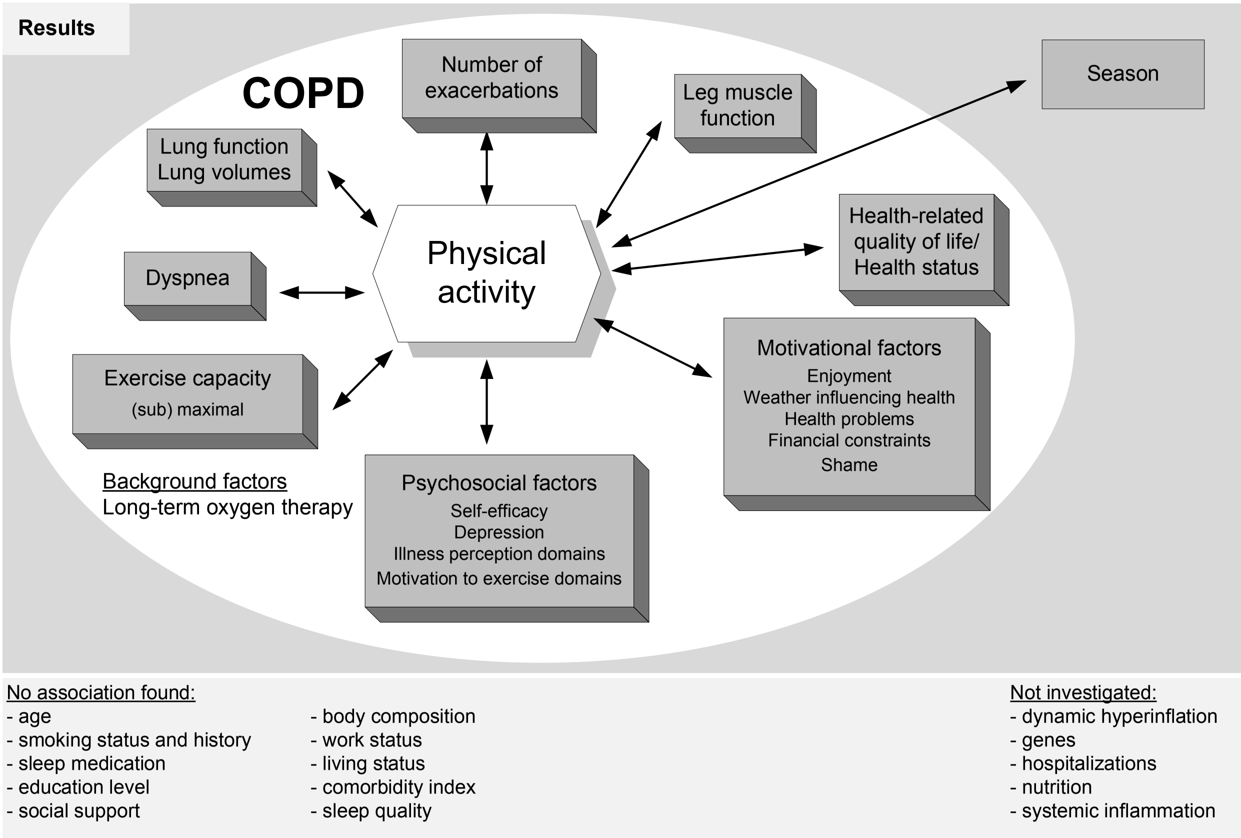

FIGURE 2. Identified associations between physical activity and various physical, psychosocial and environmental factors in 115 mild to very severe COPD patients (*chapters 3 and 4*).

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In *Chapter 7* we established the minimal important difference (MID) for residual volume (RV) in severe emphysema patients undergoing bronchoscopic lung volume reduction. Ninety-one severe emphysema patients were included. RV and total lung capacity (TLC) were measured by body plethysmography. MID estimates were calculated with anchor-based and distribution-based methods. FEV_1, 6-minute walk distance and St Georges's Respiratory Questionnaire total score were used as anchors and Cohen's effect size was used as distribution-based method. The calculated MID estimates according to the different anchors and methods ranged between -0.31 and -0.43L for RV, -6.1 and -8.6% for percentage change in RV from baseline and -2.8 and -4.0% for RV%TLC. These MID estimates are useful for sample size determination in new studies on interventions aimed at reducing RV and for interpreting the results from clinical trials in severe emphysema patients.

GENERAL DISCUSSION

We reviewed and investigated various potential predictors of physical activity. As expected, disease-specific physical factors, like dyspnea, exercise capacity and muscle function, affected the physical activity level in COPD patients. However, besides physical predictors we identified psychosocial, including motivational, and environmental factors that affected the physical activity level as well (figure 2). In patients with mild to moderate COPD the predictors of physical activity were found to be more generic in contrast to the physical and disease-specific determinants in more severe stages. Lung hyperinflation was found to be an important independent predictor of physical activity but improving lung hyperinflation with bronchoscopic lung volume reduction did not automatically increase physical activity in patients with severe emphysema. Furthermore, we found that when applying current general physical activity recommendations with small differences in frequency, intensity or time and measured by different instruments led to large differences in classifying whether COPD patients are physically active or not. In the following part of this thesis we will reflect on the results presented in this thesis and discuss the implications for clinical practice and future research.

Predictors of physical activity and implications

Information on factors that are related to physical activity participation, could guide clinicians and therapists and provide starting points for the enhancement of physical activity. We will discuss some identified predictors of physical activity and their possible implication.

Physical activity not one-dimensional

It is important to acknowledge that physical activity is part of a patient's lifestyle and has a large behavioral component. Physical activity was not only affected by physical capabilities but we showed that psychosocial and environmental factors also play a role. Treating one dimension will probably not change a patient's physical activity behavior. This is illustrated by our results described in *chapter 7*. Reducing static lung hyperinflation by bronchoscopic lung volume reduction (LVR) did not automatically lead to an improvement in physical activity, although static lung hyperinflation was an independent predictor of physical activity. In *chapter 3* we showed that in (very) severe COPD patients next to lung hyperinflation, dyspnea, leg muscle function and use of long term oxygen therapy were independent predictors of physical activity. Therefore, besides improving lung hyperinflation, it may be important to also increase muscle function and improve dyspnea and thus a physical activity enhancement program or pulmonary rehabilitation after bronchoscopic LVR could be important. It would be interesting to investigate whether such a multi-component program after bronchoscopic LVR does increase physical activity. In line, another study found a weak to moderate relationship between change in exercise capacity and change in physical activity and concluded that interventions not only need to target exercise but also should target behavioral change with regard to physical activity.[1] A final example showing that physical activity should not be treated as a one-dimensional condition is derived from a study that showed that providing lightweight ambulatory oxygen to COPD patients using long term oxygen therapy (LTOT) did not increase their physical activity level.[2] In our study, the use of LTOT was a predictor of lower physical activity in patients with (very) severe COPD as well as a predictor of sitting time. In order to change physical activity behaviour only diminishing the burden of LTOT is probably not sufficient. These examples indicate that treating one factor that affects physical activity will not automatically lead to an increase in physical activity in COPD patients. Probably, the focus should also be on physical activity itself and therefore behavioural change should be a target as well.

Lung hyperinflation

One of the aims of this thesis was to study the association between lung hyperinflation and physical activity more in depth. We found that static lung hyperinflation was an independent predictor of physical activity, as opposed to airway obstruction. This could indicate that regardless of the severity of airflow obstruction the development of static hyperinflation highly affects the physical activity level. This is in line with the observation that lung hyperinflation is more strongly associated with functional exercise capacity (like 6MWD) than with FEV_1.[3] It would be interesting to also investigate dynamic lung hyperinflation next to static lung hyperinflation as demonstrated in another study.[4] Probably, dynamic lung hyperinflation is at least as important for perceived dyspnea and exercise tolerance as static lung volume. Therefore, it would be interesting to investigate if treating static and dynamic lung hyperinflation in combination with a physical enhancement program would lead to an increase in physical activity.

Comorbidity

It is known that many COPD patients have comorbidities[5,6] and we believe that certain comorbidities can easily affect the level of physical activity. Unexpectedly, comorbidity was not associated with physical activity in our study population. The literature on the association with comorbidity is inconsistent: two other studies also found no association[4,7], while six other studies did.[8-13] However, in general the significant associations were based on surrogate markers of disease, like blood pressure or ECG readings, instead of specific diseases or on self-reported diseases by patients. We used a composite index-score in our study. Comorbidity indeces apply severity ratings for the various diseases and a COPD-specific comorbidity index probably would have been better. Recently, a first COPD-specific comorbidity index was developed and it would be interesting to investigate this index in relation to physical activity and compare it with general indices.[14] However, this disease-specific comorbidity index, like most other indices, is based on mortality as outcome. We recognize that mortality is indeed an important clinical outcome. However, with respect to physical activity enhancement, we believe it would be of greater interest to identify specific comorbidities that affect physical activity or functional capacity. Consequently, we recommend that future research should pay more attention to the identification of specific diseases or combinations of diseases that affect physical activity.

Combining quantitative and qualitative research

We investigated for the first time the relationship between physical activity and multiple psychosocial and environmental factors both in a quantitative and qualitative manner in the same study population. In the quantitative analyses, we found that physical activity was associated with psychosocial factors like illness perception and motivation to exercise. However, the associations were only moderate, which might be caused by the questionnaires we used. Variables like motivation or social support are difficult to measure and few suitable questionnaires are available. Moreover, COPD specific questionnaires are lacking. It would be useful to develop COPD specific questionnaire(s) that target these variables related to physical activity. Our qualitative analysis enabled us to gain more insight in these psychosocial factors. Combining these 2 methods gave use the opportunity to compare the results, and this strengthens our findings. In both analyses we found that motivation to be physically active, self-efficacy and weather significantly affected physical activity. We found no association between physical activity and social support.

Motivation to be physically active

Motivation to be physically active was related to physical activity (*chapter 3 and 4)*. In *chapter 4* we asked the patients about their motives to be physically active or to be sedentary and some of these motives were also related to the actually measured physical activity level. Measured with a questionnaire, more autonomous motivation to be physically active was associated with a higher physical activity level (*chapter 3)*. More autonomous motivation means that patients are more intrinsically motivated (by themselves) than extrinsically motivated (by others). This could indicate that for the maintenance of an active lifestyle it is important that COPD patients are physically active for their own reasons and not forced by others. An often applied technique in healthcare that addresses the patient's own motivation is motivational interviewing. Motivational interviewing uses a guiding rather than a directing style, to engage with patients, clarifying their strengths and aspirations, evoke their own motivations to change, and promote autonomy of decision making.[15] Two pilot studies that combined motivational interviewing with feedback of a pedometer showed positive effects in increasing physical activity in COPD patients.[16,17]

Self-efficacy in physical activity

In both our quantitative and qualitative study, higher self-efficacy for physical activity was related to higher physical activity (*chapter 3 and 4)*. Self-efficacy is someone's belief in his/her capabilities to successfully execute a specific type of behavior, in this case physical activity. It is known that self-efficacy is a strong and consistent predictor of exercise adherence and that it is essential for the process of behavioral change.[18-20] This underlines the importance of high self-efficacy for physical activity in the enhancement of physical activity. In *chapter 4* we have described some factors that have shown to increase self-efficacy: performance experience, vicarious experience, social persuasion and physiological and emotional arousal. If necessary, such factors could easily be incorporated in physical activity enhancement programs.

Social support for physical activity

Unexpectedly, social support for physical activity was not related to physical activity and thus might not affect physical activity (*chapter 3 and 4)*. However, patients reported low social support (*chapter 3)* which could indicate that patients experience little social support for physical activity at all. Actually involving significant others in physical activity programs might be an important factor in the enhancement of physical activity. In general, social support has been shown to improve exercise behavior.[21] But the actual effect of involving social support on physical activity enhancement in COPD patients needs to be investigated in further detail. Social support could include buddy systems, support or participation from family or friends, and encouragement and positive feedback from therapist, physicians or fellow participants.

Weather

Physical activity level was lower in autumn and winter compared to spring and summer. This is confirmed in *chapter 4* as weather was the most frequently reported reason to be sedentary. In general weather is not a disease-specific determinant of physical activity, but in our population it often was. A lot of patients reported that their respiratory symptoms increase with specific weather types and furthermore weather influencing health was related to a lower level of physical activity. Of course, we cannot change weather conditions but it is important to acknowledge the effect of weather on symptoms and consequently on physically activity. When composing a physical activity enhancement program it is probably important to discuss the influence of weather and adjust physical activity types to the season.

Physical activity in different severity stages of COPD

To investigate differences between patients with different COPD severity we used the GOLD stages, which are based on arbitrary cut off points of airflow limitation. It is questionable whether airflow limitation is the best method to discriminate between COPD patients, but currently there is no better method available. For example, in line with other studies, we could not demonstrate that the BODE index (containing besides lung function also exercise capacity, dyspnea and body mass index) was superior in detecting differences in physical activity of patients with COPD.[4,8] Two large studies showed that reduced levels of physical activity were most prevalent in severe or very severe COPD patients (GOLD stage III or IV)[22,23] and since our study confirmed this, we compared mild to moderate COPD (GOLD stage I and II) with severe to very severe patients (GOLD stage III and IV). The discussion whether severity stages based on airflow limitation alone reflect the differences in disease severity sufficiently, recently led to the new combined GOLD COPD assessment. This assessment includes besides airflow limitation also symptoms and exacerbation risks.[24] It should be investigated if this assessment is more suitable to detect differences in physical activity between COPD patients.

Mild to moderate COPD patients

Patients with mild or moderate COPD did not differ in physical activity but had significantly higher physical activity levels than patients with (very) severe COPD. Two other studies showed that the physical activity level of patients with GOLD stage I did not significantly differed from matched controls, whereas patients with GOLD stage II did not differ in some physical activity outcomes.[22,23] Furthermore, we found that the predictors of physical activity in mild to moderate COPD patients (GOLD stage I or II) were more generic instead of disease-specific (self-efficacy and weather). This could indicate that, with regard to physical activity, patients with mild to moderate COPD might not be very different from the general healthy elderly population and that disease symptoms leading to reduced physical activity particularly play a role in more severe COPD. Unfortunately, our study did not have a control group, but it would of course be interesting to know whether the determinants of physical activity differ between COPD patients and healthy controls. This does not mean that enhancing physical activity is not indicated in patients with less severe COPD, as we showed that the ranges of physical activity within the disease stages were very large. In addition, many patients with mild to moderate COPD had very low physical activity levels. Furthermore, one frequently reported reason for patients to be physical active was 'having a continuous active lifestyle in the past', underlining the importance of preventing sedentary lifestyles in an early stage of the disease. Whether sedentary patients with mild to moderate COPD should follow a COPD-specific or general physical activity enhancement program remains questionable.

Severe to very severe COPD patients

The predictors of physical activity in patients with severe to very severe COPD were disease-specific and physical. It is easy to understand how these factors, being lung hyperinflation, dyspnea, leg muscle function and LTOT, limit exercise capacity and affect physical activity in daily life. Some sub domains of the motivation to exercise questionnaire were statistically related to physical activity in these more severe patients, but probably the physical factors were more dominant. The identified predictors are all potential targets for treatment. For example, several treatment methods have been shown to improve lung hyperinflation temporarily, such as pursed-lip breathing, exercise training and oxygen use, while bronchodilators or lung volume reduction surgery have been shown to improve lung hyperinflation in COPD patients more definitively.[3,25] However, physical activity did not automatically increase after successfully reducing residual volume (*chapter 6*). And also, as described earlier, increasing the portability of oxygen cylinders does not immediately increase physical activity. During the slow progression of COPD, patients may unconsciously adapt their physical activity level to avoid feelings of dyspnea. Usually, this will lead to a cycle of decline as physical deconditioning (cardiac and muscle) aggravates dyspnea even more, which in turn leads to avoiding even more physical activities.[26] This could indicate that after successful treatment of lung hyperinflation, impaired muscle function and dyspnea, also specific attention should be paid to the enhancement of physical activity, assuming that patients are completely adapted to their sedentary life style.

Other practical implications regarding physical activity

Tailoring

Our results confirm the importance of tailoring a physical activity enhancement program instead of a 'one-size-fits-all' program. The findings that enjoyment as reason to be physically active was related to a higher level of physical activity and the broad spectrum of preferred physical activity types underline this. Therefore, tailoring a program to an individual patient's opportunities and preferences will probably lead to longer physical activity maintenance. One study that tailored physical activity advices on patients' stage of readiness to change, exercise goal, motives for and perceived barriers to reaching the goal and preferred type of physical activity found that patients who received these advices were more likely to increase physical activities of daily living than patients who received general physical advices or no advices.[27] Tailoring can be defined as 'any combination of change strategies intended to reach one specific person, based on characteristics that are unique to that person, related to the outcome of interest and have been derived from an individual assessment'.[28] Our study identified several factors that could be useful for the individual assessment of COPD patients additional to those mentioned in the study on tailored physical activity advices.[27] Those factors are shown in box 1. Such an individual assessment should consequently lead to an individualized program for the patient.

BOX 1: Factors individual assessment

- Knowledge on health benefits of physical activity
- Patient's own goal
- Readiness to change
- Reasons to be physically active
- Barriers in being physically active
  - *weather*
  - *health problems*
  - *financial constraints*
  - *shame*
- Physical activity preferences
  - *opportunities*
  - *history of physical activity*
- Self-efficacy

Physical activity monitoring

Subjective measures of physical activity by patients, overestimated the actual level of physical activity (*chapter 5*). Therefore measuring physical activity with performance based instruments is highly recommended. Triaxial and multisensory devices that monitor physical activity in a performance based manner were shown to be more valid.[29] Currently, these monitors are small, lightweight and thus wearable and become more and more affordable. We measured physical activity in our study with a highly validated triaxial accelerometer in COPD[30], which was worn by the patients day and night for one week. Our patients reported a good wearability of the device. Besides measuring physical activity with an accurate device, using it as a feedback tool for the patient has been investigated and has shown promising results.[31] For example, physical activity enhancement with feedback of a pedometer has shown to be effective in COPD patients.[16,17] Currently, accelerometers can easily be connected to mobile phones or computers, which may lead to even more advanced feedback signals and makes home telemonitoring also possible.

Physical activity versus physical inactivity

An unexpected observation of our study was that the predictors of physical activity and sitting time were not the same. Furthermore, sitting time was not significantly different between patients in different severity stages (*chapter 3)*. Interestingly, sitting time has been associated with an increased risk of mortality, even independent of leisure time physical activity.[32] Furthermore, sedentary time has been shown to be an independent risk factor for several health outcomes, like the metabolic syndrome and cardiovascular risk factors, independent of physical activity.[33,34] Promoting breaks in sitting time could be beneficial as it has been shown that a higher number of interruptions in sedentary time, independent of total sedentary time, was beneficially associated with metabolic risk variables.[33,35] This indicates that, in addition to promoting physical activity, it is also important to reduce sedentary behaviour, for example by promoting breaks in sitting time.

Minimal important difference for physical activity

For interpreting the results of physical activity enhancement programs or for determining sample size of new studies, a minimal important difference (MID) estimation, like we calculated in *chapter 7*, would also be useful for physical activity. Such a MID could indicate which improvement in physical activity is meaningful and worthwhile in the perception of the patient. The questions arises what factor represents a meaningful and worthwhile change in physical activity for a patient and how this MID should be estimated. Health status or HRQL measured with a questionnaire are probably suitable anchors when using an anchor-based approach. Also patient-based anchors could be used in which the patients rate their own experienced change on for example a 15-point global scale.[36] A problem with calculating a MID is that currently many different physical activity outcome parameters are being used, like steps, distance, activity counts, body positions, estimated energy expenditure and minutes at activity intensity levels. Furthermore, the duration of the measurement during the day or measured number of days also differs. Reaching consensus on the preferred outcome parameter and measurement duration would be helpful for the comparison of studies.

8

Physical activity advice and reference values

The latest GOLD guidelines state that all patients should be advised to participate in regular physical activity.[24] What is 'regular' physical activity? It is important to know how much physical activity is necessary to obtain health benefits and to give an evidence-based tailored advice to a COPD patient. Currently, the classification whether a patient is sufficiently physically active depends on the applied recommendation or used instrument and there is no COPD-specific physical activity recommendation yet (*chapter 5)*. Longitudinal studies are needed to determine how much physical activity in terms of frequency, intensity and time is actually sufficient in the various disease stages of

COPD. Additionally, COPD-specific reference values should be developed that identify sedentary COPD patients who need physical activity enhancement. Individualizing a recommendation to a patient's body weight, sex and fitness level and thus tailoring a physical activity advice seems appropriate, especially in patients with (very) severe COPD. However, how to determine the exact dose-response relationship between physical activity and health benefits for the individual patient is a challenging new area of research. Furthermore, it is important that a patient can incorporate a physical activity recommendation in his/her daily life routine and therefore a recommendation should be clear and easy to monitor.

Unfortunately, the actual global guidelines on how to treat a patient who does not meet the recommendation are often vague and impractical. One important treatment modality for COPD patients in this perspective is pulmonary rehabilitation, that has shown to be effective in increasing exercise capacity, quality of life and reducing dyspnea[37] and that consists of multi-dimensions. However, an increase in physical activity is not guaranteed after a rehabilitation program.[38] Another problem is that not all patients have access to these programs, often because of the high-costs. For example the new GOLD guidelines state 'all patients who get short of breath when walking on their own pace on level ground should be offered rehabilitation'. Unfortunately, this would exclude a lot of COPD patients who do in fact have a sedentary lifestyle. Besides pulmonary rehabilitation, structured exercise programs or physical activity counseling programs are useful tools in the enhancement of physical activity, but the optimal contents and setting of these programs are unclear. Obviously, there is a high need for more practical guidelines that are useful for physical therapists or physicians.

Future research in physical activity in COPD

The studies presented in this thesis have answered many research questions, but as research naturally generates new questions, new questions and potential research aims have been suggested in the discussion above.

Overall, in research on physical activity in COPD, longitudinal studies should be performed more often. Our results on the predictors of physical activity were obtained from cross-sectional data and therefore definite conclusions regarding possible cause-effect relationships are difficult to draw and longitudinal studies are necessary. For example, it would be very useful to perform follow up measurements 5 years after baseline in our study population. This would also provide more insight in physical activity patterns over time. Furthermore, longitudinal research would be helpful to determine how much physical activity in terms of frequency, intensity and time is actually sufficient to obtain health benefits. This could help to compose a more concrete physical activity advice to an individual patient.

In general, studies aiming at enhancing physical activity are necessary to optimize physical activity enhancement programs. It would be interesting to investigate a tailored multi-dimensional physical activity enhancement program that specifically targets physical activity as well. In these programs self-efficacy and autonomous motivation for physical activity should play an important role and besides promoting physical activity, reducing sitting time should be a target. Furthermore, the influence of involving social support should be investigated in new studies. Specifically in patients with mild to moderate COPD, it would be interesting to compare the effects of a general or COPD-specific physical activity enhancement program.

Future research will hopefully further improve our knowledge on optimal physical activity enhancement in COPD patients and consequently reduce the prevalence of sedentary lifestyles and its negative consequences in this patient population.

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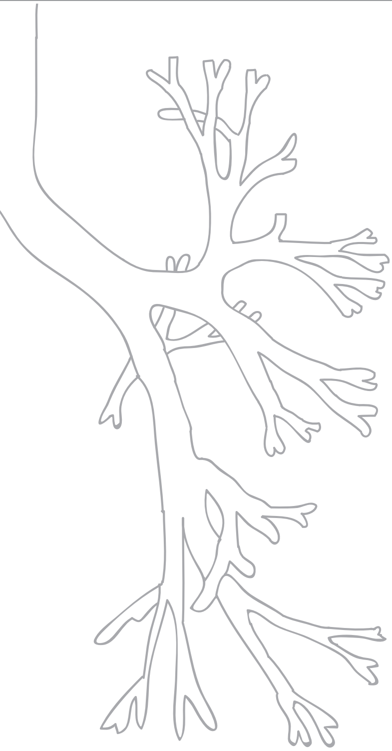
Abbreviations

6MWD	Six-minute walk distance
6MWT	Six-minute walk test
ACSM	American college of sports medicine
ATS	American thoracic society
BDI	Beck depression inventory
BMI	Body mass index
CCQ	Clinical COPD questionnaire
COPD	Chronic obstructive pulmonary disease
CIRS-G	Cumulative illness rating scale for geriatrics
DM	Diabetes mellitus
EE	Energy expenditure
ERS	European respiratory society
FEV_1	Forced expiratory volume in 1 second
FFM	Fat free mass
FVC	Forced vital capacity
GOLD	Global initiative for chronic obstructive lung disease
HR	Heart rate
HRQL	Health-related quality of life
Hs-CRP	High-sensitivity C-reactive protein
ITGV	Intra thoracic gas volume
LIVAS	Dutch version of the perceived physical ability subscale questionnaire
LTOT	Long term oxygen therapy
LVR	Lung volume reduction
IPQ-R	Illness perception questionnaire- revised version
MET	Metabolic equivalent of task
MID	Minimal important difference
mMRC	modified medical research council dyspnea index
PAL	Physical activity level
PSQI	Pittsburgh sleep quality index
RA	Rheumatoid arthritis
RV	Residual volume
SGRQ	St. George's respiratory questionnaire
SRQ-E	Exercise self-regulation questionnaire
SSQ	Social support for exercise behaviours scale questionnaire
SQUASH	Short questionnaire to assess health enhancing physical activity
TLC	Total lung capacity
VO_2	Oxygen uptake
W_{max}	Maximum workload (wattage)
WHO	World health organization

Nederlandse samenvatting

9 CHAPTER



INTRODUCTIE

COPD

Chronisch obstructieve longziekte (COPD) is een chronische longaandoening die gekenmerkt wordt door een niet volledig reversibele luchtwegobstructie die in het algemeen progressief is en wordt veroorzaakt door een abnormale ontstekingsreactie van de longen op schadelijke deeltjes of gassen.[1] Bij volwassenen vanaf 40 jaar komt COPD bij ongeveer 10% van de bevolking voor en in 2002 was COPD de 5^{e} belangrijkste doodsoorzaak wereldwijd.[2,3] De voornaamste symptomen van COPD zijn kortademigheid (dyspneu), hoesten en slijmproductie. COPD is niet alleen een ziekte van de longen, vaak zijn er ook ziekteverschijnselen buiten de long (extrapulmonaal) aanwezig en veel patiënten hebben ook nog andere aandoeningen (comorbiditeit).[4] Vaak voorkomende extrapulmonale ziekteverschijnselen en comorbiditeiten zijn: spierdysfunctie, hypertensie, botontkalking en depressiviteit.[4] De behandeling van COPD kan bestaan uit stoppen met roken, medicatie, revalidatie, zuurstoftherapie en chirurgische behandelingen.[1,5] Verder wordt in de laatste COPD richtlijn van het ‘Global Initiative for Chronic Obstructive Lung Disease’ (GOLD) ook regelmatige lichamelijke activiteit aangeraden in de behandeling van alle COPD patiënten.[1,5,6]

Lichamelijke activiteit

Lichamelijke activiteit wordt gedefinieerd als ‘elke krachtsinspanning van skeletspieren die resulteert in meer energieverbruik dan in rust’.[7] Lichamelijke activiteit reflecteert wat iemand daadwerkelijk doet en is daarmee verschillend van inspanningsvermogen of fitheid welke weergeven wat een persoon kan doen. Lichamelijke activiteit heeft dus ook een grote gedragsmatige component. Regelmatig lichamelijk actief zijn heeft grote voordelen. Verschillende studies hebben aangetoond dat regelmatige lichamelijke activiteit leidt tot verlaagde mortaliteit en verminderde kans op aandoeningen zoals diabetes type 2 en hart- en vaatziekten.[8] Ook is aangetoond dat het kan leiden tot een verhoogd inspanningsvermogen en spierfitheid, gezondere lichaamssamenstelling en verbetering van cognitieve functies.[8] Wereldwijd blijkt 1/3 van de volwassenen lichamelijk inactief te zijn ondanks dat lichamelijke inactiviteit door de World Health Organization in 2004 is uitgeroepen tot de 4^{e} grootste risicofactor voor overlijden.[9,10]

Lichamelijke activiteit en COPD

COPD patiënten zijn niet alleen vaker lichamelijk inactief dan gezonde volwassenen maar ook vaker dan andere patiëntpopulaties zoals diabetes en reumatoïde artritis.[11,12] COPD patiënten ervaren naar mate de ziekte ernstiger wordt steeds vaker kortademigheid bij lichamelijke inspanning en gaan daardoor deze lichamelijke activiteiten vermijden of verminderen. Hierdoor kunnen ze in een neerwaartse spiraal terecht komen aangezien lichamelijke inactiviteit leidt tot verminderde conditie, hetgeen de kortademigheid juist verergert.[13] Naast de eerder genoemde voordelen van regelmatige lichamelijke activiteit is aangetoond dat specifiek in COPD patiënten het ook leidt tot verminderde kortademigheid en verbeterde spierfunctie en kwaliteit van leven.[14,15] Lichamelijke activiteit is veranderbaar en zou daarom een belangrijk behandeldoel in deze patiëntpopulatie moeten zijn. Meer inzicht in de voorspellers van lichamelijke activiteit geeft aanknopingspunten voor het verbeteren van beweegstimuleringsprogramma's en dus het verminderen van lichamelijke inactiviteit in deze patiënten.

Voorspellers van lichamelijke activiteit

In de algemene volwassen populatie is aangetoond dat lage lichamelijke activiteit geassocieerd is met oudere leeftijd, vrouwelijk geslacht, lager opleidingsniveau, hoger lichaamsgewicht, gezondheidsproblemen, lagere self-efficacy (geloof in eigen kunnen), ervaring met lichamelijke activiteit en weersomstandigheden.[16-18] In COPD patiënten zijn de voorspellers van lichamelijke activiteit nauwelijks systematisch onderzocht en weinig studies hebben gekeken naar zowel fysieke als psychosociale voorspellers. Ook zijn de patiënten zelf nog nauwelijks over hun eigen gedachten en perspectieven over lichamelijke activiteit ondervraagd. Onderzoek naar de redenen waarom COPD patiënten lichamelijk actief of inactief zijn en de ervaren barrières zou nuttige informatie kunnen opleveren voor het stimuleren van lichamelijke activiteit in deze patiëntenpopulatie.

Beweegnormen

Regelmatige lichamelijke activiteit heeft dus vele voordelen maar een belangrijk vraag hierbij is wat 'regelmatig' lichamelijk actief zijn inhoudt en wat een patiënt dus zou moeten worden geadviseerd. Ongeveer 40 jaar geleden is een eerste richtlijn voor lichamelijke activiteit opgesteld en op dit moment worden de richtlijnen van de American College of Sports Medicine (ACSM) het meest gehanteerd.[19-21] Deze richtlijnen adviseren dat volwassenen minimaal 5 dagen per week, 30 minuten op matig intensiteit lichamelijk actief zouden moeten zijn of 3 dagen per week 20 minuten op hoge intensiteit of een combinatie hiervan. Over het algemeen zijn deze richtlijnen gebaseerd op volwassenen zonder aandoening, terwijl de richtlijnen voor volwassenen met een chronische aandoening zoals COPD minder duidelijk zijn. De ACSM raadt aan om de intensiteit voor deze populatiegroepen aan te passen aan de individuele fitheid en dit zou ook geschikt kunnen zijn voor COPD patiënten.[22] Maar tot nu toe zijn de beweegnormen nauwelijks onderzocht in deze patiëntenpopulatie.

Longhyperinflatie en lichamelijke activiteit

Een belangrijke voorspeller van lichamelijke activiteit in COPD patiënten lijkt hyperinflatie van de long te zijn. COPD patiënten hebben problemen met de uitademing en veel minder met de inademing. De lucht kan dus wel makkelijk naar binnen maar minder makkelijk naar buiten en sommige COPD patiënten pompen zich als het ware op. Hierdoor ademen ze op een hoger niveau waardoor het residuaal volume (de hoeveelheid lucht die in de longen achterblijft na een normale rustige uitademing) toegenomen is. Dit wordt hyperinflatie van de long genoemd. In het afgelopen decennium is er steeds meer onderzoek verricht naar behandelingen waarbij getracht wordt het longvolume te verkleinen door middel van bronchoscopische interventies. Hierbij worden met behulp van een kijkingreep kleine apparaatjes, zoals ventielen, in slecht ventilerende gebieden van de long aangebracht, die deze gebieden ontluchten en daardoor het longvolume verkleint. Deze technieken zijn weinig belastend vergeleken met een operatie, en laten goede resultaten zien wat betreft longhyperinflatie, kwaliteit van leven en inspanningsvermogen.[23-26] In theorie leiden deze behandelingen tot een verminderde kortademigheid bij inspanning en verbetering van de functionele capaciteit van het lichaam, waardoor het lichamelijke activiteitenniveau kan toenemen. Maar tot nu toe is hier nog geen onderzoek naar gedaan. Ook is nog geen onderzoek gedaan naar welke verbetering in residuaal volume door de patiënten zelf als belangrijk wordt ervaren.

Doelstellingen proefschrift

Samenvattend, lichamelijke activiteit heeft vele gezondheidsvoordelen en zou een belangrijk behandeldoel voor COPD patiënten moeten zijn. Maar over het algemeen is het lichamelijke activiteitenniveau in deze patiëntenpopulatie laag, zelfs in de mildere stadia van de aandoening. Het is onduidelijk wat bepaalt waarom de ene patiënt wel lichamelijk actief is en een andere niet. Het eerste doel van dit proefschrift was het krijgen van meer inzicht in het lichamelijke activiteitenniveau en voorspellers ervan in COPD patiënten met verschillende ernst van de ziekte, waarbij zowel fysieke als psychosociale factoren bestudeerd worden. Een tweede doel was onderzoeken of de huidige beweegnormen ook toepasbaar zijn in COPD patiënten. Een laatste doel was onderzoeken of een verbetering van longhyperinflatie geassocieerd is met een verbetering in lichamelijke activiteit.

RESULTATEN

Voorspellers van lichamelijke activiteit

In *hoofdstuk 2* hebben we potentiële voorspellers van lichamelijke activiteit geïdentificeerd. Lichamelijke activiteit bij COPD patiënten blijkt verband te houden met belangrijke COPD-specifieke factoren zoals longfunctie, spierfunctie, systemische inflammatie, comorbiditeiten en gezondheidspecifieke kwaliteit van leven. In tegenstelling tot in de algemene gezonde populatie, blijkt lichamelijke activiteit bij COPD patiënten niet samen te hangen met lichaamsamenstelling parameters (zoals BMI). Verder zijn er een aantal studies die actieve COPD patiënten vergeleken met inactieve COPD patiënten. In deze studies was een inactieve leefstijl geassocieerd met slechtere longfunctie, meer kortademigheid, hoger aantal ziekenhuisopnames voor COPD, slechtere inspanningscapaciteit en slechtere gezondheidsspecifieke kwaliteit van leven, maar de resultaten van de studies waren niet consistent. Verder waren er maar een paar studies die de relatie tussen lichamelijke activiteit en psychosociale factoren zoals self-efficacy (geloof in eigen kunnen) of depressiviteit hebben onderzocht. Over het algemeen was de literatuur beperkt en inconsistent en de meeste correlaties waren matig. Figuur 1 komt voort uit dit hoofdstuk en geeft een theoretisch raamwerk van de rol van lichamelijke inactiviteit in COPD.

Hoofdstukken 3, 4 en *5* zijn gebaseerd op data van een cross-sectionele studie die we hebben uitgevoerd in het UMCG en waarvan het hoofddoel was om de voorspellers van lichamelijke activiteit in COPD te identificeren. De deelnemende COPD patiënten voerden verscheidene fysieke tests uit en vulden meerdere psychosociale vragenlijsten in tijdens 3 studievisites. Lichamelijke activiteit werd gemeten met een accelerometer, een stappenteller en een vragenlijst. Ook werden alle patiënten geïnterviewd. In totaal hebben 115 patiënten met milde tot zeer ernstige COPD aan het onderzoek deelgenomen (68% man, gemiddelde leeftijd 65 jaar, FEV_1 57.5% van voorspeld, ernst stadia van COPD (volgens GOLD): 30 stadium I (mild), 31 stadium II (matig), 33 stadium III (ernstig), 21 stadium IV (zeer ernstig)). Het gemiddeld aantal stappen per dag varieerde van 236 tot 18433 stappen (gemeten met de accelerometer).

De studie in *hoofdstuk 3* had als doel om lichamelijke activiteit en zitduur in COPD patiënten te bepalen en om de potentiële voorspellers hiervan te bestuderen (geïdentificeerd in *hoofdstuk 2*). 113 COPD patiënten hadden de accelerometer gedragen en werden in de analyses meegenomen. De gemiddelde duur van wandelen en schuifelen was 6.8% van de dag (range: 0.7-20.4%). Lage lichamelijke activiteitenniveaus waren het meest aanwezig in patiënten met ernstige tot zeer ernstige COPD (GOLD stadia III en IV). Voorspellers van hogere lichamelijke activiteit waren betere self-efficacy en inspanningscapaciteit en mindere longhyperinflatie. In patiënten met milde en matige COPD (GOLD stadia I en II), waren hogere self-efficacy en de lente/zomer seizoen voorspellers, terwijl in patiënten met GOLD stadia III en IV slechtere longhyperinflatie, beenspierfunctie en het gebruik van zuurstof voorspellers waren. Voorspellers van zitduur in de totale groep waren een positievere perceptie op de controle van de ziekte, minder eigen motivatie om te bewegen, het niet gebruiken van slaapmedicatie en het gebruik van zuurstof.

Geconcludeerd kon worden dat zowel fysieke als psychosociale factoren het niveau van lichamelijke activiteit in COPD patiënten beïnvloeden. De voorspellers van lichamelijke activiteit in de mildere stadia van COPD waren algemeen, in tegenstelling tot de fysieke en COPD-specifieke voorspellers in de ernstigere stadia. De voorspellers van zitduur waren anders dan de voorspellers van lichamelijke activiteit.

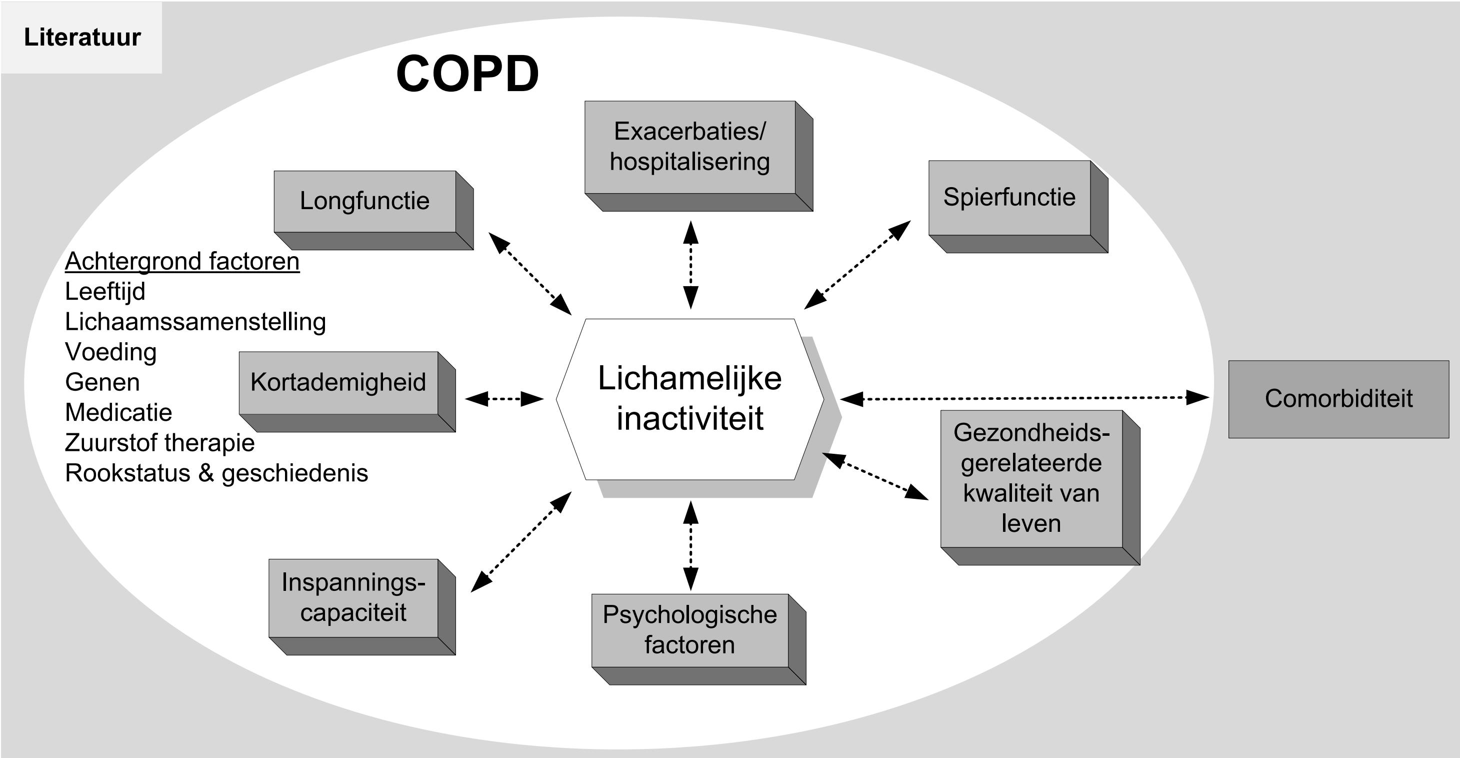
Als we de resultaten van de analyses in *hoofdstuk 3* vergelijken met de potentiële voorspellers die we identificeerden in *hoofdstuk 2* dan vonden we in overeenstemming met de literatuur dat gezondheidsgerelateerde kwaliteit van leven en gezondheidsstatus positief geassocieerd waren met lichamelijke activiteit. Ook vonden we een significante associatie tussen hogere lichamelijke activiteit en de volgende variabelen: betere longfunctie, longvolumes en beenspierfunctie, hogere (sub)maximale inspanningscapaciteit en self-efficacy, minder kortademigheid, lager aantal exacerbaties en het niet gebruiken van zuurstof therapie. Tevens vonden we geen associatie tussen lichamelijke activiteit en lichaamssamenstelling.

In tegenstelling tot de literatuur vonden we geen significante associatie tussen hogere lichamelijke activiteit en mindere depressiviteit en tussen lichamelijke activiteit en comorbiditeit.
In aanvulling op de literatuur vonden we een significante associatie tussen betere ziekteperceptie en motivatie om te bewegen. Ook was het lichamelijke activiteitenniveau lager in de herfst of winter vergeleken met de lente of zomer. Verder vonden we geen significante associatie tussen lichamelijke activiteit en sociale steun, slaapkwaliteit, gebruik van slaapmedicatie, werksituatie, woonsituatie, opleidingsniveau, leeftijd, rookstatus en rookgeschiedenis.

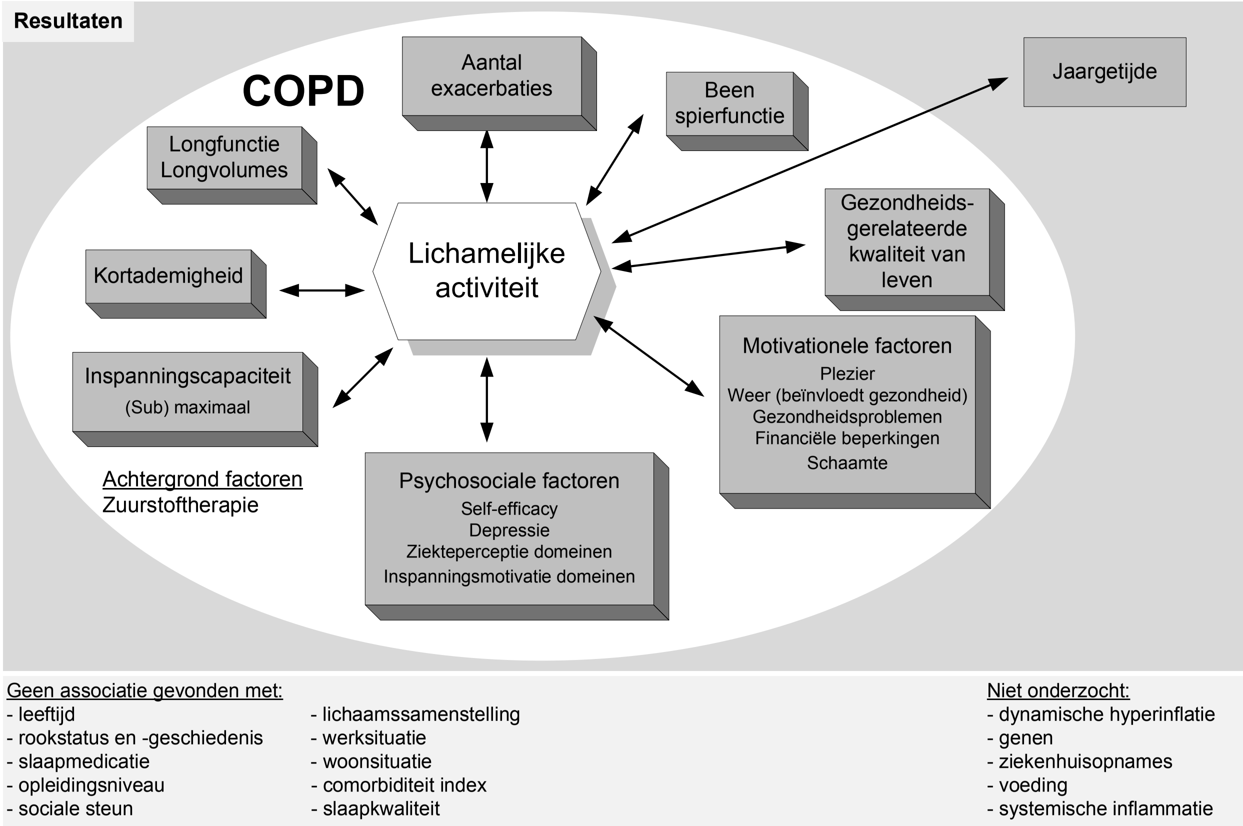
In *hoofdstuk 4* beschrijven we de resultaten van een studie waarin we de persoonlijke redenen om wel of niet lichamelijk actief te zijn hebben bestudeerd door 115 COPD patiënten te interviewen over lichamelijke activiteit. Ook hebben we in dit hoofdstuk de relatie tussen deze persoonlijke redenen en het gemeten lichamelijke activiteitenniveau bestudeerd. De meest genoemde reden om te bewegen was gezondheidsvoordelen, gevolgd door plezier in bewegen, actieve leefstijl in het verleden en functionele redenen om te bewegen. De meest genoemde reden om niet te bewegen was weersomstandigheden, gevolgd door gezondheidsproblemen en gebrek aan intrinsieke motivatie om te bewegen. Verder was een hoog lichamelijke activiteitenniveau gerelateerd aan plezier in bewegen en hoge self-efficacy in bewegen. Een laag lichamelijke activiteitenniveau was gerelateerd aan gezondheidsklachten door het weer, financiële beperkingen, gezondheidstatus en schaamte.

Concluderend hebben we belangrijke stimulerende factoren en barrières geïdentificeerd om lichamelijk actief te zijn, die erg bruikbaar kunnen zijn voor de stimulering van lichamelijke activiteit in sedentaire COPD patiënten.

Figuur 2 geeft een overzicht van de factoren die gerelateerd waren aan lichamelijke activiteit in onze studiepopulatie van 115 COPD patiënten (*hoofdstukken 3 en 4)*.



FIGUUR 1. Theoretisch raamwerk van de rol van lichamelijke inactiviteit in COPD *(hoofdstuk 2)*.
De mogelijke rol en consequenties van lichamelijke activiteit voor belangrijke COPD factoren zijn weergegeven. Deze relaties zijn ingebed in COPD gerelateerde achtergrondfactoren. Naast COPD gerelateerde factoren, kan de aanwezigheid van andere aandoeningen dan COPD (comorbiditeit) lichamelijke activiteit beïnvloeden.



FIGUUR 2. Geïdentificeerde significante associaties tussen lichamelijke activiteit en verschillende fysieke, psychosociale en omgevingsfactoren in 115 patiënten met milde tot zeer ernstige COPD *(hoofdstukken 3 en 4)*.

9

Beweegnormen

In *hoofdstuk 5* hebben we 7 verschillende beweegnormen vergeleken en de bruikbaarheid in COPD patiënten bestudeerd. De beweegnormen verschilden in frequentie, intensiteit en tijd en werden gemeten met een accelerometer, stappenteller of vragenlijst in onze studiepopulatie van 115 COPD patiënten. De beweegnormen waren gebaseerd op absolute maten van intensiteit of individuele maten van intensiteit. Individuele maten van intensiteit waren gebaseerd op het inspanningsniveau van de patiënt (vastgesteld met een maximale fietstest). Het percentage patiënten dat werd geclassificeerd als voldoende actief volgens de verschillende beweegnormen varieerde van 22 tot 86% en maar 8 patiënten (7%) voldeden aan alle 7 beweegnormen. De overeenstemming tussen de verschillende beweegnormen was laag. Het individualiseren van de mate van intensiteit resulteerde in een hoger percentage patiënten met (zeer) ernstig COPD dat de relatieve beweegnormen haalde in vergelijking met een lager percentage dat de absolute beweegnormen haalde. In tegenstelling tot de patiënten met milde tot matige COPD die minder vaak de relatieve beweegnormen haalden. De conclusie was dat het toepassen van verschillende beweegnormen met kleine verschillen in frequentie, intensiteit en tijd in lichamelijke activiteit tot grote verschillen leidt in het bepalen of COPD patiënten voldoende lichamelijk actief zijn. Dit heeft als gevolg dat de beweegnorm die gebruikt wordt voor een groot deel het beweegadvies voor de patiënt zal bepalen.

Hyperinflatie van de long en lichamelijke activiteit

Hoofdstuk 6 beschrijft de resultaten van een pilot studie waarin we de effecten van bronchoscopische longvolume reductie op het lichamelijke activiteitenniveau van patiënten met ernstig emfyseem hebben onderzocht. Ook hebben we in deze studie onderzocht of verbeterde longhyperinflatie geassocieerd was met een stijging in lichamelijke activiteit. Emfyseem is een vorm van COPD waarbij de longblaasjes (alveoli) zijn beschadigd en de gaswisseling minder goed verloopt. Veertien patiënten met ernstige emfyseem droegen een week een accelerometer voor de behandeling en 6 maanden na de behandeling nogmaals. Ondanks significante verbeteringen in statische longhyperinflatie vonden we geen stijging in het lichamelijke activiteitenniveau 6 maanden na de bronchoscopische longvolume reductie behandeling. Verder was de verbeterde longhyperinflatie niet geassocieerd met een verbetering in lichamelijke activiteit of inspanningscapaciteit, maar wel met een vermindering in kortademigheid. We concludeerden dat speciale aandacht voor het stimuleren van lichamelijke activiteit nodig is na bronchoscopische longvolume reductie om het lichamelijke activiteitenniveau van deze patiënten te verhogen.

In *hoofdstuk 7* hebben we de 'minimal important difference' (MID) bepaald voor veranderingen in het residuaal volume van patiënten met ernstig emfyseem die een bronchoscopische longvolume reductie ondergaan. Een MID kan worden gedefinieerd als een drempelwaarde voor een verandering die door de patiënt als zinvol en de moeite waard wordt ervaren en waarbij de patiënt de behandeling opnieuw zou overwegen als hij/zij deze keuze opnieuw zou maken. 91 patiënten met ernstig emfyseem werden geïncludeerd. Residuaal volume en de totale longcapaciteit werden gemeten met de bodybox.

MID schattingen werden berekend met de zogenaamde anker- en distributiemethoden. FEV_1, 6-minuten wandelafstand en kwaliteit van leven (SGRQ totaal score) werden gebruikt als ankers en de Cohen's effect size werd gebruikt als distributiemaat. De berekende MID schattingen volgens de verschillende methoden varieerden tussen -0.31 en -0.43 liter voor residuaal volume, -6.1 en -8.6% voor percentage verschil in residuaal volume van baseline en -2.8 en -4.0% voor residuaal volume% van totale longcapaciteit (RV%TLC). Deze MID schattingen zijn nuttig voor het berekenen van een steekproefomvang voor nieuwe studies met als doel het verminderen van residuaal volume en voor het interpreteren van de resultaten van klinische studies in patiënten met ernstig emfyseem.

INTERPRETATIE VAN DE RESULTATEN

Samenvattend hebben we verschillende potentiële voorspellers van lichamelijke activiteit onderzocht. Zoals verwacht beïnvloeden fysieke voorspellers, zoals dyspneu, inspanningscapaciteit en spierfunctie, het lichamelijke activiteitenniveau in COPD patiënten. Naast fysieke factoren bleken ook psychosociale factoren, inclusief motivatie- en omgevingsfactoren, het lichamelijke activiteitenniveau van COPD patiënten te beïnvloeden (figuur 2). In patiënten met milde tot matige COPD waren de voorspellers vergelijkbaar met de algemene populatie terwijl in (zeer) ernstige COPD patiënten de voorspellers fysiek en COPD specifiek waren. Longhyperinflatie was een belangrijke onafhankelijke voorspeller van lichamelijke activiteit maar een verbetering van longhyperinflatie door bronchoscopische longvolume reductie leidde niet automatisch tot een verbetering in lichamelijke activiteit. Verder vonden we dat het gebruik van verschillende beweegnormen met kleine verschillen in frequentie, intensiteit en tijd tot grote verschillen leidden in het classificeren of een COPD patiënt voldoende lichamelijke actief is.

Voorspellers van lichamelijke activiteit en de implicaties ervan

Onze resultaten laten zien dat lichamelijke activiteit niet door één factor wordt beïnvloed en dat dus het behandelen van één factor niet automatische leidt tot een stijging van het lichamelijke activiteitenniveau. Een goed voorbeeld hiervan is de in *hoofdstuk 6* beschreven studie. Ondanks dat de bronchoscopische longvolume reductie behandeling wel significant de hyperinflatie van de long verminderde, wat een belangrijk voorspeller van lichamelijke activiteit is, verbeterde het lichamelijke activiteitenniveau van de patiënten niet significant. Waarschijnlijk zijn deze patiënten zo gewend aan hun dagelijkse activiteitenpatroon dat hier ook specifiek aandacht aan besteed zou moeten worden, naast andere factoren zoals verminderde spierfunctie. Verder is dit een goed voorbeeld van het feit dat lichamelijke activiteit naast een fysieke component ook een gedragsmatige component heeft en onderdeel is van de levensstijl van de patiënt.

Combinatie kwantitatieve en kwalitatieve analyse

We hebben voor het eerst de voorspellers van lichamelijke activiteit met een kwantitatieve en kwalitatieve (interview) benadering onderzocht in dezelfde studiepopulatie van COPD patiënten. Psychosociale factoren zijn lastig te meten en de vragenlijsten zijn vaak van slechte kwaliteit of niet COPD-specifiek. Het combineren van de kwantitatieve en kwalitatieve analyses versterkt de bevindingen over de relaties tussen lichamelijke activiteit en psychosociale factoren. In beide analyses vonden we dat motivatie om lichamelijk actief te zijn, self-efficacy voor lichamelijke activiteit en weersomstandigheden significant lichamelijke activiteit van COPD patiënten beïnvloeden. We vonden in beide analyses geen verband tussen lichamelijke activiteit en sociale steun voor bewegen.

Motivatie om lichamelijk actief te zijn

In *hoofdstuk 4* bleek dat een aantal persoonlijke redenen van de patiënten om lichamelijk actief te zijn inderdaad geassocieerd waren met meer lichamelijke activiteit. Verder bleek in *hoofdstuk 3* dat meer autonome motivatie om lichamelijk actief te zijn geassocieerd was met hogere lichamelijke activiteit. Meer autonome motivatie betekent dat patiënten meer intrinsiek gemotiveerd zijn om te bewegen (omdat ze er zelf van overtuigd zijn) dan extrinsiek gemotiveerd (overtuigd door anderen). Oftewel dat COPD patiënten het zelf belangrijk vinden om lichamelijk actief te zijn. Een steeds meer gebruikte techniek in de gezondheidszorg die hier gebruik van maakt is 'motivational interviewing'. Deze techniek gebruikt counseling die gericht is op de patiënt, waarbij getracht wordt de patiënt zelf de motivatie om te veranderen te laten benoemen en uit te laten voeren. Twee pilot-studies die deze techniek hebben toegepast in COPD patiënten lieten goede resultaten zien.[27,28]

Self-efficacy om lichamelijk actief te zijn

Self-efficacy is het vertrouwen van een persoon in de eigen bekwaamheid om met succes invloed uit te oefenen op zijn of haar omgeving, bijvoorbeeld door een bepaalde lichamelijke activiteit te volbrengen. In zowel *hoofdstuk 3* als *4* was self-efficacy voor lichamelijke activiteit gerelateerd aan een hoog lichamelijke activiteitenniveau. Het is bekend dat self-efficacy een belangrijk voorspeller is van het volhouden van lichamelijke activiteit en essentieel is voor het proces van gedragsverandering.[29-31] In *hoofdstuk 4* hebben we een aantal factoren beschreven die self-efficacy kunnen verhogen, en die makkelijk in beweegstimuleringprogramma's kunnen worden geïntegreerd.

Sociale steun voor lichamelijke activiteit

In tegenstelling tot wat we vooraf verwachtten was sociale steun voor lichamelijke activiteit niet gerelateerd aan lichamelijke activiteit. Omdat patiënten lage scores voor sociale steun voor lichamelijke activiteit rapporteerden, zou dit ook kunnen betekenen dat patiënten eigenlijk weinig sociale steun voor lichamelijke activiteit ervaren. In het algemeen is aangetoond dat sociale steun voor lichamelijke activiteit gedrag positief beïnvloedt.[32] Dit zou kunnen betekenen dat het verhogen van sociale steun voor lichamelijke activiteit een belangrijke factor is in het stimuleren van lichamelijke activiteit in COPD patiënten, maar dit zou verder onderzocht moeten worden. Sociale steun voor bewegen kan komen van familie of vrienden maar ook van aanmoedigingen van therapeuten, artsen en medesporters.

Rol van het weersomstandigheden bij lichamelijke activiteit

De meest genoemde reden om niet lichamelijk actief te zijn was weersomstandigheden en lichamelijke activiteit was ook lager gemeten in de herfst of winter vergeleken met de lente of zomer. In het algemeen zijn weersomstandigheden niet een ziektespecifieke determinant van lichamelijke activiteit maar in onze studiepopulatie was dit meestal wel het geval. Veel patiënten ervaren meer longklachten bij specifieke weertypes zoals mist en extreme temperaturen. We kunnen het weer natuurlijk niet beïnvloeden maar de resultaten impliceren wel dat het belangrijk is om rekening te houden met het weer bij het opstellen van een lichamelijke activiteiten programma. Bijvoorbeeld door na te denken over back-up activiteiten.

Lichamelijke activiteit in verschillende ernststadia van COPD

Milde tot matige COPD

Patiënten met milde tot matige COPD hadden een significant hoger lichamelijke activiteitenniveau dan patiënten met ernstig tot zeer ernstig COPD. Twee studies lieten al eerder zien dat het lichamelijke activiteitenniveau van milde COPD patiënten niet significant verschilt van de algemene populatie. Voor patiënten met matige COPD gold dit voor bepaalde lichamelijke activiteit uitkomstmaten ook.[33,34] De voorspellers van lichamelijke activiteit in deze mildere groep patiënten in onze studie waren gelijk aan die in de algemene bevolking, namelijk self-efficacy en jaargetijde. Het zou kunnen betekenen dat wat betreft lichamelijke activiteit milde tot matige COPD patiënten vergelijkbaar zijn met mensen zonder COPD. Dit zou mogelijk komen omdat deze patiënten nog nauwelijks fysiek beperkt worden in hun dagelijkse activiteiten door hun longklachten. Dit betekent echter niet dat deze mildere patiëntengroep dus uitgesloten zouden moeten worden van beweegstimuleringsprogramma's aangezien er ook veel patiënten met milde tot matige COPD een laag lichamelijke activiteitenniveau hadden. Verder was een veel genoemde reden om te bewegen 'een actieve leefstijl in het verleden' wat impliceert dat het ook voor de preventie van sedentaire leefstijlen in een later stadium van COPD belangrijk is om lichamelijke activiteit in deze stadia al te stimuleren. Het is wel de vraag of patiënten met milde of matige COPD beter een COPD specifiek of algemeen beweegstimuleringsprogramma zouden moeten volgen.

Ernstige tot zeer ernstige COPD

De voorspellers van lichamelijke activiteit in patiënten met ernstige tot zeer ernstige COPD waren ziektespecifiek en fysiek (longhyperinflatie, kortademigheid, beenspierfunctie en zuurstofgebruik). Al deze voorspellende factoren zijn potentiële behandeldoelen maar zoals we eerder beschreven leidt het aanpakken van één van deze factoren niet automatisch tot een verbetering van lichamelijke activiteit. Tijdens de langzame progressie van COPD kunnen patiënten onbewust door de ervaren kortademigheid bepaalde lichamelijke activiteiten gaan vermijden. Dit zal vaak leiden tot een neerwaartse spiraal omdat een verslechterde conditie ontstaat wat de kortademigheid bij inspanning doet toenemen, en daardoor het lichamelijke activiteitenniveau verder verlaagt. Succesvolle behandeling van één van deze factoren is waarschijnlijk onvoldoende om in een opwaartse spiraal te komen. Daarom zal ook aandacht besteed moeten worden aan het stimuleren van lichamelijke activiteit aangezien patiënten volledig zijn aangepast aan hun sedentaire leefstijl.

Overige praktische implicaties

'Tailoring'

Onze resultaten bevestigen dat het belangrijk is om een beweegstimuleringsprogramma op maat te maken voor een patiënt in plaats van een algemeen programma te maken voor alle COPD patiënten. Dit wordt bevestigd door onze waarneming dat plezier in bewegen was gerelateerd aan een hoger lichamelijke activiteitenniveau, en dat er een grote variatie was in het soort lichamelijke activiteiten dat patiënten het liefst doen. Waarschijnlijk zal een voor de COPD patiënt op maat gemaakt programma ervoor zorgen dat ze het programma beter kunnen volhouden. Een andere studie liet zien dat een op maat gemaakt beweegadvies vaker leidde tot een stijging in lichamelijke activiteit dan algemene beweegadviezen.[35] Onze studie identificeerde een aantal factoren die gebruikt kunnen worden voor het opstellen van een op maat gemaakt programma, naast algemene factoren genoemd in de eerder beschreven studie[35] (Box 1).

BOX 1: Factoren individuele assessment

- Kennis over gezondheidsvoordelen van lichamelijke activiteit
- Eigen doelen van de patiënt
- Bereidheid tot veranderen
- Redenen om lichamelijk actief te zijn
- Barrières in lichamelijke activiteit
  - *weer*
  - *gezondheidsproblemen*
  - *financiële beperkingen*
  - *shaamte*
- Voorkeuren in lichamelijke activiteit
  - *mogelijkheden*
  - *beweeggeschiedenis*
- Self-efficacy

Het meten van lichamelijke activiteit

De eigen inschatting van de patiënt van het lichamelijke activiteitenniveau bleek een overschatting te geven van het daadwerkelijke lichamelijke activiteitenniveau (*hoofdstuk 5)*. Daarom is het meten van lichamelijke activiteit met objectieve meetinstrumenten zoals accelerometers aan te raden. Tegenwoordig worden deze apparaten steeds kleiner, lichter, makkelijker draagbaar en goedkoper. In onze studie werd lichamelijke activiteit onder andere gemeten met een gevalideerde accelerometer.[36] De patiënten droegen het apparaat gedurende 1 week en hadden weinig klachten over het dragen van het apparaat. Beweegstimulering met feedback van een stappenteller heeft goede resultaten laten zien in het toenemen van lichamelijke activiteit.[37] Tegenwoordig kunnen accelerometers verbonden worden met mobiele telefoons en computers, waardoor patiënten kunnen worden gemonitord op afstand en stimulerende feedback signalen aan de patiënten gegeven kunnen worden. Dit zou gedragsverandering kunnen ondersteunen.

Lichamelijke activiteit versus lichamelijke inactiviteit

Een onverwachte observatie van onze studie was dat de voorspellers van lichamelijke activiteit anders zijn dan de voorspellers van zitduur. Ook was de zitduur niet verschillend tussen patiënten in verschillende ernststadia van COPD. Andere studies hebben laten zien dat zitduur een onafhankelijke risicofactor is voor verschillende aandoeningen zoals het metabool syndroom.[38,39] Verder bleek dat het stimuleren van onderbrekingen in zitduur, onafhankelijk van totale zittijd, leidt tot vermindering van de risicofactoren van lichamelijke inactiviteit.[38,40] Ook bij COPD patiënten kan het dus nuttig zijn om naast het stimuleren van lichamelijke activiteit ook het verminderen van lichamelijke inactiviteit te stimuleren, bijvoorbeeld door onderbrekingen in zitduur te adviseren.

Beweegadvies en referentiewaarden

De laatste GOLD richtlijn adviseert dat alle patiënten regelmatig lichamelijk actief zouden moeten zijn.[1] Maar wat is 'regelmatig' lichamelijke actief zijn? Daarom is het belangrijk om te weten hoeveel lichamelijke activiteit nodig is om de gewenste gezondheidsvoordelen te behalen en om een concreet advies te kunnen geven aan een COPD patiënt. Op dit moment is de classificatie of een patiënt 'genoeg' lichamelijk actief is mede afhankelijk van de beweegnorm die wordt toegepast of met welk meetinstrument het wordt gemeten. Daarom is longitudinaal onderzoek nodig om te bepalen hoeveel lichamelijke activiteit in termen van frequentie, intensiteit en tijd daadwerkelijk nodig is in de verschillende stadia van COPD. Ook zou het nuttig zijn om referentiewaarden te ontwikkelen voor COPD patiënten om zo te kunnen bepalen welke COPD patiënten voor een beweegstimuleringsprogramma zouden moeten worden geselecteerd. Het individualiseren van de beweegnorm op basis van het fitheidniveau van een patiënt lijkt aantrekkelijk, vooral bij patiënten met (zeer) ernstig COPD. Bij het maken van een keuze voor een beweegnorm is het belangrijk dat patiënten een beweegnorm makkelijk kunnen inpassen in hun dagelijks leven en daarom zou een norm duidelijk moeten zijn en makkelijk navolgbaar en meetbaar.

De praktische richtlijnen hoe je een patiënt die een beweegnorm niet haalt zou moeten stimuleren om lichamelijk actiever te worden, zijn tot nu toe vaag en geven weinig praktische handvaten. Een vaak gebruikte behandelvorm waarin beweegstimulering plaatsvindt is longrevalidatie. Longrevalidatie is vaak multidisciplinair en er is aangetoond dat longrevalidatie het inspanningsvermogen, kwaliteit van leven en mate van kortademigheid significant verbetert.[41] Maar andere studies hebben ook laten zien dat een verhoging in lichamelijke activiteit niet automatisch gegarandeerd is na een revalidatieprogramma.[42] Een ander probleem is dat deze programma's vaak erg duur zijn en maar een zeer beperkt aantal patiënten in aanmerking komen voor longrevalidatie. Naast revalidatieprogramma's zijn gestructureerde sport- of fitnessprogramma's of lichamelijke activiteit counselingprogramma's nuttige behandelvormen, maar de optimale inhoud en plaatsing van deze programma's is op dit moment niet strak vastgelegd. Concluderend, is er duidelijk behoefte aan meer praktische beweegrichtlijnen die bruikbaar zijn voor fysiotherapeuten en andere behandelaars van sedentaire COPD patiënten.

Toekomstig onderzoek naar lichamelijke activiteit in COPD

Als eerste, raden we meer studies met een longitudinale opzet naar lichamelijke activiteit in COPD patiënten aan. Onze resultaten zijn verzameld op één tijdstip waardoor het moeilijk is om conclusies te trekken over oorzaak-gevolg verbanden. Het zou bijvoorbeeld heel interessant zijn om dezelfde patiënten na 5 jaar nog eens dezelfde metingen te laten uitvoeren. Dit geeft meer inzicht in veranderingen in lichamelijke activiteitpatronen van patiënten in de loop van de tijd. Longitudinaal onderzoek is ook nodig om te bepalen hoeveel lichamelijke activiteit daadwerkelijk nodig is om te leiden tot gewenste gezondheidsvoordelen, wat betreft frequentie, intensiteit en tijd in lichamelijke activiteit. Dit kan artsen en fysiotherapeuten helpen om concretere beweegadviezen aan een patiënt te geven.

Daarnaast zijn meer studies nodig die de meest optimale vorm van beweegstimulering bij COPD onderzoeken. Het zou interessant zijn om een op maat gemaakt, multidimensioneel beweegstimuleringsprogramma te onderzoeken dat zich specifiek richt op lichamelijke activiteit. In deze programma's zouden dan self-efficacy en intrinsieke motivatie een belangrijke rol moeten spelen. Naast het stimuleren van lichamelijke activiteit zou het verminderen van zitduur ook een doel moeten zijn en de rol van sociale steun voor lichamelijke activiteit zou verder onderzocht kunnen worden. Bij patiënten met milde tot matige COPD zou het interessant zijn om te onderzoeken of een algemeen beweegstimuleringsprogramma net zo effectief is als een COPD specifiek programma.

Toekomstig onderzoek zal hopelijk leiden tot dieper inzicht in het optimaal stimuleren van lichamelijke activiteit in COPD patiënten. Dit zal leiden tot een vermindering van sedentaire levensstijlen en de negatieve gevolgen ervan in deze patiëntpopulatie.

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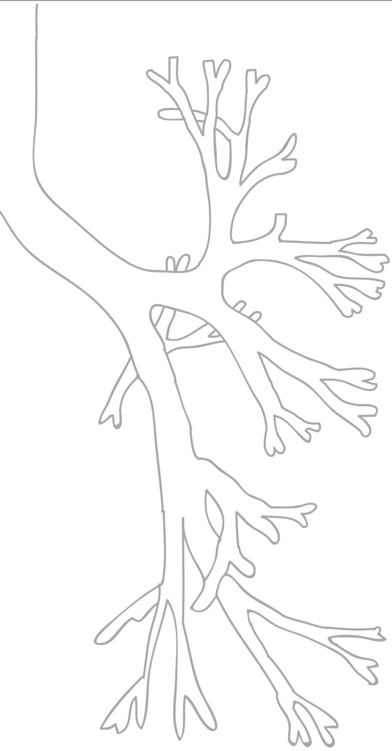
Dankwoord



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