Physical therapy in COPD

- effects on exacerbations and influence of comorbidity -

Emmylou Beekman

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- effects on exacerbations and influence of comorbidity -

Title page: `Lungtree`

A tree does not get most of its mass from the soil (Jan Baptist van Helmond, 1580-1644); it is mostly made out of air,[1] eventually *our* breath.

The research presented in this thesis was conducted at the Care and Public Health Research Institute (CAPHRI), which participates in the Netherlands School of Primary Care Research (CaRe). It was conducted at the Department of Epidemiology, Faculty of Health, Medicine and Life Sciences, at Maastricht University.

This research and printing of this thesis was funded by the Scientific College Physical Therapy (WCF) of the Royal Dutch Society for Physical Therapy (KNGF). The financial support by the WCF is gratefully acknowledged and enabled the research programme 'Designing Optimal Interventions in physical Therapy' (DO-IT), a unique national cooperation of four universities in The Netherlands.

Support for finalising this thesis was kindly provided by ParaMedisch Centrum Zuid and the Research Centre for Autonomy and Participation of Persons with a Chronic Illness at Zuyd University.

Coverdesign: EVELIENJAGTMAN.COM
Layout: Tiny Wouters
Production: Gildeprint Drukkerijen, Enschede

ISBN: 9789462335134

[1] The dry mass of a tree comes mainly from the air as CO2. Most of the plant dry matter is carbohydrate, with the general composition ratio of CH2O. The C and O come from CO2. The H comes from H2O. Between 50180% of a tree dry mass comes from moister (CO2 and H2O). Fromm JH, Sautter I, Matthies D, Kremer J, Schumacher P, Ganter C. Xylem water content and wood density in spruce and oak trees detected by highresolution computed tomography. *Plant physiology* 2001; 127(2): 416-25.

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PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. dr. Rianne M.
Letschert volgens het besluit van het College van Decanen, in
het openbaar te verdedigen op vrijdag 27 januari 2017, om
16.00 uur

door

Emmylou Beekman

Promotores:
Prof. dr. R.A. de Bie
Prof. dr. O.C.P. van Schayck
Prof. dr. R. Gosselink (KU Leuven, België)

Copromotor:
Dr. I. Mesters

Beoordelingscommissie:
Prof. dr. M. Drent (voorzitter)
Prof. dr. A.J.H.M. Beurskens
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Prof. dr. J.A.M.C.F. Verbunt
Dr. P.J. van der Wees (Radboudumc Nijmegen)

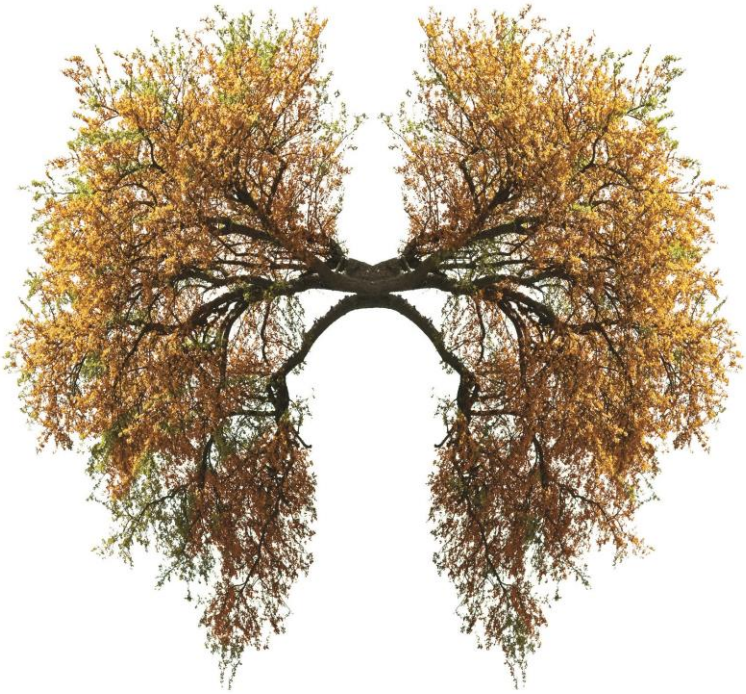
voor Peter, Lucas en Tristan
en voor mijn ouders

TABLE OF CONTENTS

It is most definitely noticeable that a lung (tracheobronchial tree) is
like an upside-down tree.
The bark and resin are like mucus; it protects against viruses from the outside.
The branches are like bronchi; the main passageways.
The twigs are like bronchioli; the smaller peripheral passageways. The
leaves are like alveoli; where the gas exchange happens.
Human blood haemoglobin is like plant chlorophyll; it carries O2 or CO2.
The sap is like blood; it runs gasses through the body.
Trees do not flourish in fire and smoke, just like lungs; they become sick…

- Emmylou -

CHAPTER 1



General introduction

1

BACKGROUND

Respiratory diseases are among the leading causes of death worldwide, which is a public health problem that is currently challenging our society. Respiratory infections (mostly pneumonia and tuberculosis), lung cancer and chronic obstructive pulmonary disease (COPD), together accounted for 9.5 million deaths worldwide during 2008, onesixth of the global total. Within this top four respiratory diseases, COPD accounted for 35% of the mortality and 21% of the disability- adjusted life-years (DALYs) lost worldwide (2008-2012).[1,2]

Among the leading causes of death, COPD was ranked 4th in 1990 and 3rd in 2010. In the next two decades, the proportion of deaths caused by respiratory disease in Europe is likely to remain stable, with a decrease in deaths from respiratory infections, however, this is countered by a rise in lung cancer and COPD mortality.[1]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The definition of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is "a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced inflammatory response in the airways and the lung to noxious particles or gasses."[3] The chronic airflow limitation is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema),[3] as displayed in Figure 1.1. The key risk factor for COPD is tobacco smoke inhalation (either primary or secondary), but environmental and occupational agents as well as genetic factors and early-life events also play a role.[1,2] The disease mostly concerns adults aged over 40 years, with a higher prevalence in men than women.[3] However, in 2016 the disease affected men and women almost equally in high-income countries, due in part to increased tobacco use among women in the past few decades.[2] The most important symptoms are breathlessness on exertion and chronic cough with or without mucus. Serious systemic consequences, also called extra-pulmonary manifestations of COPD, like deconditioning, exercise intolerance, skeletal muscle dysfunction and metabolic impact (e.g. cachexia) can arise as the disease progresses.[1,4,5]

In the Netherlands, patients with COPD are treated in primary care by a general practitioner or in secondary care by a pulmonologist. Clinicians consider a diagnosis of COPD in any patient who has dyspnoea, chronic cough or sputum production, and a history of exposure to risk factors for the disease.[3] Spirometry is required to make a confident diagnosis of COPD.[3]

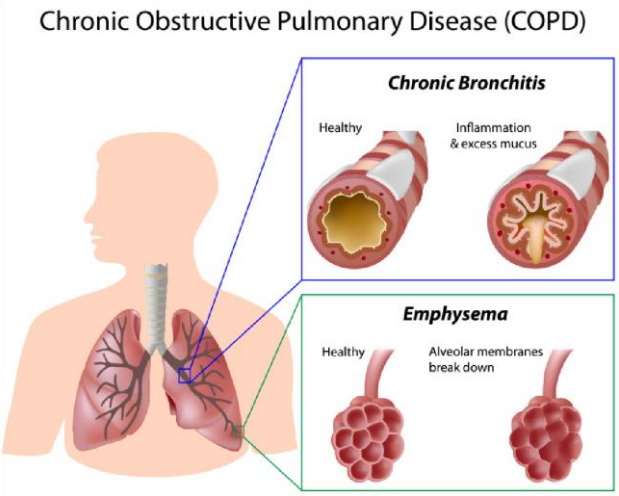


Figure 1.1 The pathophysiology of chronic obstructive pulmonary disease.[6]

EXACERBATIONS AND COMORBIDITY

In 2008, the idea for this dissertation stemmed from the great clinical impact that acute exacerbations have on people with COPD.[7-9] A COPD exacerbation is defined as "an event in the natural course of the disease characterised by an increase in dyspnoea, cough and/or sputum beyond normal day-to-day variations. The onset is seemingly acute and may require a change in regular medication or hospitalisation".[3] Exacerbations are mostly precipitated by bacteria and common pollutants and viruses causing an infectious systemic inflammation of the tracheobronchial tree.[3,10] The oneyear prevalence of exacerbations increases with the worsening limitation of airflow.[3] The lack of complete recovery of exacerbations is likely to explain this relationship between exacerbations and decline of lung function, with exacerbations contributing to around 25% of the decline.[11] This decline in lung function along with exacerbations result in reduced physical activity, poorer quality of life, significant morbidity, more hospital admissions and an increased risk of death.[1,12-14] Consequently, exacerbations are also responsible for a large proportion of the healthcare costs attributable to COPD. About 7% of all hospital admissions in Europe are due to lung disease. Almost half of these are attributable to exacerbations.[1] Given these consequences of exacerbations,

the assessment of exacerbation risk can also be seen as an assessment of the risk of poor outcomes in general.[3] Mild and severe COPD exacerbations frequently occur despite maximum pharmacological interventions.[15] Early rehabilitation after exacerbations is important. In unstable COPD (exacerbations), treatment is multimodal, including smoking cessation, medical treatment with bronchodilators as well as inhibitors of inflammation, exercise training and oxygen therapy. But the most powerful component of pulmonary rehabilitation is exercise training.[1,3] Although prevention and treatment of exacerbations is given by the World Health Organisation as one of the main goals of effective COPD management,[16] the potential impact of nonpharmacological physical therapy interventions on exacerbation frequency, duration and severity altogether has not yet been studied.

Another consideration for new research emerged from the difficulty of implementing relevant results from clinical studies into daily practice; 'COPD does not come alone'. In a Dutch cohort study in a tertiary care centre, 97.7% of patients with COPD had one or more comorbidities.[17] Precise prevalence numbers differ in the published epidemiological studies, but the majority of studies agree that the most prevalent comorbidities include cardiovascular disease (e.g. hypertension), metabolic syndrome, diabetes, mental disorders (e.g. anxiety/depression), osteoporosis, gastroesophageal reflux disease, (lung) cancer, dysfunctional skeletal myopathies and other respiratory diseases (e.g. asthma and obstructive sleep apnoea syndrome).[18,19] Moreover, patients with the frequent exacerbator phenotype develop higher cardiovascular and stroke risk,[20,21] increased depression[22] and related gastroesophageal reflux[23] over time and the presence of these comorbid conditions increases along with disease severity.[24] However, clinical trials investigating treatment of COPD routinely exclude significant comorbid conditions like cardiovascular diseases or cancer, while some comorbidities like depression and anxiety are included.[18,25] This does not provide enough indications for health care professionals on how to handle patients with COPD and comorbidities in practice nor on what to expect from the influence of comorbidity on health care outcomes. Neither do clinical practice guidelines.[18]

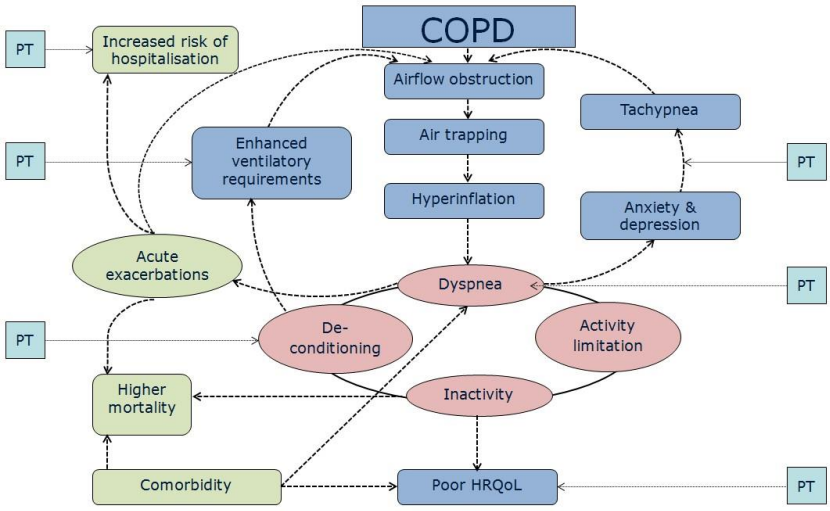
Much has changed in the past ten years since the first GOLD report was published. This dissertation closely relates to these developments. The definition of COPD was extended by the words "Exacerbations and comorbidities contribute to the overall severity in individual patients".[26] Another important example of this change is the classification system for COPD severity. Whereas spirometry was previously used for staging the disease, the severity of spirometric abnormality and current level of patients symptoms should now be assessed in conjunction with future risk of exacerbations and the presence of comorbidities.[3] This resulted in a four categoryassessment; A: low risk, less symptoms, B: low risk, more symptoms, C: high risk, less symptoms, D: high risk, more symptoms. Although comorbidity was not integrated in this classification, it should be combined with assessment of potential comorbidities. This combined approach reflects the complexity of COPD better than the

one-dimensional analysis of airflow limitation and forms the basis of the guide to individualised management.[3] Although both exacerbations and comorbidity are now acknowledged as having a greater role in terms of disease management in the GOLD report, the attention both traits is given in clinical practice is still little.

PHYSICAL THERAPY IN COPD

Care for patients with COPD is increasingly given by multidisciplinary care teams ('ketenzorg' in Dutch) including a general practitioner and pulmonologist and other health care professionals such as a physical therapist, nurse and dietician.[27] Besides drugs, such as bronchodilators and corticosteroids, non-pharmacological treatment is an important part of COPD care,[3] in which smoking cessation is the most important step.[3,27] Additionally, physical activity is recommended for all patients with COPD.[3] There is a plethora of evidence to support recommendations for physical activity by means of pulmonary or respiratory rehabilitation, in which individually tailored exercise training is considered the cornerstone of pulmonary rehabilitation.[3,28,29] If a patient cannot comply with sufficient daily physical activity, he or she is referred to a physical therapist (preferably one specialised in exercise training for COPD).[27] Physical therapists offer protocol-directed physical therapy including several effective treatment modalities (specifically exercise training, breathing exercises, peripheral and respiratory muscle training).[9] Protocol-directed physical therapy in the Netherlands qualifies as pulmonary rehabilitation, defined in the policy statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) as: "programmes including, at the very least, comprehensive baseline and post-pulmonary rehabilitation outcome assessments; a structured and supervised exercise training programme; an education/behavioural programme intended to foster long-term health-enhancing behaviour; and provision of recommendations for home-based exercise and physical activity".[30] In accordance with McCarthy et al. (2015) physical therapy in this thesis can be considered to be pulmonary rehabilitation because exercise training for at least four weeks with or without education and/or psychological support was included.[29] Shortterm goals of physical therapy incorporate improvement of patients' knowledge, selfmanagement and confidence to accomplish activities. Medium-term goals are relief of dyspnoea, improvement of impaired airway (mucus) clearance, and improving or retaining exercise performance and physical activity in everyday life. Long-term goals entail improvement or preservation of disease related quality of life.[9] Pulmonary rehabilitation (at least including exercise training) has proven its effectiveness on reduction of symptoms, improvement of exercise capacity, improvement of healthrelated quality of life, reduction in hospitalisation, reduction in anxiety and depression.[3]

Figure 1.2 shows how physical therapy covers a range of non-pulmonary problems that may not be adequately addressed by medical therapy for COPD, including exercise deconditioning, relative social isolation, altered mood states (especially anxiety and depression), muscle wasting, and weight loss.[3] Physical therapy aims to break the vicious circle illustrated in Figure 1.2.



Abbreviations: PT = physical therapy, HRQoL = health-related quality of life.

Figure 1.2 The (potential) reversible impact of physical therapy in COPD related to the vicious circle of symptoms, inactivity, systemic consequences and exacerbations, adapted from and based on the literature.[3,11,19,29,31-39]

Chronic Obstructive Pulmonary Disease comes with air trapping and hyperinflated lungs, which results in increased dyspnoea. Increased dyspnoea provokes anxiety, accompanied by subsequent inefficient breathing, which inevitably leads to further air trapping and dyspnoea.[31,32] Now a vicious circle emerges with exacerbations of COPD symptoms, dyspnoea causing activity limitation, whereby any activities that involves physical exertion are avoided, causing muscle decondition. The pulmonary and skeletal muscle abnormalities further reduce capacity to engage in physical activity and enhance the ventilatory requirements during exercise resulting in exercise-associated symptoms such as dyspnoea and fatigue.[29,32,33] These symptoms make exercise an unpleasant experience, which many patients try to avoid. The unpleasant experience, along with a depressive mood status in up to 30% of patients further accelerates the process and leads to an inactive life-style.[32]

Physical inactivity is therefore a key-predictor in mortality in people with COPD.[29] Exacerbations are also a predictor of mortality[34] and lead to an increased risk of hospitalization[35], to increased airflow limitation[3,11] eventually followed by a poorer quality of life[32,36] (Figure 1.2). Also the presence of comorbidity in patients with COPD is a predictor of high mortality,[19,37-39] as it is a predictor of exacerbations, dyspnoea and poor quality of life.[19]

Consequently, the joint ATS/ERS guidelines highlight the importance of physical exercise in the management of COPD.[40] The physical therapist is the health care professional par excellence to provide competent exercise training for COPD.[9]

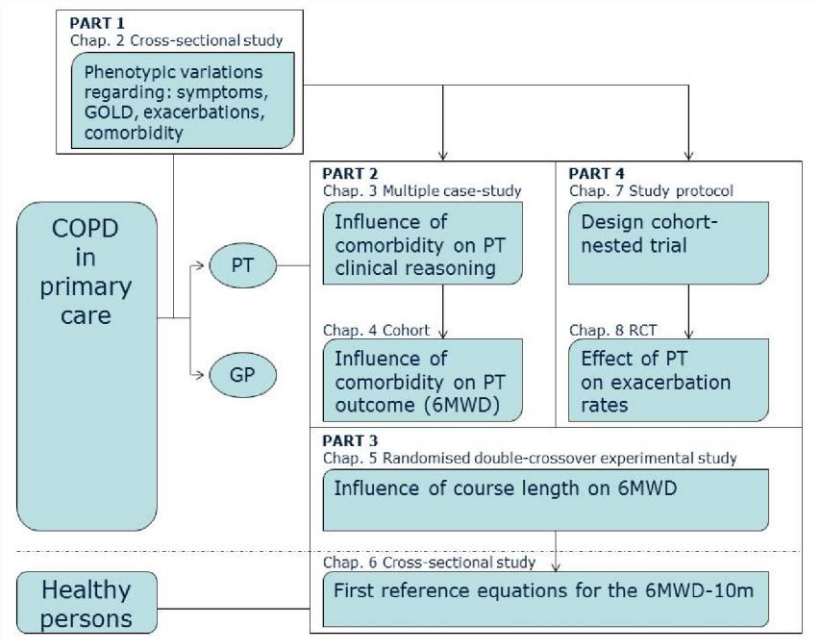
In the past decade, measurement instruments have also evolved in COPD healthcare. At first, symptom assessment did not have a direct relation to the choice of management, and health status measurement was a complex process.[3] Nowadays, there are applicable and reliable measurement instruments designed for routine use in daily clinical practice. They enable the new approach to management – one that matches assessment to treatment objectives. [3] Common and suitable measurement instruments physical therapists in the Netherlands use are the six-minute walk test to quantify functional exercise capacity and a Clinical COPD Questionnaire to assess health-related quality of life, which can be used to quantify health status. However, not always are measurement protocols feasible in clinical practise. The six-minute walk test is advised over a course of 30 metres,[41] whereas most primary care physical therapy practices have limited space. Consequently, existing reference equations to interpret measurement outcome were used for a non-corresponding test course. Due to the broader use of measurement instruments in all kinds of clinical settings anywhere in the world, a critical view towards validity, reproducibility, practicality and generalizability is still required.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to provide new evidence concerning the interactions between physical therapy, comorbidity and exacerbations in patients with COPD. This thesis provides data to enable physical therapists and physicians to deliver competent treatment, to obtain optimal treatment results that can be interpreted correctly, and to tailor individual health care for patients with COPD and comorbidity and with the frequent exacerbator phenotype. These topics generate a lot of interest, as seen from the many scientific publications in the field. However, the essential role of specialised COPD physical therapy in relation to the great benefits of physical therapy in COPD needs more attention.

The aim of the work summarised in this thesis was (1) to explore phenotypic variations in (inactive) patients with COPD treated in different primary care settings (general practitioner practice versus physical therapy practice), (2) to illustrate clinical consequences of comorbidity in COPD for physical therapy, (3) to extend the applicability of functional exercise capacity assessment (the six-minute walk test) for patients with COPD and patients with other chronic conditions, and (4) to study the effect of physical therapy on exacerbation frequency, duration and severity in patients with COPD.

The outline of the thesis body is schematically presented in Figure 1.3.



Abbreviations: Chap. = Chapter, GOLD = disease stage by the Global Initiative of Lung Diseases classification, PT = physical therapy, GP = general practitioner, 6MWD = six-minute walk distance, RCT = randomised controlled trial, 6MWD-10m = six-minute walk distance over a 10 metre course.

Figure 1.3 A schematic representation of the thesis.

Part 1 gives an introduction to the study population of this dissertation, with special attention to exacerbations and comorbidity. In Chapter 2, differences in patient characteristics between inactive patients treated by a general practitioner and inactive patients treated by a general practitioner combined with a physical therapist are

presented. Additionally an overview is given of the phenotype of patients with COPD in a physical therapy practice.

Part 2 explains the influence of comorbidity on physical therapy in two ways. Firstly, the therapeutic consequences for physical therapy practise during treatment of patients with COPD and multiple comorbidities are addressed in Chapter 3. Secondly, the effect of physical therapy on the primary outcome functional capacity (six-minute walk test) is presented within prognostic profiles of patients with COPD and comorbidity in Chapter 4.

Consequently, Part 3 considers optimisation of functional exercise capacity assessment as a consequence of bottom-up observations during the research for this dissertation. Chapter 5, proves that course length of 30 metre versus 10 metre has a significant and clinical influence on six-minute walk distance in patients with COPD. Chapter 6 presents the first reference equations for the six-minute walk distance over a 10 metre course in healthy adults. Subsequently, a published correspondence between the co-chairs of the joint ATS/ERS task force and the authors of this thesis is given regarding the question: what determines which six-minute walk test is conventional?

Part 4 studies the potential of physical therapy to reduce COPD exacerbations. Chapter 7 presents a study protocol of a cohort-nested randomised controlled trial to study the effect of physical therapy on exacerbation rates in patients with COPD (including comorbidity). In Chapter 8, the results of this trial are presented.

The general discussion in Chapter 9 summarises the main findings reported in this thesis and discusses their implications for clinical practice and future research.

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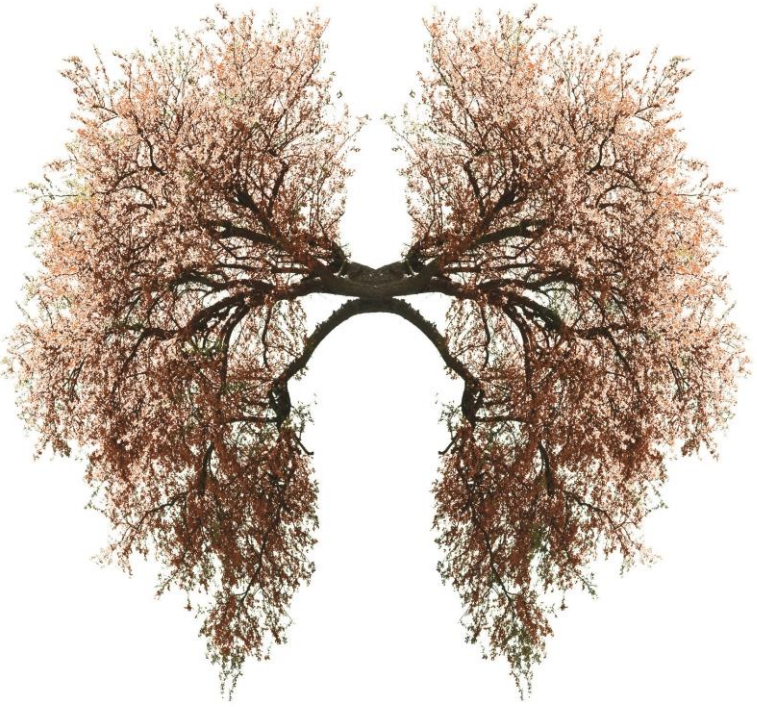
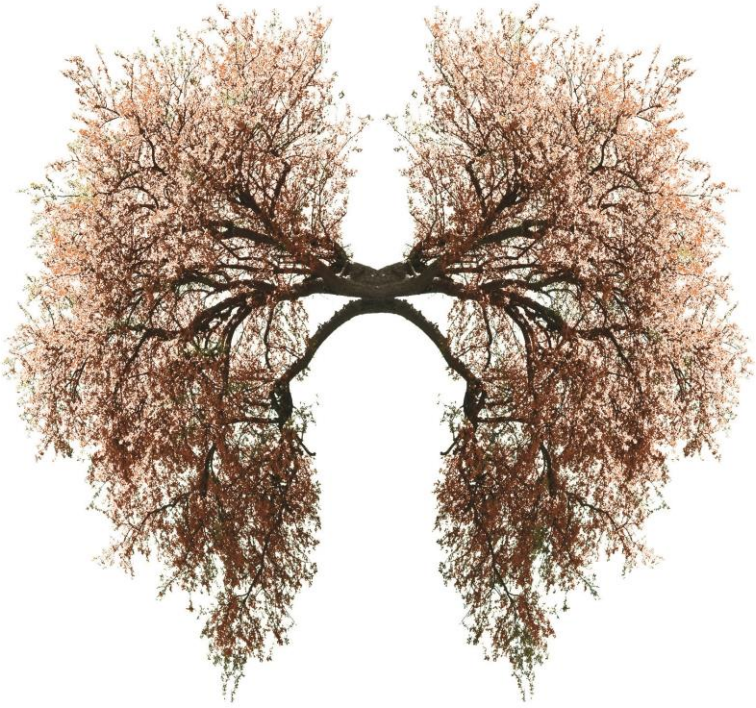
PART 1



An introduction to the study population of this dissertation

CHAPTER 2



Phenotypic variation in patients with chronic obstructive pulmonary disease in primary care

Emmylou Beekman, Ilse Mesters, Mark G. Spigt, Eva A.M. van Eerd, Rik Gosselink, Rob A. de Bie, and Onno C.P. van Schayck

BioMed Research International 2016:8108717

ABSTRACT

Introduction

Despite the high number of inactive patients with COPD, not all inactive patients are referred for physical therapy, unlike recommendations of general practitioner (GP) guidelines. It is likely that GPs take other factors into account, determining a subpopulation that is treated by a physical therapist (PT). The aim of this study is to explore the phenotypic differences between inactive patients treated in GP practice and inactive patients treated in GP practice combined with PT. Additionally this study provides an overview of the phenotype of patients with COPD in PT practice.

Methods

In a cross-sectional study, COPD patient characteristics were extracted from questionnaires. Differences regarding perceived health status, degree of airway obstruction, exacerbation frequency, and comorbidity were studied in a subgroup of 290 inactive patients and in all 438 patients.

Results

Patients treated in GP practice combined with PT reported higher degree of airway obstruction, more exacerbations, more vascular comorbidity, and lower health status compared to patients who were not referred to and treated by a PT.

Conclusion

Unequal patient phenotypes in different primary care settings have important clinical implications. It can be carefully concluded that other factors, besides the level of inactivity, play a role in referral for PT.

INTRODUCTION

Physical activity is beneficial for patients suffering from chronic obstructive pulmonary disease (COPD). Physical activity can improve symptoms, quality of life, and physical and emotional participation in everyday activities,[1] whereas a decline from moderate/high physical activity to low physical activity is associated with an increased mortality risk.[2] To describe the number of active or inactive COPD patients the physical activity norm for healthy persons is applied as the norm for physical activity in patients with COPD. To be considered sufficiently physically active, a healthy adult has to carry out moderate intense physical activities for at least five days a week, 30 minutes a day (Dutch standard)[3] or 20 min of vigorous-intensity physical activity on at least 3 days every week, or an equivalent combination, which can also be accumulated in shorter bouts of 10 min exercise (international standard).[3–7] The extent to which this framework, on which to base recommendations for physical activity promotion, applies to patients with COPD is currently unknown.[6] Since no definite directives are available about how much physical activity COPD patients should carry out, the standard for healthy persons is used in health care.[7]

Epidemiological data show that 84% of patients with COPD do not reach the Dutch standard for daily physical activity.[8] Systematic literature reviews conclude that the number of inactive patients with COPD is some 30% (range 17–43%) higher compared to inactive healthy adults[5,9–11] and higher compared to other patients with chronic diseases like diabetes mellitus and rheumatoid arthritis.[12] Lower levels of physical activity were already present in the earlier stages of the disease, and an increasing severity of COPD was associated with a further decrease in physical activity.[13]

The Dutch general practitioners (GPs) practice guidelines advice to refer patients with COPD to a physical therapist (PT) if they do not or cannot comply with the Dutch standard for physical activity due to dyspnoea or fear of dyspnoea.[14] Although inactivity is a referral criterion for physical therapy, there is a discrepancy between the numbers of patients with COPD who are inactive (the earlier mentioned 84%) and those with COPD treated by a PT (27%).[15] Indeed, patients may decide (not) to opt for physical therapy; for example, patients with COPD perceive their health condition (dyspnoea) as less severe compared to the objective degree of severity.[16] However, it is more likely that GPs take severity of obstruction, symptoms (dyspnoea), exacerbation risk, and presence of comorbidities into account, besides inactivity, to refer patients with COPD for physical therapy.[1,17] Other patients' symptoms and perceived level of limitations may additionally play a role in referring patients to the PT.[17] Patients' perceptions of limitations are a stronger predictor of behaviour (like physical activity) than objective measures of limitation severity,[18] as they contribute to the larger patients' burden of disease. From a patient perspective, COPD can be held responsible for disability that restricts many everyday activities, such as walking upstairs.[19] Hence, when assessing the patients' burden of COPD, patient reported outcome measures should be

incorporated, for instance, the Clinical COPD Questionnaire (CCQ) that assesses a broader range of health status than dyspnoea only.[20–22] We hypothesise that the referral for patients to PT is based on the patients' burden of disease and that this is not necessarily coherent with the level of inactivity.

General practitioner's considerations to refer for physical therapy are likely to determine patient flow in primary care. GPs treat a wide spectrum of patients from less severe to very severe COPD. PTs however seem to treat a subpopulation of this spectrum. Although the descriptions of COPD populations in the literature are limited to in-patients or out-patients who are under supervision of pulmonary clinics,[23,24] PTs in primary care settings believe that they are involved with patients with a high burden of disease. Since physical therapists are expected to tailor their clinical reasoning and their choice for exercise therapy to the population that visits the PT,[25] insight in the overall phenotype of their patients is crucial for PTs. Depending on the level of inactivity but also depending on other patient characteristics like the presence of comorbidities[25] and future risk of exacerbations,[1] PTs may have to take into account extensive interdisciplinary consultation, adapted training intensity, or longer treatment duration. We hypothesise that patient phenotypes are unequal in different primary care settings. This study explores the phenotypic differences between inactive patients treated in GP practice and inactive patients treated in GP practice combined with PT, with regard to patients' perceived health status, degree of airway obstruction, exacerbation frequency, and comorbidity. Additionally it provides an overview of the overall phenotype of patients with COPD in PT practice.

METHODS

Participants

In 2012, cross-sectional data were collected in collaboration with ten multidisciplinary primary health care centres (collaboration "SGE") providing care to 64,602 people in Eindhoven, The Netherlands.[26] In this population, 1,248 patients were diagnosed with COPD, as registered with code R95 in accordance with the International Classification of Primary Care (ICPC) in the general practice patient documentation system. In December 2012, questionnaires were sent by post to all 1,248 patients.

Measurements

The questionnaire was developed by Maastricht University in collaboration with the participating health centres. It contained items regarding personal characteristics and disease severity (self-reported). Disease-related health status was measured with the Clinical COPD Questionnaire,[27] addressing symptoms, functional state, and mental state

(CCQ, rating from 0 “good” to 6 “bad”). General health status was measured with the first question on The Short Form Health Survey (SF36, rating from 1 “excellent” to 5 “poor”).[28] Information regarding physical activity (Physical Activity questionnaire, rating from 0“not physically active” to 8 “very physically active”),[29] smoking, and comorbidities (for 15 different disease categories) was collected. Exacerbation history was measured by an event-based approach (the number of hospitalisations and medication intake (0, 1, 2, 3, or 3>)). Whether patients were treated by a PT for COPD or another health condition was collected as well. Inactivity was defined as moderate intense physically active for less than five days a week (30 minutes a day) and vigorousintense physically active for less than three days a week (20 minutes a day) or an equivalent combination. This corresponds with a score between zero and three on the Physical Activity questionnaire[7,29] and is in agreement with the international standard for physical activity.[3-6]

Data analyses

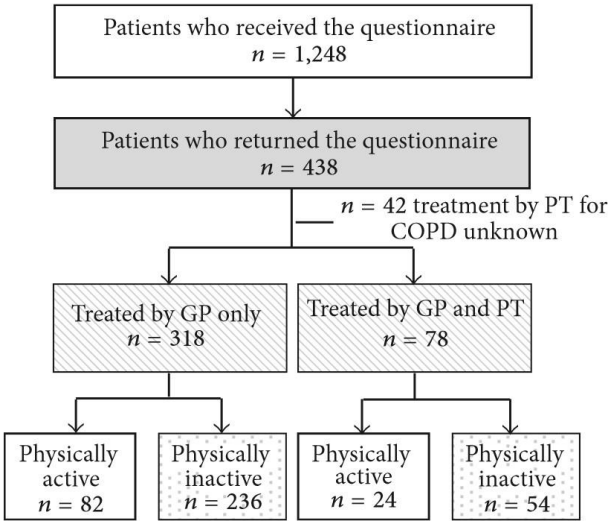
From the questionnaires returned, individual anonymised data were used. Phenotypic variations in inactive patients with COPD and in all patients with COPD treated by a GP versus a PT were analysed, based on the patient reported outcome measures. The following factors were treated as categorical data: sex, Global Obstructive Lung Disease (GOLD stages I–IV),[1] general health status (SF36), comorbidity (yes or no for 15 different disease categories), exacerbation frequency (number of hospitalisations and medication intake (0, 1, 2, 3, or 3>)), and physical therapy treatment (yes or no). Age, disease-related health status (CCQ), physical activity (Physical Activity questionnaire), and smoking history (pack years) were treated as continues data. Double answers were treated as was specified in the original questionnaires. If not specified, the less favourable answer was taken (e.g., “GOLD 3” AND “GOLD 4” were replaced by GOLD 4; “1-2 days a week physical active” AND “3-4 days a week physical active” were replaced by 1-2 days a week; “25 cigarettes a day” AND “15 cigarettes a day” were replaced by 25 cigarettes).

Between-group differences (GP treatment versus GP combined with PT treatment) were analysed for the inactive population and for the whole population by crosstabs with Pearson χ^2 and odds ratios (OR) for sex, GOLD stage, presence of comorbidity, exacerbation frequency, and general health perception, with an independent *t*-test for age, and with the Mann-Whitney test for smoking, physical activity, and disease-related health status.

2

RESULTS

Four hundred and thirty-eight completed questionnaires were returned, with a response rate of 35%. Missing data was treated by case wise deletion for each statistical run (41 in physical activity; 24 in smoking history; 4 in comorbidity; 126 in GOLD stage; 40 in exacerbations; 121 in health status; 42 in health perception; and 42 in treatment GP versus PT). Data was sampled independently from the populations being compared, with equal variances. According to the respondents, eighteen percent of the respondents were treated for COPD by a PT. Of those patients, 69% were physically inactive. In the group that did not receive PT, 74% were physically inactive. Moreover, a total of 73% of patients with COPD registered by the GP were physically inactive. Figure 2.1 presents the flow of patients and the subgroups analysed.



Abbreviations: PT = physical therapist, GP = general practitioner.

Figure 2.1 Flowchart of patients registered and treated in primary care. GP: general practitioner; PT: physical therapist; COPD: chronic obstructive pulmonary disease. Subgroups in the dotted boxes were compared for the first aim of this study. Subgroups in the striped boxes were compared for the second aim of this study.

Phenotype of inactive patients in primary care

Table 2.1 presents characteristics of all inactive patients, based on patient reported outcome measures. Patients who were referred for PT did not differ significantly from patients who were treated by a GP only regarding the demographic characteristics sex ($\chi^2(1)=0.53$, $p=0.55$) and age ($t(287)=-0.36$, $p=0.72$).

Table 2.1 Characteristics of 290 inactive patients with COPD treated in primary care.

Characteristic	Treated by GP only (*n*=236)	Treated by GP and PT for COPD (*n*=54)	*p* value
Sex, *n* male (%)	122 (52)	31 (57)	0.55
Age (yr), mean (SD)	70.29 (11.07)	70.87 (8.76)	0.72
Smoking (pack years), mean (SD)	31.14 (23.54)	40.90 (23.39)	0.001
GOLD stage, *n* (%)			<0.0001
I	92 (52)	5 (11)	
II	68 (39)	18 (39)	
III	10 (6)	15 (33)	
IV	6 (3)	8 (17)	
Comorbidity, *n* (%)			
Cardiovascular	71 (44)	21 (39)	0.317
Cardiac	51 (22)	13 (24)	0.543
Vascular	21 (9)	11 (20)	0.020
Stroke	11 (5)	5 (9)	0.160
Respiratory (asthma)	26 (11)	5 (9)	0.456
Psychological (depression)	32 (14)	5 (9)	0.226
Metabolic (diabetes)	35 (15)	12 (22)	0.137
Nutritional	64 (27)	15 (28)	0.536
Exacerbations in the past year, *n* (%)			0.001
0	127 (54)	16 (30)	
1; of which hospitalised	55 (23); 7 (13)	12 (22); 4 (33)	
2; of which hospitalised	24 (10); 1 (4)	9 (17); 1 (11)	
3 or more; of which hospitalised	29 (12); 15 (52)	17 (32); 8 (47)	
Disease-related health status (0–6), mean (SD)			
Total CCQ	1.40 (0.95)	1.80 (0.95)	<0.0001
Symptoms subscale	1.85 (1.11)	2.35 (1.07)	0.004
Functional state subscale	1.32 (1.14)	2.40 (1.25)	<0.0001
Mental state subscale	0.68 (0.99)	0.92 (1.02)	0.038
General health perception (0–5), *n* (%)			<0.0001
1, excellent	1 (1)	1 (2)	
2, very good	8 (3)	0	
3, good	96 (45)	9 (17)	
4, moderate	90 (43)	35 (66)	
5, poor	17 (8)	8 (15)	

Abbreviations: GP = general practitioner, PT = physical therapist, SD = standard deviation, GOLD = the Global Initiative for Chronic Obstructive Lung Disease; GOLD stages: I: mild COPD, $FEV_1/FVC<0.7$, and $FEV_1 \geq 80\%$ of predicted; II: moderate COPD, $FEV_1/FVC<0.7$, and $50\% \leq FEV_1 < 80\%$ of predicted; III: severe COPD, $FEV_1/FVC<0.7$, and $30\% \leq FEV_1 < 50\%$ of predicted; IV: very severe COPD, $FEV_1/FVC<0.7$, and $FEV_1<30\%$ of predicted or $FEV_1<50\%$ of predicted plus chronic respiratory failure, FVC = postbronchodilator forced vital capacity, FEV_1 = postbronchodilator forced expiratory volume in one second, CCQ = Clinical COPD Questionnaire: rating from 0 “good” to 6 “bad”.

Inactive patients treated by GP combined with PT reported a statistically significant higher degree of airway obstruction compared to patients treated by a GP only ($\chi^2(3)=49.10$, $p<0.0001$). Patients with GOLD II or higher were 9 times more likely to be treated by a PT compared to patients with GOLD I; for patients with GOLD III or higher it was 10 times more likely.

Also, higher comorbidity rates were reported in the group treated by GP combined with PT, but only vascular disease was significantly more present ($\chi^2(1)=5.77$, $p=0.020$); those with an additional vascular disease were 2.3 times more likely to be treated by a PT. Other disease groups, like neoplasms, musculoskeletal, skin, endocrine, digestive, or neurological disease, were not statistically different between the groups. Moreover, these subgroups were very small and therefore not shown in Table 2.1.

Significantly higher exacerbation rates were reported by patients treated by PT ($\chi^2(3)=17.02$, $p=0.001$). The chance for treatment by a PT increased gradually with higher exacerbation frequencies (OR=2.8 with one or more exacerbations; OR=3.2 with two or more exacerbations; OR=3.3 with three or more exacerbations).

General health perception was significantly lower in the group treated by PT ($\chi^2(2)=16.44$, $p<0.0001$); those who rate their general health as poor or moderate were almost two times more likely to be treated by GP and PT combined. Comparably, disease-related health status was significantly lower based on the total CCQ scale ($U=5762.500$, $p<0.0001$) and based on the subscales for symptoms ($U=6541.500$, $p=0.004$), functional state ($U=7904.000$, $p<0.0001$), and mental state ($U=5016.500$, $p=0.038$).

Phenotype of patients in PT practice

Characteristics of patients treated by PT versus patients treated by a GP only can be found in Table 2.2. All patients (active and inactive) who received PT did not differ significantly from patients who did not receive PT regarding the demographic characteristics sex ($\chi^2(1)=0.71$, $p=0.45$) and age ($t(393)=-1.06$, $p=0.29$).

Patients treated by both a GP and a PT reported a statistically significant higher degree of airway obstruction compared to patients treated by a GP only ($\chi^2(3)=79.75$, $p<0.0001$). Patients with GOLD II or higher were 15 times more likely to be treated by a PT compared to patients with GOLD I.

Also, high comorbidity rates were reported in the group treated by PT (Table 2.2), but only vascular disease was significantly more present ($\chi^2(1)=7.51$, $p=0.009$); those with an additional vascular disease were 2.7 times more likely to be treated by a PT.

Significantly higher exacerbation rates were shown in patients treated by PT ($\chi^2(4)=35.91$, $p<0.0001$). The chance for treatment by a PT increased gradually with higher exacerbation frequencies (OR=3.4 with one or more exacerbations; OR=3.7 with two or more exacerbations; OR=3.8 with three or more exacerbations).

Table 2.2 Characteristics of all 438 patients with COPD treated in primary care.

Characteristic	All patients	Treated by GP only (*n*=318)	Treated by GP and PT for COPD (*n*=78)	*p* value
Sex, *n* male (%)	235 (54)	166 (52)	45 (58)	0.71
Age (yr), mean (SD)	69 (11)	69 (11)	69 (11)	0.29
Physical activity (0–8), mean (SD)	2.38 (2.31)	2.20 (2.33)	2.92 (1.99)	0.001
Smoking (pack years), mean (SD)	31.14 (23.54)	30.45 (23.30)	38.27 (22.32)	0.004
GOLD stage, n (%)				<0.0001
I	141 (32)	133 (55)	5 (7)	
II	116 (27)	88 (36)	27 (41)	
III	35 (8)	14 (6)	21 (32)	
IV	20 (5)	7 (3)	13 (20)	
Comorbidity, *n* (%)				
Cardiovascular	116 (27)	88 (26)	25 (32)	0.171
Cardiac	82 (19)	61 (19)	16 (21)	0.440
Vascular	38 (9)	22 (7)	13 (17)	0.009
Stroke	20 (5)	14 (4)	6 (8)	0.177
Respiratory (asthma)	56 (13)	44 (14)	9 (12)	0.381
Psychological (depression)	60 (14)	44 (14)	10 (13)	0.499
Metabolic (diabetes)	70 (16)	50 (16)	13 (17)	0.469
Nutritional	115 (27)	87 (28)	23 (30)	0.390
Exacerbations in the past year, *n* (%)				<0.0001
0	204 (51)	181 (57)	22 (28)	
1; of which hospitalised	89 (22); 12 (13)	70 (22); 8 (11)	18 (23); 4 (22)	
2; of which hospitalised	47 (12); 4 (9)	32 (10); 3 (9)	14 (18); 1 (8)	
3; of which hospitalised	19 (5); 6 (32)	14 (5); 5 (36)	5 (7); 1 (20)	
>3; of which hospitalised	39 (10); 21 (54)	19 (6); 11 (58)	19 (24); 10 (53)	
Disease-related health status (0–6), mean (SD)				
Total CCQ	1.51 (1.06)	1.32 (0.97)	2.19 (1.01)	<0.0001
Symptoms subscale	1.95 (1.19)	1.76 (1.14)	2.49 (1.13)	<0.0001
Functional state subscale	1.52 (1.28)	1.20 (1.13)	2.48 (1.29)	<0.0001
Mental state subscale	0.75 (1.06)	0.67 (1.00)	1.02 (1.13)	0.004
General health perception (0–5), *n* (%)				<0.0001
1, excellent	6 (2)	4 (1)	1 (1)	
2, very good	13 (3)	11 (4)	0	
3, good	168 (42)	133 (47)	15 (20)	
4, moderate	172 (44)	112 (39)	51 (66)	
5, poor	37 (9)	26 (9)	10 (13)	

Abbreviations: GP = general practitioner, PT = physical therapist, SD = standard deviation, physical activity: rating from 0 “not physically active” to 8 “very physically active”, GOLD = the Global Initiative for Chronic Obstructive Lung Disease; GOLD stages: I: mild COPD, $FEV_1/FVC<0.7$, and $FEV_1 \geq 80\%$ of predicted; II: moderate COPD, $FEV_1/FVC<0.7$, and $50\% \leq FEV_1 < 80\%$ of predicted; III: severe COPD, $FEV_1/FVC<0.7$, and $30\% \leq FEV_1 < 50\%$ of predicted; IV: very severe COPD, $FEV_1/FVC<0.7$, and $FEV_1<30\%$ of predicted or $FEV_1<50\%$ of predicted plus chronic respiratory failure, FVC = postbronchodilator forced vital capacity, FEV_1 = postbronchodilator forced expiratory volume in one second, CCQ = Clinical COPD Questionnaire: rating from 0 “good” to 6 “bad”.

General health perception was significantly lower in the group treated by PT ($\chi^2(2)=23.71$, $p<0.0001$); those who rate their general health as poor or moderate were four times more likely to be treated by GP and PT combined. Also, disease-related health status was significantly lower based on the total CCQ scale ($U=11923.000$, $p<0.0001$) and based on the subscales for symptoms ($U=13806.500$, $p<0.0001$), functional state ($U=16485.000$, $p<0.0001$), and mental state ($U=9962.000$, $p=0.004$). Patients treated by a PT were significantly more physically active in their daily life ($U=9438.000$, $p=0.001$) but had a significantly higher history of pack years ($U=8863.500$, $p=0.004$).

DISCUSSION

This study showed that there are phenotypic differences between patients with COPD in primary care. More specifically, inactive patients treated in GP practice combined with PT had a higher degree of airway obstruction, more exacerbations, and more vascular comorbidity and a lower health status was reported. It may be that patients who are referred for PT have a higher burden of disease compared to patients who are not referred for a PT. Moreover, this study gave an overview of the overall phenotype of patients with COPD in PT practice. We showed that the group of patients that were not treated by PT had a low burden of disease compared to the group of patients treated by a PT. Indeed, these patients had a double burden of disease (inactive and significantly more exacerbations) or even a triple burden of disease (inactive, significantly more exacerbations and more vascular comorbidity).
Thus, the hypotheses that the referral of patients for PT is based on the patients' burden of disease and that this is not necessarily coherent with the level of inactivity and that patient phenotypes are unequal in different primary care settings were confirmed by the study results.

Considerations in patient referral

Although based on patient reported data only, this study confirmed that the majority of patients with COPD are inactive. The large proportion of patients within PT practice who are inactive (69%) is not surprising, since GP practice guidelines advise referring the patient to a PT if the physical activity standard is not achieved.[14] Interestingly, however, this study showed also that the group of inactive patients that was not treated by a PT is extremely large (74%). This can be clarified by different reasons. A GP might not refer patients for PT when physical training is not a feasible option. Alternatively, GPs might consider other patient characteristics needed for referral for PT than inactivity alone.

Solely based on the inactivity referral criteria, it means that the GP could have referred more patients to a PT. However, this statement needs some consideration. According to the patient reported outcomes, 73% of patients with COPD registered by the GP were physically inactive, while not more than 20% were referred to and treated by a PT. On the one hand, the respondents are a relatively small subgroup (35%) of the GP population, from which they were recruited. It is possible that patients who were treated by a PT responded less often to the questionnaire compared to patients who were not treated by a PT. However, the National Primary Care Collaboration LESA reported that 27% of patients with COPD were referred to a PT in one year,[15] which is a number approximating the patients reported percentage (20%).

On the other hand, GPs might not have referred *inactive* patients to a PT when they showed no unfavourable prognosis based on other criteria such as exacerbations, comorbidity, or limitations in activity. Reversely, by taking into account these other criteria, GPs might have referred *active* patients that showed an overall higher burden of disease. Our findings confirmed the latter hypothesis, since referred patients for PT had higher exacerbation rates, more vascular comorbidity, higher degree of airway obstruction, worse symptom scores (CCQ-subscale symptoms), more limitation in daily activity (CCQ-subscale functional state), and lower health perception (GPE) or health status (CCQ-total scale).

Clinical implication of phenotypic variation

The phenotype of patient populations in different primary care settings varies. This finding may have several clinical implications.

The results of this study can provide both GPs and PTs with a realistic perspective from which prior expectations are set and treatment results are being evaluated. In the light of (potential) referral criteria, it is useful to understand why part of the inactive patient population is not referred to or treated by a PT.

This study increases GPs awareness of the phenotypes of patients treated by a PT. Our data also shows that GPs might deviate from the GP guidelines regarding referral criteria for good reasons such as disease-related criteria mentioned in the GOLD report.[1] GPs consider comorbidity as an important part of COPD management, including referring patients to a PT. This is a relevant finding, since it is apparent that COPD clinicians should focus their attention not only on the management of COPD itself, but also on the investigation and management of COPD comorbidities.[30]

For physical therapists it is important to have insight into the phenotype of COPD patients who receive PT in terms of tailoring their clinical reasoning and treatment. This study showed that PTs, treating patients with COPD, cope with a patient population that has a relatively higher burden of disease compared to the patient population treated by a GP only. This insight is also necessary to improve COPD care workflows in

primary care in order to achieve proactive maintenance instead of acute rescue in COPD management.[31]

Patients may not seek medical attention until their symptoms become troublesome and persistent and significant respiratory impairment and comorbidities are present.[32] The more severe and complex patient population in the PT practice may be one of the reasons that PTs treat patients with COPD for long-term periods. Studies with longterm exercise programmes for patients with COPD generally achieve more favourable results regarding functional exercise capacity, skeletal muscle function, and healthrelated quality of life.[33] Although long-term exercise programmes are more expensive and take more effort for patients, neither health care insurance companies nor patients are well served by programmes that yield only modest benefit.[33]

Health care insurance companies should bear in mind the existence of phenotypic variations in their target population before comparing and judging treatment results across different primary care settings. Patients with COPD who are treated in PT practices are more complex and may need longer treatment because of their higher burden of disease (more exacerbations, more comorbidity, and lower quality of life). Moreover, health care insurers better not base the reimbursement for PT in COPD solely on the degree of airway obstruction (GOLD stage). Parameters that define the burden of disease and those that can be improved by PT (as part of pulmonary rehabilitation) should be taken into account to determine reimbursement policy. Exacerbation frequency,[34,35] limitations in daily activities,[35-37] and comorbidities, but not necessarily airway obstruction,[38] should be considered as criteria for PT reimbursement.[39]

From the patients' perspective, it seems favourable to be treated by a PT earlier in the disease process, which can yield favourable results like higher functional exercise capacity (walk distance), more muscle strength, quality of live (mastery), and daily physical activity (steps).[40] Referral for PT should not be delayed until their activity rate has dropped below threshold (international standard for physical activity) and their burden of disease is high enough (e.g., only patients with a forced expiratory volume in one second (FEV_1) of 50% of the predicted or higher are eligible for PT reimbursement in The Netherlands). It is important to assess and encourage physical activity in the earliest stages of COPD in order to maintain a physical activity level that is as high as possible, as this is associated with better prognosis.[2]

Limitations of the study

The response rate in this study was 35%. Compared to studies that used paper-based questionnaires that reached response rates within 33-75%,[41] our response rate can be considered relatively low. Response rates are probably more dependent on the population sampled than on any other factor.[42] The questionnaire was combined with multiple questions about smoking for the benefit of another study. The number of

patients with COPD who did not want to fill out these specific questions may have reduced the response rate. Since we are unable to compare the patient characteristics of the nonrespondents with the respondents, it is important that our 35% is a representative sample of the base population.[41] The distribution of GOLD stages in this study is comparable with population-based samples mentioned in international literature.[43] The percentages of the comorbidities present in our study correspond relatively well with other COPD populations.[1,44] The number of exacerbations is slightly higher than the populations mentioned by the Global Initiative for Chronic Obstructive Lung Disease, whereas the number of hospitalisations is similar per GOLD stage.[1] The respondent characteristics in this study approximate the characteristics of the COPD population described in the literature. Nevertheless, the statistical significance of the specific differences between the subpopulations in this study needs to be interpreted with care as the external validity can be compromised.[45]

Due to the transversal study design, no causal effect can be assured for the influence of other referral criteria on the actual referral by GPs. However, the aim of this study was to reveal any differences in phenotypes between patients with COPD treated by PT versus GP only, and this was answered with the present study design. The demonstrated higher burden of disease can be seen as a reason for referral for PT. Indeed, it is less likely that a higher burden of disease emerges as a consequence of PT, since PT has shown its effect on reduced hospital admission and mortality and improved health-related quality of life in COPD in other studies.[35] The higher burden of disease in the group treated by GP combined with PT was accompanied by the remarkable lower smoking rate and higher physical activity rate. It is possible that the physical activity rate was increased after referral for PT and not vice versa. Some studies showed a significant increase in daily physical activity after pulmonary rehabilitation; however other studies did not find an increase in the level of physical activity.[46] Moreover, once or twice a week guided therapy for COPD (which includes at least 30 minutes of moderate exercise) will not necessarily increase the patient reported physical activity rate per week to cross the inactivity threshold of the physical activity standard.

Another limitation might be the use of questionnaires, introducing potentially social desirable answers. But patient reported outcome measures cannot be left out when determining differences between patients' burdens of disease in primary care. It has been shown that perceptions of limitations and reported limitations are a stronger predictor of behaviour or disease severity than objective measures of severity.[16,18]

CONCLUSION

General practitioners treat inactive patients with COPD who are not referred to or treated by a PT. Inactive patients treated by a GP combined with a PT differ significantly from those treated by a GP only. The COPD patient population in PT practices showed a higher burden of disease, regarding higher exacerbations rates, more vascular comorbidity, more severe airway obstruction, worse symptoms, more limitations in daily activity, and, consequently, lower health perception or health status. Besides the specified inactivity criterion in GP guidelines, these factors may play a role in the referral for physical therapy by a GP. These observations have implications for clinical expectations regarding therapy outcomes, for the way health care reimbursement for PT is organised and for generalizability of study results in future research.

AKNOWLEDGEMENTS

The authors thank the collaboration of ten multidisciplinary primary healthcare centres (collaboration “SGE”) in Eindhoven and all questionnaire respondents for their cooperation to collect the data for this study. The authors thank the taskforce members of the research programme “Designing Optimal Interventions in Physical Therapy” (DO-IT), a national cooperation of four universities in Netherlands, for their contribution to the conception of the study. This study was financially supported by the Dutch Scientific College of Physiotherapy (WCF) of the Royal Dutch Society for Physical Therapy (KNGF).

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