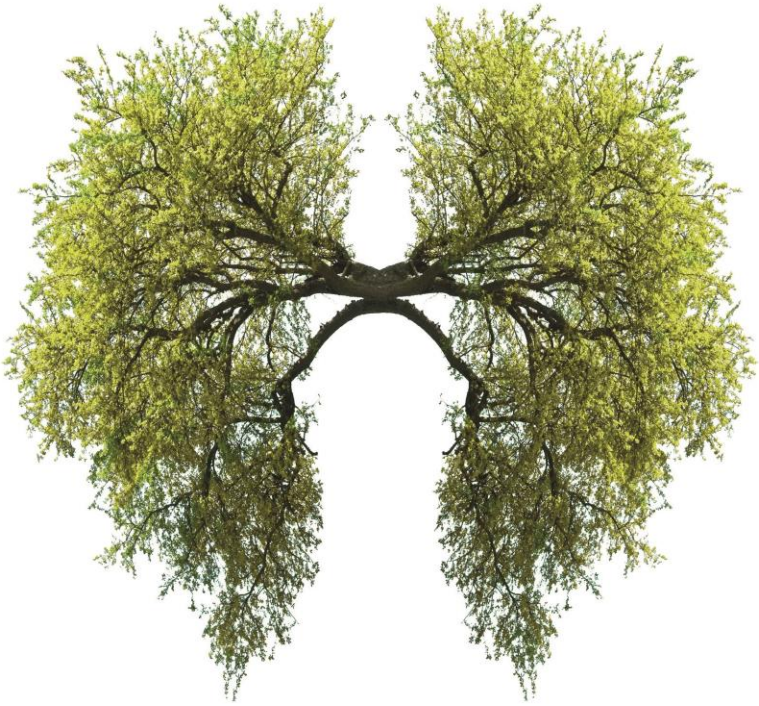
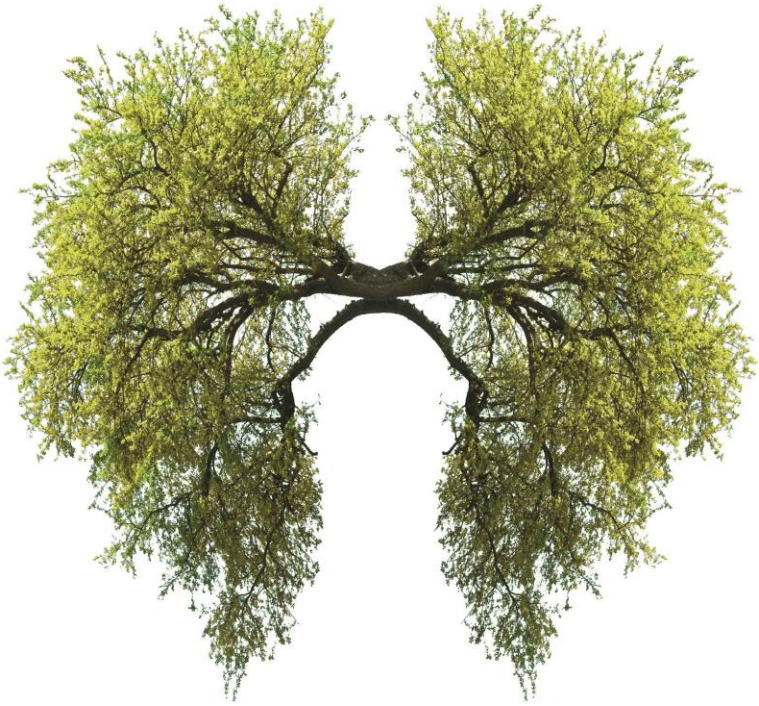
PART 4



Physical therapy to reduce COPD exacerbations

CHAPTER 7



Exacerbations in patients with chronic obstructive pulmonary disease receiving physical therapy: a cohort-nested randomised controlled trial

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BMC Pulmonary Medicine 2014;14:71

ABSTRACT

Background

Physical exercise training aims at reducing disease-specific impairments and improving quality of life in patients with chronic obstructive pulmonary disease (COPD). COPD exacerbations in particular negatively impact COPD progression. Physical therapy intervention seems indicated to influence exacerbations and their consequences. However, information on the effect of physical therapy on exacerbation occurrence is scarce. This study aims to investigate the potential of a protocol-directed physical therapy programme as a means to prevent or postpone exacerbations, to shorten the duration or to decrease the severity of exacerbations in patients with COPD who have recently experienced an exacerbation. Besides, this study focuses on the effect of protocol-directed physical therapy on health status and quality of life and on costeffectiveness and cost-utility in patients with COPD who have recently experienced an exacerbation.

Methods/Design

A prospective cohort of 300 COPD patients in all GOLD stages will be constructed. Patients will receive usual multidisciplinary COPD care including guideline-directed physical therapy. Patients in this cohort who have GOLD stage 2 to 4 (post-bronchodilator FEV_1/FVC<0.7 and FEV1<80% of predicted), who receive reimbursement by health insurance companies for physical therapy (post-bronchodilator Tiffeneau-index <0.6) and who experience a COPD exacerbation will be asked within 56 days to participate in a cohort-nested prospective randomised controlled trial (RCT). In this RCT, the intervention group will receive a strict physical therapy programme for patients with COPD. This protocol-directed physical therapy (pdPT) will be compared to a control group that will receive sham-treatment, meaning no or very low-intensity exercise training (ST). An economic evaluation will be embedded in the RCT. Anthropometric measurements, comorbidities, smoking, functional exercise capacity, peripheral muscle strength, physical activity level, health related quality of life, patients' perceived benefit, physical therapy compliance, motivation level, level of effective mucus clearance, exacerbation symptoms and health care contacts due to COPD will be recorded. Follow-up measurements are scheduled at 3 and 6 weeks, 3, 6, 12 and 24 months after inclusion.

Discussion

Ways to minimise potential problems regarding the execution of this study will be discussed.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is currently defined as "a common preventable and treatable disease, characterised 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 gasses. Exacerbations and comorbidities contribute to the overall severity in individual patients".[1] The World Health Organisation (WHO) lists COPD as the tenth most prevalent disease worldwide and the fourth most common cause of death in the world, responsible for 5% of overall mortality.[2] Due to the ageing population, expanding smoking behaviour, earlier diagnosis of COPD and reduced mortality from other common causes of death, the total number of people with COPD will increase in the near future. This will rank COPD fifth worldwide in burden of disease by 2020.[1]

Common clinical pulmonary manifestations that can be seen in COPD patients are dyspnoea with chronic cough, sputum production and recurrent respiratory infections. Additionally, with disease progression significant extrapulmonary systemic effects can be observed in patients, especially in patients with moderate to severe airway obstruction: skeletal muscle dysfunction and weakness, nutritional abnormalities and weight loss.[1,3] Nowadays, systemic effects of COPD are acknowledged as an important characteristic of the disease, which contribute significantly to decreased exercise capacity, decreased health status, reduced health related quality of life (HRQL), more utilisation of health care resources and increased mortality.[3-5]

The impact of COPD exacerbations

The definition of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) explicitly mentions COPD exacerbations as an enormous burden for patients[1] and health care systems.[6] Exacerbations are 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".[1,7] They are mostly precipitated by an infectious systemic inflammation of the upper respiratory tract and the tracheobronchial tree.[1]

Since exacerbations are a significant cause of morbidity (e.g. acute muscle deconditioning and muscle weakness), hospital admissions, impaired health status, impaired quality of life and even death in patients,[8-10] prevention is indicated. A relatively small percentage of patients (10%) experiencing frequent exacerbations

account for over 70% of all medical costs due to COPD.[6] A study of Pitta et al. (2006) showed that COPD patients tend to be severely inactive during and after an exacerbation; which is worrying since there seems to be a strong association between physical inactivity in patients who recently exacerbated and an elevated risk of (re)hospitalisation due to a COPD exacerbation.[11,12] It appears that patients with recurrent exacerbations show a more rapid decline in their physical activity level than stable patients and their functional capacity gradually decreases faster over time.[11] Besides, their more pronounced skeletal muscle weakness and decreased six-minute walk distance (6MWD, a measure of functional exercise capacity), are risk factors for future exacerbations and higher mortality.[9,13] Consequently, unstable patients, who frequently experience exacerbations, enter a downward spiral of inactivity and exacerbations. Hence, adequate management of exacerbation (prevention) in patients is considered worldwide as one of the main goals in controlling COPD.[1]

Although medical treatment modalities for COPD have improved, there is still no pharmacological therapy available that reduces the progression of the disease.[4] Though, patients with COPD, irrespective of disease stage, have shown to benefit from exercise programmes[12] resulting in improved exercise performance and health status.[4,5,14-17]

Physical exercise training in COPD

Evidence, to support the biological plausibility of the positive effects of physical exercise training on COPD, points towards longer high-intensity exercise training programmes. High-intensity exercise training has shown to increase exercise tolerance.[18,19] Firstly, exercise training improves muscle oxidative capacity and oxygen recovery kinetics in patients with COPD.[20] Secondly, patients with COPD who experience lactic acidosis during exercise can attain physiologic training responses from a physical exercise training programme.[21,22] Exercise performance can be improved by reducing the ventilatory requirement for a certain activity level. As the bioenergetics of skeletal muscle improve, blood lactate levels are reduced at a given level of exercise; thereby decreasing the amount of non-metabolic carbon dioxide (CO_2) that is produced by the bicarbonate buffering system.[12,21] Since lactic acid stimulates ventilation, decreasing lactate production during exercise can be very helpful for patients with COPD. Physical exercise training, in addition to optimal bronchodilatation, can reduce breathing frequency during exercise and consequently lower the degree of dynamic lung hyperinflation that many patients with severe COPD develop.[22,23] In turn, decreased hyperinflation may mediate improvement in

exercise endurance by delaying the attainment of a critically high inspiratory lung volume.[22,23] Moreover, high-intensity exercise training, engendering high levels of blood lactate, are more effective than training work rates eliciting low lactate levels.[21] Although measurable physiological changes may occur within weeks, behavioural changes may require longer time periods and may be the reason that greater effects were shown in long-term exercise programmes.[19] In conclusion, extensive physical exercise training is beneficial in patients with COPD.

Physical exercise training to reduce COPD exacerbation frequency, duration or severity

Patients with COPD often experience sudden worsening of symptoms, i.e. exacerbations. Previous studies already demonstrated that physical exercise training (the component that has shown to provide the most benefit of pulmonary rehabilitation programmes)[1] has important benefits for patients, such as improved exercise capacity and HRQL.[9,15,24] However, the effect of pulmonary rehabilitation and physical exercise training on the occurrence of exacerbations is less clear.[4,19,25,26] Observational studies demonstrated that patients who perform regular physical activity have a reduced risk of hospital admission due to COPD and decreased all-cause and respiratory mortality,[12,27,28] but neither of these outcomes are a substitute for reduction of exacerbation frequency, duration or severity. The factors determining utilisation of health care resources in patients with COPD are poorly understood.[29] Few studies reported significantly fewer exacerbations after a pulmonary rehabilitation programme (including physical exercise training).[30,31] Reduction of exacerbations may be at least one of the factors explaining the reduction in health care utilisations as reported in observational studies. Moreover, a recent study suggested that an acute bout of exercise resulted in a reduction in sputum proinflammatory cytokines, suggesting some anti-inflammatory effect of exercise in the airways of patients with COPD.[32] Based on these few findings it is plausible to hypothesise that physical exercise training for patients with COPD may result in fewer exacerbations, or at least in less severe exacerbations, meaning exacerbations with a shorter duration or exacerbations without the necessity for hospital admission.

Prevention of exacerbations by means of physical exercise training would fit the prime management goal for COPD.[27] Based on expert's opinion, it was stated that teaching patients how to recover quickly from an exacerbation will probably minimise the risk for relapse and improve long-term outcome.[26] Exercise training improves recovery in patients with COPD after an acute exacerbation.[33] Also, from previous studies it has been shown that especially early pulmonary rehabilitation (including physical therapy) after an acute

exacerbation is most likely to result in clinically relevant improvements in functional exercise capacity and health-related quality of life.[5,16] Puhan et al. (2011) found in nine small trials of moderate methodological quality that effects of pulmonary rehabilitation programmes immediately after an acute COPD exacerbation were visible when at least physical exercise was included.[24] However, they also concluded that more studies are needed to further investigate the role of pulmonary rehabilitation after an acute exacerbation and its potential to reduce costs.[24,34] Evidence based physical exercise training and advice on physical activity can be delivered by physical therapists that follow evidence based guidelines for physical therapy in COPD patients, such as the guideline COPD developed by the Royal Dutch Society for Physical Therapy (KNGF).[35] This study protocol hypothesis that early protocol-directed physical therapy for patients with COPD may reduce COPD exacerbation frequency, duration or severity.

METHODS/DESIGN

Study aim

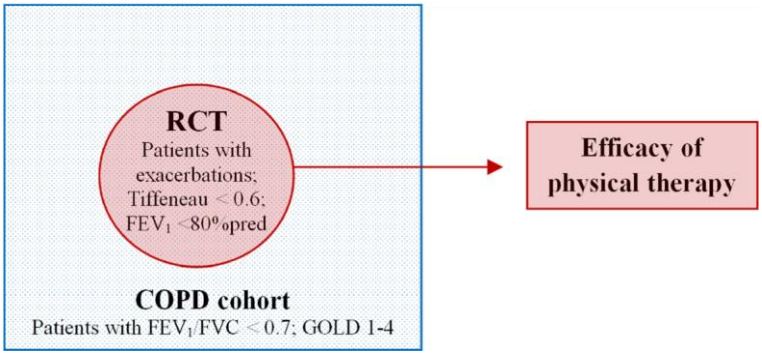
The aim of this study is to assess the clinical effectiveness, cost-effectiveness and costutility of early protocol-directed physical therapy for patients with COPD on exacerbations (frequency, duration and severity), health status and quality of life in patients who have recently experienced a COPD exacerbation.

Study design

A cohort-nested, prospective, randomised controlled trial (cohort-nested RCT) will be conducted. This means that a RCT will be embedded within a COPD cohort (Figure 7.1). The cohort will consist of COPD patients who receive usual multidisciplinary COPD care and guideline-directed physical therapy (gdPT). The cohort will serve as an optimal recruitment population for the RCT to show the surpassing importance of physical therapy interventions on exacerbations. Therefore, a RCT that holds a large contrast of protocol-directed physical therapy (pdPT) versus sham treatment (ST) will be constructed. This means that when patients from the COPD cohort report an exacerbation, with an occurrence no longer than 56 days ago (a trade-off between threshold values of 35–91 days in which the majority of exacerbations have returned to baseline[36]), they are either randomised to the experimental group (protocol-directed physical therapy (pdPT)) or the control group (sham treatment (ST)). This RCT will be used to study effectiveness of physical therapy in addition to an economic evaluation. The ethics committee of Maastricht University has approved the study protocol, procedures and informed consent (NL28718.068.09).

Study population

The study population consists of patients who are treated by COPD-specialised physical therapists, after referral by a general practitioner (GP) or pulmonologist. Physical therapy practices, GPs and pulmonologists, in southern districts of The Netherlands, who are willing to participate in the study, will be recruited. Once a patient is referred to a participating physical therapy practice (with post-bronchodilator $FEV_1/FVC<0.7$, GOLD 1−4), the patient will be asked to participate in the COPD cohort study. Patients in the cohort are monitored for health outcomes and exacerbation occurrence. Participants for the RCT will be recruited within the cohort by physical therapists, as soon a patient suffers from an exacerbation. Additionally, advertisements in local papers in southern regions of The Netherlands are used to reach potential COPD patients for the RCT who were missed out on inclusion with the former recruitment method. Those patients who are reached through advertising and presenting with an exacerbation will be recruited for the RCT by the researcher, while the mechanisms for alert and continuous trial recruitment are automatically organized within the cohort. By means of this unique cohort-nested RCT design (Figure 7.1), the likelihood that patients with a COPD exacerbation will be picked up is higher. A flowchart of the RCT is presented in Figure 7.2.



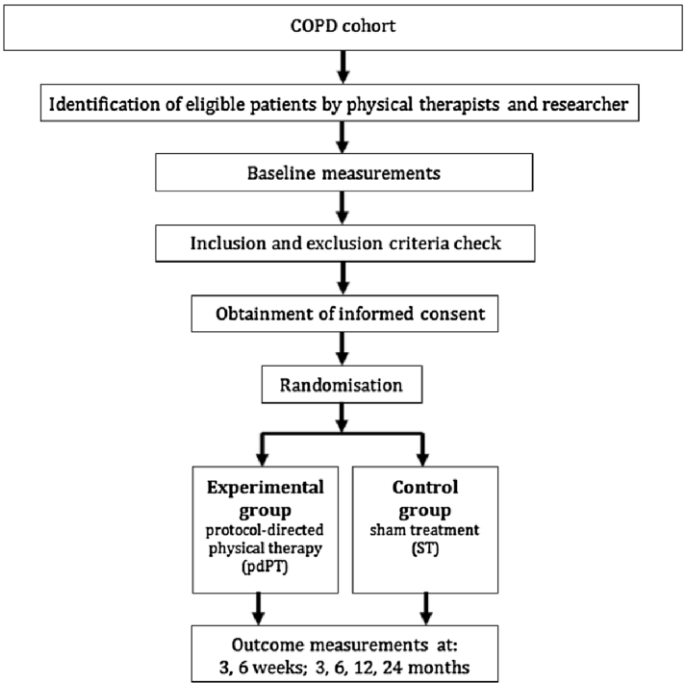
Abbreviations: COPD = Chronic Obstructive Pulmonary Disease, RCT = Randomised Controlled Trial, Tiffeneau<0.6 = Tiffeneau index (FEV_1/VC)<0.6*, FEV_1=Forced Expiratory Volume in one second*, FVC=Forced Vital Capacity*, GOLD I = mild COPD, $FEV_1/FVC<0.7$ and FEV1≥80% of predicted*, GOLD II = moderate COPD, $FEV_1/FVC<0.7$ and 50%≤FEV_1<80% of predicted*, GOLD III=severe COPD, $FEV_1/FVC<0.7$ and 30%≤FEV_1<50% of predicted*, GOLD 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. *All lung functions are post-bronchodilator values.

Figure 7.1 Framework of the study: a cohort-nested, prospective, randomised controlled trial.

The following inclusion criteria will be checked during the eligibility screening of patients for the RCT: a GP/pulmonologist diagnosed COPD in GOLD stage 2, 3 or 4 (supported by a post-bronchodilator $FEV_1/FVC<0.7$ and $FEV_1<80\%$ of predicted); eligible for reimbursement by health insurance companies for physical therapy (postbronchodilator Tiffeneau-index <0.6); experienced an COPD exacerbations in the past 56 days (defined as: unscheduled visit to their GP/pulmonologist or hospitalisation and possibly receiving a course of antibiotics and/or prednisone); having an adequate and optimal medication (inhalation) regimen by their referring physician; willing to sign informed consent before randomisation; competent enough to speak and understand the Dutch language; above 18 years of age.

Patients who meet the following criteria will be excluded from the RCT: suffering from significant exercise limitations or comorbidities that would prevent a patient from following the required intervention in this study; and expected to be lost for follow-up (for example because of a planned change of residency).

All patients entering the cohort have to give informed consent on the following two levels, whereas patients entering the RCT have to give informed consent on three levels: (1) oral consent to exchange patient information between physical therapists and other related health care providers (usual physical therapy procedure); (2) oral consent to participation in the COPD cohort (registration and use of data for research purposes); and (3) written consent to participate in the RCT, after experiencing an acute exacerbation.



Abbreviations: COPD = Chronic Obstructive Pulmonary Disease, pdPT = protocol-directed physical therapy, ST = sham-treatment, including no or very low-intensity exercise training.

Figure 7.2 Flowchart of the RCT.

Size of the study population

For the cohort study 300 patients with COPD will be recruited. This number is based on the calculated sample size for the RCT part of the study. The sample size calculation for this RCT is based on the identification of a minimal relevant clinical difference in exacerbation frequency between the experimental and the control group. The difference in exacerbation rate is expected to be 22% (based on exacerbation rates found in previous studies with rehabilitation programmes).[37,38] The probability that the study will detect a treatment difference is 80% at a two-sided 5% significance level. This is based on the assumption that the intervention period will be 12 months, the follow-

up period will be 24 months and the ratio control subjects to intervention subjects is 1:1. A sample size calculation for comparing event rates between two independent groups is used, resulting in 79 participants per group.[39,40] Assuming outcome data will be analysed prospectively and considering a drop-out rate of 20%, 100 patients per group will be needed in this two treatment parallel-design study.

Randomisation and blinding

After taking baseline measurements and eligibility screening within 56 days after the start of the past exacerbation, informed consent is obtained and stratified block randomisation will take place (Figure 7.2). Pre-stratification will be applied for exacerbation severity and GOLD stage (six levels in total), since both factors are suspected to influence treatment outcome. Therewith, the influence of selection bias for severity of the disease on group configuration or comparability between groups may be minimized. The patients will be randomly assigned to the experimental group or the control group in a 1:1 ratio. The concealed randomisation procedure will be performed by a blinded, independent research assistant using a computerised system. A block-randomisation will be used with blocks of size four, six or eight, with random block sequences. A computerised system will refer the patients to a group, after which a blinded, independent research assistant will notify the treating physical therapist after receiving instructions on treatment group allocation through computer generated random number tables.

In this RCT full blinding of the patients and physical therapists is not feasible. However, Hawthorne effects are non-differential, since patients in the experimental group as well as patients in the control group will get attention from their physical therapist. Both groups receive periodic questionnaires and measurement sessions, avoiding nonrandom effect optimisation. Several measures are taken to avoid bias due to blinding issues. Although patients will be aware of the existence of two treatment arms, they are not informed about the exact content of the other treatment arm (e.g. determining intensity) to prevent influence on outcomes. The control group will be assessed at the same time intervals as the experimental group by trained physical therapists that do not assess the patients in the experimental group at the same time. The researcher is fully blinded, because all outcome measures are quantified by the patients and physical therapists. Physical therapists are blinded for a number of outcomes measurements (questionnaires CCQ, CRQ-SR, GPE, EQ-5D, DS14 and physical activity level), since part of the data that are provided by the patient alone and will be captured through an electronic patient record system. Moreover, a number of

important objective outcomes (exacerbation frequency, duration and severity, mechanically assessed physical activity level and cost diaries) are less liable to patient manipulation in order to please their physical therapist, as these outcomes are directly collected by the researcher.

Cohort

All participants in the cohort receive usual multidisciplinary COPD care including guideline-directed physical therapy. In The Netherlands usual COPD care is given by a pulmonologist and/or a GP. This usual COPD care entails lung function testing, medication prescription for COPD and counselling, including education about the disease, symptoms and risks and tailor-made advice, which basically comes down to two major aspects; stop smoking and increase physical activity in everyday life.[41] In the light of the latter, all patients in the cohort are referred for usual physical therapy and physical activity advice. Usual physical therapy in The Netherlands is guideline-directed physical therapy (gdPT), provided by registered physical therapists and based on the KNFG physical therapy guidelines for COPD.[35] These guidelines provides assistance for applying physical therapy intervention (diagnosis and treatment) in COPD patients coping with impairments in mucus clearance, pulmonary function, muscle function and exercise capacity, and with limited physical activities due to dyspnoea or exercise intolerance. In the guidelines the effectiveness of several treatment modalities (specifically exercise training, breathing exercises, peripheral and respiratory muscle training) was reported and evidence based recommendations for the application of these modalities in physical therapy programmes were made. Moreover, disease management strategies are integrated. Short-term goals incorporate improvement of patient's knowledge, self-management 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.[35] Long-term goals entail improvement or preservation of disease related quality of life. Physical therapists are free to compile a patient-centred programme at one's professional discretion, within the limitations of the guideline. Hence, frequency of the guideline-directed physical therapy for COPD in The Netherlands varies; patients visit their physical therapist generally one to three times a week, for one hour, ranging from one-time consultation to multiple consultations during 3–12 months, depending on disease severity (based on usual care given in participating physical therapy practices) (Table 7.1).

Intervention	*Content*	*Intensity*	*Frequency*	*Start*
Guideline-directed physical therapy (gdPT) A programme made by individual PTs, within the limitations of the KNFG physical therapy guideline for COPD (usual care)	One or more of: Exercise training, peripheral muscle strength training, respiratory muscle training, breathing exercises, electrical muscle stimulation, physical activity in daily life homework	Ranging on the full intensity scale	On average: 30 minutes to 1 hour 1 to 3 times a week During 3 months to multiple years	
Protocol-directed physical therapy (pdPT) A complete programme by protocol, according to the KNGF physical therapy guideline for COPD, but with strict conditions	Both exercise training and peripheral muscle strength training When indicated: respiratory muscle training, breathing exercises, electrical muscle stimulation Always: physical activity in daily life homework	Endurance/interval training ≥60% of sub maximum, muscle strength training ≥80% of maximum, always: borg-scale ≥5	Minimal: 1 hour Twice a week During 12 months	Early PT: starting within 56 days after an acute exacerbation
Sham-treatment (ST) No physical therapy Or	One-time consultation: advice to be physically active in daily life		Maximal: 30 minutes Once a week	
Very low-intensity exercise training	Exercise training only	Endurance/interval training ≤15% of sub maximum or borg-scale ≤2	During 12 months	

Table 7.1 Contrasts between RCT experimental and control group and cohort.

	Cohort	RCT Experimental group	RCT control group

Abbreviations: RCT = randomised controlled trail, COPD = Chronic Obstructive Pulmonary Disease, KNGF = the Dutch Society for Physical Therapy.

Randomised controlled trial

As patients enter the RCT, after experiencing a COPD exacerbation, they may be assigned to either the experimental group or control group. Contrasts between the experimental group, control group and the cohort, based on content, intensity, frequency and timing, are displayed in Table 7.1.

Experimental group

Patients in the experimental group receive protocol-directed physical therapy (pdPT). The content of the pdPT is based on the on the KNGF physical therapy guidelines for COPD, like the guideline-directed physical therapy in the cohort.[35] However, in the RCT the physical therapy follows a strict protocol. The therapy specifically concerns early physical therapy, starting within 56 days after an acute COPD exacerbation. Patients in the experimental group receive a programme of one hour, twice a week for one year. The programme includes high-intensity exercise training, which entails endurance and/or interval training with an intensity of 60% or higher of (sub) maximum physical exertion, based on the results of a maximal cardiopulmonary exercise test (CPET) and six-minute walk test. In addition, ratings of perceived exertion and dyspnoea of five or higher on the modified Borg-scale (0–10) are used to tailor exercise intensity.[42] Peripheral muscle strength training is provided (a programme combining upper and lower extremities) with an intensity of 80% or higher of maximum physical exertion, based on the results of one-repetition maximum tests or handheld dynamometer measurements. Again, ratings of perceived exertion and dyspnoea of five or higher on the modified Borg-scale are used to adjust exercise intensity.[9] When indicated, the programme includes respiratory muscle training, breathing exercises and electrical muscle stimulation. In addition, much emphasis is given to the assessment and treatment of physical inactivity in daily life. Patients are asked to increase their total physical activity on their own. At least 30 minutes of moderately intense physical activity on at least five days a week is the current recommended level. All visits for treatment and all advice for home training are part of standard procedure, following the KNGF guideline physical therapy for COPD and the Dutch Standard for Healthy Exercise (NNGB).[35,43] Published Supplement 7.1 shows the intervention in more detail according to a framework based on the International Classification of Functioning, Disability and Health (ICF).[44]

Control group

Patients in the control group receive sham-treatment (ST), which entails no or very low-intensity exercise training, for one year. The latter applies only if the participant in the control group insists on training in a physical therapy practice. The very lowintensity exercise training is limited to a maximum of 30 minutes once a week, with an intensity of 15% or lower of (sub) maximum physical exertion, based on the results of a maximal CPET and six-minute walk test. In addition, ratings of perceived exertion and dyspnoea of two or lower on the modified Borg-scale (0–10) are used to tailor exercise intensity.[42] There will be no further peripheral muscle strength training, respiratory muscle training, breathing exercises nor electrical muscle stimulation.[35] Furthermore, patients will be advised to do at least 30 minutes moderately intense physical activity on their own for at least five days a week according to the physical activity norm.[43]

Physical therapists

All interventions are carried out in primary care physical therapy practices. Registered physical therapists, experienced in COPD care, who are willing to participate in the study, will be recruited through local physical therapy networks in The Netherlands that already have mapped the specialised skills of these health professionals and registered who treats a sufficient number of patients with COPD (with a minimum of 5-10 per week).

Therapists will be invited to attend information/training sessions given by the research group and related COPD experts. Information will be given about the aim and content of the cohort and RCT along with information about the necessary clinical measurements. Lectures will be given on the latest information on COPD and updates on the current COPD guidelines and on counselling (in line with the Dutch college of general practitioners (NHG) standard COPD). Furthermore, a COPD master class will be given to the network of participating physical therapists in cooperation with the Dutch Paramedical Institute (NPi).

Data collection

Participants will be monitored by physical therapists with the help of a high quality electronic patient record system that is COPD-specific and serves simultaneously as a research database for the experimental group as well as for the control group. Moreover, the system will be used by physical therapists as guidance for treatment of the experimental group, since the KNGF guidelines physical therapy for COPD is fully incorporated within this system (for example: an alert will be visible on the computer

screen when a patient's performance is below 80% of the predicted peripheral muscle strength or when FEV_1<50% and Medical Research Council dyspnoea score (MRC) ≥2 an advice to initiate multidisciplinary evaluation and rehabilitation is given).
Primary and secondary study-specific outcome measures will be assessed with the help of the COPD-specific record system. In addition, the system will contain information about the content of physical therapy, the duration of physical therapy, the total amount of physical therapy sessions, the duration per session, and the adherence to physical therapy.

Primary outcome measure

The primary outcome measure will be exacerbation frequency, calculated as the number of COPD exacerbations experienced by the patient in a post exacerbation period of two years. A COPD exacerbation will be identified as a sustained worsening of the patient's condition occurs from the stable state and beyond normal day-today variations that is acute in onset and may warrant additional treatment.[45] A recurrent exacerbation will be defined as a subsequent occurrence; exacerbations are assumed to be independent of each other. The follow-up period is twelve months (twenty-four months for the long-term outcome measurement) to overcome time confounding, since exacerbation frequency is seasonal and particularly related to influenza and other viral epidemics.[45]
In the cohort, exacerbations will be identified by means of an event-based approach, whereas in the RCT exacerbations will be identified by means of an event based approach (health care contact) and symptom based approach (clear increase of respiratory symptoms). Usual assessment of exacerbations is done by recording health care contacts. However, there are many underreported exacerbations in COPD patients when using this event based method.[46] On average, these underreported exacerbations have similar severities to reported exacerbations.[45] Therefore, increase of respiratory symptoms will also be recorded in the RCT. When measuring the appearance of exacerbations with these two methods, this trial is able to compare event based and symptoms based methods in relation to the primary and some of the secondary outcome measures.

1. Event based approach

The onset of an exacerbation will be the first day of an unscheduled health care contact with a GP/pulmonologist due to a COPD exacerbation and the start of additional medication intake or the first day of an unscheduled hospitalisation or emergency visit

to the hospital due to an exacerbation. The exacerbation lasts until the last day of this extra medication intake or until the last day of hospital admission.[45] To identify these events, physical therapists will monitor patients' reasons for absenteeism on physical therapy appointments and relapse in treatment (as an exacerbation might be the reason). In addition, records of health care contacts and additional medication use due to COPD are registered on patients' prospective daily diary cards. Overall, good compliance to register for instance symptoms, can be achieved using daily diaries in COPD.[47]

2. Symptom based approach

Respiratory symptoms will be monitored using prospective daily diary cards. In these diary cards patients have to report, according to Anthonisen et al. (1987), whether their major symptoms (breathlessness, sputum production, sputum colour) and minor symptoms (cough, wheeze, running nose, score throat, and fever (>38.5°C) were beyond normal.[7] Prospective diary card assessments are best recorded as changes from an agreed baseline, rather than absolute symptom severities. Comparable to the COPE-II study by Effing et al. (2009), at inclusion all patients will receive a 'what is normal for me' card, which describes their individual levels of major symptoms at baseline.[48] When patients experience no deterioration of any of the symptoms listed on the diary, they should check 'no change in symptoms'. When patients experience deterioration, they should check 'yes' and report on all symptoms in the diary whether the level of each symptom was 'normal', 'slightly increased', or 'clearly increased'.
The onset of an exacerbation will be defined as the first day of at least two consecutive days at which the patient checks 'clear increase' from baseline in two major symptoms or one major and one minor symptom. The day that an exacerbation is resolved will be defined as the first day of: (1) three successive days that the patient has returned to his normal health state; or (2) seven consecutive days on which patients continuously reported no or only a 'slight increase' in symptoms, compared to baseline, with no fever or change in sputum colour.[7,48,49] Besides the daily diary card, symptoms during COPD exacerbations will also be recorded by the physical therapists, in order to receive additional information about the number and type of perceived symptoms and to add missing information to the daily diary cards in cooperation with the patient.

Secondary outcome measures

Exacerbation duration is defined as the duration of the medical intervention per occurrence and the number of days with clear increase of respiratory symptoms. For the event based approach: the duration of an exacerbation will be equal to the time of

the medical intervention.[45] For the symptom based approach: the duration of an exacerbation will be equal to the time between onset and resolution of exacerbation based on the above mentioned definitions.[7,48,49]

Furthermore, a distinction is made between various levels of exacerbation severity. For the event based approach, a scale for exacerbation severity is proposed, which distinguishes two levels of exacerbation severity: (1) mild/moderate and (2) severe. Level one exacerbations can be treated at home by means of a health care contact with a GP/pulmonologist and the start of additional (temporarily) medication intake (e.g. corticosteroids or antibiotics). Level two exacerbations require hospitalisation or an emergency visit to the hospital [45,46]. For the symptom based approach: the severity of an exacerbation day will be calculated with help of symptom scores. The major symptoms are scored as: normal = 0; small increase = 1; or clear increase = 2. The minor symptoms are scored 0, 0.5 and 1, respectively. Sputum colour will be scored as: normal = 0, different from normal = 2; and fever: no = 0, yes = 1. Adding all scores, results in a daily symptom score ranging from 0–11 points. When patients are admitted to the hospital for their COPD, a daily score of the maximum 11 points will be assigned.[7,48]

Generic health related quality of life (HRQL) of the patients will be assessed by means of the Euro-Qol (EQ-5D-3L). Disease-specific HRQL will be assessed with the Clinical COPD Questionnaire (CCQ) and the Chronic Respiratory Questionnaire – self reported (CRQ-SR). In addition, negative affectivity, social inhibition, and type D personality will be assessed by means of the DS14 questionnaire.

The level of dyspnoea (MRC), effective mucus clearance, physical activity in daily life and motivation will be assessed by standardised questions from the KNGF guidelines [35]. Furthermore, to estimate the patients' perceived benefit of the physical therapy, the Global Perceived Effect (GPE) will be scored by patients on a 9-point scale.[35] Objective assessment of physical activity in daily life will be done by means of an accelerometer-based activity monitor (Dynaport Move-Monitor).[50]

Height, weight, Body Mass Index (BMI) and Fat Free Mass (FFM) will be measured. The peripheral muscle strength of the patient will be measured as maximal voluntary isometric contraction (MVIC) of the dominant hand, shoulder abduction and knee extension (m. quadriceps), tested in standardised positions by means of the break method by a handheld dynamometer.[42,51] Functional exercise capacity is measured by the six-minute walk test (6MWT), in accordance with the guidelines by the American Thoracic Society.[52] If a straight floor-walking course of 30 metres is not available in the physical therapy practice, a course with a distance of 10 metres is the required

minimum.[35] Outcome is measured by total walking distance in metres (6MWD) and in percentage of the predicted value. Reference equations by Hill et al. (2011) will be applied to calculate the predicted value if a straight 30 metre walking course was used, whereas reference equations for a straight 10 metre walking course may be necessary to develop within this study, as no reference equations exist for this frequently used test layout.[53] During the walk test, perceived fatigue and dyspnoea will be measured on a modified Borg scale ranging from zero (nothing at all) to ten (very, very severe).[42] Transcutaneous oxygen saturation and pulse rate will be measured with a finger pulse oximeter (Onyx 9500).[52] The modified Get Up and Go test (mGUG) is used to measure basic functional mobility. The outcome is the time it takes a subject to stand up from a chair and walk a distance of 10 metres.[54] After the mGUG, perceived exertion is measured with the modified Borg scale.

Comorbidities of all participants will be recorded thoroughly, as well as smoking history (pack years and cessation moment) and physical therapy compliance (scored by the therapist as insufficient, moderate or good and scored whether comorbidity has any influence on this compliance), as being important potential confounders in this study. Number and type of adverse events will be registered during the one-year treatment period. After randomisation, patients are discouraged to participate in interventions other than those in the study (like hydrotherapy or drug studies) that may influence the outcome measures. When they still decide to participate in other interventions, these interventions will be registered during the study period.

Finally direct and indirect costs will be assessed with three-monthly retrospective questionnaires, including questions about health care contacts, medications use, residential status, occupational status, domestic care service and use of medical aids. The economic evaluation will be analysed from a societal perspective. This means that the most appropriate set of costs captured from the data, regardless of where the costs or benefits occur, will be applied.

Planning of outcome assessment

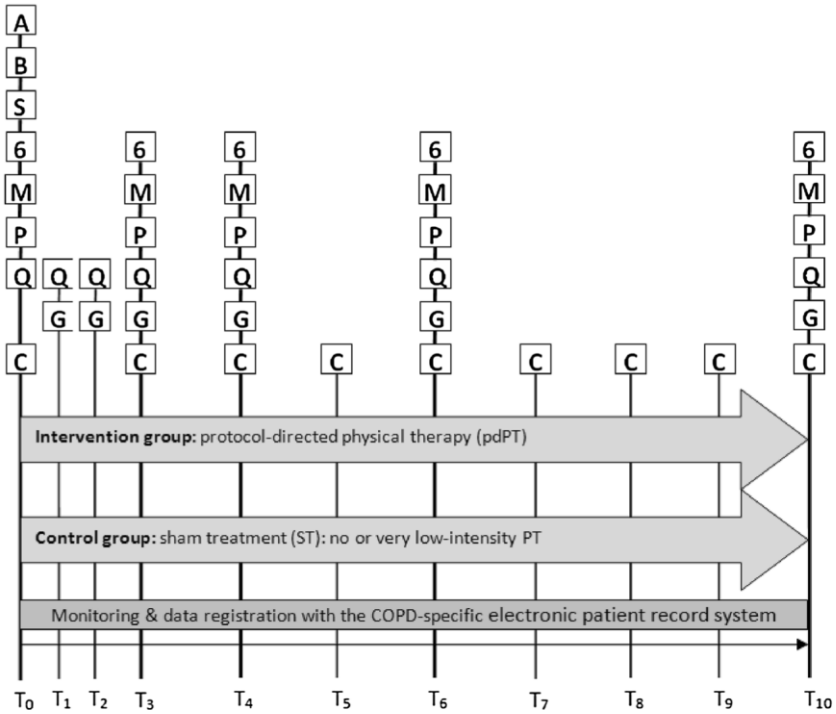
In all eligible patients, entering the cohort and the RCT, baseline assessment will be performed. In the baseline assessment, demographic variables, anthropometric data, healthcare/medical variables, lifestyle factors, health related quality of life and clinical status will be recorded of the participants.

The lung function of the patients is already assessed by the GP/pulmonologist or assistant, by means of pulmonary function tests, as part of standard procedure in patients with COPD. Forced expiratory volume in one second (FEV_1 (L)), forced vital

capacity (FVC (L), the FEV_1/FVC ratio and Tiffeneau-index (FEV_1/VC) are measured by means of post-bronchodilator spirometry and are known to the physical therapist in order to construct a tailored-made programme adjusted to the severity of the pulmonary component of the disease. The clinical status, maximal exercise capacity and physiological restrictions of the patients should in most cases have been assessed by a maximal CPET and communicated to the physical therapist in order to enable the physical therapist to construct a safe and tailored-made programme for the patient. If the clinical status of the patient in the RCT is not yet assessed in the hospital or rehabilitation clinic, the treating physical therapist will be asked to refer the patient for a maximal CPET to a sports medicine physician, who is contacted by the researcher. After the baseline visit, participants in the cohort will be assessed every three months for 12 months or longer. Participants from both the experimental and the control group in the RCT will be measured at three and six weeks, and three, six, twelve and twenty-four months during follow-up visits at the physical therapy practice for various outcome measures (Figure 7.3).

In the RCT, prospective daily diary cards are distributed every month for twenty-four consecutive months and are returned by the patient at the end of every month. The retrospective questionnaire on the use of health care is send to the patient once every three months for twenty-four consecutive months.

Time point	T_0	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}
Moment in time	Base-line	3 week	6 weeks	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months



Abbreviations: T0 = baseline measurement, T1-T10 = consecutive measurements in time after the baseline measurement, A = Anthropometric measures, B = Bicycle test results (maximal cardiopulmonary exercise test (CPET)), S = Spirometry results, 6 = 6MWT + Borg score and mGUG + Borg, M = peripheral muscle strength, P = physical activity in daily life with accelerometer, Q = CCQ*, CRQ-SR, EQ-5D*, DS14, MRC and level of effective mucus clearance, level of motivation, physical activity, physical therapy compliance*, C = questionnaire to assess direct and indirect costs, G = Global Perceived Effect*.
Measurement occasions are explained in the Table above the Figure. *The
only measurements on T1 and T2.

Figure 7.3 Planning of outcome measurements in the RCT. The diary cards are not included in the Figure, but they are used by the patient every day of every month until T6. In the cohort, the baseline measurement is followed by the same measurements as on T3 in the RCT and are repeated every three months for at least twelve consecutive months.

Data analysis

Clinical effectiveness

The descriptive characteristics are presented quantitatively as mean (±standard deviation) or median (5^{th} - 95^{th} percentile), depending on the data distribution, whenever the variable is continuous or as a percentage whenever the variable is dichotomous or categorical. Data will be analysed with SPSS-19. Assumptions accompanying the following statistical methods will be checked and all data analyses will be applied by a blinded analyst.

Data from the RCT will be analysed to examine intervention main effect on the counts for the primary outcome (exacerbation frequency) and the secondary outcomes. All exacerbations from each patient will be used as the dependent outcome to evaluate the effect of physical therapy at the end of the intervention (12 months) and follow-up (24 months). Measurement moments for secondary outcomes are baseline, three and six weeks, three, six, twelve and twenty-four weeks. The effects of the variable of primary interest, physical therapy (pdPT), will be analysed in a generalized linear model (GLM) for group (intervention vs. control) analysis of covariance with adapted regression for count data distribution. Analyses of secondary outcomes will be done with linear regression analysis and generalized linear models. Since exacerbation outcome in the RCT is measured with two methods, analyses will be based on the event-based approach, on the symptom-based approach and on a combination of both. Potential confounding by variables like, age, gender, GOLD stage, smoking, physical activity in daily life, exacerbation history, severity of latest exacerbation, and comorbidity, will be controlled for. Results from a 'per-protocol' and an 'intention-totreat' principle will be compared. At a minimal statistical power of 80%, p-values smaller than 0.05 will be considered as significant.

Economic evaluation

From the RCT data cost-effectiveness and a cost-utility of physical therapy in COPD patients experiencing exacerbations compared to usual care will be established using a one and two year time horizon.

A cost-effectiveness analysis will be performed, weighing incremental costs against the mean incremental effect in terms of quality of life based. For assessing patient outcome, the score of the disease specific quality of life measures CCQ and CRQ-SR will be used at the 12 months follow up moment. For this purpose, a societal perspective will be administered, indicating the relevance of direct medical, direct non-medical and

indirect costs, as adding measurement of indirect costs will provide a more comprehensive picture of the burden of exacerbations.[55] For defining the content of care 'consumed', out of pocket costs, lost productivity costs and direct non-medical costs for each patient in the RCT, resource use will be measured using patient questionnaires. These frequently used retrospective questionnaires will cover a three months retrospective period. Moreover, patients' daily diary cards will be assessed, to incorporate each exacerbation experienced by a patient that involves 'consumed' care. The costs of the experimental physical therapy will be assessed using micro-costing and time-and-motion techniques in several participating practices and patients' dossiers of the physical therapist will be assessed.
For the cost-utility analysis, quality adjusted life year (QALY) will be calculated based on the EuroQol questionnaire (EQ-5D-3L). The EQ-5D-3L is a generic quality instrument that will make it able to calculate utilities at each outcome measurement (on a 12 months' and 24 months' basis). Thus, societal cost will be used to calculate the incremental cost-effectiveness based on CCQ and CRQ-SR and to calculate the incremental costutility based on QALYs. Besides, the cost of the physical therapy intervention will be assessed against the incidence of exacerbation in both groups within the RCT.

Project time frame

The project in total will take five years. During the first three years of the project, physical therapy practices and COPD patients will be recruited. Patients in the cohort will be followed at least until the end of the project. Patients included in the RCT will be followed for two years by means of the COPD-specific electronic patient record system, while the treatment will be one year. The last year of the project is reserved for the processing and analysis of data, as well as the publication of results.

DISCUSSION

In this article the protocol of a cohort-nested randomised controlled trial is presented, concerning a study about the effect and cost-effectiveness of standardised physical therapy as a supportive measure to prevent or postpone future exacerbations, to shorten the duration or to decrease the severity of future exacerbations in COPD patients experiencing acute exacerbations. The focus on prevention of exacerbations by means of physical therapy fits one of the prime management goals for COPD, which

is 'reducing the frequency of hospitalisations due to exacerbations'.[1] It is expected that the outcomes of this study will provide useful information about the effects of physical therapy on exacerbations, which may alter the role of physical therapy in managing COPD in the future.

Healthcare utilisation is not an optimal substitute for exacerbation frequency, exacerbation duration and exacerbation severity, depending on many unrelated social factors and comorbidity. It is an outcome in its own right.[45] Therefore, not only will this event based approach be applied in this trial, also a symptom based approach will be used. Both approaches will be used separately and together and their influence on outcome will be compared during statistical analyses.

Bias and confounding

To assure a high quality treatment according to KNGF guidelines physical therapy for COPD, the participating physical therapists will be trained before the start of the study. It is obvious that physical therapists as well as patients cannot be fully blinded during this study, since both groups are aware of the treatment procedures. Moreover, due to practical reasons physical therapists perform some exercise measurements instead of the researcher. This can lead to subjective interpretations of the research findings. Therefore, participating physical therapists will be instructed to make correct use of the measurement instruments for standardisation. To minimise social desirability answering, patients are told that there are no right or wrong answers before filling out questionnaires. In order to minimize differential Hawthorne effects, all patients from the cohort, the intervention group and the control group in the RCT will be monitored very precisely in a standardised way on first signs of exacerbations and other outcome measurements. To minimise bias, research findings will be analysed by a blinded researcher.

Potential problems

Potential problems regarding the execution of this study are twofold. Because COPD is a complex disease the KNGF guidelines for physical therapy for COPD patients requires a lot of effort from participating physical therapists regarding patient assessment, apart from the general KNGF Guidelines on Reporting in Physical Therapy. Although the outcome measures in this study are very well connecting to the requirements of these guidelines, complete registration remains difficult and costs time, so problems may be expected regarding the full registration of COPD patients in this study.

Besides, patients who enter the RCT may be assigned to the control group, which may come with some problems. To include patients in the control group means physical therapists are only allowed to offer no or very low-intensity exercise training. Due to the lower frequency of treatments, participation in the RCT may be financially unattractive to the physical therapy practice and physical therapists. Moreover, there is a chance that patients in the intervention group of the RCT are doing much better compared to the control group.

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PUBLISHED SUPPLEMENT 7.1

Description of the main goals and content of the protocol-directed physical therapy intervention for a patient with COPD within the cohort-nested RCT, according to a framework based on the International Classification of Functioning, Disability and Health (ICF).[1]

Intervention protocol

Phase 1 (12 months, including individual adjustments to the programme regarding adjustment of treatment goal, type of exercises and intensity at least every 3 months)

General information:

Note: This physical therapy intervention is reserved to COPD-specialised physical therapists, meaning registered physical therapists who are experienced in COPD care, who acquired specialised skills through COPD education and who treat a sufficient number of patients with COPD (with a minimum of 5-10 per week).

- Physical therapy is part of respiratory rehabilitation.
- The physical therapy starts with history-taking and clinical examination and assessment of exercise performance, respiratory and peripheral muscle function, physical activity and quality of life to determine goals for physical therapy.
- After an exacerbation the patients is motivated to resume with the physical therapy sessions as soon as possible.
- The intervention is based on the latest Royal Dutch Society for Physical Therapy (KNGF) guideline for physical therapy in patients with COPD (2008). The objective of this guideline is to describe evidencebased physical therapy – with regard to effectiveness, efficiency and tailored care – for COPD patients with impairments in mucus clearance, pulmonary function, peripheral and respiratory muscle function, exercise capacity, and quality of life, and with physical activity limitations in daily life due to dyspnoea or exercise intolerance.

Intervention treatment goals:

The treatment goals[a] for the physical therapy interventions are: (1) to reduce dyspnoea; (2) to improve exercise capacity and physical activity; (3) to improve mucus clearance; (4) to improve knowledge, selfmanagement and self-efficacy. In this elaboration of the intervention the main focus of physical therapy is on reducing dyspnoea and improving exercise capacity.

Above treatment goals according to ICF-classification:

On the level of body functions:	For the treatment goals, the main focus is based on the most limiting factor of the exercise limitation:
b410 Heart functions (+ b460 sensations associated with cardiovascular functions) b440 Respiration functions (e.g. respiration rate, rhythm, depth) (+ b460 sensations associated with respiratory functions) b445 Respiratory muscle functions b740 Muscle endurance functions b152 Emotional functions (e.g. fear of activity, fear of dyspnoea, anxiety, depression)	1. Cardiocirculatory limitation 2. Ventilatory limitation 3. Oxygen transport limitation 4. Peripheral muscle weakness 5. Psychologic limitation

[a] The global treatment goals need to be individualised and formulated according to SMART-criteria

On the level of activities:	
d410 Changing basic body position d455 Moving around d460 Moving around in different locations d498 Mobility, other specified (carrying out daily routine, doing housework, dressing)	

NB: On the level of functions: if serious weight loss occurs in a patient (>10% in the past half year or 5%> in the past month) or if the patient experiences a COPD exacerbation, multidisciplinary consultation/referral may be indicated.

Exercises:
The protocol-directed physical therapy programme takes one hour, twice a week for one year. Since it is not possible to fully disentangle the effect of the exercises on the above mentioned levels of body functions, because COPD is a chronic disease with systemic effects, an individual exercise is not assigned specifically to an individual level of body function. However, depending on the most limiting factor(s) in functions: guided endurance training, interval training, muscle strength training, breathing exercises, body positioning, relaxation exercises, education, counselling or a combination will be provided.

- Cardiocirculatory: endurance training
- Ventilatory limitation or if oxygen transport in the lungs is disturbed: endurance training versus interval training: If hypoxemic / hypercapnic during exercising, than interval training. If walking on 70% of $Watt_{max}$ for at least ten minutes is possible, than endurance training, if not interval training.
- Consequently, if hyperinflation is present, than advises and exercises targeting body position and various breathing exercises (active expiration, slow and deep breathing, pursed lips breathing (PLB), diafragmal respiration).
- Consequently, if respiratory muscle weakness is present, than inspiratory muscle training (IMT)
- Peripheral muscle strength limitation: endurance / interval training and muscle (resistance) training of both upper and lower extremities and possibly electric muscle stimulation (NMES) in the case of serious decreased muscle strength.
- Psychologic limitation: relaxation therapy, education or counselling on physical activity (to enhance compliance and improve self-management skills) (For the behavioural component of physical therapy knowledge of behavioural change is necessary).

Settings:
Cardiorespiratory endurance / interval exercises:
Frequency: 2 x per week during therapy
Intensity: 60% ≥ of $Watt_{max}$ in maximal cardiopulmonary exercise test (CPET) or maximum walking speed in six-minute walk test and/or a score of 5 ≥ on the modified Borg scale (0-10) Duration: 20-60 minutes per session (depending on duration of other exercises).
Exercises examples: walking on a treadmill, walking on a cross trainer including arm movements, cycling or rowing on an ergometer.

Muscle strength and muscle endurance capacity:
Frequency: 2 x per week during therapy
Intensity: 80% ≥ of KgF or Nm and/or a score of 5 ≥ on the modified Borg scale (0-10)
Duration: 2 to 5 sets of 8 to 15 repetitions, with 30 seconds of rest between sets.
Main muscle (groups): quadriceps, hamstrings, leg/arm adductors, leg/arm abductors, biceps, triceps, deltoids, pectoralis major.
Exercises examples for upper extremities: lat pull down, upright rowing with a weight or theraband, vertical rowing with a pulley.
Exercises examples for lower extremities: knee extension, leg press, leg abduction/adduction with a pulley, dumbbell squat, sit to stand/chair squat, steps aerobic workout.

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Depending on the most limiting factor(s) in activity and participation: education and advice, guided endurance training, interval training and optimising posture, supplemental oxygen, counselling or a combination will be provided.

- Education and advice about risk factors and prognostic factors for COPD, course of the disease, exacerbations.
- Education, instruction and stimulation to be physically active in everyday life, apart from the activity in the physical therapy practice (e.g. time aspects, modalities – kind of exercise, frequency, and etcetera), and regarding use of aids. Meanwhile, feedback by means of questionnaires and accelerometer.
- Optimising body posture (e.g. during sitting/standing: forward leaning posture and spreading the knees, while keeping the spine relatively straight, placing hands on thighs or knees, and then bracing the upper arms and shoulders for more efficient use of the accessory breathing muscles, during the use of a 'rollator'
- (rolling walker)).
- When indicated: The use of supplemental oxygen during exercises (only on medical prescription). The use of short-acting bronchodilators before the therapy starts (only on medical prescription).
- When indicated: Specific education and counselling must be addressed or patient must be referred to a psychologist, when a psychological factor (e.g. lifestyle, coping strategies, social context, personality factors, fear of activity or dyspnoea) seems one of the most limiting factor during exercise (For the behavioural component of physical therapy knowledge of behavioural change is necessary).

Home exercises:
Perform at least 30 minutes of moderately intense physical activity (e.g. walking, cycling) on at least five days a week, according to the physical activity norm.

Phase 2 (12 months – 24 months follow-up period)

- After the 12 month-intervention the patient is free to decide to stop the physical therapy intervention or to continue or adjust the physical therapy programme in consultation with the physical therapist.
- The advice to be physically active in everyday life, according to the physical activity norm (perform on at least five days a week physical activity with moderate intensity for at least 30 minutes per activity), applies in every way

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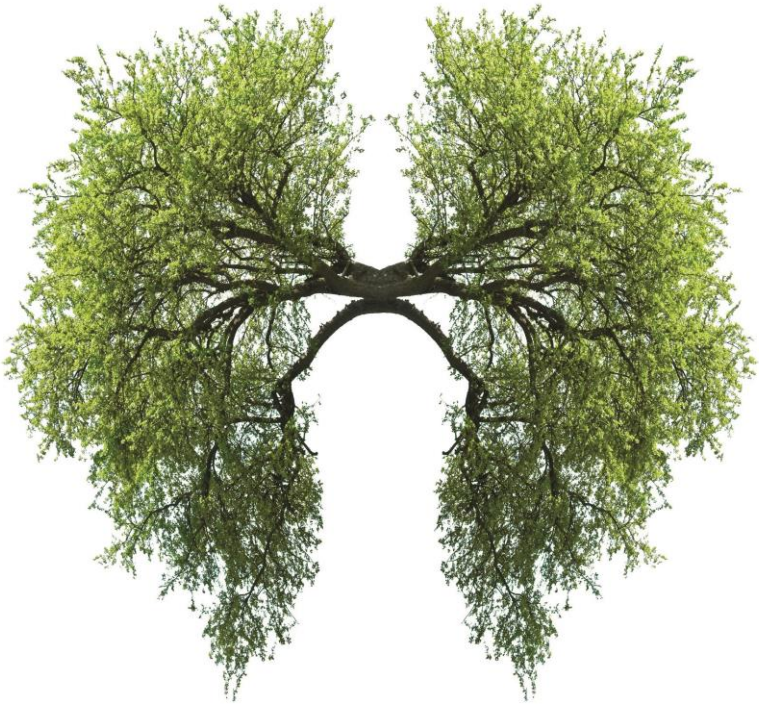
CHAPTER 8



Physical therapy reduces exacerbations in COPD: a randomised controlled trial

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Submitted

ABSTRACT

Introduction

This study investigates the potential of physical therapy, including intensive physical exercise training, to decrease exacerbation frequency, duration and severity in patients with chronic obstructive pulmonary disease (COPD) after an acute exacerbation.

Methods

A randomised controlled trial was conducted in primary care. Twenty-nine patients with COPD (GOLD-stage 2-4, age 45-81) who suffered an acute exacerbation were randomly placed into one of two groups: physical therapy intervention (high-intensity exercise training) or sham-treatment (very low-intensity exercise training). The primary outcome variable was exacerbation frequency, calculated as the number of COPD exacerbations. Exacerbations were identified by a *symptombased* approach (clear increase of respiratory symptoms) in addition to an *event-based* approach (health care contact). Secondary outcomes were exacerbation duration, exacerbation severity, quality of life, and exercise capacity.

Results

Ninety-four exacerbations were counted. Exacerbation frequency was significantly higher in the control group (6.15±1.82 counts) compared to the intervention group (1.17±1.27, p<0.001). Average exacerbation duration was shortened by 10 days, perceived exacerbations were 2.7 points less severe and exercise capacity and quality of life in the intervention group improved significantly relative to the control group.

Conclusion

Physical therapy, including high intensity exercise training after an acute exacerbation, thus reduced the frequency, duration and severity of exacerbations in patients with COPD.

INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) are important events in the course of the disease, negatively affecting symptoms, lung function and quality of life and increasing mortality.[1] A COPD exacerbation is defined as 'an acute event characterised by respiratory symptom worsening that is beyond normal day-to-day variations, leading to change in medication and potentially requiring hospitalisation.'[1] Prevention of COPD exacerbations is fundamental to COPD control.[1] Physical therapy, i.e. supervised physical exercise training in combination with breathing exercises, sputum clearance techniques and education, may favourably affect exacerbation frequency, duration and severity, and is considered to be the most beneficial component of pulmonary rehabilitation (PR) programmes.[1] High intensity exercise programmes (endurance and resistance training) result in improved skeletal muscle function, exercise capacity, health status and health-related quality of life,[2-5] in particular when administered soon after an acute COPD exacerbation.[5-7] Improvement in peripheral muscle strength and exercise capacity might serve as intermediate outcomes that eventually also influence exacerbation rates. However, whether PR, and in particular physical therapy, affects exacerbation rates remains uncertain.[4,5]

There is a biological explanation for a potential anti-inflammatory effect of exercise on the airways. Davidson et al. showed a reduction in sputum pro-inflammatory cytokines after a bout of intense exercise, suggesting an anti-inflammatory effect of exercise in the airways of patients with COPD.[8] A few observational studies[9-12] and nine small-scale trials of moderate methodological quality[6] showed a relationship between physical exercise and reduced hospital admissions and mortality in COPD patients after an acute exacerbation. Although this may indicate that decreased exacerbation rates may be at least one of the factors explaining reduction in contact with health care providers (event-based), none of these outcomes is a substitute for reduction of exacerbations.[13] Only two studies that measured on an event basis found reduced exacerbation frequency or duration as a result of physical exercise[14,15] and one study using diary cards (symptom-based) reported significantly fewer mild exacerbations.[16] So far, no study has combined event-based with symptom-based measurement of exacerbation in studying the effect of physical therapy.[6] The hypothesis in this study was that the physical therapy component in particular may result in fewer exacerbations, as well as less severe or shorter exacerbations, in patients with COPD after an acute exacerbation, measured both event-based and symptom-based.

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METHODS

Study design

A multicentre RCT, conducted between 2010 and 2014 in physical therapy practices in the south of The Netherlands, studied the effectiveness of physical therapy on exacerbation rates. After baseline measurements, concealed randomisation was determined by computerised blocks (random block sizes between 4-8), with

prestratification applied for severity of the most recent exacerbation (1-2) and GOLD stage (2-4).[1,17] Although patients were aware of the existence of two treatment groups, they were not informed about the exact nature of the other treatment (randomised consent). Physical therapy practices saw patients in the intervention or control group, or both. In the latter case, physical therapists treated and assessed patients in the intervention group in isolation from patients in the control group. The assessor (EB) of the primary and some of the secondary outcomes was fully blinded for treatment allocation. Elaboration on the handling of potential bias is available in Supplement 8.1. The calculated study sample size was 79 participants per group (the study protocol contains further information).[18]

Study subjects

A cohort of patients with COPD, referred to 27 physical therapy practices, served as a recruitment population for a randomised clinical trial (RCT). A pulmonologist and respiratory nurse practitioner (Maastricht University/Hospital) as well as general practitioners could refer COPD patients to participating physical therapy practices. Additionally, advertisements in local newspapers were used to reach potential patients with COPD. Physical therapists identified eligible patients at their practices and a researcher (EB) determined which subjects were included in the trial (eligibility criteria in Table 8.1). In accordance with a holistic approach, patients with comorbidity were not excluded from the trial so as to enhance generalisability of study results.[19,20] Written informed consent was obtained prior to randomisation. The study was approved by the ethics committee of Maastricht University/Hospital (NL28718.068.09). More detailed information of this trial, registered in The Netherlands National Trial Register (NTR1972), was published earlier.[18]

Table 8.1 Eligibility criteria for the trial subjects.

- A general practitioner/pulmonologist diagnosed COPD in GOLD stage 2, 3 or 4 (confirmed by a postbronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ of predicted).
- Eligible for reimbursement by health insurance companies for physical therapy (post-bronchodilator Tiffeneau-index < 0.6).
- The patient experienced a recent COPD exacerbation (defined as an unscheduled visit to their general practitioner/pulmonologist or hospitalisation due to COPD, and (optionally) receiving a course of antibiotics and/or prednisone within the past 56 days*).
- Having an adequate and optimal medication (inhalation) regimen.
- Competent to speak and understand the Dutch language.

*A trade-off between threshold values of 35-91 days in which the majority of exacerbations have returned to baseline (study protocol).[18]

Abbreviations: RCT = randomised controlled trial, COPD = chronic obstructive pulmonary disease, GOLD = the Global Initiative for Chronic Obstructive Lung Disease, GOLD stages: 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=forced vital capacity, FEV_1=forced expiratory volume in one second.

Intervention

Patients received protocol-directed physical therapy (PT) or sham-treatment (ST). Contrasts between both groups were based on the FITT-principle: frequency, intensity, type (therapy components) and time.[21] PT was based on the COPD guideline of the Royal Dutch Society for Physical Therapy (KNGF)[22] and followed a strict protocol. Patients received a high-intensity exercise programme of one hour, twice a week for one year. ST ranged from no to very low-intensity exercise training, limited to a protocol of which no effect could be expected, for one year.
Additionally, patients in both groups were advised to increase their total daily physical activity on their own.

Intervention group: protocol-directed physical therapy (PT)

The programme included high-intensity exercise training, which entails endurance and/or interval training with an intensity of 60% or higher of (sub) maximum physical exertion, based on the results of a maximal cardiopulmonary exercise test (CPET) and a six-minute walk test (6MWT). Peripheral muscle strength training, combining upper and lower extremities, was provided with an intensity of 80% or higher of the onerepetition maximum tests. In addition, ratings of perceived exertion and dyspnoea of five or higher on the modified Borg-scale (0-10) were used to tailor exercise intensity.[1,23] The patient received the therapy components respiratory muscle training, breathing exercises, sputum clearance techniques and electrical muscle stimulation as per their medical indication.
In patients who received protocol-directed physical therapy, much emphasis was given to the assessment and treatment of physical inactivity in daily life. Patients were advised to increase their total daily physical activity on their own. At least 30 minutes of moderately intense physical activity at least five days a week is the current recommended level. All visits for treatment and all advice for home training were in compliance with the KNGF guideline physical therapy for COPD and the Dutch Standard for Healthy Exercise (NNGB).[22,24]

Control group: sham-treatment (ST)

The very low-intensity exercise training was limited to a maximum of 30 minutes once a week, with an intensity of 15% or lower of (sub) maximum physical exertion, based on the results of a maximal CPET and a 6MWT. In addition, ratings of perceived exertion and dyspnoea of two or lower on the modified Borg-scale (0-10) were used to tailor exercise intensity.[1] There was no further peripheral muscle strength training, respiratory muscle training, breathing exercises, sputum clearance techniques nor electrical muscle stimulation.[22] Patients who received sham-treatment were advised to engage in at least 30 minutes of moderately intense physical activity on their own for at least five days a week according to the exercise norm.[24]

Registered physical therapists, educated and experienced in COPD care and treating at least 5 patients with COPD per week, were recruited through local physical therapy networks in The Netherlands to treat the included patients. They attended information/training sessions given by the research group and a COPD expert network.

Outcome assessment

The primary outcome was exacerbation frequency, the number of COPD exacerbations experienced by the patient. Initially, the primary outcome in the study protocol was listed as "time to exacerbation".[18] However, the outcome exacerbation frequency was more informative given the insight that a history of previously treated events is the best predictor of having frequent exacerbations (2≥ per year).[17] Both intervention and follow-up periods lasted twelve months each to overcome time confounding, since exacerbation frequency is subject to seasonal variation and is particularly related to influenza and other viral epidemics.[25] Exacerbations were identified using both a symptom-based approach (clear increase of respiratory symptoms) as well as an eventbased approach (health care contact), to avoid underreporting exacerbations.[26]. On average, underreported exacerbations seem to be similar in severity compared to reported exacerbations.[25]

The event-based approach defines the onset of an exacerbation as the first day of an unscheduled health care contact with a general practitioner or pulmonologist due to a COPD exacerbation and the start of additional medication intake, or the first day of an unscheduled hospitalisation or emergency visit to the hospital due to an exacerbation. The exacerbation lasts until the last day of this extra medication intake or until the last day of hospital admission.[25] These events were identified by prospective patients' daily diary cards[27] and by physical therapists, who monitored patients' reasons for absenteeism, health care contacts and extra medication intake.

For the symptom-based approach, respiratory symptoms were monitored with prospective daily diary cards. In these diary cards patients report, following the method of Anthonisen et al., whether their major symptoms (breathlessness, sputum production, sputum colour) and minor symptoms (cough, wheeze, running nose, sore throat, and fever (>38.5°C)) were more severe than normal.[28] Upon inclusion in the study all patients received a 'what is normal for me' card, which described their individual levels of major symptoms at baseline. When patients experience no deterioration of any of the symptoms listed in the diary, they should check 'no change in symptoms'. When patients experienced a deterioration, they should check 'yes' and report for all symptoms in the diary whether the level of each symptom was 'normal', 'slightly increased', or 'clearly increased'.[29] The onset of an exacerbation was defined as the first day of at least two consecutive days at which the patient checks 'clear increase' from baseline in two major symptoms or one major and one minor symptom. The day that an exacerbation is resolved was defined as the first day of: (1) three successive days that the patient has returned to his normal health state; or (2) seven consecutive days

on which patients continuously reported no or only a 'slight increase' in symptoms, compared to baseline, with no fever or change in sputum colour.[28-30]

Secondary outcomes were exacerbation duration and severity, disease-specific healthrelated quality of life (Clinical COPD Questionnaire (CCQ) total, symptom, mental health and functional scores) and the patients' perceived benefit of the physical therapy (Global Perceived Effect (GPE) score).[22] Intermediate outcomes – between physical therapy and exacerbation rates – were exercise capacity (10 m-6MWT) and peripheral muscle strength (maximal voluntary isometric contraction of the dominant hand and shoulder abduction and knee extension).

The secondary outcome exacerbation duration was defined as the duration of the medical intervention per occurrence, and the number of days with clear increase of respiratory symptoms (based on the above mentioned definitions).[25,28-30] Exacerbation severity was defined as level 1: 'mild/moderate', allowing home-treatment with antibiotics and/or prednisone after contact with their general practitioner or pulmonologist, and level 2: 'severe', requiring hospitalisation, and defined in terms of symptom scores on the daily diary cards (0-11).[25,26,28,29]

Functional exercise capacity was measured by the six-minute walk test on a 10-metre course (10 m-6MWT), in accordance with the guidelines by the American Thoracic Society except for the course length due to practical restrictions in primary care practices.[31] Group differences were calculated based on absolute distance in metres. Peripheral muscle strength was measured as maximal voluntary isometric contraction (MVIC) of the dominant hand with the Jamar dynamometer, and the shoulder abduction and knee extension (m. quadriceps), tested in standardised positions by means of the break method by the MicroFET handheld dynamometer.[1,32]

Potential confounding variables were exacerbation history (patient-reported number of treated events in the previous year); GOLD stage; smoking history (pack years); physical activity in daily life (Physical Activity Questionnaire (0-8))[22]; severity of the latest exacerbation before study entry (mild/moderate or severe); and comorbidity (Cumulative Illness Rating Scale (CIRS 0-52))[33]. Other baseline characteristics measured were dyspnoea (modified Medical Research Council dyspnoea questionnaire (mMRC 0-4))[1], FEV_1 (%predicted) and FEV_1/FVC.

Analysis

Descriptive statistics were presented quantitatively as means (± standard deviation) or medians (25^{th}–75^{th} percentiles) for the continuous variables, depending on the data distribution; as percentages for the dichotomous variables severity and gender; and as categorical variables for GOLD stage and mMRC.

Group differences at baseline and group differences regarding change in intermediate outcomes (12 months versus baseline) and secondary outcomes (CCQ and GPE) were analysed with independent samples t-tests and Mann-Whitney U tests respectively.

8

Missing data at 12 months were imputed by last-observation-carried-forward. All data analyses were done by a blinded analyst.

The effect of physical therapy (PT) on exacerbation frequency was analysed in a generalized linear model (GLM) with a logarithm link function and Poisson distribution for count data. Based on the data, a negative binominal distribution was abandoned in favour of a Poisson distribution. The model was adjusted for missing diaries by an offset variable 'ln(12–number of months missing)'. Exacerbation duration and severity were analysed with backward linear regression analysis and frequency calculations in percentages. Analyses were based on respectively the event-based approach, symptom-based approach and a combination of both (all event-based plus all symptom-based exacerbation counts, minus double counts). Exacerbation history, GOLD stage, age, gender, smoking pack years, physical activity in daily life, severity of latest exacerbation and comorbidity were entered in the model as covariates. Results of per-protocol and intention-to-treat analyses were presented of those returning at least nine out of twelve diaries, with a p-value <0.05 and minimal probability of 80% indicating statistical significance.

RESULTS

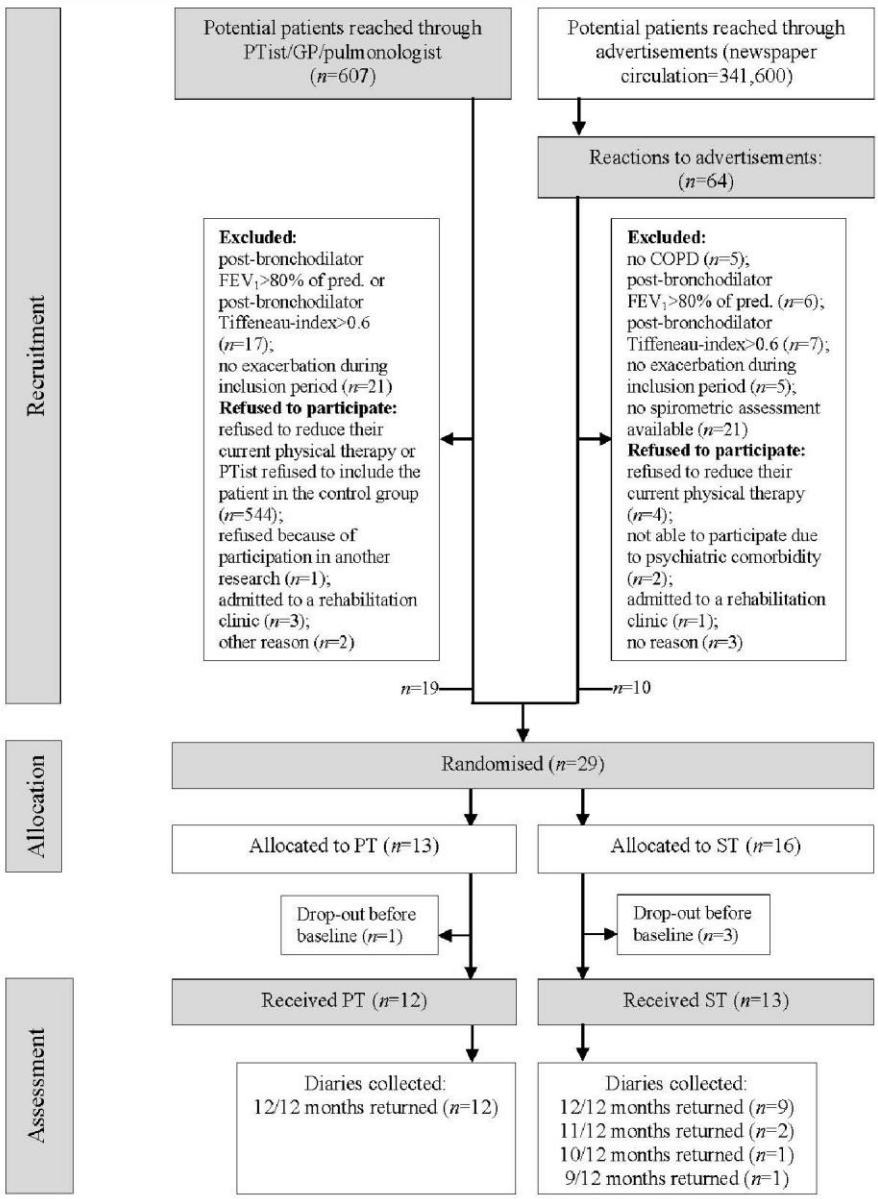
The CONSORT flowchart (Figure 8.1) shows the study flow after 671 persons were contacted to participate in the trial. After positive response and eligibility check twenty-nine patients were randomised. At this point, inclusion of patients in the trial was stopped prematurely due to disappointing participation rates and for ethical reasons. Patients and physical therapists believed in the effectiveness of physical therapy regarding exacerbations and exercise capacity in the short term. Many physical therapists withdrew their participation from the recruitment for the trial. The resulting low participation rate was more pronounced than anticipated. Four patients died during the trial (*n*=3 in the ST-group; *n*=1 in the PT-group). There were no significant differences between participants (*n*=25) and four early drop-outs (*n*=1 cancer; *n*=2 psychiatric complaints; *n*=1 refused participation in ST-group after randomisation) based on gender, age, GOLD-stage and severity of latest exacerbation.

Twenty-five patients had 77 event-based and 86 symptom-based exacerbations. Combined, this resulted in 94 single exacerbations: 8 exacerbations in which the patient received healthcare without subjectively experiencing the exacerbation according to the pre-specified criteria,[18,28] plus 17 exacerbations based on subjective experience without any healthcare contact, plus 69 exacerbations where both subjective experience and healthcare contact occurred.

Time between the most recent exacerbation and inclusion in the study in the PT-group (28 days) was not significantly different from the ST-group (19 days, *p*=0.21). Table 7.2 presents participants' demographic and clinical characteristics. All continuous variables were distributed normally, except for smoking history in the ST-group (*D*(13)=0.29, *p*=0.01). Exacerbation history in the PT-group showed a positively skewed distribution. Groups seemed comparable after randomisation for all variables, including the strongest predictors for exacerbation frequency (GOLD-stage: *U*=76.00, *p*>0.5 and

exacerbation history: *U*=76.50, *p*>0.5). Only age was significantly higher in the ST-group (67y) compared to the PT-group (59y, *p*=0.04). Based on the sample size (*n*=25), alpha error level (5%) and measured average and standard deviations (6.15±1.82 versus 1.17±1.27) in the primary outcome, the power achieved in this study was 99%.[34]

Figure 8.1 Flow of participants through the study.



Abbreviations: PTist = physical therapist, GP = general practitioner, PT = protocol-directed physical therapy, ST = sham-treatment.

Table 8.2 Baseline characteristics of the subjects.

Characteristic	PT-group (*n*=12)	ST-group (*n*=13)
Gender, *n* male (%)	6 (50)	8 (62)
Age *(yr),* mean (SD)	59.2 (8.1)	67.1 (9.7)*
FEV_1 *(%$_{pred}$)*, mean (SD)	50.6 (18.9)	52.7 (16.5)
FEV_1/FVC *(%)*, mean (SD)	45.9 (13.8)	49.2 (7.9)
GOLD Stage, *n* (%)		
II	5 (42)	7 (54)
III	6 (50)	3 (23)
IV	1 (8)	3 (23)
Comorbidity *(CIRS 0-52)*, mean (SD)	7.1 (2.6)	8.6 (2.5)
Smoking *(pack-yr)*, mean (SD)	44.0 (31.3)	42.2 (52.4)#
median (25^{th}-75^{th} percentiles)	46.0 (23.1-65.1)	24 (14.2-56.3)#
Physical activity level *(0–8)*, mean (SD)	2.7 (1.8)	2.6 (2.1)
Dyspnoea *(mMRC 0-4)*, n (%)		
1	3 (25)	2 (15)
2	2 (17)	6 (46)
3	7 (58)	3 (23)
4	0 (0)	2 (15)
Exacerbation frequency over 12m-retrospectively, mean (SD)	3.2 (3.2)#	2.4 (1.2)
median (25^{th}-75^{th} percentiles)	2.0 (1.3-3.0)#	2.0 (1.0-3.5)
Severity of latest exacerbation, n (%)		
mild/moderate	10 (83)	9 (69)
severe	2 (17)	4 (31)

Abbreviations: FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second, GOLD = the Global Initiative for Chronic Obstructive Lung Disease, GOLD stages: II = moderate COPD, FEV_1/FVC<0.7 and 50% ≤FEV_1<80% of predicted, III = severe COPD, FEV_1/FVC<0.7 and 30%≤FEV1<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, CIRS=Cumulative Illness Rating Scale, mMRC=modified Medical Research Council dyspnoea questionnaire.
* p<0.05, # non-normal distribution.

Exacerbation frequency

Exacerbation frequency was significantly higher in the ST-group (6.15±1.82 counts) compared to the PT-group (1.17±1.27), when *combining event-based and symptombased* measurement ($\chi^2(1)=36.25$, $p<0.001$). PT showed a protective effect regarding exacerbation frequency with an incidence rate ratio (IRR) of 0.15 (*95%CI*: 0.08-0.28), indicating a seven-fold increased risk of an expected exacerbation in the ST-group compared to the PT-group during the 12-month intervention. The model was adjusted for 'exacerbation history'; one event-based measured exacerbation increased the risk of another expected exacerbation in the year after by 14% (*exponentiated unstandardised coefficient*=1.14, *95%CI*: 1.03-1.26). Other potential covariates did not significantly contribute to the model.

Event-based exacerbation frequency differed significantly between the ST-group (5.08±1.89 counts) versus PT-group (0.92±1.31 counts) ($\chi^2(1)=31.52$, p<0.001). The IRR was 0.11 (95%CI: 0.05-0.24), indicating a nine-fold increased exacerbation risk in the ST-group.

Higher exacerbation frequencies were recorded with the symptom-based approach compared to event-based. Still, the number of *symptom-based* exacerbations was significantly lower in the PT-group (1.08±1.24 counts) versus ST-group (5.62±1.76 counts) ($\chi^2(1)=32.69$, $p<0.001$). The IRR was 0.16 (*95%CI*: 0.08-0.30), indicating a sixfold increased exacerbation risk. Irrespective of the event-based or symptom-based approach, again 'exacerbation history' appeared to be a significant confounder.

Exacerbation duration

Duration of an *event-based* exacerbation was 14 days (*SD*: 10) in the ST-group and 5 days (*SD*: 7) in the PT-group. Duration was shortened by 10 days on average by PT ($F(1,21)=6.22$, $b_1=-9.52$, $p<0.05$).

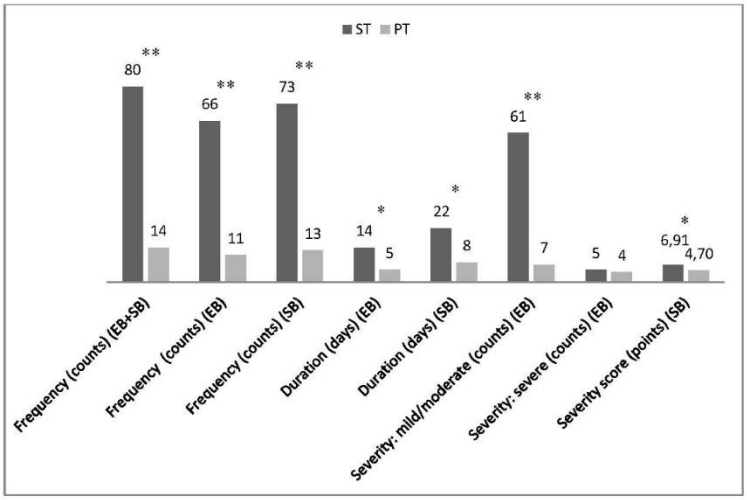
Using the *symptom-based* approach, duration was 22 days (*SD*: 16) in the ST-group and 8 days (*SD*: 12) in the PT-group. Although the confounder 'age' independently correlated with exacerbation duration it did not add significantly to the models, whereas 'exacerbation history' did in the symptom-based approach only. On the one hand, duration was shortened by 16 days on average by PT, while on the other hand each previous exacerbation (during the previous year) increased the duration of a future exacerbation by 3 days ($F(2,20)=5.46$, $b_1=-15.87$, $b_2=2.67$, $p<0.05$).

Exacerbation severity

Severity of an *event-based* exacerbation was scored mild/moderate or severe in 61 and 5 of all exacerbations in the ST-group, respectively, and 7 and 4 in the PT-group, respectively, without a significant difference between the counts of severe exacerbations.

Based on the *symptom-based* approach, average severity of an exacerbation was higher in the ST-group (6.91±1.25 points) than in the PT-group (4.70±4.40 points) and only significantly influenced by the intervention in combination with 'exacerbation history'. PT decreased the average severity score by 2.70 points (*95%CI*: -5.24 - -0.17) whereas each exacerbation increased the severity of a next exacerbation with 0.63 points (*95%CI*: 0.09-1.18). ($F(2,20)=4.62$, $b_1=-2.70$ $b_2=0.63$, $p<0.05$). Effects of the interventions on primary (frequency) and secondary outcomes (duration and severity) are shown in Figure 8.2.

Figure 8.2 Exacerbation frequency, duration and severity in the control (ST) and intervention group (PT).



Abbreviations: ST = sham-treatment, PT = protocol-directed physical therapy, EB = event-based approach, SB = symptoms-based approach.
* p<0.05, ** p<0.001.

Exercise capacity and muscle strength

Functional exercise capacity improved significantly more in the PT-group (51±50m) compared to the ST-group by non-parametric testing (-29±72m, p=0.005).
Peripheral muscle strength improved significantly more in the PT-group compared to the ST-group with regard to knee extension (p=0.016) and strength of the dominant hand (p=0.001), but not with regard to shoulder abduction (p=0.13).

Quality of life and perceived benefit

The PT-group scored significantly higher on disease-specific health-related quality of life by non-parametric testing. The CCQ total score was reduced by -0.6±0.6 points in the PT-group compared to an increase in the ST-group (0.17±0.93, p=0.04). From the subscales only the functional score differed significantly (0.46±0.95 versus -0.52±0.82, p=0.01).
The patients' perceived benefit of the therapy at 12 months appeared higher in the PTgroup (5.15±1.91), but not significantly different from the ST-group (3.58±2.07, p=0.05).

Follow-through with the protocol

Twenty-five patients started the intervention after giving informed consent and were randomly assigned to either the intervention group (PT, n=12) or the control group (ST, n=13), equally distributed over 11 practices. Three practices had patients both in the

intervention group and patients in the control group, but treated and assessed them separately.

Follow-through with the protocol was checked (physical therapy practice data and patient report) and the applied physical exercise was in accordance with the study protocol regarding intensity and time.[18] The intensity in the PT-group was between 60-90% of the CPET (*n*=4) or of the 6MWT (*n*=8), with a median Borg-score of 6 (5-7). Four patients in the ST-group received advice only, apart from the measurement session at the practice, for one year. For the remaining participants in the ST-group intensity of endurance or interval training was between 0-20% of the CPET (*n*=3) or of the 6MWT (*n*=10), with a median Borg-score of 2 (0-5). Not all patients in the ST-group managed to exercise below the maximum perceived exertion rate of two (*n*=3). The planned frequency in the PT-group (twice a week) was reduced due to holidays and missed treatments (mainly due to comorbidity) to an average of 1.5±0.3 times a week. In multiple cases comorbidity restricted exercise intensity in the PT-group. In the ST-group frequency was only 0.3±0.2 times a week, mainly due to frequent exacerbations and comorbidity, preserving the intended contrast between the intervention and control group regarding frequency. Regarding the content of the therapy (type), all patients in the PT-group received a combination of interval and endurance training and the therapy components breathing exercises and sputum clearance techniques as per their medical indication. Respiratory muscle training or electrical muscle stimulation was not used during the trial in the PT-group. No other therapies outside the trial were reported in the ST-group.

During the 12-month intervention period daily diary cards were send back by each participant at the end of every month, except for one month-diary (*n*=1 drop-out in the twelfth month due to psychiatric complaints; *n*=1 forgot to send back month twelve); two month-diaries (*n*=1 forgot to send back months eight and eleven); and three month-diaries (*n*=1 drop-out in the ninth month due to death). Completion rates did not differ significantly between groups (p=0.07).

Statistical assumptions

Assumptions were met for the regression analyses (no multicollinearity, no substantial influencing cases, fairly linear and homoscedasticity). The Poisson models appeared to fit the data well without indications for bias, undue influence of outliers or deviation of the expected distribution (goodness of fit expressed in *Deviance*=0.88-0.99 ≤2, the overall models were significant with $\chi^2(10)=53.09\text{-}58.94$, with all $p<0.001$ and there was no systematic pattern in the plot of standardised deviance residual versus predicted value of mean of response).

Intention-to-treat versus per-protocol analyses

Since one patient dropped out in the ST-group and three dropped out in the PT-group, all before baseline measurement, and because the outcome of this study is based on count data over 12 months, intention-to-treat analysis is not a straightforward method.

However, when imputing 'exacerbation frequency' with the most optimistic frequency (zero) and imputing the confounder 'exacerbation history' with 1 exacerbation (as this is known information at inclusion) for all four patients, effect size of PT is comparable ($\chi^2(1)=35.95$, $p<0.001$) and in the same direction (IRR=0.15 (*95%CI*: 0.08-0.28) as in the per-protocol analysis. Moreover, the predictor exacerbation history increased the risk for an exacerbation by 15%.

DISCUSSION

This is the first known trial showing that physical therapy, including intensive physical exercise training, significantly reduced exacerbation rates in patients with COPD after an acute exacerbation. A large significant reduction of exacerbation frequency was observed with both the event-based and symptom-based approach. Furthermore, physical therapy shortened exacerbation duration and reduced severity, except severe *event-based* exacerbations. An explanation for the lack of this effect may be the small sample size, resulting in fewer possible events, or the fact that there is little possibility of improvement in this severe state of the disease.

This study confirmed underreporting of exacerbations with the event-based method[26]; 17 out of 94 exacerbations were perceived by the patients but not accompanied by a medical event. Combining both methods provided a comprehensive picture of exacerbation rates. It slightly increased the effect of physical therapy on exacerbation frequency, and did not alter the conclusion.

As expected, both exercise capacity and lower limb muscle strength improved significantly more in the PT-group.[2-6] Assuming patients' health status is a mediating factor between a high level of physical exercise and exacerbation rates, our results regarding muscle strength and exercise capacity are in line with the shown reduction in exacerbation rates by PT.

Generalisability of the results

A previous exacerbation was an important confounder, increasing the risk for an expected future exacerbation, indicating the presence of a susceptibility phenotype, independent of disease severity (GOLD-stage).[1,17] Spirometric classification did not predict exacerbation frequency in contradiction with the literature.[1] The fact that prestratification on GOLD-stage was performed upon randomisation may explain this finding. The average number of exacerbations per GOLD-stage in our study (GOLD2: 2.6; GOLD3: 3.3; GOLD4: 4.0) was much higher than the numbers found in cohort studies (GOLD2: 0.7-0.9; GOLD3: 1.1-1.3; GOLD4: 1.2-2.0),[17,35,36] due to the broader inclusion criteria for our study population (higher disease severity with Tiffeneau-index<0.6, comorbidity and a history of exacerbations). Patients showed a pronounced average of six exacerbations in the ST-group. This has implications for the generalizability of our

results. A high exacerbation risk is an indication for physical therapy, considering the close relationship between dyspnoea and physical deconditioning[37] and between exacerbations, muscle weakness and inactivity, increasing the frequency of future exacerbations.[9,38] This vicious cycle may be broken by intensive physical therapy. Recent guidelines by the American College of Chest Physicians and Canadian Thoracic Society cautiously recommend PR to prevent exacerbations with a restriction to patients with COPD GOLD 2-4 and a recent hospitalisation within the past four weeks. Our inclusion period lasted until eight weeks after an event-based exacerbation, but the average time between exacerbation and inclusion in the study was eventually 28 days (PT-group) and 19 days (ST-group) on average, supporting the guidelines recommendation. In these guidelines, however, an all-cause hospitalization was assumed to reflect a COPD-specific hospitalization. In our trial only COPD-specific hospitalizations were analysed, and symptom-based exacerbations were also measured, accounting for the largest effect.[39]

Cost-effectiveness and clinical impact

After reimbursement by health insurance companies for physical therapy (in The Netherlands for GOLD 2-4), with average costs of 1,830 euros per patient on an annual basis in this study,[40] physical therapy may recover costs by decreasing exacerbation frequency and duration. Frequency reduction alone resulted in a total cost reduction of 8,226 euros for event-based exacerbations during this study, on average 531 euros per patient.[41-45]

Not only did physical therapy have a statistical and financial advantage, the reduction of exacerbations also had a clear clinical impact. When the new combined assessment of GOLD-stage, symptoms and exacerbations[1] is applied to the study participants, patients-profiles in the ST-group increased negatively, while patient-profiles of those receiving PT changed favourably during the trial. These changes in patient-profile mean COPD medication was stepped down,[1] indicating a positive clinical implication of physical therapy for the patient. Detailed information on cost calculations and clinical impact is available in Supplement 8.1.

Methodological and ethical limitations and considerations

For ethical-related recruitment considerations patient inclusion was stopped prematurely: 1) the majority of patients who received physical therapy in the past did not want to risk randomisation into ST, since they wanted to overcome their recent exacerbation (inclusion criteria); 2) most patients who were unfamiliar with physical therapy declined participation in an exercise programme; 3) during the inclusion period healthcare insurance policies changed, lowering physical therapy reimbursement; 4) physical therapists declined withholding patients the expected short-term benefits from PT, preventing them from including patients in the study after an exacerbation; 5) an indirect argument for physical therapists not to include patients could also have been the financial loss due to fewer treatment sessions for patients allocated to ST.

Comparably, a recent review found that other studies on PR (including at least exercise training) were also stopped before the recruitment target was reached due to the use of random allocation to different types of post-exacerbation management in a situation of poor health.[6] During the trial and follow-up period more patients died in the control group than in the intervention group. It seems unlikely that the study results have been overestimated given this important observation. The reasons for the difficult recruitment in this study, in combination with the observed positive effects of physical therapy on exacerbations in patients with a recent COPD exacerbation (this study) and on other health outcomes (this study and other studies),[1,6] may indicate that similar future trials cannot be justified in this form. This conclusion corresponds with a recent review, stating that additional RCTs comparing pulmonary rehabilitation and conventional care in COPD are not warranted.[2] Detailed information on ethical considerations regarding the small sample size is available in Supplement 8.1.

Like other trials that studied the effects of physical exercise interventions in PR in patients with COPD, the observed effect in this study is so large (99% power) that it is unlikely that the effect can be attributed to bias only.[6] But because of the small sample size[6] and trial truncation our study results may overestimate its effects.[46] Therefore, the results of this study should be interpreted with caution and should be confirmed by other studies with a different methodology and populations with lower exacerbation frequency.

In conclusion, protocol-directed physical therapy after an acute exacerbation can reduce exacerbation frequency, duration and severity in patients with COPD. These fairly cautiously interpreted results apply to patients with moderate to very severe COPD and comorbidity, with a high exacerbation risk.

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SUPPLEMENT 8.1

In this supplementary file more detailed information regarding the discussion is given.

DISCUSSION

Handling bias

Hurst and colleagues showed that exacerbations are not random events, but cluster together in time.[1] They found a high-risk period for a recurrent exacerbation in the eight-week period after an initial exacerbation, which may be problematic for the analyses of count data. In this study, exacerbation history (including initial exacerbations) was taken into account as a covariate. A second unscheduled event or second medication prescription that followed the first medication intake directly (within one day) was considered to be the same exacerbation. In all other cases, each exacerbation was treated as a single event. During the study analyses, a time period of at least fifteen days between all registered single events was noticed.

Several measures were taken in this study to avoid bias due to blinding issues. Patients in the PT-group as well as patients in the ST-group received attention from their physical therapist to avoid Hawthorne effects as much as possible. Both groups received periodic questionnaires and measurement sessions. Patients were kept naïve on the exact content of the other treatment group (randomised consent) to prevent influence on outcomes. Physical therapists could not be blinded in this study, but were not involved in the diary-monitoring of exacerbation. The outcome of this study was partly objective (event-based) and less liable to patients' manipulation in order to please their physical therapist, as the diaries were directly collected by the researcher. Assessment of the primary and secondary outcomes by the researcher and analyses of the data was fully blinded.

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Contamination occurred in some patients in the ST-group who received (very low) exercise training. Therefore, the intention-to-treat analysis showed conservative estimates.

Cost-effectiveness

The demonstrated reduction of event-based exacerbation frequency and duration may also be relevant for governments and health insurance companies, as a relatively small percentage of all patients (10%) experiencing exacerbations account for over 70% of all medical costs due to COPD.[2] This study confirmed that a small group of patients can have multiple exacerbations in 12 months. In The Netherlands, health insurance companies provide reimbursement for physical therapy in COPD GOLD 2-4. Therefore, the costs of physical therapy (on average 1.5 treatments a week for 30.76 euros per

treatment)[3] should be taken into account. Costs for physical therapy (based on the PTgroup) were on average 2,445 euros per patient on an annual basis. In The Netherlands, patients generally pay for the first twenty treatments themselves, leaving 1,830 euros to be paid by the health insurance companies. However, this study suggests that these costs may be reduced by a clear decrease of exacerbation frequency and duration. Multiple studies have calculated the costs involved in a COPD exacerbation in The Netherlands, and in all studies a distinction was made between a less-severe exacerbation (contact with their general practitioner or pulmonologist plus antibiotics and/or prednisone, costs on average 84 euros per exacerbation) versus a severe exacerbation (hospitalisation, costs on average 3,690 euros per exacerbation), similar to the distinction in our study.[4-8] Due to frequency reduction, 54 mild/moderate (61 exacerbations in the ST-group minus 7 exacerbations in the PT-group) and one severe (5 minus 4) exacerbations occurred more in the ST-group than in the PT-group, leading to a probable total cost reduction of 8,226 euros for event-based exacerbations during 12 months in the PT-group. Per patient, this may mean an average of 4.12 (61/n=13 minus 7/n=12) fewer mild/moderate exacerbations per year and an average of 0.05 (5/n=13 minus 4/n=12) fewer severe exacerbations per year, resulting in an average reduction of 531 euros per patient per year. Based on the study results and these numbers, making physical therapy after an exacerbation more accessible might also be in the interest of health insurance companies from a financial perspective.

Clinical impact

Not only did physical therapy in this study have a statistical and financial advantage, the reduction of exacerbations also had a clear clinical impact. To understand the impact of COPD on an individual patient, assessment of the patient's spirometric classification alone is insufficient. A new combined assessment of GOLD-stage, symptoms (mMRC) and exacerbation frequency into four profiles (A: low risk, less symptoms, B: low risk, more symptoms, C: high risk, less symptoms, D: high risk, more symptoms) was recommended by the GOLD in 2011-2015.[9] When this assessment is applied to the participants of this study at baseline, two patients would have been assigned to profile A, two to B, three to C and eighteen to D. After the intervention two patients (ST) shifted up from profile B to C, one patient (ST) shifted up from profile C to D and three patients (PT) shifted down from profile D to B, because of the changes in exacerbation frequency. These changes in patient profile mean COPD medication was stepped down,[9] indicating a positive clinical implication of physical therapy for the patient. Some of the objective conclusions above may be reflected by the perceived improvement in health-related quality of life by the patients in the PT-group. This positive influence of the PT programme in patients with moderate to very severe COPD is confirmed by the literature, which showed a similar benefit from exercise programmes on other objective and subjective outcomes, irrespective of disease stage.[10-12] The higher patients' perceived benefit from the physical therapy at 12 months in this study, however, did not reflect the improved quality of life statistically.

Ethical considerations

An important limitation of this study is the small sample size. Because of ethical considerations, inclusion of participants in this study was stopped prematurely. Because of the small sample size our study results may overestimate its effects. A review ('STOPIT-2' study) showed that truncated RCTs were associated with greater effect sizes compared to RCTs that were not stopped prematurely (including nonpharmacological therapeutic interventions).[13] In general, an overestimation of treatment effects for the outcome, related to early stopping for benefit, was reported for RCTs with fewer than 200-500 events (including all kinds of outcomes; in this study 94 exacerbations). However, this study was not stopped earlier for benefit and no analysis was done before the decision to discontinue recruitment was made. Still, the results of this study should be interpreted with caution because the small sample size does not allow estimating the treatment effect very precisely.[12]

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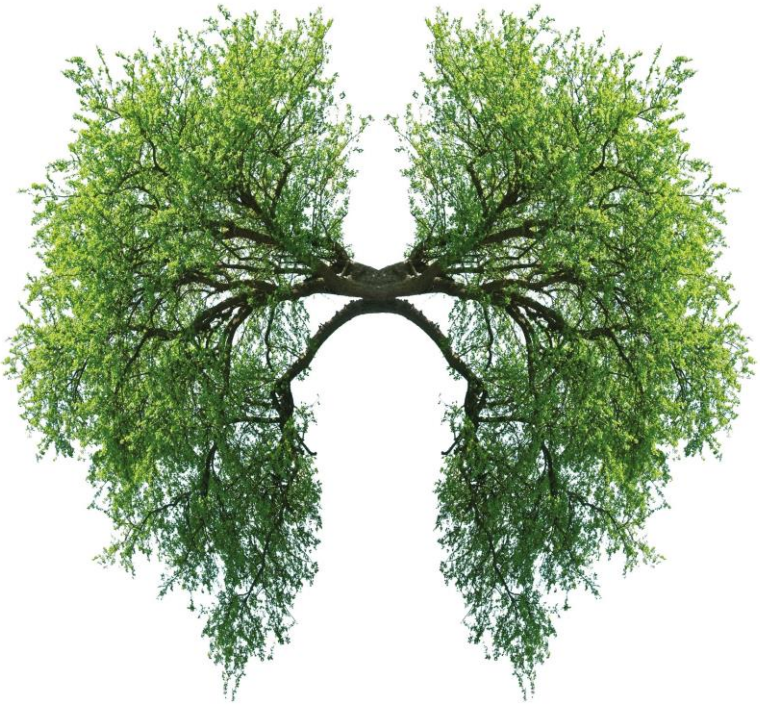
CHAPTER 9



General discussion

GENERAL DISCUSSION

This chapter presents an overview of the main findings of this thesis; it gives a general reflection on the studies performed and discusses methodological considerations. Moreover, it places the results of the studies in the context of other scientific evidence in the field of pulmonary rehabilitation and physical therapy along with measurement of performance in patients with COPD, comorbidity and exacerbations. This general discussion concludes with the main implications for clinical practice and directions for future research.

MAIN FINDINGS

This thesis provides evidence of multiple interactions between physical therapy, comorbidity and exacerbations in patients with COPD and shows that these interactions play a central role in the management of patients with COPD and in the interpretations of health outcomes.

In accordance with recommendations from general practitioner (GP) guidelines it was expected that a lower patient physical activity level played a role in the choice of management of patients with COPD in primary care. However, Chapter 2 showed that the target population referred by general practitioners and treated by physical therapists in primary care had an *overall* higher burden of disease compared to patients not treated by a physical therapist. We found that unequal patient phenotypes occur in different primary care settings and that other factors – like a higher degree of airway obstruction, more exacerbations, more vascular comorbidity, and lower health status – play a role in referral for physical therapy (Part 1 of this thesis). This strengthened the need for a more comprehensive evaluation of physical therapy in: a) patients with COPD and comorbidity (Part 2 of this thesis); and b) patients with COPD after an acute exacerbation (Part 4 of this thesis).

A. Evaluation of physical therapy in patients with COPD and comorbidity

Clinical consequences of comorbidity in COPD for physical therapy practice were explained in two ways; the therapeutic consequences of treating patients with COPD combined with high prevalent comorbid conditions and the modifying influence of comorbidity on longitudinal improvements of functional exercise capacity in patients with COPD following physical therapy, particularly in primary care (Part 2 of this thesis). First, the impact of comorbid conditions on clinical reasoning

focussed on the physical therapist's skills and knowledge, on the need for monitoring outcomes, intervention adjustment and on the level of referral information given by general practitioners and physicians to a physical therapist.[1] To obtain optimal treatment when dealing with comorbidity in COPD, our multiple case-study showed that a patient-centred approach – aiming at an individually-tailored programme - rather than a disease-oriented approach is needed. Second, health care professionals and researchers should be aware that the more comorbid conditions are present, the quicker the exercise capacity of the patients reduces over time during physical therapy. Some comorbid disease categories appeared to have no influence on the effect of physical therapy while others, like vascular diseases, had only a confounding effect, reducing the level at which physical therapy started. Whereas others like cardiac, hepatic and psychiatric diseases appeared to modify the effect of physical therapy, expressed in a lower starting level as well as a decline of functional exercise capacity in time following physical therapy.

B. Evaluation of physical therapy in patients with COPD after an exacerbation

This thesis provides evidence for the potential of physical therapy to reduce COPD exacerbations in patients with a frequent exacerbator phenotype (and comorbidity) (Part 4 of this thesis). It was shown that physical therapy (including high-intensity exercise training) was effective in reducing the frequency, duration and perceived severity of exacerbations compared to sham-treatment (very low-intensity exercise training).

Clinimetric feasibility of measuring exercise capacity in practice

In previous studies in this thesis, functional exercise capacity was taken into account either as a primary, intermediate or secondary outcome measure, depending on the aim of the study, and measured with the six-minute walk test (6MWT).[2-4] Course length of 30 m as advised in the standardised measurement protocol for the 6MWT[2] is not feasible in most primary care settings due to limited space and therefore cannot be seen as the most conventional test.[5] Most physical therapists were forced to deviate from the advised 30 m, mostly using a 10 m course length.[6] However, they still applied the existing reference equations based on a 30 m course to interpret test results from a standardised test over a 10 m course. In order to interpret 6MWD correctly additional research was necessary. For this reason, two studies were performed to extend the applicability of functional exercise capacity assessment (6MWT) for patients with COPD and patients with other chronic conditions (Part 3 of this thesis). This thesis shows that existing reference equations established for a 6MWT conducted on a 30 m (or longer) course cannot be applied to predict the distance achieved on the 6MWT on a 10 m

course, due to a substantial interpretation error.[6] Although we showed that the impact of course length on the achieved six-minute walk distance (6MWD) and on the use of reference equations in patients with COPD is substantial and statistically and clinically relevant, no reference equations were available for the 6MWT on a 10 m course. Because of the need for the 10 m reference equations in everyday practice, this thesis provides health care professionals with reliable first reference equations to evaluate 6MWD over a 10 m course and expands the usefulness of this clinical measurement instrument.[7]

GENERAL REFLECTION

All studies, described in this thesis included COPD patients with comorbid conditions unlike other studies, mainly randomised controlled trials, which have routinely excluded significant comorbid conditions like cardiovascular diseases.[8,9] Those patients who experience an acute COPD exacerbation can profit from physical therapy, as was shown in this thesis. The improvement in exercise capacity and lower limb muscle strength along with a reduction of exacerbation frequency may be a reason why previous studies showed a reduction in hospitalisation and mortality due to pulmonary rehabilitation (PR) after an acute exacerbation.[10-14] But healthcare utilisation is not an adequate substitute for severity,[15] nor for exacerbation frequency and duration, for it depends on many unrelated social and comorbidity factors. These are outcomes in their own right.[15] In a review of these studies the intervention considered was PR when at least physical exercise, the cornerstone intervention in our physical therapy programme, was included.[14] A biological explanation for a potential anti-inflammatory effect of physical therapy on the airways may come from a reduction in sputum proinflammatory cytokines after a bout of intense exercise.[16] The additional reduction of symptom-based exacerbations, exacerbation duration and perceived exacerbation severity in this thesis (Chapter 8) seem in line with reduced hospitalisation.[14] The increase in muscle strength and exercise capacity following physical therapy in our trial can be considered intermediate outcomes, acting between 'performing physical exercise' and 'reduction in exacerbations rates'.[14] However, the influence of physical therapy on exercise capacity needs to be considered in respect of other patient characteristics, like the modifying influence of comorbidity studied in our cohort study. Additionally, the influence of physical therapy on exercise capacity also needs to be considered in respect of possible interpretation errors when using reference equations for the 6MWD that are not in accordance with the test course used.

These main thesis findings can be translated into:

1) *A possible gain in health-related quality of life for patients with COPD, as exacerbations rates can be reduced by physical therapy:* Exacerbations of COPD negatively affect a patient's quality of life,[17] and conversely, a reduction in exacerbation rates may lead to a gain in quality of life. Our trial confirmed a gain in disease-specific health-related quality of life after a reduction in exacerbation rates in patients who received physical therapy after an acute exacerbation compared to the control group. Compared to PR in stable COPD patients, the effect size of rehabilitation on a health-related quality of life questionnaire was similar in patients who have recently had an acute exacerbation of COPD in studies that have used the outcome hospitalisation to quantify exacerbations.[14] Together with our study results, this proves that gain in quality of life can be achieved by physical therapy in all patients with COPD, even if patients still experience a home-treated exacerbation by a general practitioner instead of a hospitalisation, or if patients do not visit a physician but still experience a symptombased exacerbation. Both scenarios were seen in our trial, using both event-based and symptom-based definitions of an exacerbation. There is evidence that patients do not report all exacerbations that are suggested by prospective diary-card recording.[18] Therefore, we used daily diary cards that related symptoms to the usual baseline state agreed with the patient rather than to score severity.[15] The recording of both exacerbation definitions in our trial reinforces the finding that symptom-based exacerbations, not captured by the number of hospitalisation or general practitioner visits, have on average similar severities to reported or event-based exacerbations,[15] and are likely to have equal influence on improvement in quality of life.

2) *An additional reason to refer patients after an acute exacerbation for physical therapy*: Most studies on PR have been done in stable outpatients[14] and they have demonstrated large and clinically significant positive effects of PR – alike physical therapy – on dyspnoea and fatigue, health-related quality of life, functional exercise and maximal exercise.[19] Patients should be referred for primary care physical therapy on the basis of factors that show effectiveness in PR: worse symptoms, physical deconditioning and lower health-related quality of life.[20] Additionally, this thesis showed that physical therapy has a potential in *post-exacerbation management* in COPD by reducing exacerbation rates in non-stable patients (Chapter 8). Besides improvements in peripheral muscle strength, functional exercise capacity and possible additional gain in quality of life by physical therapy after an acute exacerbation, in line with other studies including post-exacerbation PR,[14] this thesis showed significant reduction in exacerbation rates.

It seems that especially early PR after exacerbation-hospitalisation[14] like early physical therapy after an event-based or symptom-based exacerbations (this thesis) may be a

particularly attractive addition to the management of *patients who have recently experienced an exacerbation*. A reason for this criterion may be a more pronounced *initial deterioration in muscle function*[21] *and physical activity*[10] following an exacerbation, that renders patients more likely to improve from physical exercise.[14] Physical activity is the strongest predictor of dying in the year after an exacerbation – those with worsened physical activity from the exacerbation to two months postexacerbation or those with very low physical activity levels are at a higher risk[22] – this can be influenced by early physical therapy after an exacerbation.[14,23]
A more pronounced initial deterioration in functional exercise capacity was also seen (Chapter 4) in *patients with specific comorbid conditions* (cardiovascular, hepatic, psychiatric, eye-ear-nose-throat-larynx, genitourinary diseases and endocrinemetabolic-lymphatic-immune diseases), making the presence of comorbidity a second important feature in referring patients for physical therapy. A third reason for referring (comorbid) patients after an acute exacerbation might be PR's strength to revert *physical inactivity in patients*.[24] This was in accordance with the higher physical activity level in primary care patients treated by a physical therapist compared to those not treated by a physical therapist in our study.[25] Those patients that improve physical activity levels have in turn less chance of being re-admitted.[10, 11] This makes physical inactivity a legitimate reason for a general practitioner to refer a patient for physical therapy,[26] but not the only legitimate criterion, in line with our study.[25] A fourth reason for referring patients may be the educational component in rehabilitation or physical therapy that may remediate *deficiencies in self-management or education among this group of patients*.[14,27] This seems to go hand in hand with a reduction in all-cause hospitalisation.[28] Another significant risk-factor for hospital readmission is *depression*, supporting early rehabilitation, since it has been shown to improve depressive symptoms after exacerbations.[14] An international standard confirms that the presence of anxiety or depression in patients with COPD is an additional reason to refer for physical therapy,[20] supporting the earlier mentioned second reason (patients with specific comorbid conditions). Concluding, specific patient characteristics – having had an acute exacerbation, reduced health-related quality of life, worse symptoms, physical deconditioning (including reduced muscle function and reduced exercise capacity), suffering from comorbid conditions (including depression), physical inactivity and deficiency in self-management or education – are useful in considering a referral for physical therapy. This insight contributes to the need for more information on patient selection criteria for PR programmes, like physical therapy.[20]
3) *An expanded applicability of the commonly used six-minute walk test*: The 6MWT is considered a reliable, valid and responsive test to evaluate functional exercise capacity in

patients with COPD, but also in other chronic diseases like heart failure.[2,3,29] Because course length substantially influences the performance of patients with COPD, in a 6MWT, using existing reference equations to establish %-predicted values for the 6MWD, causes an overestimation of the functional capacity of a COPD patient.[6] This overestimation results in a worse representation of a COPD patient's functional exercise capacity that may influence the patient's physical therapy treatment plan[30] and may interfere with correct interpretation of rehabilitation results by referring clinicians.

The influence of physical therapy on exercise capacity (in research and practice) needs to be considered in respect of correct use of clinimetric norm values. Therefore, the first reference equations for the 6MWT-10m, provided by this thesis (Chapter 6), serve as a solution to a practical problem and expand the usefulness of the 6MWT in healthy adults and patients with chronic diseases, like COPD.

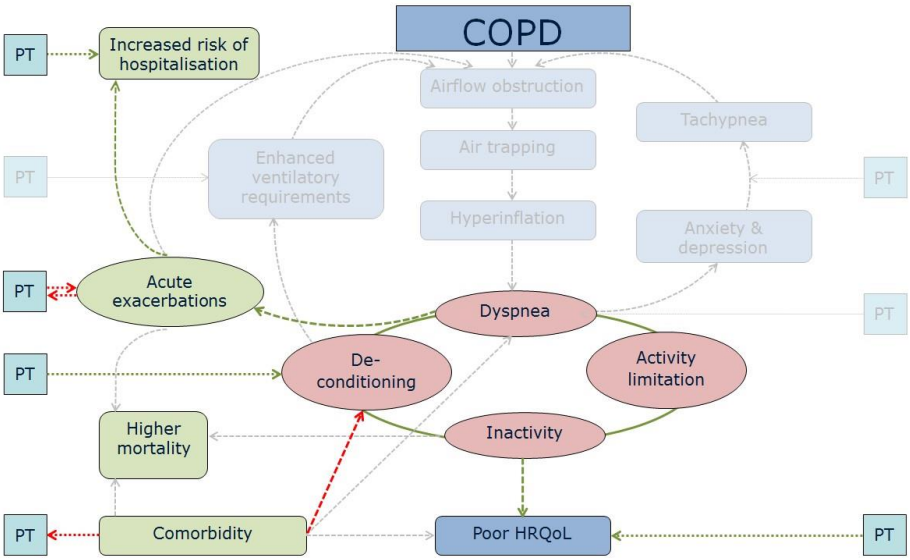
4) *A potential for societal cost reduction through physical therapy*: COPD exacerbations are invoke high socioeconomic costs.[20,31] Physical therapy is momentarily addressed in The Netherlands for known benefits like an increase in relief of dyspnoea, improvement of muscle strength, improvement of exercise performance and reduction of physical inactivity.[32,33] Annual costs involved are on average 2,445 euros per patient (on average 1.5 treatments a week for 30.76 euros per treatment),[34] with (partial) reimbursement by health insurance companies. However, due to the potential of physical therapy to reduce exacerbation frequency, costs involved with each prevented hospitalisation (on average 3,690 euros per exacerbation) or each prevented contact with a physician plus antibiotics and/or prednisone (on average 84 euros per exacerbation) can be considered profit.[35-39] Therefore, the demonstrated reduction of event-based exacerbation frequency and duration may also be relevant for governments and health insurance companies, as a relatively small percentage of all patients (10%) experiencing exacerbations account for over 70% of all medical costs due to COPD.[40,41] The economic but also prognostic impact of physical therapy is large when it causes a reduction of only one or two exacerbations in one year or one exacerbation leading to hospitalisation, as this history indicates the presence of a susceptibility phenotype, independent of disease severity (GOLD-stage), being the best predictor of having frequent exacerbations in the future.[20,42]

The latest GOLD report stated that COPD exacerbations can often be prevented by a variety of interventions such as smoking cessation, influenza or pneumococcal vaccines and long-acting inhaled bronchodilators, with or without inhaled corticosteroids.[20] We recommend that PR or physical therapy, as a potential mean for the prevention of future exacerbations should be incorporated.

COPD AND PHYSICAL THERAPY

The outcomes of this thesis underline the close relationship between exacerbations, dyspnoea and physical deconditioning[43] and between muscle weakness and inactivity, increasing the frequency of future exacerbations.[10, 21] This vicious cycle may be broken by intensive physical therapy (Figure 9.1), as confirmed by a positive effect of physical therapy on the intermediate outcomes functional exercise capacity and muscle strength in our trial, leading to a reduction of exacerbation rates, including hospitalisations (Chapter 8). Physical therapists are confronted with a population with a high burden of disease (Chapter 2) and this thesis shows (Chapter 3) that physical therapists need to tailor individual health care for patients with COPD, comorbidities and with the frequent exacerbator phenotype[1] (Figure 9.1).

This thesis fills some 'scientific gaps' in the knowledge on the influence of comorbidity during primary care physical therapy and the effect of physical therapy on exacerbation rates. While monitoring COPD-outcomes, such as decreased functional exercise capacity (an evident trait of deconditioning),[44] the modifying influence of different comorbid conditions during physical therapy (Chapter 4) should be taken into account by all health care professionals involved (Figure 9.1). Moreover, physical therapy is not only effective in reducing symptoms, improving exercise capacity, improving healthrelated quality of life, reducing hospitalisation, reducing anxiety and depression,[20] but is also likely to be effective in reducing frequency, durations and severity of eventbased and symptom-based acute exacerbations. This is a 'scientific gap' regarding the effectiveness of physical therapy that was provided by this thesis (Chapter 8) and was added to Figure 9.1.



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

Figure 9.1 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 in the general introduction[19,20,45-55] and the additive parts from this thesis: green arrows confirmed existing evidence; red arrows provided new evidence.

METHODOLOGICAL CONSIDERATIONS

Study design

A combination of several cross-sectional experimental and observational studies, a multiple case study, a longitudinal cohort study and a randomised controlled trial was used to answer the different research questions addressed in the general introduction of this thesis.

The positive effect of physical therapy on functional exercise capacity[19] can be diminished by a few specific comorbid conditions as was shown in by our cohort study (Chapter 4). However, the methodological design of this study does not allow for a comparison with a random group of patients with COPD and comorbidity that did not receive physical therapy, because differential classification bias was likely to emerge from the selective referral by general practitioners to physical therapists when patients had an overall higher burden of disease (Chapter 2).[25] It is likely that the decline in exercise capacity will be much larger if patients with COPD and the addressed comorbid conditions do not attend physical therapy. This is because exercise-based

rehabilitation programmes have the ability to revert physical inactivity in patients[24], they increase exercise capacity in patients with COPD[19] and increase exercise capacity in patients with conditions like cardiac diseases[56] or depression.[57] Moreover, despite including patients with comorbidity in our trial, physical therapy still had a significant influence on the intermediate outcome functional exercise capacity and on the outcomes of interest regarding exacerbation rates, compared to the control group (Chapter 8).

In our trial two groups were compared; the physical therapy group (high-intensity exercise training) versus the control group (sham-treatment e.g. very low-intensity exercise training). This comparison was ethically approved as the high-intensity exercise training was not considered usual care at that time. Nevertheless, we encountered disappointing participations rates as patients and physical therapists did believe in the effectiveness of physical therapy regarding exacerbation rates. A large difference in exacerbations rates between-groups and the fact that more patients died in the control group than in the intervention group led to our decision to stop the trial earlier, despite the small sample size. The power of studies is not always reflected in the study sample.[58] This can be confirmed by our trial that was adequately conducted and adequately powered (99% with confidence intervals excluding an IRR of 0 that would change the clinical decision, Chapter 8), and therefore may serve as a 'most precise trial'[58] for the outcome exacerbation rates in COPD following physical therapy after an acute exacerbation. The observed effect in our trial was so large that it is unlikely that the effect can be attributed to bias only.[14] Still, because of the small sample size[14] and trial truncation our study results may overemphasise its effects,[59] and the results should be interpreted with caution and should be confirmed by other studies, obviously with a different methodology. We feel that interventions like PR and physical therapy cannot be placebo controlled in western countries like The Netherlands, not even in regions where physical therapy is not considered usual care. In general, it is desirable to gather evidence in physical therapy settings, but methodologically it will not always be ethical (a reason for stopping our trial early), feasible (a reason for additional research and adaptations regarding clinimetrics of the 6MWT) or sustainable (a reason why comorbidity was included in the trial and cohort). A challenge exists to use and accept alternative study designs than randomised controlled trials as best evidence in physical therapy studies.

Patient populations in primary care

The overall burden of disease was higher in the study populations in this thesis compared to the general COPD population. This observation can be explained from several angles. The average number of exacerbations per GOLD-stage in our trial (GOLD2: 2.6; GOLD3: 3.3; GOLD4: 4.0) was much higher than the numbers found in other cohort studies (GOLD2: 0.7-0.9; GOLD3: 1.1-1.3; GOLD4: 1.2-2.0).[42,60,61] Methodologically, this can be explained by including the symptoms-based exacerbation definition in our study and by the specific inclusion criteria for our study population (higher disease severity with Tiffeneau-index<0.6, comorbidity and a history of exacerbations). For every eligibility criterion there is an explanation why the patients in our study appeared to have a frequent exacerbator phenotype. The more severe the spirometric classification the higher the exacerbation frequency.[20] The presence of (some) comorbidities are associated with an increased risk of exacerbations,[20] systemic inflammation is even a proven link between multiple comorbidities.[62] Finally, a history of previous event-based exacerbations is the best predictor of having frequent exacerbations.[42]

Apart from specific eligibility criteria in the trial, this thesis (Chapter 2) shows that patient phenotypes in different primary care (non-research) settings are unequal and that patients treated by a physical therapist have, on average, a higher burden of disease (higher degree of airway obstruction, more exacerbations, more vascular comorbidity and lower perceived health status) compared to patients not treated by a physical therapist.[25] This finding was again confirmed by our cohort study reflecting a natural cohort, without specific eligibility criteria, while receiving pulmonary physical therapy care. Also in this cohort the burden of disease was high regarding the presence of comorbid conditions and the exacerbation history was positively skewed with a median of 1.0 (0.0-2.0) (Chapter 4).

Outcomes measures

We recommend considering the differences in definitions for exacerbations in scientific studies. Taking into account both event-based and symptom-based exacerbations in scientific research have been worthwhile as was seen in our trial. It is essential that medical practices routinely monitor exacerbations but this is not yet a convention in physical therapy practice. Electronic patient documentation systems can assist by building in a systematic field for the evaluation of exacerbation rates. For research purposes, however, the use of electronic patient record systems to collect clinical patient data in primary care is difficult. Although in the long-term it may be promising, many complications regarding the use of a high quality electronic record system in our trial setup were exposed. The study protocol described that primary and secondary study-specific outcome measures will be assessed with the help of a COPD-

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specific record system.[63] It was a specially built electronic record system for therapists but with the goal to capture all desired research outcomes and information to monitor the intervention. Because not all eligible physical therapists were willing to use this system and not all who used the system completed all required fields after trial set-up, most research data for the trial and cohort was collected manually by the researcher at the therapy practices or retrieved from the different electronic patient record systems that were used in each participating practice during the studies.

IMPLICATIONS FOR CLINICAL PRACTICE

Referral for physical therapy

Physical inactivity is a legitimate reason for a general practitioner to refer a patient for physical therapy,[26] but not the only legitimate criterion as COPD assessment is a multifactorial concept.[20,25,64] This finding may also explain why there is a discrepancy between the high numbers of patients with COPD who are inactive (73% in our study, 84% in another cohort study[65]) and the relative low number of patients with COPD referred to and treated by a physical therapist (18% in our study, 27% in a national epidemiological study[66]). On the other hand, general practitioner use of PR, like physical therapy, for patients with COPD lags behind national and international guideline recommendations.[67] More people may be eligible for COPD treatment by a physical therapist, given the national under-reporting of the medical diagnosis COPD.[31] To facilitate inclusion of physical therapy in COPD management, (primary care) referring physicians need to decide when rehabilitation best fits in an individual's COPD treatment programme.[67] The earlier mentioned criteria for patient selection for physical therapy in this thesis contribute to recapturing referring criteria for physical therapy. A statement, that is largely in line with the international GOLD report that promotes to include symptoms, presence of comorbidities and future risk of exacerbations.[20] The Dutch general practitioners practice guidelines should incorporate these multiple factors to refer patients with COPD for physical therapy, rather than inactivity only. This altered referral strategy may improve quality of healthcare and an altered strategy is inevitable, since no specific pulmonary function inclusion criteria that indicate the need for rehabilitation like physical therapy exist.[41] Currently symptoms and functional limitations and not the severity of the underlying physiology, direct the need for rehabilitation.[26,41] This often leads to delayed referral until patients reach a stage of advanced lung disease. While these patients can derive considerable

benefit from rehabilitation, earlier referral would allow for earlier preventative strategies, like greater latitude in the exercise prescription.[41]

Delivering optimal physical therapy

This thesis aimed to provide data enabling physical therapists and physicians a) to deliver competent treatment, b) to obtain optimal treatment results that can be interpreted correctly, and c) to tailor individual health care for patients with COPD and comorbidity and with the frequent exacerbator phenotype.

Ad a: Exercise interventions in physical therapy are often not well described in research reports. Omitting details of the intervention hampers the transfer to daily clinical practice.[68] A framework for describing goals and content of exercise interventions, in order to provide structured and detailed information for use in research reports, was developed with an overarching national research group `Designing Optimal Interventions for physical Therapy (DO-IT)`.[68] This framework, based on the International Classification of Functioning, Disability and Health (ICF), was used to describe and publish goals and content of the exercise interventions in our trial and cohort.[63]

Ad b: Clinimetric skills are essential to collect and interpret treatment results correctly. In accordance to Singh and colleagues, we encourage clinicians to use published reference equations for the 6MWT related to the length of the test course.[5,7,69]

Ad c: Dealing with comorbidities and acute exacerbations in patients with COPD during an intervention is another challenge physical therapists face. This thesis (Part 2) gives more guidance for health care professionals on how to handle COPD patients with comorbidity in practice and what to expect from the influence of physical therapy, modified by comorbidity, on exacerbation rates and functional exercise capacity. This information is lacking in clinical practice guidelines.[9] Guidelines and most scientific studies that exclude comorbidity do not consider the reality of patient care with multiple chronic conditions.[70] As stated earlier in this thesis, COPD does not come alone and literature reports that up to 97.7% of patients with COPD have one or more comorbid conditions[71] (quite similar to the 89% in Chapter 4). Due to demographic changes, the absolute number of patients suffering from COPD will rise between 2011 and 2030 by 27%-49%.[72] Likewise COPD mortality will rise in Europe in the next two decades.[73] With an overall increase of the elderly population the number of comorbidities highly prevalent in patients with COPD will also increase.[53,74] According to the report by Kaljouw and colleagues (2015),[75] in several regions in The Netherlands more than half of the population will have one or multiple chronic diseases by 2030, including COPD. Although chronic conditions do not necessarily mean limitations in functioning from the patients' perspective, limitations in mobility and psychiatric diseases were clearly present in the national prognosis.[75] This thesis confirms the

presence of multiple chronic diseases like cardiovascular, psychiatric and metabolic diseases in patients with COPD treated in primary care (Chapter 3 and 4), but also confirms that the comorbid condition present did interfere with patients' daily life (established by a median severity index of 2.0 on the comorbidity scale (CIRS), meaning interference with normal activity, Chapter 4). These findings are in line with the report by Kaljouw and colleagues, who suggested 23 citizen profiles divided into low or high complex problems and the absence or presence of multiple chronic conditions (comorbidity), limitation in functioning and psychosocial problems (like interference with daily life according to the CIRS), on which healthcare by multidisciplinary teams should be based.[75] Accordingly, we suggest that the study population of this thesis should not only be considered as "patients with COPD" to optimally target therapeutic interventions and evaluate treatment results. With the knowledge that COPD is accompanied by systematic consequences, acute exacerbations and much comorbidity, we encourage physical therapists to offer a holistic patient-centred approach in order to obtain an individually tailored-programme,[1] that tries to match the physical therapy clinical guidelines for COPD and other comorbid conditions, in line with another recent publication.[70] Also, the international guidelines on COPD assessment advised to take the patient's symptoms, future risk of exacerbations and presence of comorbidities into account instead of the disease severity only.[20] Primary care physical therapists have a unique opportunity to identify patients at risk for a higher burden of disease and to provide care that encompasses a holistic approach to management and correct interpretation of health outcomes. In this light there are some tangible points of attention for physical therapists that can be derived from this thesis. The patientcentred rather than disease-centred approach should target at physical therapist's skills and knowledge of highly prevalent comorbidities, on the need for monitoring more than COPD-outcomes alone, on adequately adjusting interventions and on the level of information regarding all coexisting diseases and related medication given by general practitioners and physicians during referral of a patient to a physical therapist (Chapter 3).[1]

Reimbursement for physical therapy in COPD

Although *the need* for physical therapy does not rely on specific pulmonary function inclusion criteria but (at least) on symptoms and functional limitations,[26,41] only patients with GOLD stage II or higher will receive *reimbursement* for physical therapy in

The Netherlands.[76] This inclusion criterion that is solely based on a pulmonary function – the degree of pulmonary obstruction – may easily cause misclassification of patients with COPD to enter physical therapy treatment. Some patients may not enter physical therapy treatment until their symptoms become troublesome, they have a high exacerbator phenotype and comorbidities are present, along with a significant respiratory impairment (GOLD-II ≥).[32] The severe and complex patient population that is seen in primary physical therapy practice[25] may be one of the reasons that physical

therapists treat patients with COPD for long-term periods. Studies with long-term exercise programmes for patients with COPD generally achieve more favourable results regarding functional exercise capacity, skeletal muscle function, and health-related quality of life.[77] 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.[77]

We advise healthcare insurance companies to primarily consider symptoms and functional limitations in combination with exacerbation risk and comorbidities. These factors are included in the 'Burden of disease tool COPD' ('Ziektelastmeter COPD' in Dutch) for general practitioners and pulmonologists. This has been developed in The Netherlands by the partnership Picasso, run *under* the *auspices* of the Dutch Lung Alliance (LAN) and supported by a few health care insurance companies (Achmea and CZ). It also connects referral for physical therapy to symptoms, functional limitations, mental state, quality of life, underweight and inactivity, but not yet to recent exacerbations or presence of comorbidity.[78] Together with general practitioners, physical therapists are the health care professionals par excellence to identify patients that are most suitable for physical therapy. They work closely with the general population in primary care and are able to incorporate the selection criteria proposed by this thesis and the literature[20] (early post-exacerbation, future exacerbation risk, comorbid conditions, reduced quality of life, worse symptoms, physical deconditioning (including reduced muscle function and reduced exercise capacity), physical inactivity and deficiency in self-management or education). Still, direct access to physical therapy is not yet an option for patients with COPD who need a chronic indication. Together with an altered reimbursement strategy for physical therapy this may be a future direction for improvements in quality of health care.

FUTURE RESEARCH DIRECTIONS

Part 2 of this thesis makes clear that comorbidity should not be excluded from scientific studies that take into account functional exercise capacity as an outcome. A main goal during collecting scientific evidence should always be translating scientific findings (both generalisation and particularisation) to clinical practice.[79] Since the majority of patients with COPD have proven to be part of a complex population[25,75] capturing comorbidities in scientific studies is inevitable.

More evidence for the potential of physical therapy to reduce exacerbation frequency, duration and severity is desirable. The conclusions of the most recent update of the Cochrane Review (2015) on PR, in COPD patients are in line with its prior versions: there is a strong argument that rehabilitation is beneficial in improving quality of life.[19,80] The view that additional randomised controlled trials comparing PR and conventional care in COPD are no longer warranted, led to the unusual decision by the Cochrane Airways

editorial board that this review is now closed.[80] On the one hand this recent review and coinciding decision reinforced our earlier stopping of the trial. The recruitment related problems (many patients refrain from participation as they believed in the effectiveness of physical therapy regarding exacerbation rates) and ethical related problems (more deaths in the control group than in the intervention group) we experienced, seem to be in line with the positive influence of physical therapy on all our study outcomes (Chapter 8) as well as with the conclusion of the recent Cochrane Review. Although the quality of the review evidence is only, at best, moderate, this is inherent in the current criteria of quality and the type of intervention from which we cannot expect higher-quality evidence to be forthcoming[81] as this type of intervention cannot be double blinded.[80] On the other hand this review concerned rehabilitation in stable patients, whereas we studied a patient population after an acute exacerbation. Studies in this field so far have been captured by another Cochrane Review.[14] Closing the systematic review on PR in stable patients can be seen as good news as research money should now be directed elsewhere.[19,80]

One direction is the non-stable patient population after an acute exacerbation; another is attention for the outcome 'exacerbation rates' that was captured as a whole in our trial (exacerbation frequency, duration and severity in relation to the event-based versus symptom-based definition of exacerbations), unlike the outcome hospitalisation in the review on PR after an acute exacerbations.[14] With these future research directions accepting alternative methodological study designs as best evidence for physical therapy studies will be a challenge. This also accounts for new research opportunities in relation to PR including the intensity of the training, the degree of supervision, the ideal length and location and how long the treatment effect persists.[19] Literature suggests that these specific issues require further elucidation through randomised controlled trials and further meta-analysis.[80] However, since there is some evidence that high-intensity exercise elicits greater benefits;[82] supervised training sessions are recommended over un-supervised sessions;[19, 77] long-term exercise programmes show greater effects;[77,83] and maintenance strategies following rehabilitation are beneficial,[83] these future research direction may also ask for alternative research methodology that can still be considered ethical.

Regarding the clinimetric topic in Part 3 of this thesis, the first reference equations for the 6MWT-10m serve as a solution to a practical problem and expand the usefulness of the 6MWT in healthy adults and patients with chronic diseases, like COPD. Establishing absolute 'benchmark values' suitable for a test conducted over 10 m should be a next step.[5,69] Studies debate the usefulness of group-based point-estimates, like a minimal clinical important difference (MID), for the individual patient.[84-86] Whereas other literature mentions that the advantage of

defining norm values, like an MID, is that it can be used to determine whether important changes in health status have occurred in individual patients.[87] Indeed, a between-group criterion that needs to be met to be considered clinically meaningful may mask important changes for individual patients. Although reference-equations are also based on statistical properties of the population-based measurement, they embrace the variation that is inherent in measurements of the 6MWD. We suspect that the norm values can be applied most confidently to groups in clinical studies in primary (and secondary) care. Health care professionals can use them to get an indication of an individual's status in clinical practice, since our study established the reference equations of health individuals with a wide range of age, weight, length and heart rate – the most important predicting factors of 6MWD.[7] Further, in the literature, established values by statistical distribution-based methods only[84] are similar to thresholds reported for individuals (including anchor-based methods).[85,87] Overall, the new reference equations and future established absolute benchmark values are likely to assist in the interpretation regarding diagnosis and prognosis (reference equations) and prognosis and change (e.g. the distance below which survival is affected; MID) in exercise capacity following intervention.[5,7,84,88] Awareness concerning the need for a critical view towards clinical feasibility of current measurement instruments and corresponding norm values was created by this thesis. We therefore, recommend a clear description of the standardised measurement methods (including the course length for 6MWTs) used in scientific studies. Moreover, an update of the ATS guidelines is timely. New literature was published since 2002 and there is a need for adaptations of exercise tests in research that corresponds with different clinical settings, especially in primary care.

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Summary

SUMMARY

This thesis concerns the interactions between physical therapy, comorbidity and exacerbations in patients with Chronic Obstructive Pulmonary Disease (COPD). It provides data and tools 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 who frequently experience exacerbations.

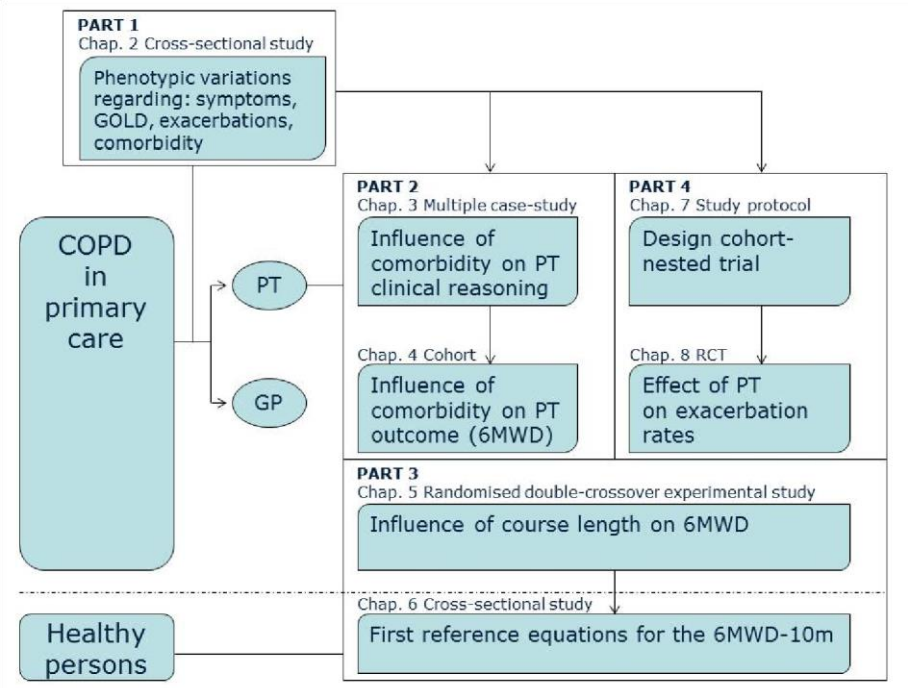
Chapter 1 is the general introduction of this thesis, which defines COPD and puts this disease in a societal, clinical and economic perspective. It describes the disease burden and pathophysiology of COPD, its risk factors and consequences for the patients. The common traits 'exacerbations' and 'comorbidy' are defined. In the light of multidisciplinary care for patients with COPD, special attention is given to protocol-directed physical therapy in the Netherlands that qualifies as the cornerstone of pulmonary rehabilitation according to the literature. The current evidence for effectiveness of physical therapy is addressed followed by 'scientific gaps' that arise when comorbidity is present in the patient population; when exacerbations are measured and exacerbation rate reduction is the outcome of interest; and when measurement of functional exercise capacity is not feasible in practice, with respect to physical therapy. This chapter concludes with the thesis' aims and a schematic outline of the thesis body to link all topics covered by this thesis (Figure 1).

Part 1: An introduction to the study population of this dissertation

The first part of this dissertation gives an introduction to the study population. Phenotypic variation in patients with COPD in primary care is illustrated, with special attention to differences in exacerbations and comorbidity.

Patients with COPD benefit from physical activity. Physical therapy is therefore recommended by general practitioner guidelines. Many patients with COPD appear

physically inactive; however, they often are not referred for physical therapy. It is likely that general practitioners take other factors into account for referral, determining a subpopulation that is treated by a physical therapist. Chapter 2 presents a cross-sectional study, which aims to determine differences in patient characteristics between inactive patients treated by a general practitioner and inactive patients treated by a general practitioner as well as a physical therapist. Additionally this study provides an overview of the phenotype of patients with COPD in physical therapy practice. Differences regarding perceived health status, degree of airway obstruction, exacerbation frequency, and comorbidity were studied with questionnaires in 438 patients, of whom 290 were physically inactive. Patients treated by a general practitioner combined with a physical therapist 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 physical therapist. Unequal patient phenotypes in different primary care settings may have important clinical implications. It seems that other factors, other than the level of inactivity mentioned in the general practitioners clinical practice guidelines, play a role in the referral of patients for physical therapy.



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 meter course.

Figure 1 A schematic representation of the thesis body.

Part 2: The influence of comorbidity on physical therapy practice and outcome in patients with COPD

This part focuses on the influence of comorbidity on physical therapy in two ways: the influence of comorbidity on physical therapy clinical reasoning and the influence of

comorbidity on the physical therapy outcome functional exercise capacity, more specifically the six-minute walk distance.
Firstly, the therapeutic consequences for physical therapy practice during treatment of patients with COPD and multiple comorbidities are addressed. Comorbidities are prevalent in patients with COPD, but current physical therapy guidelines do not incorporate clear actions related to comorbid conditions. Comorbidity may require adaptations in intervention strategies, as comorbidity (e.g. diabetes mellitus) negatively affects treatment results of the index disease COPD, or treatment for one disease (such as cardiopulmonary endurance training for COPD) may negatively interact with the treatment or natural course of a coexisting disease (e.g. severe osteoarthritis of the knee). Therefore, in Chapter 3 two case studies illustrate possible consequences of COPD (index disease) and comorbidity for physical therapy in a primary care setting. Both avoidable and inescapable problems were unfolded in the different steps of the clinical decision-making process. The first case was a very severe COPD patient (FEV1=46% predicted and chronic respiratory failure) with decompensated heart failure, using a beta-adrenergic blocker. It demonstrates the danger of missing relevant information about a comorbid condition and related medication during the intake and its consequences for physical therapy practice. The second case, a mild COPD patient (FEV1=86% predicted) with multiple inter-related comorbidities, showed the importance of monitoring outcomes of multiple diseases and adjustments to the plan of care and interventions. Dealing with comorbidity in COPD management needs a patient-centred rather than a disease-oriented approach in order to obtain optimal treatment and results. It is concluded that physical therapists should improve their skills and knowledge of high prevalent comorbidity combinations; be fully informed regarding medical patient records; also monitor comorbidity-outcomes instead of COPD-outcomes alone; and adequately adjust interventions to the multi-morbid patient. General practitioners and chest physicians can improve the level of information given to a physical therapist when a patient is referred for physical therapy, by providing information on all coexisting diseases and related medication.

Secondly, the effect of physical therapy on the primary outcome functional exercise capacity (six-minute walk test) is presented within prognostic profiles of patients with COPD and comorbidity. Although comorbidities do not preclude access to rehabilitation, they seem to affect physical therapy outcomes in patients with COPD. However, the extent to which comorbidity impacts on physical therapy outcomes over time remained unclear, especially in primary care. Chapter 4 presents a prospective cohort study including 158 patients, GOLD I-IV, receiving long-term guideline-directed physical therapy for COPD to investigate the influence of comorbidity on the progression of change in functional exercise capacity during primary care physical therapy. Functional exercise capacity was monitored by means of 1301 measurements of six-minute walk distance (6MWD). Comorbidity was registered with the Cumulative Illness Rating Scale (CIRS). To study the influence of comorbidities on repeated assessments of 6MWD over time, random slope mixed model analyses with an AR(1) correlations structure was used. Median treatment duration was 27 months (*95%CI*: 7-65). Comorbid conditions in the categories 'endocrine, metabolic, lymphatic, immune', 'cardiovascular' and 'muscle, bone, skin' were most prevalent. With every additional comorbid condition the 6MWD was significantly lower at the start of physical therapy (23 metres, *95%CI*: 31-14). Besides, with every extra condition the progression of 6MWD over time decreased with 7 metres (*95%CI*: 13-1) during 1,000 days of physical therapy. By analysing each disease category individually for its impact on the 6MWD, three different profiles were noted. Corrected for the confounding influence of the other fixed comorbidity variables, cardiac, hepatic and psychiatric disease had the strongest negative interactions with time, with a significant correlation of sequential six-minute walk tests (r=0.33, SE=0.045). In this cohort of patients with COPD receiving physical therapy, the starting level as well as improvements of functional exercise capacity was significantly reduced by comorbidity, which appeared also clinically meaningful. This is the first long-term follow-up study in COPD to illustrate the influence of comorbidity on exercise capacity during primary care physical therapy within prognostic profiles.

Part 3: Extended applicability of functional exercise capacity assessment (the six-minute walk test)

The third part of this thesis considers optimisation of functional exercise capacity assessment as a consequence of 'bottom-up' observations during the research presented in this thesis. Firstly, the influence of course length on functional exercise capacity (6MWD) in patients with COPD is explained. Secondly, the first reference equations for the 6MWD over a course of 10 metres are provided.

As primary care practice space is mostly limited to 10 metres, the six-minute walk test (6MWT) over a 10-metre course is a frequently used alternative to evaluate patients' performance in COPD. However, the question whether patients with COPD achieve a different distance on the 6MWT conducted on a 10-metre course versus on a 30-metre course remained. Furthermore, existing reference equations that were generated on longer courses may lack valid conclusions when applied to distances walked on a 6MWT conducted on a 10-metre course. Chapter 5 presents a randomised double-crossover experimental study in 45 patients with COPD in primary physical therapy care. All patients performed a 6MWT twice over a 10-metre course and twice over a 30-metre course. The 6MWTs were performed in accordance with the American Thoracic Society guidelines. 6MWD was assessed and predicted distance was calculated based on a range of reference equations. The 6MWD on the 10-metre course was 49.5 metre shorter than on the 30-metre course, which was statistically significant (*95%CI*: 39.4-59.6). By using existing reference equations for a 6MWT conducted on the 10-metre course, the predicted distance is highly overestimated (range: 30-33%). Besides, the average distance as a percentage of the predicted value is 8% lower compared to a 6MWT conducted on the 30-metre course, resulting in a worse representation of a COPD patient's functional exercise capacity. This chapter proves that the impact of course length on the 6MWD and on the use of reference equations in patients with COPD is substantial and clinically relevant (even when using the most conservative published minimum clinically important difference). Therefore, existing reference equations established for a 6MWT conducted over a 30-metre (or longer) course cannot

be applied to predict the distance achieved on the 6MWT on a 10-metre course, which is frequently used for patients with COPD in primary care physical therapy practices.

Considering that course length significantly affects 6MWD, the study in Chapter 6 developed appropriate reference equations for the 10-metre 6MWT. In a cross-sectional study, 181 healthy subjects aged 40-90 years performed two standardised 6MWTs over a straight 10-metre course. Average distance achieved was 578±108 metre and differed between males and females ($p<0.001$). Resulting sex-specific reference equations from multiple regression analysis included age, body mass index and change in heart rate, explaining 62% of the variance in 6MWD for males and 71% for females. The presented reference equations are the first to evaluate 6MWD over a 10-metre course and expand the usefulness of the 6MWT in healthy adults and patients with various chronic diseases like COPD.
Part 3 concludes with a published correspondence between the co-chairs of the joint American Thoracic Society and European Respiratory Society (ATS/ERS) task force and the authors of this thesis regarding the question: What determines which six-minute walk test is conventional?

Part 4: Physical therapy to reduce COPD exacerbations

The fourth part of this thesis studies the potential of physical therapy to reduce COPD exacerbations. Firstly, the study protocol of the cohort-nested trial design is explained. Finally, the effect of physical therapy on exacerbation rates is presented.

Physical exercise training aims at reducing disease-specific impairments and improving quality of life in patients with COPD. Exacerbations in particular negatively impact COPD progression. Physical therapy intervention seems indicated to influence exacerbations and their consequences. However, information on the effect of physical therapy on exacerbation occurrence was scarce. Chapter 7 presents a study protocol of a cohort-nested randomised controlled trial to study the potential of a protocol-directed physical therapy programme as a means to prevent or postpone exacerbations, to shorten the

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duration or to decrease the severity of exacerbations in patients with COPD who have recently experienced an exacerbation. Within a prospective cohort, patients with COPD GOLD I-IV (including comorbidity) received usual multidisciplinary COPD care including guideline-directed physical therapy. Patients in this cohort who have GOLD I-IV (post-bronchodilator FEV1/FVC<0.7 and FEV1<80% of predicted), who receive reimbursement by health insurance companies for physical therapy (post-bronchodilator Tiffeneau-index <0.6) and who experience a COPD exacerbation were asked within 56 days after the exacerbation to participate in a cohort-nested prospective randomised controlled trial (RCT). In this RCT, the intervention group received a strict physical therapy programme for patients with COPD. This protocol-directed physical therapy was compared to a control group that received sham-treatment, meaning no or very low-intensity exercise training. Anthropometric measurements, comorbidities, smoking, functional exercise capacity, peripheral muscle strength, physical activity level, health related quality of life, patients' perceived benefit, physical therapy compliance, motivation level, level of effective mucus clearance, exacerbation symptoms and health care contacts due to COPD were recorded. Subsequently, the primary outcome exacerbation frequency and seconday outcomes exacerbation duration and severity were quantified with both a symptom-based and an event-based approach. Follow-up measurements were scheduled at 3 and 6 weeks, 3, 6, 12 and 24 months after inclusion. The planed economic evaluation concerns an estimation of avoidable costs due to exacerbations.. Finally, ways to minimise potential difficulties regarding the execution of this study are discussed.

In Chapter 8, the results of this trial aimed at investigating the potential of physical therapy, including intensive physical exercise training, in order to decrease exacerbation frequency, duration and severity in patients with COPD after an acute exacerbation are presented. Twenty-nine patients with COPD (GOLD I-IV, age 45-81) who suffered an acute exacerbation were randomly assigned to one of two groups: physical therapy intervention (high-intensity exercise training) or sham-treatment (no or very low-intensity exercise training). For ethical-related recruitment considerations, including a skewed distribution of deaths in the trial patients (one in the physical

therapy group versus three in the control group), inclusion was stopped prematurely. Exacerbation frequency was calculated as the primary outcome variable. Exacerbations were identified by a *symptom-based* approach (clear increase of respiratory symptoms) in addition to an *event-based* approach (health care contact). Secondary outcomes used were exacerbation duration, exacerbation severity, quality of life and exercise capacity. Overall, ninety-four exacerbations were counted. Exacerbation frequency was significantly higher in the control group (6.15±1.82 counts) compared to the intervention group (1.17±1.27, $p<0.001$). When comparing the intervention to the control group, average exacerbation duration was shortened by 10 days, perceived exacerbations were 2.7 points less severe on a 12-point scale and exercise capacity and quality of life improved significantly in the intervention group. It is concluded that physical therapy, including high intensity exercise training after an acute exacerbation, reduced the frequency, duration and severity of exacerbations in patients with COPD. It was shown from a simple cost-effectiveness calculation that physical therapy may recover costs (on average 531 euros per patient) by frequency reduction of event-based exacerbations. The observed effect in this study is so large (99% power) that it is unlikely that the effect can be attributed to bias only. But because of the small sample size and early termination the results of this study should be interpreted with caution as our study results may overestimate its effects.

Chapter 9 presents the general discussion of this thesis. It starts with an overview of the main findings reported in this thesis. This chapter concludes that the findings from Part 1 (unequal patient phenotypes in primary care physical therapy settings, including more exacerbations and more comorbidity) strengthened the need for Part 2 – a more comprehensive evaluation of physical therapy in patients with COPD and comorbidity; and for Part 4 – a more comprehensive evaluation of physical therapy in patients with COPD after an acute exacerbation. Moreover, from a 'bottom-up' point of view, it discusses the clinimetric feasibility of measuring exercise capacity in practice (Part 3). This chapter gives a general reflection on all studies performed and discusses methodological considerations. It places the results of the studies in the context of other scientific evidence in the field of pulmonary rehabilitation and physical therapy

along with measurement of performance in patients with COPD, comorbidity and exacerbations. This general discussion concludes with the main implications for clinical practice and directions for future research.

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Samenvatting

SAMENVATTING

Dit proefschrift beschrijft de interacties tussen fysiotherapie, comorbiditeit en exacerbaties bij patiënten met 'Chronic Obstructive Pulmonary Disease' (COPD ofwel Chronische Obstructieve Longziekte) Dit proefschrift levert gegevens en handvatten die fysiotherapeuten en artsen in staat stellen om adequaat te handelen ter verkrijging van optimale behandelresultaten die correct kunnen worden geïnterpreteerd, en om individuele gezondheidszorg af te stemmen op patiënten met COPD en comorbiditeit die frequent exacerbaties hebben.

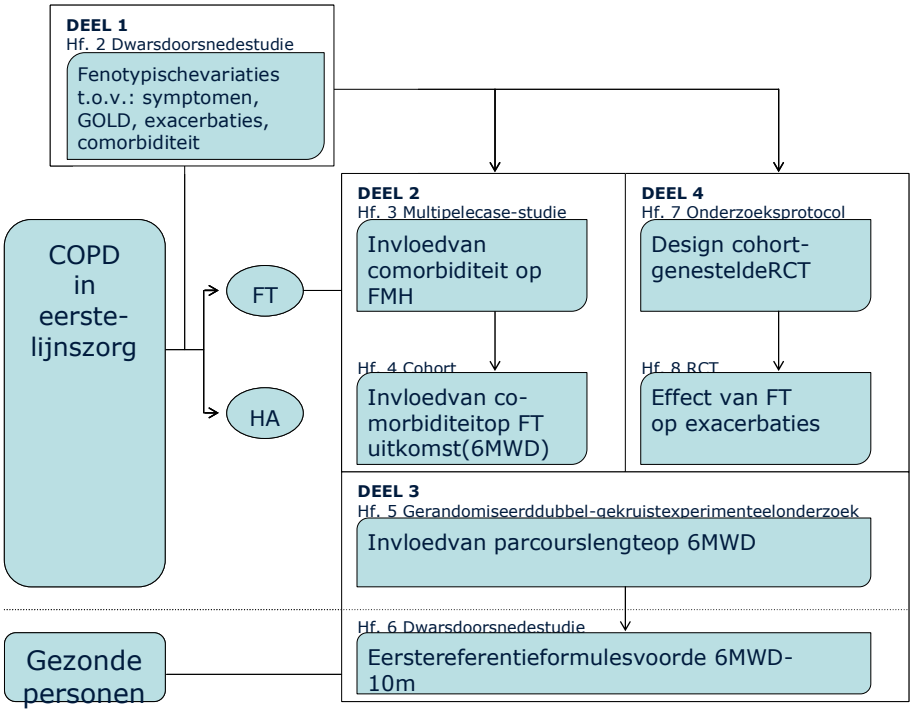
Hoofdstuk 1 is de algemene inleiding van dit proefschrift, waarbij COPD wordt gedefinieerd en de aandoening in een sociaal, klinisch en economisch perspectief wordt geplaatst. Het beschrijft de ziektelast en pathofysiologie van COPD, de risicofactoren en de consequenties voor de patiënten. Vervolgens worden de termen `exacerbaties' en `comorbiditeit' gedefinieerd. In het kader van multidisciplinaire zorg voor patiënten met COPD wordt extra aandacht besteed aan protocol-gestuurde fysiotherapie in Nederland, de hoeksteen van de pulmonaire revalidatie volgende de geldende literatuur. Het huidige bewijs voor de effectiviteit van fysiotherapie wordt toegelicht, gevolgd door het benoemen van `wetenschappelijke hiaten' met betrekking tot fysiotherapie die ontstaan door de aanwezigheid van comorbiditeit in de patiëntenpopulatie; die ontstaan bij het in kaart brengen van exacerbaties wanneer vermindering ervan een behandeluitkomst is; en die ontstaan door haalbaarheidsproblemen bij het meten van functionele inspanningscapaciteit. Dit hoofdstuk eindigt met de doelstellingen van dit proefschrift en een schematische presentatie van de inhoud van dit boek om de relatie aan te geven tussen alle onderwerpen die aanbod komen in dit proefschrift (Figuur 1).

Deel 1: Een inleiding in de onderzoekspopulatie van dit proefschrift

Het eerste deel van dit proefschrift geeft een introductie op de onderzoekspopulatie. Er wordt ingegaan op fenotypische variatie onder patiënten met COPD in de eerstelijnszorg, met speciale aandacht voor de verschillen in exacerbaties en comorbiditeit.

Patiënten met COPD zijn gebaat bij fysieke activiteit. Daarom wordt verwijzing voor fysiotherapie aanbevolen in de richtlijn voor huisartsen. Veel patiënten met COPD blijken fysiek inactief te zijn, echter, een verwijzing voor fysiotherapeutische zorg is niet vanzelfsprekend. Waarschijnlijk nemen huisartsen andere factoren in overweging bij het verwijzen van patiënten, wat bepalend is voor de subpopulatie die door fysiotherapeuten uiteindelijk wordt behandeld. Hoofdstuk 2 presenteert een dwarsdoorsnede studie die zich richt op het vaststellen van verschillen in patiënt karakteristieken tussen inactieve patiënten die behandeld worden door een huisarts en inactieve patiënten die een behandeling krijgen van zowel de huisarts als de

fysiotherapeut. Tevens geeft deze studie een overzicht van het fenotype van patiënten met COPD in fysiotherapiepraktijken. De verschillen ten opzichte van gezondheidsstatus, mate van luchtwegobstructie, exacerbatie frequentie en comorbiditeit werden met vragenlijsten in 438 patiënten achterhaalt, waarvan 290 fysiek inactief waren. Patiënten die behandeld werden door zowel een huisarts als een fysiotherapeut rapporteerden een grotere mate van luchtwegobstructie, meer exacerbaties, meer vasculaire comorbiditeit en een lagere gezondheidsstatus in vergelijking met patiënten die niet werden verwezen naar en behandeld door een fysiotherapeut. Ongelijke patiënt fenotypes in verschillende eerstelijnszorgsettingen kunnen belangrijke klinische implicaties hebben. Het lijkt erop dat inderdaad andere factoren, dan enkel de mate van inactiviteit die wordt genoemd in de praktijkrichtlijn voor huisartsen, een rol spelen in het verwijzen van patiënten naar fysiotherapie.



Afkortingen: Hf = hoofdstuk, GOLD = ziekte stadium volgens `the Global Initiative of Lung Disease` classificatie, FT = fysiotherapie, HA = huisarts, FMH = fysiotherapeutisch methodisch handelen, 6MWD = zesminuten wandelafstand, RCT = gerandomiseerd gecontroleerd onderzoek, 6MWD-10m = zes-minuten wandelafstand over een 10 m parcours.

Figuur 1 Een schematische presentatie van de inhoud van het proefschrift.

Deel 2: De invloed van comorbiditeit op fysiotherapeutisch handelen en uitkomstmaten bij patiënten met COPD

Dit deel richt zich op twee verschillende manieren op de invloed van comorbiditeit op fysiotherapie: de invloed van comorbiditeit op het fysiotherapeutisch methodisch handelen en de invloed van comorbiditeit op de fysiotherapeutische uitkomstmaat functionele inspanningscapaciteit, in het bijzonder de zes-minuten wandelafstand.

Ten eerste wordt aandacht besteed aan de consequenties voor het fysiotherapeutisch handelen tijdens de behandeling van patiënten met COPD en meerdere comorbiditeiten. Bij patiënten met COPD komen comorbiditeiten veel voor, maar huidige fysiotherapie richtlijnen omvatten geen gerichte acties die gerelateerd zijn aan comorbide condities. Comorbiditeit kan aanpassingen in interventie strategieën vergen, wanneer comorbiditeit (bijvoorbeeld diabetes mellitus) behandelresultaten van de indexziekte COPD negatief beïnvloedt, of wanneer de behandeling voor één ziekte (zoals cardiopulmonaire duurtraining voor COPD) de behandeling of het natuurlijk beloop van een andere ziekte (bijvoorbeeld ernstige knieartrose) negatief beïnvloedt. Daarom illustreren twee case studies in Hoofdstuk 3 de mogelijke consequenties van COPD (indexziekte) en comorbiditeit voor het fysiotherapeutisch methodisch handelen in een eerstelijnssetting. Zowel vermijdbare als onontkoombare problemen in de verschillende stappen van het fysiotherapeutisch methodisch handelen werden aan het licht gebracht. De eerste casus was een zeer ernstige COPD patiënt (FEV1=46% van voorspeld en chronisch longfalen) met hartfalen, die adrenerge bètareceptorblokkerende medicijnen gebruikte. De casus laat het gevaar zien van het missen van relevante informatie over een comorbide conditie en gerelateerde medicatie tijdens de anamnese en de consequenties voor het fysiotherapeutisch handelen. De tweede casus, een milde COPD patiënt (FEV1=86% van voorspeld) met meerdere gerelateerde comorbiditeiten, liet het belang zien van het monitoren van uitkomstmaten van meerdere aandoeningen en van aanpassingen aan het behandelplan. Het omgaan met comorbiditeit in de zorg voor mensen met COPD vraagt eerder een patiëntgerichte dan een ziekte-georiënteerde benadering om optimale behandeling en resultaten te verkrijgen. Er wordt geconcludeerd dat fysiotherapeuten hun vaardigheden en kennis van zeer prevalente combinaties van comorbiditeiten moeten verbeteren; volledig geïnformeerd moeten zijn over medische patiëntgegevens; niet alleen COPD-uitkomstmaten moeten monitoren maar ook die van comorbiditeiten; en interventies adequaat moeten aanpassen aan de multimobide patiënt. Huisartsen en longartsen kunnen de informatie inhoud bij verwijzing van een patiënt naar de fysiotherapeut verbeteren door te voorzien in informatie over alle nevenaandoeningen en gerelateerde medicatie.

Ten tweede, het effect van fysiotherapie op de primaire uitkomstmaat functionele inspanningscapaciteit (zes-minuten wandeltest) wordt gepresenteerd aan de hand van prognostische profielen van patiënten met COPD en comorbiditeit. Hoewel

comorbiditeit het volgen van revalidatie niet belet, lijkt het wel fysiotherapeutische uitkomstmaten te beïnvloeden bij patiënten met COPD. Echter, de mate waarin comorbiditeit invloed heeft op fysiotherapeutisch uitkomstmaten, met name in eerstelijnszorg, was onduidelijk. Hoofdstuk 4 legt een prospectieve cohort studie voor met 158 patiënten, GOLD I-IV, die richtlijn-gestuurde fysiotherapie voor COPD krijgen over lange termijn. Onderzocht wordt wat de invloed is van comorbiditeit op het verloop van de verandering in functionele inspanningscapaciteit tijdens eerstelijns fysiotherapie. Functionele inspanningscapaciteit werd gemonitord door 1301 metingen van de zes-minuten wandelafstand (6MWD). Comorbiditeit werd geregistreerd met de Cumulative Illness Rating Scale (CIRS). Om de invloed van comorbiditeit op herhaalde metingen van de 6MWD in de tijd te onderzoeken werd een `random slope mixed model` analyse methode uitgevoerd met een AR(1) correlatie structuur. De mediaan van de behandelduur was 27 maanden (*95%CI*: 7-65). De meest prevalente comorbide condities waren die in de categorieën `endocrien, metabool, lymfatisch, immuun', `cardiovasculair' en `spier, skelet, huid'. Bij iedere extra comorbide conditie was de 6MWD significant lager tijdens de start van fysiotherapie (23 meter, *95%CI*: 31-14). Daarnaast daalde de voortgang van de 6MWD in de tijd met 7 meter (*95%CI*: 13-1) per 1.000 dagen fysiotherapie, bij iedere extra comorbide conditie. Bij het analyseren van de invloed van iedere individuele ziektecategorie op de 6MWD werden drie verschillende profielen opgemerkt. Na correctie voor de vertekenende invloed van andere gefixeerde comorbiditeit variabelen bleek dat cardiale, hepatische en psychiatrische aandoeningen de sterkste negatieve interactie hadden met de tijd, waarbij sprake was van een significante correlatie van opeenvolgende zes-minuten wandeltesten (r=0.33, SE=0.045). In dit cohort van patiënten met COPD die fysiotherapie krijgen, was zowel het startniveau als de verbeteringen van functionele inspanningscapaciteit significant verminderd door de aanwezigheid van comorbiditeit, wat tevens een klinisch betekenis had. Dit is de eerste lange termijn follow-up studie die is uitgevoerd met patiënten met COPD om de invloed van comorbiditeit op inspanningscapaciteit tijdens eerstelijnsfysiotherapie te illustreren binnen prognostische profielen.

Deel 3: Uitgebreide toepasbaarheid van het meten van functionele inspanningscapaciteit (de zes-minuten wandeltest)

Het derde deel van dit proefschrift overweegt optimalisatie van het meten van functionele inspanningscapaciteit, als resultaat van `bottom-up' observaties tijdens de in dit proefschrift gepresenteerde onderzoeken. Ten eerste wordt de invloed van parcourslengte op functionele inspanningscapaciteit (6MWD) bij patiënten met COPD uitgelegd. Ten tweede worden de eerste referentie formules voor de 6MWD op een parcours van 10 meter aangereikt.

Omdat praktijkruimte in de eerstelijnszorg vaak beperkt is tot 10 meter, wordt de zesminuten wandeltest (6MWT) over een 10 meter parcours vaak gebruikt als een

alternatief om prestaties van patiënten met COPD te evalueren. Echter, de vraag is of patiënten met COPD een andere afstand afleggen bij de 6MWT op een 10 meter parcours versus een 30 meter parcours. Tevens kunnen bestaande referentie formules die op een langer parcours zijn ontwikkeld resulteren in minder valide conclusies wanneer zij worden toegepast op gelopen afstanden op een 6MWT die is afgenomen op een 10 meter parcours. Hoofdstuk 5 presenteert een gerandomiseerd dubbelgekruist experimenteel onderzoek met 45 patiënten met COPD in de eerstelijns fysiotherapie. Alle patiënten voerden de 6MWT twee keer uit op een 10 meter parcours en twee keer op een 30 meter parcours. De 6MWT`en werden uitgevoerd in overeenstemming met de American Thoracic Society richtlijn. De 6MWD werd gemeten en de voorspelde afstand werd berekend met een range van referentie formules. De 6MWD op het 10 meter parcours was 49,5 meter korter dan op het 30 meter parcours, met een statistische significantie (*95%CI*: 39.4-59.6). Door de bestaande referentie formules te gebruiken voor een 6MWT die op een 10 meter parcours is afgenomen, wordt de voorspelde afstand zwaar overschat (range: 30-33%). Daarnaast is de gemiddelde afstand als percentage van de voorspelde waarde 8% lager in vergelijking met een 6MWT die wordt afgenomen op een 30 meter parcours, wat resulteert in een slechtere weergave van de functionele inspanningscapaciteit van een patiënt met COPD. Dit hoofdstuk bewijst dat de invloed van parcourslengte op de 6MWD en op het gebruik van referentie formules bij patiënten met COPD substantieel en klinisch relevant is (zelfs wanneer het meest conservatieve gepubliceerde minimaal klinische relevant verschil wordt gehanteerd). Daarom kunnen bestaande referentie formules die zijn ontwikkeld voor een 6MWT op een 30 meter (of langer) parcours niet worden gebruikt om de loopafstand te voorspellen voor een 6MWT op een 10 meter parcours, zoals frequent wordt gebruikt voor patiënten met COPD in eerstelijnsfysiotherapiepraktijken.

Gezien de significante invloed van parcourslengte op de 6MWD, worden in Hoofdstuk 6 nieuwe referentie formules gepresenteerd die geschikt zijn voor de 10 meter 6MWT. In een dwarsdoorsnede studie hebben 181 gezonde proefpersonen in de leeftijd van 40-90 jaar twee gestandaardiseerde 6MWT`en uitgevoerd over een recht parcours van 10 meter. De gemiddelde loopafstand was 578±108 meter en verschilde tussen mannen en vrouwen ($p<0.001$). De resulterende geslacht-specifieke referentie formules voortkomend uit meervoudige regressieanalyse bevatten leeftijd, body mass index en verandering in hartslag. Deze variabelen verklaren 62% van de variantie in 6MWD bij mannen en 71% bij vrouwen. De gepresenteerde referentie formules zijn de eerste formules om de 6MWD op een 10 meter parcours te evalueren en vergroten de toepasbaarheid van de 6MWT bij gezonde volwassenen en patiënten met verscheidene chronisch aandoeningen zoals COPD.
Deel 3 eindigt met een gepubliceerde correspondentie tussen vertegenwoordigers van de verbonden American Thoracic Society en European Respiratory Society (ATS/ERS) werkgroep en de auteurs van dit proefschrift met betrekking tot de vraag: Wat bepaald welke zes-minuten wandeltest conventioneel is?

Deel 4: Fysiotherapie om COPD exacerbaties te reduceren

Het vierde deel van dit proefschrift bestudeert de potentie van fysiotherapie om COPD exacerbaties te reduceren. Eerst wordt het onderzoeksprotocol van een genest onderzoek uitgelegd. Tot slot wordt het effect van fysiotherapie op exacerbaties gepresenteerd.

Fysieke inspanningstraining doelt op het verminderen van ziekte-specifieke beperkingen en het verbeteren van kwaliteit van leven bij patiënten met COPD. Met name exacerbaties beïnvloeden COPD progressie negatief. Fysiotherapie interventies lijken exacerbaties en de consequenties ervan te kunnen beïnvloeden. Echter, informatie over het effect van fysiotherapie op het voorkomen van exacerbaties was schaars. Hoofdstuk 7 presenteert een onderzoeksprotocol van een genest cohort gerandomiseerd gecontroleerd onderzoek om de potentie van een protocol-gestuurd fysiotherapieprogramma te onderzoeken. Het fysiotherapieprogramma heeft als doel preventie of uitstellen van exacerbaties en verkorten van de duur of verminderen van de ernst van exacerbaties bij mensen met COPD die recent een exacerbatie hebben gehad. Binnen een prospectief cohort krijgen mensen met COPD GOLD I-IV (inclusief comorbiditeit) gebruikelijke multidisciplinaire COPD zorg waaronder richtlijn-gestuurde fysiotherapie. Patiënten in dit cohort met GOLD I-IV (post-bronchodilator FEV1/FVC<0.7 and FEV1<80% of predicted), die vergoeding voor COPD fysiotherapie ontvangen van hun zorgverzekeraar (post-bronchodilator Tiffeneau-index <0.6) en die een COPD exacerbatie hebben gehad, werden binnen 56 dagen na de exacerbatie gevraagd om deel te nemen aan een genest gerandomiseerd onderzoek (RCT). In deze RCT kreeg de interventie groep een strikt fysiotherapie programma voor patiënten met COPD. Deze protocol-gestuurde fysiotherapie werd vergeleken met een controle groep die en schijn (sham) behandeling kreeg, wat geen of zeer laag-intensieve inspanningstraining inhield. Antropometrische gegevens, comorbiditeiten, roken, functionele inspanningscapaciteit, perifere spierkracht, fysiek activiteitenniveau, gezondheid-gerelateerde kwaliteit van leven, het door de patiënt ervaren effect, therapietrouw, motivatie niveau, mate van effectieve mucus klaring, exacerbatie symptomen en contacten met de gezondheidszorg als gevolg van COPD werden in kaart gebracht. Daaropvolgend werd de primaire uitkomstaat `tijd tot de volgende exacerbatie' (gebaseerd op exacerbatie frequentie) bepaald aan de hand van zowel een *symptoomgerichte* als een *gebeurtenisgerichte* benadering. Follow-up metingen werden gepland op 3 en 6 weken, 3, 6, 12 en 24 maanden na instroom. De geplande economische evaluatie omhelst een schatting van vermijdbare kosten ten gevolge van exacerbaties. Ten slotte worden in dit hoofdstuk mogelijke moeilijkheden in de uitvoering van de studie en preventieve maatregelen belicht.

In Hoofdstuk 8 worden de resultaten van dit onderzoek gepresenteerd gericht op de potentie van fysiotherapie, inclusief intensieve fysieke inspanningstraining, om exacerbatie frequentie, duur en ernst te verminderen bij patiënten met COPD na een acute exacerbatie. Negenentwintig patiënten met COPD (GOLD I-IV, leeftijd

45-81) die een acute exacerbatie hebben gehad werden willekeurig toegewezen aan één van de twee groepen: fysiotherapie interventie (hoog-intensieve inspanningstraining) of schijn (sham) behandeling (geen of zeer laag-intensieve inspanningstraining). Vanwege ethisch gerelateerde overwegingen ten aanzien van de werving, inclusief a scheve verdeling van overlijdensgevallen onder de onderzoekpopulatie (één in de fysiotherapie groep versus drie in de controle groep) werd de inclusie eerder gestopt. Exacerbaties werden geïdentificeerd door middel van een *symptoomgerichte* benadering (een duidelijke toename van respiratoire symptomen) naast een *gebeurtenisgerichte* benadering (contact met gezondheidszorg). Secundaire uitkomstmaten die werden gebruikt waren exacerbatie duur, exacerbatie ernst, kwaliteit van leven en inspanningscapaciteit. In totaal werden 94 exacerbaties geteld. Exacerbatie frequentie was significant hoger in de controle groep (6.15±1.82 tellingen) vergeleken met de interventie groep (1.17±1.27, p<0.001). Wanneer de interventie met de controle groep werd vergeleken was de gemiddelde exacerbatie duur verkort met 10 dagen, waren de ervaren exacerbaties 2.7 punten minder ernstig op een 12-puntsschaal en was de inspanningscapaciteit en de kwaliteit van leven significant verbeterd in de interventiegroep. Er wordt geconcludeerd dat fysiotherapie, inclusief hoog-intensieve inspanningstraining na een acute exacerbatie, de frequentie, de duur en de ernst van exacerbaties in patiënten met COPD verminderd. Uit een simpele kosteneffectiviteitsberekening bleek dat fysiotherapie gezondheidszorguitgaven kan verminderen door de reductie van de frequentie van gebeurtenisafhankelijke exacerbaties. De geobserveerde effecten in deze studie zijn dusdanig groot (99% power) dat het onwaarschijnlijk is dat het effect enkel aan vertekening kan worden toegeschreven. Maar vanwege de kleine onderzoekspopulatie en het eerder stoppen van het onderzoek moeten de resultaten van dit onderzoek met voorzichtigheid worden geïnterpreteerd aangezien onze onderzoeksresultaten het effect kunnen overschatten.

Hoofdstuk 9 presenteert de algemene discussie van dit proefschrift. Allereerst wordt een samenvatting met de belangrijkste bevindingen van dit proefschrift gerapporteerd. Dit hoofdstuk concludeert dat de bevindingen in Deel 1 (ongelijke patiënt fenotypen in eerstelijnsfysiotherapiepraktijken, inclusief meer exacerbaties en meer comorbiditeit), de noodzaak versterken van Deel 2 – een uitgebreidere evaluatie van fysiotherapie bij patiënten met COPD en comorbiditeit; en van Deel 4 – een uitgebreidere evaluatie van fysiotherapie bij patiënten met COPD na een acute exacerbatie. Daarnaast, vanuit een `bottom-up' perspectief, bespreekt dit hoofdstuk de klinimetrische haalbaarheid van functionele inspanningscapaciteit metingen in de praktijk (Deel 3). Dit hoofdstuk geeft een algemene reflectie op alle uitgevoerde onderzoeken en bediscussieert methodologische overwegingen. Het plaatst de resultaten van de onderzoeken in de context van ander wetenschappelijk bewijs op gebeid van pulmonaire revalidatie en fysiotherapie samen met metingen van fysieke prestaties door patiënten met COPD, comorbiditeit en exacerbaties. Deze algemene discussie eindigt met de belangrijkste implicaties voor de klinische praktijk en geeft richting aan toekomstig onderzoek.

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Valorisation

VALORISATION

In this thesis, we tried to merge the top-down supply of science with the bottom-up demand of practice. We intended to improve care for patients with chronic obstructive pulmonary disease with this thesis by elucidating effects of physical therapy on exacerbation rates, by giving insight in the impact of comorbid conditions on the treatment process and treatment outcomes, and by optimising measurement tools.

VALORISATION OF THIS THESIS` RESULTS

Relevance for society

Chronic Obstructive Pulmonary Disease (COPD), at this very moment, reduces the quality of life of 65 million people worldwide. In 2030 it will be the third leading cause of death worldwide[1] and in The Netherlands it just took sixth place.[2] It causes breathlessness, cough and sputum production. Once or more times a year these symptoms get so bad by an infection requiring the patient to receive additional medication or hospitalisation for several days or even weeks; such an event is called an exacerbation. As a consequence, their psychological and physical activity levels reduce, which may lead to more exacerbations, systemic consequences (such as loss of functional exercise capacity) and additional diseases such as heart failure, diabetes or depression. The suffering of patients with COPD is high and is similar to that of, for instance, patients with cancer. Ironically, patients with COPD could be said to suffer more than those with cancer; the symptom burden is similar, but patients with COPD tend to live longer.[3]

We know that medication can reduce symptoms, but they are not the solution to prevent exacerbations.[4] There is, however, a promising treatment to reduce exacerbation rates that is widely used in the rehabilitation process for patient with COPD: COPD-specialised physical therapy (PT).

Prior research showed statistical and clinical effects of PT on functional capacity and health-related quality of life.[5,6] However, clinical impact of PT on “exacerbations” was unclear. Reduced hospitalization after PT in previous studies had set the expectation of a positive influence of PT on exacerbations. This thesis shows a reduction of symptombased and event-based exacerbation frequency, a reduction of exacerbation duration and severity by protocol-directed PT.

In addition to its scientific relevance, this reduction of exacerbation rates has shown its social relevance. The clinical impact was demonstrated by a profile shift in the new combined assessment of the Global Initiative of Lung Disease (GOLD).[7] The impact of COPD on an individual patient should be expressed by a combination of the patients` GOLD-stage, symptoms, comorbidity and reduced exacerbation frequency. The consequence of an increase in exacerbation frequency is a shift into a more negative patient profile, which was seen in the participants in the control group of our trial. A

shift to a more positive patient profile was seen in the PT-intervention group due to reduction in exacerbation frequency, along with COPD medication step down.[7] This positive clinical implication of the PT programme in patients with moderate to very severe COPD is confirmed by the literature, which showed a similar benefit from exercise programmes on other objective and subjective outcomes, irrespective of disease stage.[4,5,8]

Target groups

From a patients' perspective the reduction of all exacerbation rates, those that involve hospitalisation and those that do not, may enhance the patients` quality of life.

Moreover, because 70% of all medical costs due to COPD are mainly caused by hospitalisation and other patient-doctor contacts,[9] the reductions in exacerbations rates in our trial had economic relevance and may encourage reimbursement for PT treatment by insurance companies. Earlier research concluded that mortality could be reduced by PT as a part of pulmonary rehabilitation.[5] Although not expressed explicitly, insurance companies probably may not prefer therapies that improve life expectancy in chronically ill patients from an economical point of view. However, in line with the current societal impact of COPD, exacerbation management is the worldwide main goal in effective care for COPD.[10] Therefore, from a societal perspective it is appropriate to reimburse PT for COPD, instead of reducing reimbursement for PT as was seen in the Netherlands in the past five years.

Exacerbations rate reductions due to PT may encourage general practitioners and pulmonologists to refer their patients for physical therapy.

Not only does this thesis act on exchanging knowledge on protocol-directed PT regarding the effects on exacerbations, it also specifies the intervention given (for example training frequency, exercise intensity, timing of the intervention and type or content (the FITT principle)).[11] For, most PT research publishes a "black box"intervention, where no one knows in detail what exactly was done during the treatment, complicating the possibility of proper implementation. The PT protocol used in this thesis was described thoroughly in a published supplement, enabling physical therapist to provide more efficient treatment in COPD. The framework, based on the International Classification of Functioning, Disability and Health (ICF), that was used to describe the main goals and content of the intervention was developed with an overarching national research group `Designing Optimal Interventions for physical Therapy (DO-IT)`.[12]

Innovation

Many studies describe effects of interventions on a specific patient population and exclude those who suffer from other diseases than the disease studied, which is commendable from a methodological point of view since it diminishes bias. However, healthcare professionals seldom see patients with COPD without comorbidity; hence they cannot apply the research findings from optimal clinical trials on their population.

Unlike most studies, our study did not exclude comorbid patients, allowing for generalisation of the study results to "real" patient populations. The clinical value of our results will therefore be higher. Thus providing healthcare professionals with insight in the influence of comorbidity on clinical reasoning and addressing points of action in order to include comorbidity more often in the clinical decision-making process. On the other hand, the influence of comorbidity on the frequently used PToutcome functional exercise capacity was disentangled with help of the COPD cohort study. Patients, referring physicians and physical therapists now can adjust their expectations regarding effects of PT in complex COPD patients in primary care.

Products

From the different studies addressed in this thesis it appeared that the frequently used "six-minute walk test" to assess functional exercise capacity often could only be tested on a course of ten metres in length, due to space limitation in primary care. Not only showed this thesis that the choice for a shorter walk distance (10m versus 30m) had a statistical significant impact on walked distance, a clinical impact was illustrated by the measurement error introduced by the course length being higher than the minimal clinical important difference. Therefore, existing reference values for this test could often not be used in primary care and leads to interpretation errors. Our publication on this matter was cited twenty-two times, including in the 2015, 2016 and 2017 report by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[13], in the 2015 Polish Respiratory Society guidelines[14] and in the official European Respiratory Society / American Thoracic Society technical standard on field walking tests in chronic respiratory disease[15]. These citations show the awareness that was raised by our study results and underline the influence of track length on test performance and the importance of keeping this factor constant where within-subject comparison of 6MWD on subsequent occasions is required.[15] This thesis provides the first reference values for the six-minute walk test for healthy persons and patients with chronic diseases. The need for these reference equations by the clinical community was confirmed by the many requests for this publication by physical therapists in the Netherlands and abroad. All knowledge collected by this thesis was translated into national and international conference proceedings that have been addressed to the academic community as well as the health care community on different. Besides the publications in academic journals, most results have been or will be translated into Dutch and published in Dutch physical therapy magazines.

Finally, the online page of the research programme 'Designing Optimal Interventions in physical Therapy' (DO-IT) on the website of the Royal Dutch Society for Physical Therapy (KNGF) (https://www.fysionet-evidencebased.nl/index.php/do-itpublicaties/do-it-algemeen) displays the academic publications and summaries of the study results for the community of Dutch physical therapists.

Implementation

Implementation of the new reference equations is enabled by publication in the academic journal `Thorax`, presentations on multiple conferences and free access to the norm values through an online Dutch portal for PT measurement instruments (www.meetinstrumentenzorg.nl). So, in response to a bottom-up problem, we made sure that the product resulting from this thesis was distributed in the PT field in order to facilitate implementation. As a result, the British Thoracic Society guidelines for home oxygen use in adults, published by Thorax in 2015,[16] cited our publication and mentions that "it is recognised that due to a lack of space a modified 10m-6MWT (cones 9m apart) may be used as an alternative".

Moreover, the importance of choosing the corresponding norm values for the measurement tool used in practice and the new reference equations were included in the curriculum for physical therapy education at Zuyd University of Applies Sciences. By this act, awareness is created among students regarding the importance of choosing a clinimetric protocol and its consequences for clinical practice. Also, the development of a `benchmark value` (the minimal important difference (MID)) for the six-minute walk test on a ten-metre course is translated into a graduation subject for senior Bachelor students that started in 2015-2016, with a follow-up in 2016-2017. This follow-up student project was nominated for the annual Jaco den Dekker award for the best bachelor physiotherapy thesis of 2016 and received and lot of publicity.

Bottom-up problems about measurement issues in health care practice such as the one encountered in this thesis form the centre of doing innovative scientific research and are covered by `Meetpunt` (https://www.meetpunt.eu). Meetpunt is an open portal of services and support in which health care professional, patients/clients, students, entrepreneurs and government can submit questions regarding health measurement problems. Meetpunt is the portal of the upcoming large regional knowledge project `Limburg Meet (LIME 2017-2021) from Zuyd University of Applied Sciences in collaboration with Maastricht University, for new arising bottom-up challenges (granted by the province of Limburg).

Conclusion

Chronic Obstructive Pulmonary Disease is worldwide one of the leading causes of death and has a major impact on the physical state of every patient with COPD, especially caused by exacerbations and comorbidity. This thesis shows that exacerbations could be reduced by physical therapy and gives insight in the role of comorbidity in the health care process, so that therapists and referring physicians could classify patients better and adjust their treatment and their expectations on treatment results. During the study a practical problem occurred in the PT-field regarding a frequently used measurement test. Many health care professionals are bound to a ten-metre space for this test. We developed the first norm values for this test to expand its usefulness. The protocol of the physical therapy intervention, points of action for health care providers and the new norm values for the test and all other study results are and will be distributed by English and Dutch publications, presentations at (inter) national

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conferences, websites and used in higher education curricula and new research projects.

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Acknowledgements / Dankwoord

ACKNOWLEDGEMENTS / DANKWOORD

Dan ben ik eindelijk toegekomen aan het schrijven van dit hoofdstuk. Als ik steeds zei dat het proefschrift bijna af is wanneer ik aan het dankwoord toegekomen ben en dat dit het gemakkelijkste stuk is om te schrijven, dan spraken velen mij tegen. Het dankwoord is blijkbaar het gedeelte dat het meest wordt gelezen (of het *enige* gedeelte dat wordt gelezen door de meesten). Na jaren lang gedegen wetenschappelijk onderzoek uitgevoerd te hebben en dit methodologisch, ethisch en maatschappelijk verantwoord opgeschreven te hebben word ik dus zeer waarschijnlijk afgerekend op mijn integriteit, met andere woorden `de compleetheid van dit hoofdstuk`. Daarom moet iedereen erin staan, moet dit het liefst in het Nederlands geschreven zijn en de namen vet gedrukt zijn zodat iedereen zichzelf snel kan terugvinden.

Niets is minder waar. Want dit *is* eigenlijk toch het belangrijkste hoofdstuk voor de basis van het proefschrift. Zonder de inspiratie, de steun, de inhoudelijke kennis, het enthousiasme en de afleiding van zoveel mensen had ik dit boek nooit kunnen schrijven. Daarom wil ik heel graag gebruik maken van dit hoofdstuk om iedereen te bedanken.

Allereerst wil ik mijn promotieteam bedanken. Zonder hen was het niet mogelijk geweest om te promoveren tot doctor.

Mijn eerste promotor, Rob de Bie, wil ik bedanken voor zijn inspiratie, zijn grappen en enthousiasme tijdens het hele proces. Het was Rob die mij al tijdens mijn Master Health Sciences Research inspireerde om goed onderzoek te doen, maar ook om onderzoek *goed* te doen. Ik dank hem hierbij voor zijn methodologische kennis die hij met mij deelde. Zijn enthousiasme toen ik met een meta-analyse scriptie kwam aanzetten zal ik nooit vergeten. Hij heeft mij ervan overtuigd dat ik veel meer aan kon dan ik dacht en dat een pittig onderwerp voor een promotieonderzoek zeker zou lukken. En het is gelukt, dank daarvoor!

Mijn tweede promotor, Onno van Schayck, dank ik voor zijn scherpe en kritische blik op mijn geschreven stukken, met name zijn blik op de probleemstellingen in de inleidingen van de hoofdstukken. Zijn inhoudelijke kennis op gebied van COPD en de medische behandeling vanuit het perspectief van (huis)artsen heeft bijgedragen aan de robuustheid van de gepubliceerde artikelen. Tevens kon ik altijd bij hem binnenlopen wanneer ik mij inhoudelijk of procesmatig in een lastige positie bevond, ondanks zijn drukke agenda. Dank daarvoor!

Mijn derde promotor, Rik Gosselink, dank ik uit de grond van mijn hart voor zijn vakkundige bijdragen. Ik heb Rik altijd de goeroe op het gebied van revalidatie, fysiotherapie en COPD genoemd. Vanaf het allereerste begin van mijn promotiecarrière was Rik betrokken bij de opzet, de uitvoering en het schrijven van de hoofdstukken. Daarom was het niet meer dan logisch dat ik hem dolgraag als derde promotor

wilde toevoegen aan mijn promotieteam. Hoewel hij zijn bijdrage benaderde vanuit het perspectief van de revalidatie en vanuit de Belgische zorgsector, terwijl ik vaak keek vanuit de eerstelijns fysiotherapiehoek in de Nederlandse zorgsector, had ik altijd heel veel affiniteit met zijn ideeën over de inhoud van mijn artikelen. Dank daarvoor!

Mijn copromotor, Ilse Mesters, wil ik bedanken voor haar wekelijkse begeleiding in de jaren dat ik op de UM-locatie werkte. Ilse, bedankt voor je contacten waarvan ik gebruik heb mogen maken, vooral voor het succesvol werven van participanten voor mijn verschillende onderzoeken. Jij bekeek mijn stukken in beginsel vooral vanuit de hoek van opvoeding en voorlichting zonder fysiotherapeutische achtergrond of inhoudelijke kennis over COPD. Soms vond ik dit lastig, maar uiteindelijk heb ik zoveel voordeel gehaald uit jouw commentaren op mijn stukken. Jij las mijn stukken altijd zeer uitvoerig door van begin tot einde, wat ik enorm kon waarderen. De laatste jaren was jouw manier van input geven in mijn ogen positief veranderd. Wellicht heb je ondertussen ook meer kennis vergaard op gebied van COPD en fysiotherapie, en misschien wel omdat je dochter inmiddels vergevorderd is in de opleiding Fysiotherapie (die ik af en toe dan weer les mag geven bij Zuyd Hogeschool).

Mijn voormalige copromotor, Erik Hendriks, wil ik danken voor zijn inzet en zijn goede bedoelingen tijdens de eerste jaren van mijn promotieonderzoek. Erik heeft mij met een aantal fysiotherapeuten in het werkveld in contact gebracht, waar ik absoluut veel profijt van heb gehad. Omdat hij zelf nog werkzaam was als fysiotherapeut was het altijd leuk om met hem te sparren over onderzoeksonderwerpen die mij interesseerden.

Zonder de vrijgevigheid en flexibiliteit van mijn twee huidige werkgevers was het niet mogelijk geweest om mijn proefschrift tot een goed en mooi einde te brengen met een bijdrage aan maatschappij en onderwijs.

Ik wil mijn collega's van ParaMedisch Centrum Zuid bedanken voor hun begrip dat ik naast mijn ene dag werken in de praktijk als fysio mijn andere werkzaamheden, waaronder het proefschrift, soms ook voorrang moest geven. En wat vind ik het ontzettend leuk dat jullie samen met mij nu weer deelnemen aan nieuwe wetenschappelijke onderzoeken naar fysiotherapeutische zorg die we vanuit Zuyd Hogeschool uitvoeren.
De Maatschap, Rob, Petra en Ramon, dank voor de ondersteuning en vrije dagen die jullie mij hebben gegund voor het realiseren van deze mooie dag.
In het bijzonder wil ik Rob Ummels bedanken. Rob, ik denk niet dat jij je realiseert hoe dankbaar ik je ben voor jouw manier waarop je met mij de afgelopen jaren bent omgegaan. Ik heb mij altijd enorm gewaardeerd gevoeld voor mijn wetenschappelijke werkzaamheden binnen en buiten onze praktijk en dat is mijns inziens iets wat niet vanzelfsprekend is bij fysiotherapeuten die nog met twee benen in het vak staan zoals jij. Dank voor je geduld en het vertrouwen dat je in mij had dat ik ooit klaar zou zijn met dat proefschrift. Dan mag ik natuurlijk niet vergeten te noemen dat ik door jouw

netwerk in contact ben gekomen met Zuyd Hogeschool en daar nu heel veel profijt van heb.

Ik wil mijn `nieuwe` collega`s van het lectoraat Autonomie en Participatie van Mensen met een Chronisch Ziekte en de Opleiding Fysiotherapie van Zuyd Hogeschool bedanken voor hun begrip dat ik naast het vele leuke werk op Zuyd ook mijn proefschrift graag wilde afschrijven.
In het bijzonder wil ik lector Sandra Beurskens bedanken. Toen ik na 5 jaar promotieonderzoek aan de UM `verhuisde` naar Zuyd Hogeschool kwam ik in een warm bad terecht, waar ik mij meteen (en nog steeds) helemaal op mijn plek voelde. Dit was het type onderzoek wat ik juist zo leuk vond; toegepast onderzoek, veelal bottum-up en daardoor betekenisvol. En dan ook nog eens met super leuke collega's die mij het woord `samenwerking` opnieuw hebben leren ontdekken. Sandra, dankjewel voor je geduld en vertrouwen dat ik mijn proefschrift zou afschrijven naast de voltijdse baan. Dank je wel voor je inschikkelijkheid en flexibiliteit, en dat je mij zelfs een paar weken vrij hebt gegeven om weer een flinke slag te maken met het afschrijven van artikelen.
Ik wil Jacqueline Bruinsma bedanken voor haar hulp en interesse in mijn werk. Stephanie Cornips, bedankt voor…zo ongeveer alle…vragen en hulp waarmee ik bij jou terecht kan!
Mijn teamleiders bij de opleiding, Monique van den Broek en Maud Doveren, wil ik bedanken voor hun erkenning van mijn persoon door mij in te zetten in het onderwijs op de onderwerpen waar mijn passie ligt en op andere onderwerpen waar een uitdaging ligt.
Beste `roomies` – Josine, Miekie, Ruud, John, Andreas, Veerle en Simone – dank jullie wel voor jullie interesse die jullie toonden in mij en in de vorderingen op het gebeid van promotieonderzoek in de afgelopen jaren. Josine, met jouw heb ik er een echte vriendin bijgekregen.

Bovenal, Sandra, Rob, Monique en Maud, dank jullie wel voor jullie flexibiliteit waardoor ik mijn geliefde drie pijlers: onderzoek, onderwijs en praktijk nu kan combineren! Hierdoor heb ik nu de leukste baan die ik me kan wensen!
Ik wil het Wetenschappelijke College Fysiotherapie (WCF) van het Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF) danken voor het financieel mogelijk maken van mijn promotieonderzoek en wel in een heel bijzondere vorm waarbij vier universiteiten met vier verschillende promotietrajecten op het gebied van fysiotherapie samenwerkten in het onderzoekprogramma `Designing Optimal Interventions for physical Therapy` (DO-IT).
Aan alle leden, hoogleraren en promovendi, van onze nationale `DO-IT onderzoeksgroep`: dank jullie wel voor jullie kritische blikken, de prettige samenwerking tijdens de overleggen, jullie enthousiasme tijdens de presentaties die we samen op congressen hebben gehouden en jullie inzichten vanuit verschillende perspectieven, die andere promovendi buiten een onderzoeksgroep zoals DO-IT niet hebben kunnen ervaren maar waar ik steeds dankbaar gebruik van heb gemaakt. Joost Dekker, dank voor je mooie voorbeeld als voorzitter van onze onderzoeksgroep en je

kritische waardevolle vragen, met name op het gebied van methodologie en prioritering, en je complimenten na mijn voordrachten op congressen.
Ria Nijhuis, dank voor je meeslepende enthousiasme. Je bent voor mij een voorbeeld hoe vrouwelijke onderzoekers in het vakgebied fysiotherapie veel kunnen bereiken. Erik Hulzebos, dank voor je wijze input, met name op het gebied van inspanningsfysiologie.
Bart Staal, dank voor je wijze input en inspiratie. En vooral leuk dat de samenwerking die startte op de UM werd voortgezet binnen DO-IT.
Marieke van de Leeden, dank voor de leuke samenwerking en je betrokkenheid bij ons als promovendi.
Mede promovendi Nienke de Vries, Maarten Werkman, en Mariette de Rooij, wat was het leuk om dit traject met jullie aan mijn zij te doorlopen. Behalve dat ik denk dat we veel van elkaar geleerd hebben op inhoudelijk gebied, omdat we allen promoveerden op toch verschillende fysiotherapeutische onderwerpen, vond ik het altijd prettig om samen de meerwaarde van wetenschap voor ons vakgebied fysiotherapie te verdedigen in de gezamenlijke artikelen en op congressen.

Ik wil alle coauteurs bedanken voor ieders bijdragen aan de ideeën over onderzoeksopzet en de artikelen: Ton Ambergen, Geertjan Wesseling, Mariska Klaassen, Mark Spigt, Eva van Eerd, Jean Muris en Guus Asjiee. Annemieke Fastenau, bedankt voor de samenwerking vanaf het allereerste begin van het promotietraject.

Clive Lawrence, I would like to thank you for your feedback on my general introduction and discussion, but most of all for your inspirational lessons during the Cambridge course. You truly are a walking encyclopaedia of English language and grammar, humorous anecdotes and origins of English expressions. Thank you for your thoughtfulness, your kindness and expressing your genuine interest in someone's qualities!
Tiny Wouters, bedankt voor je hulp bij het opmaken van het proefschrift. Ondanks de vele stukken waaraan je werkte was het nooit een probleem om mijn teksten voorrang te geven wanneer dit even nodig was. Mede dankzij jou is het een mooi eindresultaat geworden.

Evelien Jagtman, dankjewel voor het realiseren van mijn idee voor de voorkant van het proefschrift en de boom die langzaam mee verandert met de kennis die met ieder volgend hoofdstuk wordt opgedaan. Fantastisch dat je zo meedacht en dank voor het uiteindelijke ontwerp.

Ik wil de leden van de beoordelingscommissie Prof. dr. Marjolein Drent, Prof. dr. Sandra Beurskens, Prof. dr. Thierry Troosters, Prof. dr. Janine Verbunt en Dr. Philip van der Wees, en de additionele leden van de corona Prof. dr. Joost Dekker en Prof. dr. Ria Nijhuis bedanken voor hun interesse en belangstelling in mijn werk en de tijd die zij genomen hebben om mijn proefschrift te lezen.

Ik wil alle mensen bedanken die hun medewerking hebben verleend tijdens de uitvoering van de verschillende onderzoeken.

In het bijzonder wil ik Melanie van der Veeke en Bep Penris danken voor hun oneindige hulp bij het werven van patiënten met COPD voor meerdere onderzoeken die in dit boek beschreven staan. Jullie grote aantallen patiënten met COPD binnen de praktijk FysioMedica was van onschatbare waarde voor mijn promotieonderzoek. Ook de andere collega`s van jullie praktijk wil ik bedanken voor hun aanpassingsvermogen wanneer ik weer eens de gangen bezette om testen uit te voeren.

Tevens wil ik Tiny Wehrens bedanken voor haar hulp bij het zoeken naar gezonde proefpersonen voor het realiseren van de nieuwe normwaarden voor de zes-minuten wandeltest. Vele van jouw deelnemers aan de 50+gym hebben met zeer veel enthousiasme deelgenomen aan mijn onderzoek.

Ik wil mijn oma Annie van der Woude en mijn moeder Toos Beekman bedanken voor hun hulp bij het zoeken naar `gezonde` deelnemers, wat nog best een klus was omdat de bovenste leeftijdsgrens 90 jaar was. We hebben vele mensen kunnen testen op de gang van de Veluwse Heuvel en daarna werd de koffie (of het wijntje) verzorgd voor de proefpersonen door mijn eigen oma van 90 jaar.

Er waren zoveel meer mensen op enig moment betrokken bij de uitvoering van mijn promotieonderzoek en gelieerde onderzoeken die ik dank verschuldigd ben.

In ieder geval wil ik Johan Peeters, Cor Zagers, Philip van der Wees en Waldemar Hogerwaard bedanken voor hun samenwerking.

Grote dank aan alle participanten, inclusief enkele collega`s van de UM en alle mensen met COPD, die hebben deelgenomen aan de verschillende onderzoeken die in dit proefschrift staan beschreven.

Ik wil alle fysiotherapeuten en fysiotherapiepraktijken bedanken die hebben meegewerkt aan het, ethisch gezien, toch lastige gerandomiseerde onderzoek dat in dit proefschrift staat beschreven.

Ik dank de Stichting Gezondheidscentra Eindhoven (SGE) en de Astma/COPD Dienst voor het beschikbaar stellen van geanonimiseerde gegevens ten behoeve van wetenschappelijk onderzoek.

D

Velen die ik heb ontmoet voor of tijdens mijn promotiecarrière wil ik bedanken voor hun interesse, inspiratie en collegialiteit.

Ik wil alle collega`s van de vakgroep Epidemiologie van de UM bedanken voor de collegiale samenwerking tijdens mijn promotieonderzoek.

In het bijzonder, alle aio`s en oud-aio`s (`JongEpid`). Ik vond de lunches, etentjes en andere uitjes altijd reuze gezellig. Hoewel ik er de laatste jaren helaas veel minder tijd voor kon vrij maken, heb ik jullie steun als medepromovendi zeker ervaren. Diegenen die al gepromoveerd zijn, heel veel succes met het zoeken en het tot een succes maken van nieuwe banen en voor allen die nog (net) niet gepromoveerd zijn, heel veel succes met het afronden…(`gewoon` doorwerken, de dag van het resultaat komt vanzelf).
Mijn lieve kamergenote Vivian ben ik dankbaar voor heel veel dingen. Niet alleen inhoudelijke kon ik goed met je praten over `het promoveren in deeltijd`, maar ik wil je vooral ook bedanken voor de momenten van psychische steun op alle vlakken die de afgelopen jaren de revue zijn gepasseerd op onze kamer.
Niet te vergeten, `de Epiladies`; Esther, Audrey, Judith, Vivian, Stephanie en Sarah! Het mooie is dat, terwijl onze onderzoeken en promoties lang niet gelijktijdig opliepen, onze werkzaamheden en kamerindelingen elkaar steeds op verschillende momenten hebben gekruist en wij altijd veel met elkaar hebben opgetrokken en nog steeds een `echt clubje` zijn gebleven. Ik heb veel aan jullie gezelligheid, hulp, steun en humor gehad, dank jullie wel daarvoor!
In het bijzonder wil ik Conny de Zwart bedanken. Conny, dankjewel voor alles wat jij voor mij hebt gedaan. Van hulp met declaraties, mails en brieven versturen tot jouw interesse in mij als persoon en altijd een fijn gesprek op de gang of op jouw of mijn kamer op de UM.
Jos Slangen en Harry van Montfort, dank jullie wel voor jullie IT-expertise als mijn computer hardware/software (of mijn eigen software op gebied van IT) te wensen overliet.

Aan de meiden van ons getrouwe Krakau-clubje; Jill, Inge en Vivian. Wat waren het mooie tijden…het bier met een rietje en mandarijntje in Café Camelot, het lekkere eten, de lakenhallen vol met souvenirs, een stressvolle avond in het hotel om onze presentaties voor te bereiden. Maar zeker ook ons indrukwekkende bezoek aan Auschwitz-Birkenau, en natuurlijk ook gewoon `strolling in the streets of Krakau` en alle andere mooie momenten die we samen hebben gedeeld en waar we nog lang van hebben nagenoten. Ik houd jullie aan onze afspraak: dat wanneer we alle vier gepromoveerd zijn, we samen nog eens terug gaan naar Krakau!

Graag wil ik Arianne Verhagen, Wendy Scholten-Peeters, Jan Pool, Bart Staal, Maurits van Tulder en Rob Oostendorp bedanken voor hun begrip toen ik had besloten om mij te concentreren op mijn promotieonderzoek en de verantwoordelijkheid voor de KNGF-richtlijn Nekpijn terug te geven.

Ik wil mijn collega`s van Onderzoek In Beweging (OIB) bedanken voor de al weer acht jaren van samenwerking ten behoeve van het organiseren van het jaarlijks fysiotherapie congres. Jacques Geraets, Mariet Mulders, Laurens Arts, Conny de Zwart, Rob de Bie, Ruud Gerards, Marc de Ruijter, Esther Bols, Josine Stammen, Sarah Dörenkamp, Alma Hilgers en Zephyr Reijnen dank voor de leuke samenwerking en ik hoop met de meesten van jullie nog lang het symposium te mogen voortzetten!

Ik wil `De Eetclub`; Nicole, Wiesje, Tobias, Simen, Niki, Eva, Joost en Malou bedanken voor de interesse die zij altijd toonden in mijn promotieonderzoek.

De leden van de Maastrichtse sambaband, PassaTempo, wil ik danken voor hun begrip dat het meespelen en repeteren met de band naast het afschrijven van mijn proefschrift op een gegeven moment te veel werd, wat ertoe leidde dat en ik ben gestopt met de band. Inmiddels heb ik jullie weer terug gevonden.

Een bijzonder dankjewel gaat uit naar Wiesje Bressers en Esther Bols, mijn paranimfen. In de aanloop naar de verdediging kon ik altijd bij jullie terecht en reageerden jullie altijd snel. Wat fijn om jullie erbij te hebben op deze mooie dag!

Hoewel het natuurlijk geen inhoudelijke of wetenschappelijke steun betrof ben ik mijn familie zo ontzettend dankbaar voor een andere steun: namelijk het geduld dat zij hebben opgebracht in de afgelopen jaren waarin ik bezig was met mijn promotiecarrière.

Ik wil mijn ouders, Herman en Toos Beekman, bedanken dat zij er waren als steun en toeverlaat. Jullie waren altijd mijn voorbeeld op het punt dat jij je niet gek moet laten maken door wat anderen vinden. Belangrijk is wat je van anderen kunt leren. Jullie oneindige geduld met mij als jullie dochter die nooit geduld heeft en bij wie niets snel genoeg kan gaan is op z`n minst bijzonder te noemen. Mijn realiteitszin heb ik zeker aan jullie te danken en daar zal ik mijn hele leven nog veel profijt van hebben. Hoewel ik weet dat jullie trots zijn op mij, ben ik omgekeerd trots op jullie dat jullie mij altijd de kans hebben gegeven om alles te bereiken in mijn leven wat ik wilde: verre reizen, 3 studies, promoveren, vele hobby's, naar het zuidelijke einde van Nederland verhuizen, en desondanks komen jullie gelukkig heel vaak op bezoek… Ik kan altijd bij jullie terecht met alles (of het nu in Nederland is of in Indonesië), oneindig veel dank daarvoor!

Mijn zussen Ezra en Denise, mijn oma Annie van der Woude, mijn schoonouders Henk en Ineke Van Slooten, mijn schoonbroer en vrouw Sander en Nikki, wil ik bedanken voor hun support. Hun interesse in mijn promotieonderzoek was oprecht en kon ik enorm waarderen.

Tristan, dankjewel dat je zo lang mogelijk bent blijven wachten in mijn buik om geboren te worden zodat ik twee weken voor de uitgerekende datum het proefschrift nog mooi kon inleveren bij de beoordelingscommissie. Hoewel ik toen nog niet wist wie je was heb je je keurig gedragen als ongeboren baby zodat ik tot drie dagen voor de bevalling nog artikelen kon afschrijven, de opmaak van het boek kon regelen, artikelen kon indienen, naast het klussen op de zolder van ons huis. Ongeveer tegelijk met jouw bevalling kreeg ik ook het bericht dat mijn proefschrift goedgekeurd was door de beoordelingscommissie (dit is op zich ook wel een `bevalling). Je was dus toch nog een beetje `een tweeling`.

Lucas, dankjewel dat je mama zo vaak met rust hebt gelaten wanneer ik aan een artikel werkte. Wat fijn dat je in het laatste jaar van mijn promotie zo fijn kon spelen met wat blokjes onder het bureau van collega Vivian op de UM op de enige zaterdagen die ik had om het proefschrift af te schrijven. Ik noemde je vaak een `proefschrift-kind` omdat je altijd zo lief was en mij de tijd gaf in de weekenden die ik nodig had om alles af te krijgen. Die momenten dat je vroeg, `mama wat doe je?,` en daarna in slaap viel op de UM totdat ik het artikel naar de coauteurs kon sturen, zijn momenten die ik niet snel zal vergeten. Daarna hebben we het weer snel goed gemaakt met een extra lang, niet-proefschrift, spelletje voor 2-jarigen.

Mijn beste maatje en allerliefste Peter, dank je voor je begrip dat mijn promotieonderzoeken en het proefschrift erg belangrijk voor mij waren. Dank je voor je geduld op de avonden (of nachten) die ik heb doorgewerkt op de universiteit en soms tot overmaat van ramp mijzelf had opgesloten omdat ik tijdens het werken (weer) vergeten was dat de UM-autogarage op vrijdag om 19.30 uur sluit. Dank je voor die keren dat je mij hebt opgehaald, hebt getroost als ik het even niet zag zitten, hebt gefeliciteerd als er weer een artikel werd geaccepteerd door een tijdschrift, hebt teruggebracht naar de realiteit wanneer ik me teveel liet meeslepen in feedback van anderen of te veel van mezelf eiste. Je zei vaak `Wanneer je er geen invloed op hebt moet jij je er niet druk over maken`. Dank voor deze en nog veel meer van je wijze lessen die je mij, soms onbewust, hebt meegegeven. Je bent er altijd voor mij, en daarom blijf ik er altijd voor jou! Als de liefde niet bestond…

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Curriculum vitae

CURRICULUM VITAE

Emmylou Beekman was born in Zwolle in the Netherlands on March 7, 1983.

After secondary school and travelling through Australia, New-Zealand en Asia, she studied Health Sciences at Maastricht University in 2002. During this study she chose for a major in Movement Sciences and decided to combine this study with another Bachelor study, Physiotherapy at the Hogeschool Zuyd in Heerlen. She was board member of a student fraternity. In 2007 she received her diploma for Health Sciences with merit and for Physiotherapy cum laude. With these results she was able to enter the two-year Health Sciences Research Master at Maastricht University, were she received her master's degree cum laude in 2009 (major subject Clinical Epidemiology). Meanwhile she worked as a physiotherapist in the primary care practice ParaMedisch Centrum Zuid in Sittard.

Inspired by treating chronically ill patients as a physiotherapist and doing physiological research, she decided to continue in this field of health care and research by means of a PhD track at the research School for Public Health and Primary Care (CAPHRI), at the Department of Epidemiology of the Faculty of Health, Medicine and Life Sciences at Maastricht University. In 2008 she started as a PhD-student on a five-year project, studying the effectiveness of physiotherapy in patients with chronic obstructive pulmonary disease. The aim of this project was to reduce exacerbations in patients with moderate and severe chronic obstructive pulmonary disease with physiotherapy. Moreover, interactions between comorbidity and physiotherapy had an important role in this project, as well as the feasibility of clinimetrics in everyday practice. Meanwhile she specialized in Health Technology Assessment, i.e. trial-based economic evaluations. She continued her work as a physiotherapist and specialized in chronic obstructive pulmonary disease and asthma. She has given many lectures and workshops on this topic for health care professionals and researchers in the Netherlands, at the Jagiellonian University of Poland (2010-2011) and at the American Physiotherapy Association in Florida, USA (2012).

After a five-year period she started to work as a researcher at Zuyd University of Applied Sciences. Her PhD thesis was approved in October 2016.
Currently her work involves a combination of: researcher at the Research Centre for Autonomy and Participation of Persons with a Chronic Illness at Zuyd University;

lecturer for bachelor and master health care students at Zuyd University; and physiotherapist at ParaMedisch Centrum Zuid.

Since 2009 she is a member of the COPD-expert group of the Dutch Paramedical Institute (NPi) and her work is closely related to the Royal Dutch Society for Physical Therapy (KNGF), in the Netherlands. She is a member of the organising committee of “Onderzoek In Beweging”, which is an annual symposium for paramedical professionals at Maastricht University. Since 2014 Emmylou is registered as `Epidemiologist A` at the Netherlands Epidemiology Society (VvE).

List of publications

LIST OF PUBLICATIONS

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