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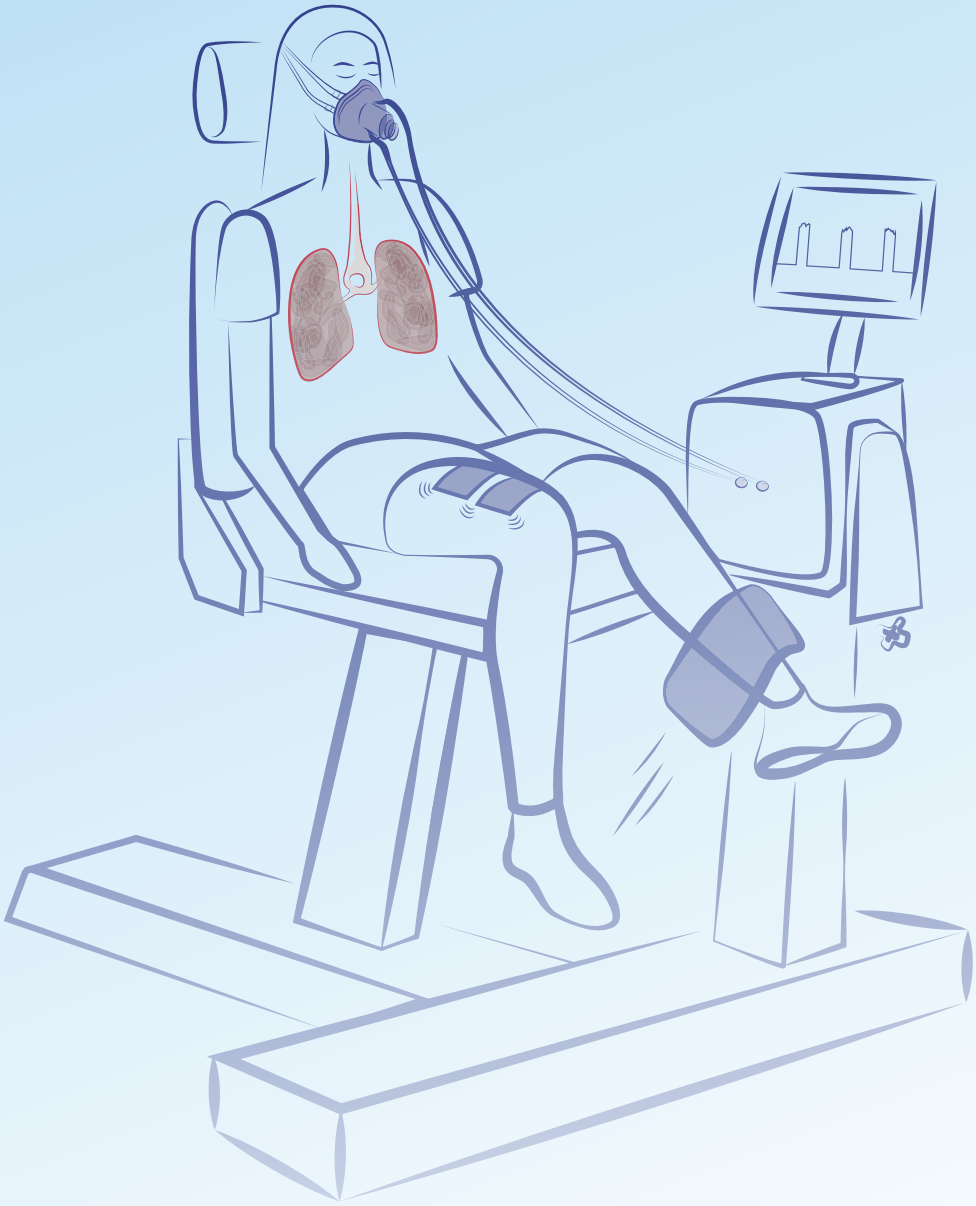

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Anouk Antoinette Franciscus Stoffels

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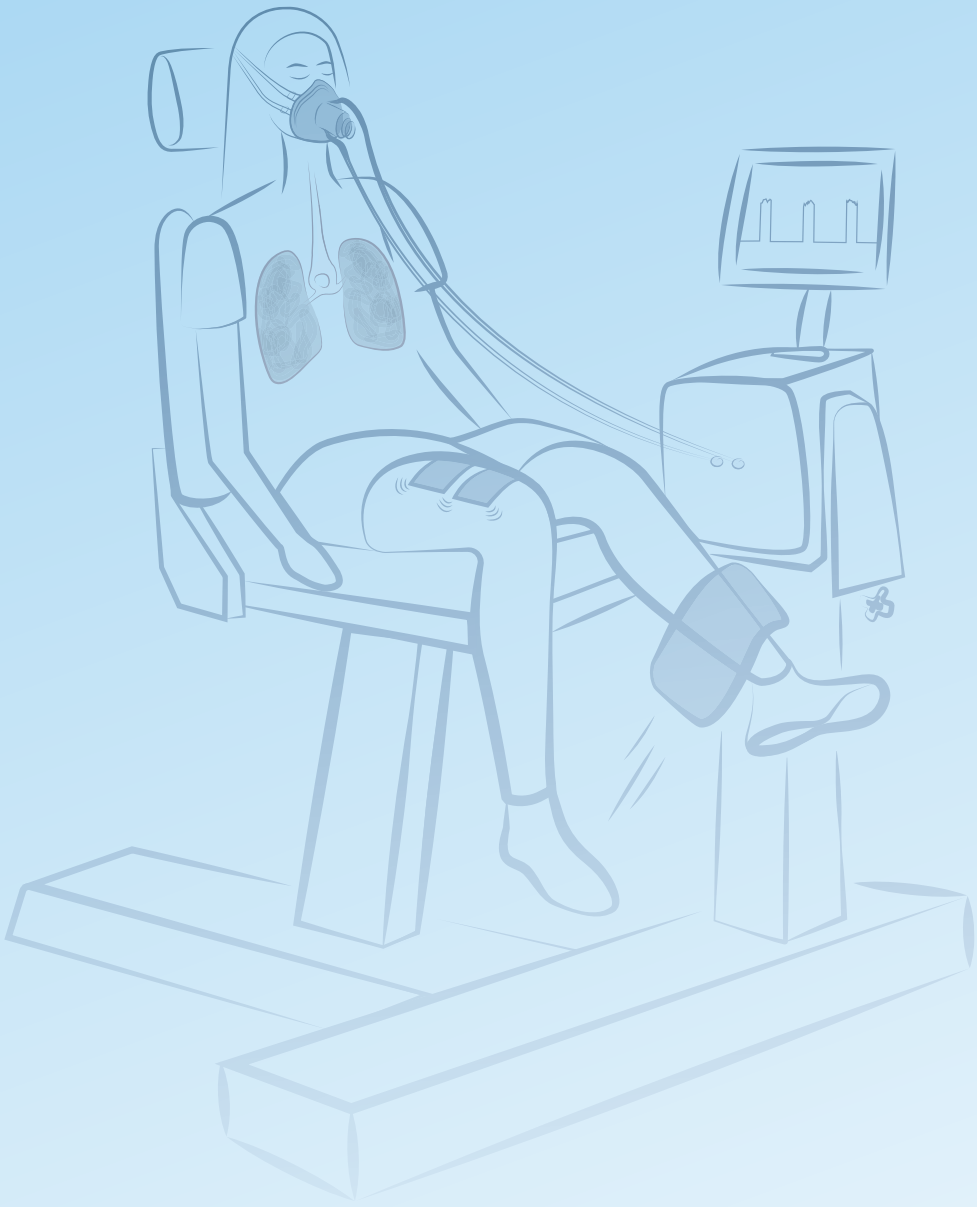

CHAPTER 1

General introduction

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is defined as *"a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnoea, cough, expectoration) due to persistent abnormalities of the airways and/or alveoli, that often results in progressive airflow limitation".*[1] This disease includes two pulmonary conditions, i.e., chronic bronchitis and emphysema. Chronic bronchitis is marked by mucus formation and narrowing of the airways due to chronic inflammation of the bronchi. Emphysema is characterized by parenchyma destruction caused by damaged alveoli walls.[2] The main risk factors for the development of COPD are environmental exposures to tobacco smoking, the inhalation of toxic particles and gases from household and outdoor air pollution, and to a lesser extent genetic mutations.[3, 4] COPD is an important health problem as it is the third leading cause of death worldwide and was estimated to affect over 384 million people with 3.23 million deaths in 2019.[5] The prevalence and burden of COPD are even expected to increase due to continued exposure to COPD risk factors and the aging of the world's population.[6] Besides pulmonary manifestations, patients frequently experience extra-pulmonary complications such as cardiovascular disease, skeletal muscle dysfunction, weight loss, metabolic syndrome, osteoporosis, depression, anxiety, and cognitive impairment.[2] Both pulmonary impairments and extra-pulmonary comorbidities contribute to limiting the patient's physical function.[7]

PHYSICAL FUNCTION

Physical function is described as the ability to perform activities of daily living that require physical actions, ranging from basic to more complicated activities.[8] A complex interplay of multiple physiological systems (e.g., neuromotor, musculoskeletal, and cardiorespiratory system) is required to perform those activities properly and successfully, which can be influenced by clinical, sensory, environmental, and behavioural factors.[8, 9] In the literature, different terminologies and classifications are used interchangeably to indicate physical function. Van Lummel et al. proposed a subdivision that classifies physical function into physical performance (i.e., person's ability or capability to perform physical activities) and physical activity (i.e., bodily movement produced by skeletal muscles that results in energy expenditure beyond that of the resting state).[10, 11] This subdivision recently lead to the development of a physical performance – physical activity quadrant concept and was used to subdivide patients with COPD along axes of what they physically "can do" (physical performance), and what they actually "do do" (physical

activity). Over a third of the patients fell within a quadrant where levels of physical performance were not congruent with levels of physical activity.[12] Therefore, a thorough assessment of both physical performance and physical activity is necessary to design interventions that optimally improve physical function in patients with COPD. In this thesis, we will merely focus on the assessment of physical performance.

Limitations in physical performance are frequently present in patients with COPD across all disease severities.[13] Reduced physical performance has a major clinical impact on patients as it is related to reduced physical activity, poor quality of life, an increased risk of hospitalization, and even premature mortality.[14, 15] Many (exercise) interventions are proven to be effective in enhancing physical performance in patients with COPD.[16] In addition, underlying mechanisms for impaired physical performance in patients with COPD are multifactorial and widely diverse between patients.[14] Therefore, timely and adequate assessment of physical performance is clinically relevant and highly essential as proper (exercise) interventions can (partly) counteract limitations in physical performance.

DETERMINANTS OF IMPAIRED PHYSICAL PERFORMANCE

Dyspnoea and leg fatigue are the two main reasons for patients with COPD to terminate exercise and are therefore major determinants of reduced physical performance. The increased sensations of these symptoms result predominantly from impaired functioning of the respiratory system and the peripheral muscles (Figure 1).[17-19]

Dyspnoea

The sensation of dyspnoea arises from a mismatch in the brain between efferent motor command output to the respiratory muscles and afferent input from diverse sensory receptors throughout the respiratory system.[20] This mismatch can already be present at rest in patients with COPD but becomes more prominent during exercise. The neural respiratory drive (i.e., efferent signals) is increased upon exertion in order to maintain gas exchange and respiratory homeostasis. However, the afferent feedback signals from for example pulmonary stretch receptors, intercostal muscle spindles, and chemoreceptors do not match the predicted response.[21] Impairments in the lungs and respiratory and peripheral muscles are the main causes of this mismatch. Derangements of pulmonary function and mechanics are responsible for aberrant afferent sensory signals and put an excessive load on the respiratory muscles.

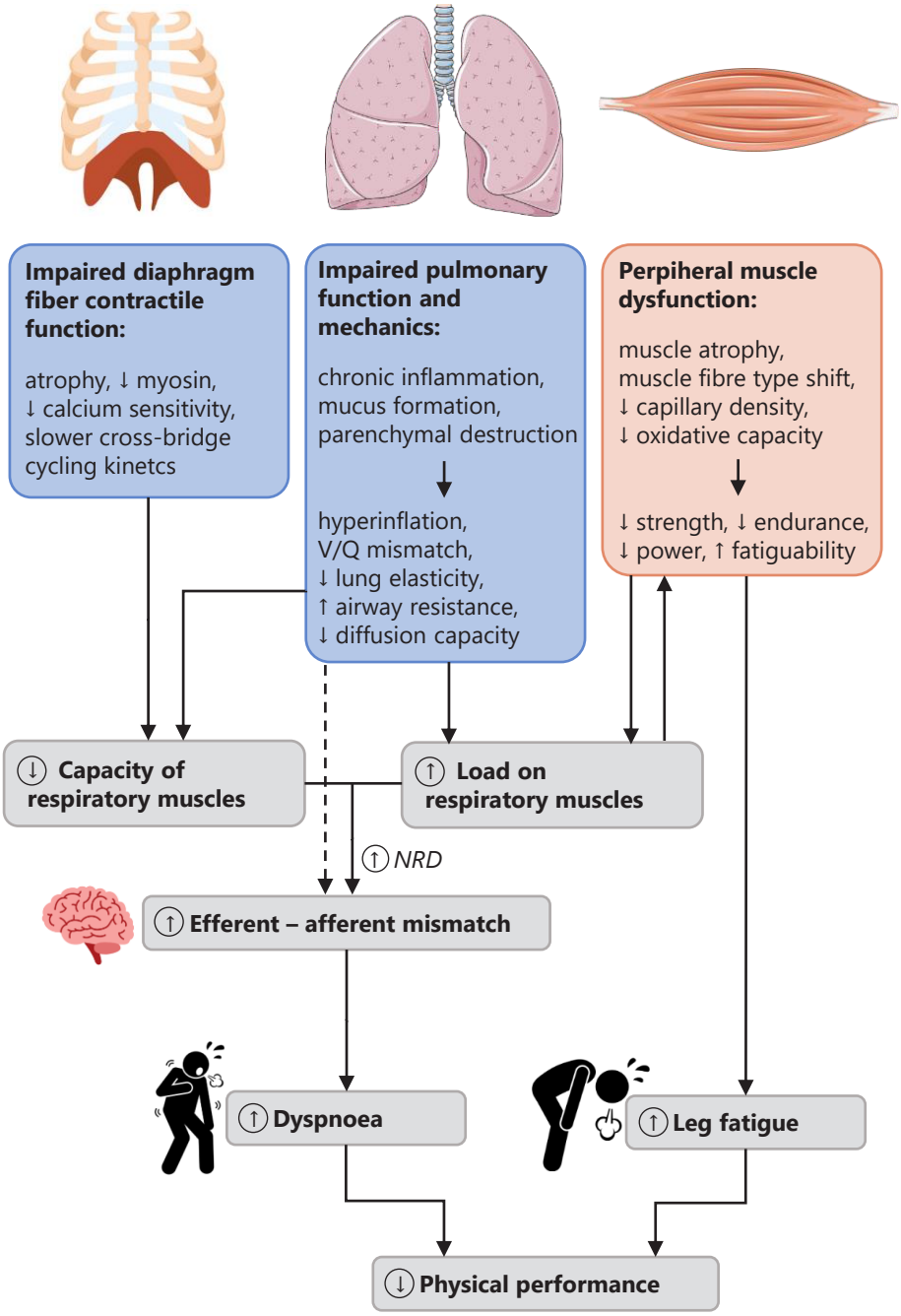

Figure 1. A schematic overview describing the major determinants of reduced physical performance in patients with COPD.

Abbreviations: NRD, neural respiratory drive; V/Q mismatch, ventilation/perfusion mismatch.

These derangements include airway obstruction, loss of lung elasticity, increased airway resistance, static or dynamic hyperinflation, reduced diffusion capacity, and abnormal distribution of ventilation/perfusion ratio. While the load on the respiratory muscles is excessively high in patients with COPD during exercise, the force generating capacity of these respiratory muscles is reduced.[21] The majority of studies on respiratory muscle dysfunction in patients with COPD focus on the diaphragm, as this is the main muscle of inspiration. Already early in the development of COPD, diaphragm fibre contractile function is impaired, characterized by atrophy, decreased calcium sensitivity of force generation, slower cross-bridge cycling kinetics, and reduced myosin content.[22, 23] In addition, hyperinflation-induced diaphragm shortening forces the muscle to contract at a less optimal (shortened) length.[21, 24] These alterations reduce the pressure generation and chest displacement and thus negatively impact the force generating capacity of the respiratory muscles.[25, 26] The reduced capacity of the respiratory muscles contributes to the excessive neural respiratory drive because more respiratory muscle fibres need to be recruited for adequate pressure generation.

Finally, hypoxemia and intrinsic alterations in the muscles (explained below) provoke anaerobic energy production in the peripheral muscles of patients with COPD already at low exercise levels. This leads to the accumulation of metabolites that stimulate the respiratory centre to further augment neural respiratory drive.[2, 16, 27]

Leg fatigue

Fatigue of lower-limb muscles contributes to limitations in physical performance in patients with COPD, independently of the severity of airway obstruction.[28, 29] The increased sensations of leg fatigue are primarily caused by peripheral muscle dysfunction, characterized by reduced muscle strength, endurance, and power, and increased muscle fatiguability.[14, 28, 30, 31] Underlying structural impairments that impact the functioning of the muscles include muscle atrophy, muscle fibre type shift, reduced capillary density, and decreased oxidative capacity.[14] Muscle atrophy is indicated by a reduction in muscle fibre cross-sectional area due to an imbalance between protein degradation and synthesis,[32] and causes muscle weakness. Furthermore, a fibre type shift from type I (i.e., slow oxidative fibres) to type IIx (i.e., fast glycolytic fibres) muscle fibres is observed in peripheral muscles of patients with COPD, which is opposite to the fibre type shift normally seen during the aging process.[14, 33, 34] This fibre type shift makes the active peripheral muscles more reliant on anaerobic and glycolytic metabolism, resulting in a rapid rise of blood lactate, a fall in muscle pH, and systemic acidosis. In addition, capillary density and capillary-to-fibre ratio are reduced[33, 34] and oxidative capacity (i.e., maximal ability of

the muscle to use oxygen) is impaired in the limb muscles of patients with COPD.[14] Lastly, the increased load on the respiratory muscles initiates a blood flow 'stealing effect' (i.e., blood flow redistribution from the peripheral muscles to the respiratory muscles) that compromises oxygen delivery to and removal of metabolic by-products from the active peripheral muscles. This makes the peripheral muscles even more reliant on anaerobic metabolism and thereby causing an increased sensation of leg fatigue.[35, 36] Furthermore, the excessive production of carbon dioxide and hydrogen by the peripheral muscles stimulates the respiratory centre and results in a higher load on the respiratory system.[21] Thus, impairments in the peripheral muscles of patients with COPD affect physical performance by contributing to leg fatigue as well as dyspnoea sensations.

ASSESSMENT OF PHYSICAL PERFORMANCE

Extensive assessment of physical performance in patients with COPD is recommended by the European Respiratory Society/American Thoracic Society to: individualize exercise prescription; evaluate potential need for additional aid; help rule out potential contraindications; ensure the safety of the intervention; and determine intervention efficacy.[16] The wide range of exercise tests currently available facilitate the comprehensive evaluation of patients but also hamper the selection of suitable tests. Therefore, a number of measurement properties will be addressed in the following paragraph which are relevant for exercise tests.

Test properties

Feasibility, reliability, validity, and responsiveness are crucial to consider before implementing or performing an exercise test in practice. Table 1 describes the definitions of these test properties, based on the Consensus-based Standards for the selection of health status Measurement Instruments taxonomy and guideline.[37-40]

Firstly, it is important to evaluate the feasibility of exercise tests in patients with COPD. In general, this population is characterized by an older age, poor lung function, high sensations of dyspnoea and leg fatigue, multiple comorbidities, and reduced physical function that can influence test performance.[2, 41] Therefore, exercise tests that are feasible in healthy individuals are not necessarily practicable and achievable to perform in patients with COPD. Commonly used measures for feasibility are patient's and clinician's comprehensibility, type and ease of administration, completion time, required equipment, costs of the instrument, and availability in different settings.[42]

Table 1. Definitions of feasibility, reliability, validity, and responsiveness.

	Definition
Feasibility	The extent to which a measurement tool: is suitable for the target population; can be successfully delivered in the target population/context; shows promise of being successful within the intended population.
Reliability	The extent to which a tool gives measurements that are consistent, stable and repeatable or the degree to which the measurement is free from measurement error.
Test-retest, inter-rater, intra-rater reliability	The extent to which a measure can obtain similar results for repeated measurements over time (test-retest), by different persons on the same occasion (inter-rater), or by the same persons on different occasions (intra-rater).
Internal consistency	The extent to which items among a measurement tool that propose to measure the same construct are interrelated.
Measurement error	The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured.
Validity	The ability for a measure to accurately reflect the construct it is designed to measure.
Construct validity	The extent to which the measurement tool actually tests the hypothesis or theory they are measuring.
Content validity	Extent to which a measure covers all aspects of the intended domains or dimensions that it claims to measure.
Criterion validity	Output of a measure produces similar results to a 'gold standard'.
Responsiveness	The ability of an outcome measure to detect changes over time in the construct to be measured.

Furthermore, an exercise test should be reliable, indicating that the test provides the same result on multiple occasions and that the measurement is free from measurement error. This test property is subdivided in (test-retest, inter-rater, and intra-rater) reliability, internal consistency, and measurement error.[38] To determine the reliability of a test, patients should be clinically stable, the time interval between the administrations must be appropriate, and the test conditions (e.g., type of administration, setting, provided instructions) need to be similar.[37] In patients with COPD, psychological complications (e.g., anxiety and depression) are common and are known to impair physical performance.[43] Thus, highlighting the importance of assessing the reliability of a test in patients with COPD

Validity describes the extent to which differences found with the test reflect true differences among those being tested. Different types of validity are construct, content, and criterion validity.[38] When evaluating the validity, it should be clear what the comparator instrument measures and whether the measurement properties of the comparator instrument are sufficient.[37] In patients with COPD, dyspnoea can influence physical performance and thus might lead to early test termination or submaximal performance.[21] Consequently, the outcome might partially reflect dyspnoea instead

of the patient's true physical performance. Therefore, it is important to determine the validity of exercise tests in patients with COPD.

Exercise interventions are effective in enhancing physical performance in patients with COPD across all severity stages of the disease.[16, 44] Although these improvements have been reported at group level, individual responses to exercise training are highly variable.[45-49] Therefore, it is clinically relevant to identify non- or poor-responders (i.e., patients that do not, or only poorly, improve in physical performance) timely to avoid inclusion of patients in intensive and demanding exercise training programs when no improvements in physical performance are to be expected. Secondly, it is important to determine why these patients do not respond to the intervention in order to make adjustments to the current program or provide a better alternative. Thus, it is important that the exercise tests used in clinical and research settings are able to pick up these improvements and that the observed changes reflect the actual improvements or deteriorations (i.e., responsiveness).[38] Three main aspects need to be considered in terms of responsiveness: whether information is interpreted on individual or group level; the timing of data collection and duration of intervention; and the kind of change that needs to be determined (e.g., statistical change, clinical change).[50, 51] The most common methods to evaluate responsiveness are classified into distribution-based and anchor-based methods. Distribution-based methods (e.g., effect size, standardized response mean, and minimal detectable change) are based on statistical significance and do not necessarily reflect a (clinically) meaningful change for the patient or clinician.[51] Anchor-based methods can be used to determine clinically meaningful differences using external anchors.[51, 52] A combination of both methods is recommended when evaluating the responsiveness of a test.

Exercise tests

Numerous exercise tests are currently used to assess physical performance in patients with COPD. Here we will discuss a number of commonly used tests in view of the test properties described above. Because tests also differ as to which domain of physical performance they asses, the following subdivision will be used: functional performance, exercise capacity and tolerance, and peripheral muscle function (upper part of Figure 2).

Functional performance

Functional performance or functional capacity is defined as *"an individual's capability, under controlled conditions, to perform tasks and activities that people find necessary or desirable in their lives".*[53] Functional tests are widely used in clinical practice as they allow identification of specific limitations in tasks that are relevant for daily

living. Therefore, they can be meaningful for patients with COPD and clinicians to improve individualization of (rehabilitation) interventions.[54-56] A frequently used and easy-to-perform functional performance measure is the short physical performance battery (SPPB), which comprises three components: three standing balance tests, the 4-meter gait speed test, and the 5-repetition sit-to-stand test.[57] Execution of the SPPB is recommended in older patients to evaluate the physical aspects of mobility and balance.[58] Furthermore, the SPPB has a prognostic value because it identifies patients with COPD at risk for a disability, a subsequent decline in activities of daily living, rehospitalization, and mortality[59-61] and might detect a phenotype with functional impairments, loss of muscle mass, and structural muscle abnormalities in patients with COPD.[62] To date, the SPPB seems valid for identifying mobility limitations in patients with COPD and classifying patients in a low-, moderate-, and high-performance in mobility and balance.[60, 62-64] Medina-Mirapeix et al. reported a high interobserver reliability[65] and the test appears to be responsive[66, 67] in patients with COPD. However, the latter has only been described in one peer-reviewed manuscript and one congress abstract, highlighting the need for a more extensive evaluation of the responsiveness of the SPPB in patients with COPD. As previously mentioned, determination of minimal important differences is essential to identify whether improvements are statistically and/or clinically relevant and enhances the interpretation of intervention efficacy. For the SPPB, minimal important differences have only been established for the 4-meter gait speed test and the 5-repetition sit-to-stand test,[68, 69] and are currently lacking for the standing balance tests and SPPB summary score in patients with COPD.

Exercise capacity and tolerance

Exercise capacity and tolerance are two distinctive determinants of physical performance and will therefore be addressed separately in the following paragraphs.

Maximal exercise capacity is defined *as "the maximum amount of physical exertion that a patient can sustain",*[70] and is commonly assessed using the incremental shuttle walk test, cardiopulmonary exercise test, and 6-minute walk test.[71] During these tests, and in particular during the cardiopulmonary exercise test, several concomitant physiological variables are accurately monitored. This is valuable in clinical settings as it allows clinicians and researchers to evaluate the safety of exercise, identify factors contributing to exercise limitation, and prescribe a personalized exercise program.[16, 72] However, exercise capacity tests are more time-consuming and/or more exhausting for patients with COPD and require often more costs and trained personnel than a subjective evaluation of patient-reported outcomes (PROs). PROs are assessed using health-related questionnaires that require patients to report on

their symptoms and quality of life and are relevant to understand the burden of the disease from a patient's perspective. Its usage is intended to reflect outcomes relevant to the patient which can be used as a target during interventions.[73] As PROs are easy and patient-friendly to evaluate in clinical practice, it is important to determine whether and to what extent PROs mirror maximal exercise capacity in patients with COPD. Punekar et al. systematically reviewed correlations between different exercise test outcomes and PROs and reported that higher 6-minute walk distances are associated with better health-related quality of life and reduced breathlessness. However, they highlighted the need for future research to determine the relation between PROs and outcomes of other physical performance tests than the 6-minute walk test.[74]

Exercise tolerance or endurance capacity can be defined as the ability of an individual to sustain submaximal exercise. Submaximal constant load tests (e.g., endurance shuttle walk test (ESWT) and constant work rate test (CWRT))[71] are used to evaluate exercise tolerance. They are more sensitive to improvements following an intervention than maximal exercise capacity tests.[75] However, it is important to note that the submaximal load of these exercise tolerance tests should be carefully chosen, because improvements of test duration depend on the load of the test. This can be explained by considering the power-duration relationship, which indicates the hyperbolic relation between tolerated test duration (i.e., limit of tolerance) and power (i.e., load) (Figure 3). The asymptote on the load axis is defined as the critical power, which reflects the highest load that can be sustained in a steady state of aerobic energy supply.[76, 77]

A large variation in tolerated test duration (Tlim) among patients with COPD has been observed for both the CWRT and the ESWT, despite the same relative workload was chosen.[78-82] As effect sizes of interventions depend on pre-intervention values (as explained in Figure 3), a large variability in pre-intervention Tlim complicates the statistical analysis of intervention efficacy and increases the number of patients required in clinical studies.[77, 83] Vivodtzev et al. evaluated pulmonary and physiological variables that may contribute to the variations in Tlim on the CWRT. They reported that Tlim was independently related to exercise capacity and leg fatigue at the end of the test, but a large fraction of the variability could not be explained by the investigated parameters.[83] To date, studies are lacking regarding determinants of the variation in Tlim during the ESWT.

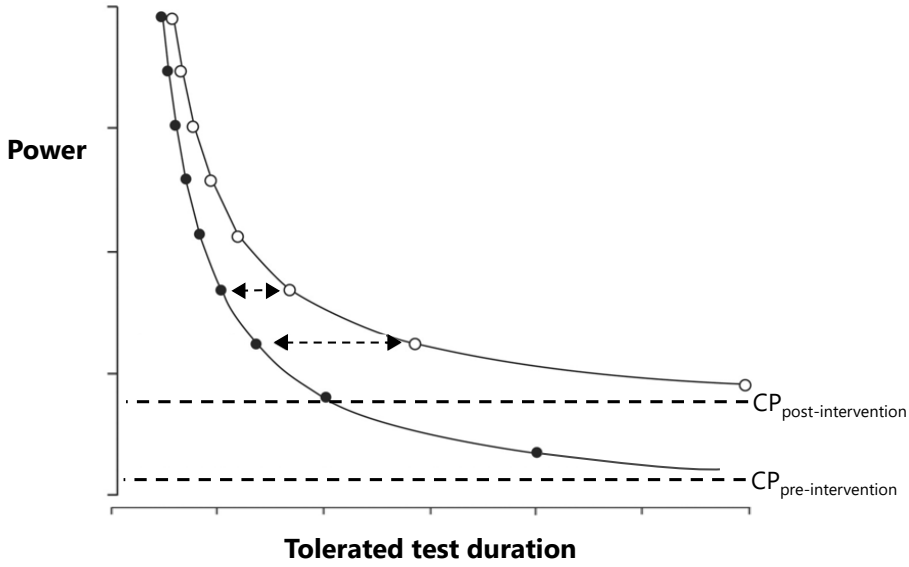

Figure 3. The hyperbolic power-duration curve that defines the limit of tolerance for whole-body exercises pre- and post-intervention.
Hypothetical curves of tolerated test duration during exercise test at multiple constant loads performed by one subject, both before an intervention (closed points) and after an intervention (open points). The lines represent the power-duration relationships pre- and post-intervention. The relationships approach asymptotes which are defined as the critical powers (CP). This figure shows that the closer the load of the test (i.e., power) approximates the critical power, the larger the potential effect of an intervention can be. Adapted from Whipp et al.[77]

Peripheral muscle function

Peripheral lower-limb muscle impairments are important determinants of exercise capacity and tolerance in patients with COPD and are therefore also related to the patient's physical performance.[54, 84] Furthermore, moderate correlations between peripheral muscle function tests and functional performance tests imply that both type of exercise tests assess different constructs and cannot replace each other.[54] Assessment of peripheral muscle function can be performed at intramuscular level, but is more common and practical at functional level for which various methods are available. The choice of the measurement technique depends on: the aim of the measurement, measurement quality, equipment, type(s) of muscle contraction, aspect(s) of muscle function, and target muscle(s).[54] Most clinicians and researchers focus on the aspect muscle strength, as this is an accessible way to investigate the extent of impairment and to prescribe adequate loads for resistance training. However, peripheral muscle endurance is even greater reduced in patients with COPD than muscle strength, and strongly related to exercise capacity and performance of daily life activities.[85, 86] Furthermore, muscle strength and endurance are two

different components of muscle function that require different training strategies.[87] This provides a great rationale for the additional assessment of peripheral muscle endurance in these patients. To date, there is no gold standard to evaluate peripheral muscle endurance in COPD, but dynamic testing of quadriceps muscle endurance using volitional isokinetic contractions is more common than static isometric or dynamic isotonic contractions.[88] Isokinetic testing allows to control for angular velocities, amplitude and duration of movement. In addition, it is feasible and has a great reliability, especially when using a computerized dynamometer.[89, 90] However, most studies have been performed in research settings with small sample sizes. Hence, an extensive evaluation regarding the feasibility, validity and responsiveness of isokinetic quadriceps test performance in a clinical setting (e.g., pulmonary rehabilitation) is essential.[54] In addition, evaluation using volitional contractions may be affected by external factors such as motivation and cooperation of the patient.[14] Non-volitional assessment using either electrical or magnetic twitch stimulations is not affected, or to a lesser extent, by these external factors.[91] Recent studies in patients with spinal cord injury have already reported a great reliability and reproducibility of non-volitional evaluation of isometric quadriceps contractile properties using electrical stimulations.[92, 93] In addition, a lower day-to-day variability of non-volitional assessment of muscle strength in comparison to volitional measures has been observed in patients with COPD.[94, 95] However, non-volitional assessment of peripheral muscle function is less practical and more time-consuming in clinical settings. Therefore, it is important to determine the validity of the volitional assessment of quadriceps muscle endurance by comparing it to non-volitional measures.

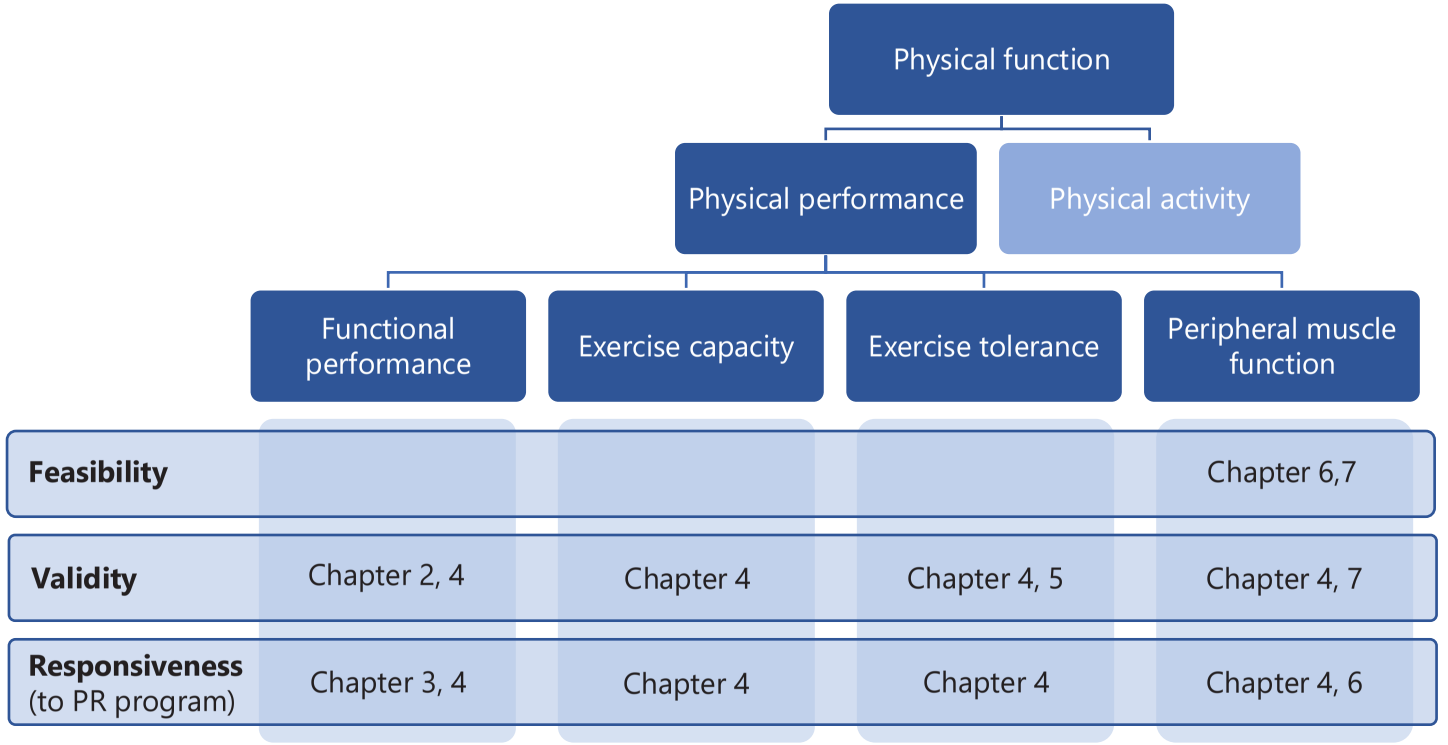

Figure 2. Subdivision of physical performance used in this thesis and corresponding chapters.

Abbreviation: PR, pulmonary rehabilitation.

AIM AND OUTLINE OF THIS THESIS

The main aim of this thesis is to expand the existing knowledge on feasibility, validity and responsiveness of commonly used physical performance outcome measures in patients with COPD.

Chapters 2 and 3 focus on the validity and responsiveness of a functional performance measure, namely the SPPB. **Chapter 2** presents the phenotypic characteristics of patients with COPD after stratification for SPPB summary score and the relations between phenotypic characteristics and the SPPB summary score at the start of pulmonary rehabilitation (i.e., validity). **Chapter 3** explores the responsiveness and minimal important differences for the SPPB subtests and summary score in patients with COPD following pulmonary rehabilitation.

Chapters 4 and 5 focus on the validity of exercise capacity and exercise tolerance measures. **Chapter 4** describes the correlations between different exercise test outcomes and commonly used PROs that describe health-related quality of life, anxiety, depression and disease-specific symptoms (e.g., dyspnoea) in patients with COPD before and after pulmonary rehabilitation. **Chapter 5** focuses on the validity of the ESWT to assess the exercise tolerance in patients with COPD. In this Chapter we explore whether pulmonary function, physical and incremental shuttle walk test performance variables are associated with ESWT Tlim in patients with COPD.

Chapters 6 and 7 focus on the feasibility, validity and responsiveness of peripheral muscle function in patients with COPD. **Chapter 6** describes whether and to what extent the isokinetic testing of quadriceps function meets the pre-defined test criteria in patients with COPD assessed pre and post pulmonary rehabilitation (i.e., feasibility); the differences in clinical characteristics between patients with a correct and incorrect isokinetic test performance (i.e., validity); and the response to pulmonary rehabilitation and minimal important differences of isokinetic quadriceps function (i.e., responsiveness). **Chapter 7** presents the results of a cross-sectional study that evaluated the relation between volitional isokinetic and isometric quadriceps muscle endurance and non-volitional electrically evoked quadriceps muscle endurance in patients with COPD (i.e., validity). Finally, **Chapter 8** is a general discussion, in which clinical implications of this thesis and future perspectives are described.

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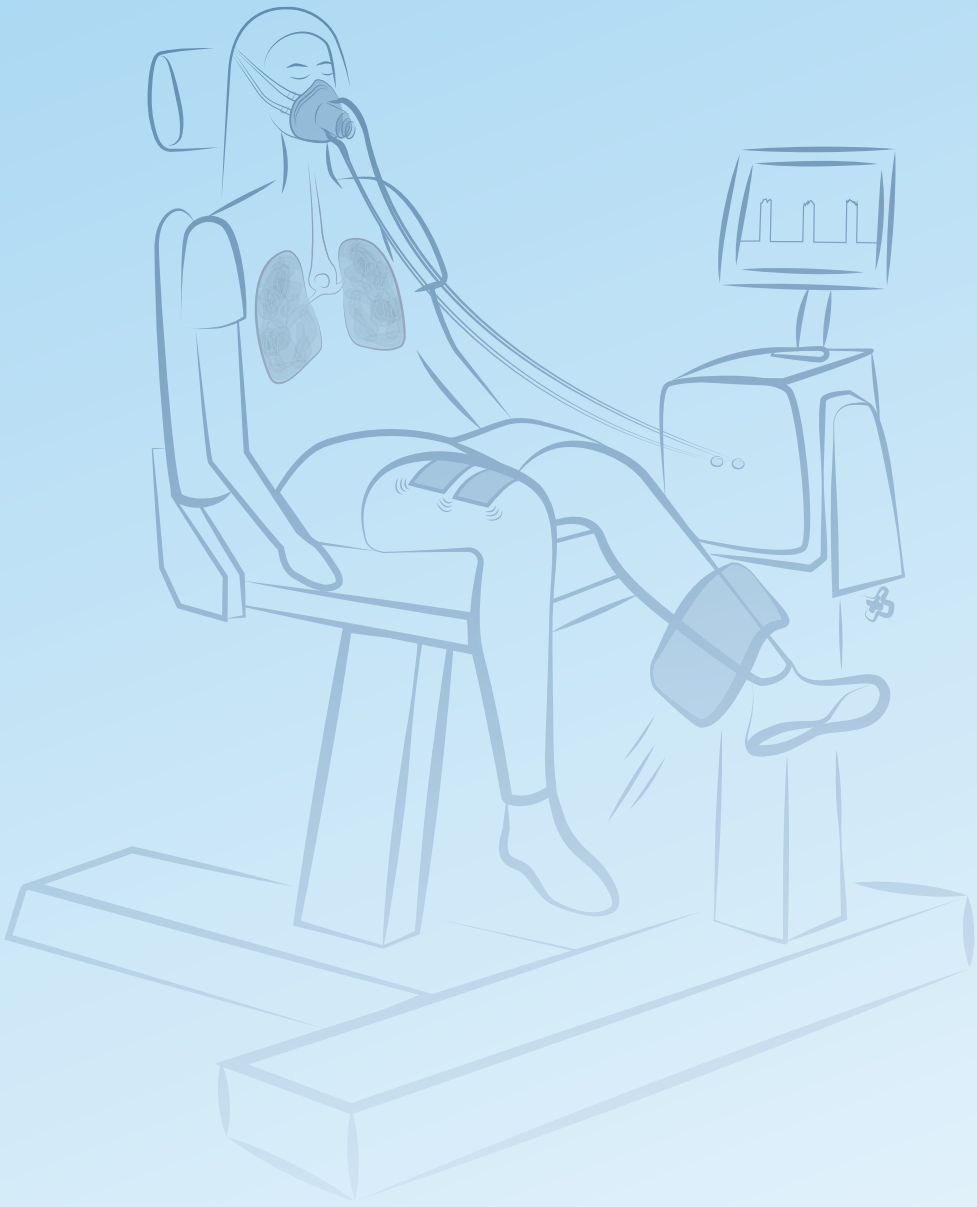
PART I: FUNCTIONAL PERFORMANCE



CHAPTER 2

Phenotypic characteristics of patients with chronic obstructive pulmonary disease after stratification for the short physical performance battery summary score

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ABSTRACT

Objective: To assess the phenotypic characteristics of patients with chronic obstructive pulmonary disease (COPD) after stratification for short physical performance battery (SPPB) summary scores and to determine phenotypic characteristics of the SPPB summary score at the start of pulmonary rehabilitation (PR).

Design: Retrospective, cross-sectional.

Setting: Baseline assessment for PR program.

Participants: Patients with COPD (n=900; age 65±8y, 52% male, forced expiratory volume in the first second of expiration, 43% [interquartile range, 31%-62%] predicted).

Interventions: Not applicable.

Main Outcome Measures: Patients were stratified according to their SPPB summary scores into low-performance (LP), moderate-performance (MP), or high-performance (HP) groups. Furthermore, lung function, arterial blood gases, body composition, physical capacity, lower limb muscle strength and endurance, and symptoms of anxiety and depression were assessed.

Results: Generally, physical capacity and muscle function were lower and scores for symptoms of anxiety and depression were higher in LP patients than MP and HP patients (all P-values <0.01). However, 25% of HP patients with COPD scored high on symptoms of anxiety and/or depression (≥10 points), and HP patients still had on average an impaired physical capacity (median, 6-minute walk test [6MWT] distance of 69% predicted). Furthermore, age and 6MWT distance (m) were the only independent predictors in a multivariate regression model, explaining 29% of the variance in SPPB summary score.

Conclusions: In COPD, LP patients have the worst physical and emotional functioning. However, HP patients can still exhibit physical and emotional impairments. Because the explained variance in SPPB summary score is low, SPPB should not be considered as a test to discriminate between patients with COPD with a low or preserved physical capacity and emotional status.

INTRODUCTION

Airflow limitation is a cardinal feature of patients with chronic obstructive pulmonary disease (COPD).[1] Additionally, evidence shows extrapulmonary consequences, such as impairment in balance control and mobility,[2-4] which are mainly caused by lower limb muscle weakness.[5] Mobility and balance deficits may induce more falls[6] and provoke difficulties in performing activities of daily living safely and independently.[7-9] Furthermore, it can be the first sign of further functional decline, and, therefore, it is important to identify patients with COPD with reduced balance and mobility to prevent disability in activities of daily living.[10-12]

The short physical performance battery (SPPB) is a commonly used, simple, and quick performance measure to evaluate mobility and balance and is recommended in older patients by the European Medicines Agency.[13] Furthermore, the SPPB score has prognostic value because it might identify a subsequent decline in activities of daily living status, rehospitalization, and mortality in elderly patients, including COPD, after hospital discharge.[14] Individuals can be grouped based on their SPPB summary score into a low-performance (LP), a moderate-performance (MP), and a high-performance (HP) group.[11] Patel et al. and Mohan et al. were the first to evaluate the physical phenotypic characteristics of the abovementioned SPPB performance groups in patients with COPD.[15,16] Indeed, LP patients with COPD had more functional impairment, loss of muscle mass, and structural muscle abnormality than HP patients.[15] Furthermore, a longer 6-minute walk test (6MWT) distance, greater quadriceps maximal voluntary contraction strength, lower age, self-reported hypertension and dyspnoea, and being married decreased the likelihood of being in the LP group.[16] These data need further corroboration in non-United Kingdom based settings because geographic differences in clinical characteristics and management of COPD are known.[17]

Symptoms of anxiety and depression are also common in patients with COPD[18] and significantly correlate with mobility and balance in healthy elderly persons.[19, 20] However, it remains unclear whether and to what extent a similar pattern occurs in emotional status (i.e., symptoms of anxiety and depression) after stratification for SPPB summary scores. Furthermore, it is unclear whether and to what extent physical and emotional impairment is also present in HP patients. This is important to know because HP patients may give a first impression that they have a normal physical and emotional functioning.

The current study aimed to assess phenotypic characteristics of patients with COPD after stratification for SPPB summary scores and to investigate which phenotypic characteristics determine the SPPB summary score at the start of pulmonary rehabilitation (PR).

METHODS

This retrospective analysis of an observational, cross-sectional study included anonymized data of 953 patients, evaluated during baseline assessment of a comprehensive PR between January 2016 and January 2018 in CIRO, a specialized PR clinic in the Netherland.[21] All measurements were performed by a highly trained and skilled team of biomedical engineers and laboratory technicians. The medical ethical committee informed the authors that the Medical Research Involving Human Subjects Act (WMO) does not apply to this retrospective study using deidentified, pre-existing data and that an official approval of this study by our committee is not required (METC 2018-0541). This study was conformed to the principles of the Declaration of Helsinki.

Inclusion criteria were a primary diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[1] and complete data available regarding SPPB. The latter may result in selection bias. Furthermore, patients were excluded from this analysis if they participated in the PR program for the second time during the inclusion period and/or if they were younger than 40 years.

Baseline characteristics

Age, sex, weight, body mass index, the degree of dyspnoea (modified Medical Research Council (mMRC)),[22] health status (COPD Assessment Test (CAT)),[23] exacerbation and all-cause hospitalization frequency in the past 12 months, Charlson Comorbidity index,[24] and use of long-term oxygen therapy were systematically assessed. An mMRC dyspnoea grade ≥2[1], CAT score ≥10 points, and CAT score ≥18 points[25,26] were used to classify patients as highly symptomatic.

Short physical performance battery

Patients performed the SPPB according to the National Institute on Aging protocol.[27] First, the standing balance measurement was performed in which the patient is required to maintain 3 stances for 10 seconds (feet placed side-by-side, semi-tandem, and tandem). The 4-meter gait speed (4MGS) test assessed the time needed to walk 4 meters at habitual gait speed from a standing position. This test was performed twice, and the best time was used to score the test. In the 5-repetition sit-to-stand (5STS) test, the time was measured to complete 5 sit-to-stand manoeuvres as quickly as possible with arms folded in front of their chest.

Each component was scored from 0 (mobility impairment) to 4 points (no mobility impairment), resulting in a SPPB summary score ranging from 0-12 points. The scoring

system can be found in Supplemental Table 1. Additionally, patients were classified as LP (0-6 points), MP (7-9 points), or HP (10-12 points).[11]

Table 1. Characteristics of patients with COPD stratified for SPPB summary score.

Baseline characteristics	Patients with COPD (n=900)	Short physical performance battery levels			P-value
		Low-performance (n=98)	Moderate-performance (n=393)	High-performance (n=409)	
General Characteristics					
Age (years)	65±8	69±8	66±8	63±8	<0.001*,#,†
Gender (male, %)	52	44	52	54	0.221
Weight [a] (kg)	74±20	76±25	74±19	73±19	0.603
BMI [a] (kg/m^2)	26.2±6.3	27.4±7.8	26.3±6.1	25.7±5.9	0.049
mMRC [b] (grade)	2 (2-3)	4 (3-4)	3 (2-3)	2 (2-3)	<0.001*,#,†
mMRC ≥ 2 [b] (% patients)	87	100	92	78	<0.001*,#,†
CAT [c] (points)	21±7	25±6	22±6	20±7	<0.001*,#,†
CAT ≥ 10 [c] (% patients)	95	100	96	93	0.020
CAT ≥ 18 [c] (% patients)	75	89	78	69	<0.001#,†
Exacerbations in the past 12 months [d] (n)	2 (1-4)	3 (2-5)	2 (1-4)	2 (1-3)	<0.001*,#
≥ 2 exacerbations in the past 12 months [d] (% patients)	63	77	62	59	0.006*,#
Hospitalizations in the past 12 months [e] (n)	0 (0-1)	1 (0-3)	0 (0-1)	0 (0-1)	<0.001*,#
≥ 1 hospitalization in the past 12 months [e] (% patients)	44	64	46	39	<0.001*,#
CCI (points)	1 (1-2)	2 (1-3)	1 (1-2)	1 (1-2)	0.006#
CCI ≥ 2 (% patients)	45	55	47	40	0.017
Long-term O_2 use [f] (yes, % patients)	22	42	22	16	<0.001*,#

*Data is presented as mean±SD, median (IQR), or percentages. * indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. # indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. † indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB scores 10-12. Alphabetic characters in superscript indicates a sample size deviant from n=900 with the following: a. n=897 (low, moderate, and high resp. 98, 390, 409), b. n=899 (low, moderate, and high resp. 98, 393, 408), c. n=844 (low, moderate, and high resp. 87, 374, 383), d. n=895 (low, moderate, and high resp. 98, 390, 407), e. n=897 (low, moderate, and high resp. 96, 392, 409), f. n=883 (low, moderate, and high resp. 95, 387, 401). Abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index; kg, kilogram; m, meters; mMRC, Modified Medical Research Council; n, numbers; O_2, oxygen; SPPB, Short physical performance battery.*

Phenotypic characteristics

The GOLD classification[28] and arterial blood gases were evaluated. Furthermore, spirometry, static lung volumes, and transfer factor for carbon monoxide by single-breath method were executed according to the European Respiratory Society recommendations[29] (MasterScreen PFT/Body).

Waist circumference was measured, and fat-free mass (FFM) and T scores of the hip (trochanter) and lumbar spine (L2-L4) were evaluated using dual energy x-ray absorptiometry (Lunar iDXA).[30] The FFM index was calculated by dividing FFM by height*height. The reference values of the International Diabetes Federation were used for waist circumference.[31]

Physical capacity was assessed using the 6MWT, maximal incremental cardiopulmonary exercise test, and constant work rate test (CWRT). The 6MWT was performed indoors on a flat and straight walking course of 30 meters, following the European Respiratory Society/American Thoracic Society guidelines.[32,33] Reference values from Troosters et al.[34] were used, and a cut-off value of 350 meters according to Spruit et al. was applied to predict respiratory-related hospitalization.[35] The maximal cardiopulmonary exercise test was performed on an electromagnetically braked cycle ergometer (Ergoselect) according to the recommended guidelines.[36] The maximal workload (Wmax) was calculated as a percentage of the predicted value.[37] The CWRT was performed on the same ergometer at 75% of the predetermined Wmax. Patients cycled until symptom limitation or until pedalling rate decreased under 60 rpm (with a maximum of 20 minutes).[38]

Isotonic muscle strength was measured by 1-repetition maximum leg press, leg extension, upper back and chest press using standard weight training apparatus (Technogym) and was corrected for the FFM of the legs or arms. Isokinetic quadriceps peak torque (Nm) and endurance (total amount of delivered work, J) of the right leg were assessed with a computerized dynamometer (Biodex Multi-joint System 3) and corrected for the FFM of the legs. The reference values of Borges et al. were used for isokinetic peak torque.[39] Patients performed a set of 30 repetitions at an angular speed of 90°/s.

The Hospital Anxiety and Depression Scale was used as a screening tool to detect symptoms of anxiety and depression. A cut-off point of >10 points was used for each domain.[40]

Statistical analyses

Statistical analyses were performed using SPSS, version 25.0. Descriptive data were presented as mean±SD, median (interquartile range, 25%-75%), or percentages as

appropriate. Differences between included and excluded patients were tested by an unpaired t test or Mann-Whitney U test as appropriate. Differences between LP, MP, and HP groups were tested by 1-way analysis of variance or Kruskal-Wallis test as appropriate. Categorical data were tested with a chi-square test. When a statistically significant difference was obtained, a pairwise post-hoc test was performed, and Bonferroni post-hoc testing was applied to correct for multiple comparison. Because of the many statistical tests performed in this study, a P-value <0.01 was considered significant.

Univariate and multivariate regression models were used to assess the associations between the phenotypic characteristics and the SPPB summary score, both using the ENTER method. Explanatory variables, based on univariate models, with a P-value <0.20 and not highly correlated with another variable of interest were used to build the multivariate linear regression model. Variables with a P-value <0.05 were considered as independent predictors of SPPB summary score.

RESULTS

Nine hundred of the 953 patients with COPD were analysed. Reasons for exclusion were absence of SPPB data (n=1), age younger than 40 years (n=5), participation in the PR program for the second time (n=20), and erroneous download from the database (n=27). Differences between included and excluded patients are depicted in Supplemental Table 2.

Clinical characteristics

The included patients had a mean age of 65±8 years, 52% were male, 63% of the patients experienced ≥2 exacerbations <12 months, and 44% experienced ≥1 hospitaliz[a]tion <12 months. Furthermore, 87% were highly symptomatic (mMRC≥2), and 45% of patients were multimorbid. A 6MWT distance <350 m was found in 38% of patients, and the median time-to-exhaustion on the CWRT was 230 seconds (interquartile range, 165-334 s). The isokinetic quadriceps peak torque was 61±19% of predicted, and the total work was 1487±632 Joules. Furthermore, 30% and 31% of the patients with COPD had a score ≥10 points on symptoms for anxiety and depression, respectively. All details can be found in Tables 1 and 2.

Table 2. Phenotypic characteristics of patients with COPD stratified for SPPB summary scores.

Phenotypic characteristics	Patients with COPD (n=900)	Short physical performance battery			P-value
		Low-performance (n=98)	Moderate-performance (n=393)	High-performance (n=409)	
Lung function and arterial blood gasses					
GOLD I/II/III/IV (% patients)	9/29/38/24	2/30/31/38	11/27/39/23	10/30/39/22	0.009[*,#]
GOLD A/B/C/D [a] (% patients)	5/24/8/63	0/15/0/85	3/27/5/66	9/24/13/54	<0.001[*,#,†]
FEV_1 (% predicted)	43 (31-62)	35 (24-54)	43 (31-62)	44 (32-63)	0.001[*,#]
FEV_1 (L)	1.07 (0.76-1.54)	0.81 (0.53-1.22)	1.05 (0.73-1.58)	1.13 (0.84-1.59)	<0.001[*,#]
FEV_1/FVC	0.35 (0.28-0.47)	0.34 (0.25-0.46)	0.36 (0.28-0.49)	0.35 (0.27-0.47)	0.253
TL_{CO}-SB [b] (% predicted)	50.1±17.1	42.7±16.3	49.7±17.4	51.9±16.6	<0.001[*,#]
RV-BB [c] (% predicted)	165.5±55.7	181.0±72.2	161.4±56.5	166.0±49.8	0.011
TLC-BB [d] (% predicted)	117.3±19.7	116.5±24.7	115.3±19.9	119.6±17.9	0.009[†]
paO_2 [e] (kPa)	9.1 (8.3-10)	8.6 (7.7-9.8)	9.0 (8.2-10.1)	9.3 (8.4-10.1)	0.001[*,#]
$paCO_2$ [f] (kPa)	5.3 (4.9-5.9)	5.8 (5.1-6.8)	5.3 (4.9-5.9)	5.2 (4.9-5.7)	<0.001[*,#]
Saturation [g] (%)	94 (92-95)	92 (90-95)	93 (92-95)	94 (93-95)	0.181
Body composition					
FFMI [h] (kg/m^2)	16.6±2.5	16.3±2.8	16.6±2.6	16.7 ±2.4	0.456
FFMI below predicted values [i] (% patients)	11	19	13	7	0.001[#,†]
FFM of the arms [j] (kg)	5.1 (3.9-6.5)	4.5 (3.6-6.0)	5.0 (3.9-6.3)	5.3 (4.2-6.7)	0.002[#]
FFM of the legs [k] (kg)	15.1 (12.2-17.9)	14.0 (11.7-17.0)	15.0 (12.0-17.7)	15.4 (12.6-18.0)	0.015
Waist circumference [l] (cm)	97.8±17.1	101.3±20.2	98.6±16.9	96.1±16.4	0.011
Waist circumference above predicted values [l] (% patients)	74	76	77	71	0.130
T-score L2-L4 [m]	-0.79±1.72	-0.60±1.90	-0.81±1.70	-0.83±1.69	0.498
T-score trochanter [n]	-1.76±1.02	-1.95±0.95	-1.81±1.01	-1.66±1.04	0.022[#]
Normal bone mineral density/ osteopenia/ osteoporosis [o] (% patients)	20/47/32	17/45/38	19/47/34	22/49/29	0.368
6MWT [p] (m)	389 (300-459)	194 (139-259)	359 (290-420)	445 (386-497)	<0.001[*,#,†]
6MWT <350 m [p] (% patients)	38	96	46	15	<0.001[*,#,†]
6MWT [q] (% predicted)	62 (50-72)	33 (24-46)	58 (49-67)	69 (60-78)	<0.001[*,#,†]
6MWT: Patients with ≥ 1 stop [r] (% patients)	16	52	16	8	<0.001[*,#,†]
Wmax [s] (W)	59 (43-80)	36 (23-53)	56 (41-75)	66 (50-91)	<0.001[*,#,†]
Wmax [t] (% of predicted)	44 (32-57)	27 (18-43)	41 (31-52)	49 (37-62)	<0.001[*,#,†]
CWRT TTE [u] (s)	230 (165-334)	145 (111-260)	215 (160-308)	258 (183-365)	<0.001[*,#,†]
Isotonic muscle strength					
Leg press [v] (kg)	70 (50-100)	40 (20-60)	60 (40-90)	80 (60-110)	<0.001[*,#,†]
Leg extension [w] (kg)	28 (20-38)	18 (10-25)	25 (20-35)	30 (25-40)	<0.001[*,#,†]
Upper back [x] (kg)	23 (15-35)	15 (10-20)	20 (15-30)	25 (20-35)	<0.001[*,#,†]

Table 2. Continued.

Physical status	Patients with COPD (n=900)	Short physical performance battery			P-value
		Low-performance (n=98)	Moderate-performance (n=393)	High-performance (n=409)	
Isotonic muscle strength corrected for FFM					
Leg press [z]	4.83±2.26	3.16±1.98	4.39±2.05	5.62±2.20	<0.001*,#,†
Leg extension [za]	1.91±0.70	1.36±0.59	1.76±0.67	2.17±0.64	<0.001*,#,†
Upper back [zb]	4.67±1.68	3.37±1.60	4.45±1.63	5.17±1.56	<0.001*,#,†
Chest press [zc]	4.63±1.68	3.58±1.43	4.41±1.71	5.06±1.56	<0.001*,#,†
Isokinetic muscle strength/endurance					
Peak torque [zd] (Nm)	86±33	60±31	83±32	94±31	<0.001*,#,†
Peak torque [ze] (% predicted)	61±19	46±18	59±19	65±17	<0.001*,#,†
Total work [zd] (J)	1487±632	889±550	1399±631	1654±572	<0.001*,#,†
Isokinetic muscle strength/endurance corrected for FFM					
Peak torque [zf] (Nm/kg)	5.57±1.40	4.01±1.45	5.36±1.36	5.99±1.21	<0.001*,#,†
Peak torque [zg] (%/kg)	4.06±1.17	3.22±1.23	3.95±1.17	4.28±1.09	<0.001*,#,†
Total work [zf] (J/kg)	95.5±29.8	60.1±29.5	89.8±29.2	105.9±24.3	<0.001*,#,†
Emotional status					
HADS anxiety [zh] (points)	7.5±4.2	9.2±4.6	7.7±4.1	6.9±4.1	<0.001*,#,†
HADS anxiety ≥ 10 [zh] (% patients)	30	46	32	24	<0.001*,#
HADS depression [zh] (points)	7.4±4.0	9.0±4.4	7.8±3.8	6.7±4.0	<0.001*,#,†
HADS depression ≥ 10 [zh] (% patients)	31	52	31	25	<0.001*,#

*Data is presented as mean±SD, median (IQR), or percentages. * indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. # indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. † indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB scores 10-12. Alphabetic characters in superscript indicates a sample size deviant from n=900 with the following: a. n=892 (low, moderate, and high resp. 96, 390, 406), b. n=835 (low, moderate, and high resp. 72, 363, 400), c. n=864 (low, moderate, and high resp. 90, 370, 404), d. n=865 (low, moderate, and high resp. 90, 371, 404), e. n=843 (low, moderate, and high resp. 81, 370, 392), f. n=843 (low, moderate, and high resp. 82, 370, 391), g. n=124 (low, moderate, and high resp. 13, 57, 54), h. n=891 (low, moderate, and high resp. 95, 389, 407), i. n=889 (low, moderate, and high resp. 95, 387, 407), j. n=892 (low, moderate, and high resp. 95, 390, 407), k. n=892 (low, moderate, and high resp. 96, 389, 407), l. n=897 (low, moderate, and high resp. 96, 393, 408), m. n=881 (low, moderate, and high resp. 94, 384, 403), n. n=875 (low, moderate, and high resp. 91, 381, 403), o. n=888 (low, moderate, and high resp. 94, 388, 406), p. n=893 (low, moderate, and high resp. 95, 390, 408), q. n=893 (low, moderate, and high resp. 94, 390, 409), r. n=895 (low, moderate, and high resp. 95, 391, 409), s. n=822 (low, moderate, and high resp. 64, 359, 399), t. n=819 (low, moderate, and high resp. 64, 356, 399), u. n=796 (low, moderate, and high resp. 57, 347, 392), v. n=865 (low, moderate, and high resp. 87, 373, 405), w. n=834 (low, moderate, and high resp. 79, 366, 389), x. n=801 (low, moderate, and high resp. 80, 343, 378), y. n=794 (low, moderate, and high resp. 77, 342, 375), z. n=858 (low, moderate, and high resp. 85, 370, 403), za. n=828 (low, moderate, and high resp. 78, 363, 387), zb. n=796 (low, moderate, and high resp. 79, 341, 376), zc. n=789 (low, moderate, and high resp. 76, 340, 373), zd. n=690 (low, moderate, and high resp. 53, 285, 352), ze. n=689 (low, moderate, and high resp. 53, 285, 351), zf. n=684 (low, moderate, and high resp. 53, 281, 350), zg. n=683 (low, moderate, and high resp. 53, 281, 349). zh. n=843 (low, moderate, and high resp. 87,*

374, 382). Abbreviations: BB, Body Box; COPD, Chronic obstructive pulmonary disease; CWRT, Constant Work Rate Test; FEV_1, Forced Expiratory Volume in the first second; FFM, fat-free mass; FFMI, fat-free mass index; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; J, Joule; kg, kilogram; L, liters; L2-L4, Lumbar spine (L2-L4); m, meters; Nm, Newton-meter; $paCO_2$, Partial pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; SPPB, Short physical performance battery; SB, single-breath; RV, Residual Volume; TLC, Total Lung Capacity; TL_{CO}, Diffusion capacity for carbon monoxide; TTE, time-to-exhaustion; Wmax, maximal wattage; W, wattage; 1-RM, 1-Repetition Maximum; 6MWT, 6-Minute Walk Test.

Short physical performance battery

The SPPB summary score of the whole group was 9 points (interquartile range, 8-10 points). Ninety-eight patients (11%) had LP scores, 393 patients (44%) had MP scores, and 409 patients (45%) had HP scores. The frequency distribution of the SPPB summary score can be found in Supplemental Figure 1.

The balance standing test score differed significantly among the levels of performance, with the LP group performing the worst (P<0.001). Furthermore, the LP group executed the 4MGS and 5STS (after excluding patients [n=70; whereof n=54 in LP group] who were not able to perform the 5STS test) the slowest in comparison to the MP group and the HP group (P<0.001) (Table 3). The frequency distribution of the SPPB components can be found in Figure 1.

Table 3. Short physical performance battery (SPPB) results of patients with COPD stratified for SPPB summary scores.

SPPB score	Patients with COPD (n=900)	Short physical performance battery levels			P-value
		Low-performance (n=98)	Moderate-performance (n=393)	High-performance (n=409)	
Balance side-by-side (s)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	<0.001*,#
Balance semi-tandem (s)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	10.0 (10.0-10.0)	<0.001*,#
Balance tandem (s)	10.0 (10.0-10.0)	0.0 (0.0-5.5)	10.0 (7.3-10.0)	10.0 (10.0-10.0)	<0.001*,#,†
4MGS (s)	3.8 (3.2-4.7)	6.3 (4.9-7.9)	4.2 (3.6-5.0)	3.4 (3.0-3.8)	<0.001*,#,†
4MGS [a] (m/s)	1.04±0.29	0.62±0.20	0.97±0.24	1.20±0.22	<0.001*,#,†
5STS (s)-all patients	15.0 (12.3-18.4)	0 (0.0-22.0)	18.1 (15.6-21.2)	13.0 (11.6-14.6)	<0.001*,†
5STS [b] (s)-only patients able to perform the test	15.4 (12.9-18.8)	23.3 (19.3-31.4)	18.3 (16.1-21.4)	13.0 (11.6-14.6)	<0.001*,#,†
Total SPPB score (points)	9 (8-10)	5 (4-6)	9 (8-9)	11 (10-11)	<0.001*,#,†

*Data is presented as mean±SD or median (IQR). * indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. # indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. † indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB scores 10-12. Alphabetic characters in superscript indicates a sample size deviant from n=900 with the following: a. n=884 (low, moderate, and high resp. 82, 393, 409), b. n=830 (low, moderate, and high resp. 44, 377, 409). Abbreviations: COPD, Chronic obstructive pulmonary disease; m, meters; s, seconds; SPPB, Short physical performance battery; 4MGS, 4-meter gait speed; 5STS, 5-repetition sit-to-stand.*

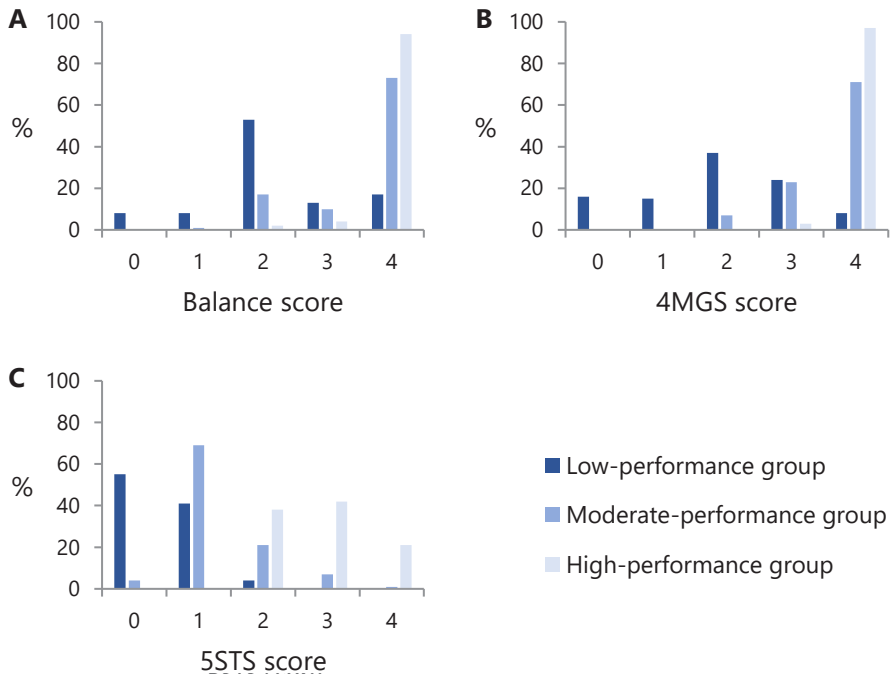

Figure 1. Percentages of patients of LP, MP, and HP groups that scored 0-4 on the (**A**) standing balance tests, (**B**) 4MGS, and (**C**) 5STS.

Characteristics after stratification for SPPB

According to stratification for SPPB score, patients with LP scores were older, experienced more dyspnoea, had a lower health status, had a higher percentage of ≥2 exacerbations and ≥1 hospitalizations in the past 12 months, and were more likely long-term oxygen therapy users than the MP and HP groups. Furthermore, 89% of the LP group and 79% of the MP group scored ≥18 points on the CAT, which was higher than the HP group (68%) (P<0.001) (Table 1).

The LP group had a higher GOLD classification and lower forced expiratory volume in the first second of expiration percentage predicted than the MP and HP groups. The LP group showed lower arterial oxygen pressures and higher carbon dioxide pressures than the MP and HP group. The FFM of arms was lower in the LP group than the HP group (P=0.003). The proportion of patients with a normal bone mineral density, osteopenia, and osteoporosis was comparable between groups (Table 2).

Physical capacity was lowest in the LP group and highest in the HP group (all P-values <0.001). In the LP group 96% of the patients had a 6MWT distance <350 meters.[35] This

proportion was lower in the MP group (46%) and HP group (16%). Furthermore, the LP group had on average a lower CWRT time-to-exhaustion than the MP and HP groups.

The muscle strength and endurance differed among the groups, with the LP group performing the worst, even after correcting for FFM (all P-values <0.001) (Table 2). Additionally, the LP group scored higher on symptoms of anxiety and depression and had a higher proportion of patients scoring ≥10 points on anxiety (46%) and depression (52%) than the MP and/or HP groups (all P-values <0.001) (Table 2).

Even though the HP group scored better on physical capacity and emotional status, 8% of patients needed ≥1 stop during the 6MWT, the median Wmax on the maximal incremental cycle test was 54% (interquartile range, 40%-71%) of the predicted value, and one-fourth of the patients had symptoms of anxiety and/or depression (Table 2).

Determinants of SPPB summary score

Almost all absolute phenotypic characteristics were univariate predictors of SPPB summary score (Supplemental Table 3). Explanatory predictors without a high correlation with another variable of interest were entered in a multivariate linear regression model. This model ($F_{15,508}$=13.673, P<0.001) explained 29% of the variance in SPPB summary score. Age (β=-0.085, P=0.043) and 6MWT (m) (β=0.454, P<0.001) were the only significant independent predictors (Supplemental Table 4).

DISCUSSION

The present study shows that the phenotypic characteristics differ between patients with COPD after stratification for SPPB summary scores, with the worst values reported in the LP group. Moreover, patients with a SPPB summary score ≥10 points (HP group) can still exhibit impairments in physical capacity and emotional traits. Age and 6MWT (m) were the only independent predictors in a multivariate regression model, explaining only 29% of the variance of SPPB summary score.

In this study, 55% of the patients with COPD scored <10 points on the SPPB at the pre-PR assessment, indicating a reduced functional capacity and increased risk of developing mobility and/ or activities of daily living.[11,41]

The LP group performed worse on all SPPB subtests than the MP and HP groups. Furthermore, a lower quadriceps strength and 6MWT is reported in the LP group; this may, at least partly, explain the reduced SPPB performance. Recently, associations

between the isometric quadriceps muscle strength, 6MWT, SPPB summary score, and SPPB subtests scores have been reported, which are confirmed by our results.[15,16,42]

Patients performed the 5STS worst of all SPPB subtests, which is consistent with the study of Larsson et al.[43] Bernabeau-Mora et al. reported only an association between CAT and the 5STS (partial R^2=0.073, P<0.001) in the multivariable regression model and not with the other subtests. This supports the concept that the 5STS is a better screening tool for poor health status[42] than the other SPPB subtests. One possible reason is that ventilatory demands during the 5STS are higher than during the standing balance tests and 4MGS,[43,44] and therefore the 5STS is more sensitive in obtaining differences between the performance groups.

Overall, the phenotypic characteristics are worse in the LP group than the MP and HP groups. The reduced lung function in the LP group is in accordance with other studies because an impaired lung function is known to contribute to mobility and balance deficits.[13] Furthermore, Eisner et al. suggested that lung functional impairment may contribute to muscle weakness in the upper and lower extremities of patients with COPD, which is consistent with systemic involvement from the disease.[45]

The body composition, physical capacity, and quadriceps muscle strength and endurance were worse in the LP group, which is consistent with the studies of Patel et al. and Mohan et al.[15,16] They reported lower quadriceps strength and bulk, physical activity, exercise capacity, and performance in the LP and/or MP group than the HP group[15] and decreased odds of being in a lower category for the SPPB summary score for a longer 6MWT and greater quadriceps maximal voluntary contraction strength.[16] Additionally, a decrease in FFM is correlated with a decline in postural stability and mobility.[46,47] A possible explanation can be that a reduction in muscle mass is related to a loss in muscle function and strength,[48] which are both necessary to maintain balance and mobility and execute functional activities.[7,49-51]

The emotional status differed between the 3 performance groups, with the highest prevalence of anxiety and depression symptoms present in the LP group. The difference in anxiety between the LP group and the MP and HP groups and in depression between the LP and HP groups reaches the minimal important difference.[52] Other studies have already reported associations between anxiety, depression, mobility, and balance, which might explain the higher prevalence of symptoms of anxiety and depression in the LP group.[19,20,53] A suggestion could be the increased risk of falls due to the inattention to potential environmental hazards in people with depression[54] or due to greater fear of falls in patients exhibiting anxiety or depression.[9] Physical activity is known to improve

one's self-esteem and reduce depressive and anxiety symptoms, and less active patients may therefore develop more often emotional impairment.[55] Future studies are needed to determine the exact causal relationship and evaluate emotional status more extensively.

Even though the values for phenotypic characteristics were the highest in the HP group, 16% of the patients had a 6MWT distance <350 meters, which is a risk factor for respiratory-related hospitalization.[35] Additionally, 1 of 4 HP patients experienced symptoms of anxiety and/or depression. These results indicate that even the HP patients with COPD at the start of PR can exhibit impairments in physical capacity and emotional status that cannot be determined by the SPPB alone. This emphasizes the importance of additional assessment in patients with COPD during baseline assessment in PR because SPPB alone cannot identify all patients at risk and/or in need of PR.

Many phenotypic factors were univariate predictors of the SPPB summary score, but age and 6MWT were the only independent predictors in a multivariate regression model. This finding is consistent with the literature[15,16,42] and highlights the importance of age and physical capacity in maintaining balance and mobility.

Study limitations

The strength of the study is the large sample size of patients with COPD with well-defined and well-characterized data that provides for the first time an extensive overview on phenotypic characteristics per SPPB performance of patients with COPD in a non-United Kingdom PR setting. The study confirms the high prevalence of physical and emotional impairment among all performance groups.

Obviously, the cross-sectional design prevents us from establishing causality between patients' phenotypic factors and mobility and balance. Second, the data are obtained retrospectively from 1 location, which reduces the generalizability of the results. Current studies also need corroboration in the primary care setting.

CONCLUSIONS

In COPD, patients with a LP SPPB summary score have the worst physical and emotional functioning. However, HP patients can still exhibit physical and emotional impairments. Because the explained variance in SPPB summary score is low, the SPPB should not be considered as a screening tool to discriminate between patients with COPD with a low or preserved physical capacity and emotional status.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. The scoring system of the standing balance, 4-meter gait speed (4MGS) and 5-repetition sit-to-stand (5STS) tests.

Scores	Balance: side-by-side test (s)	Balance: semi-tandem test (s)	Balance: tandem test (s)	4MGS (s)	5STS (s)
4				<4.82	<11.20
3				4.82–6.20	11.20–13.69
2			10.00	6.21–8.70	13.70–16.69
1	10.00	10.00	3.00-9.99	>8.70	16.70–60.00
0	<10.00	<10.00	<3.00	Unable	Unable (>60.00)

Supplemental Table 2. Differences in patients' characteristics between included and excluded patients.

Patients' characteristics	Included (n=900)	Excluded (n=53)	P-value
Age (y)	65±8	63±12	0.140
Sex (male, % of patients)	52	55	0.397
Weight (kg)	74±20	75±16	0.728
BMI (kg/m^2)	26.2±6.3	26.4±5.7	0.806
mMRC (grade)	2 (2-3)	3 (2-4)	<0.001
CAT (points)	21±7	23±6	0.047
Exacerbations in the past 12 mo: 0/1/2/3/4/>4 (% of patients) [d]	20/17/20/14/8/21	11/10/17/13/6/43	0.006
Hospitalizations in the past 12 mo: 0/1/2/3/4/>4 (% of patients) [e]	55/25/9/5/2/4	39/26/13/20/2/0	0.001
CCI (points)	1 (1-2)	1 (1-2)	0.600
Long-term O_2 use (yes, % patients) [f]	22	37	0.015
Lung function and arterial blood gases			
FEV_1 (L)	1.07 (0.76-1.54)	0.86 (0.69-1.47)	0.070
paO_2 (kPa)	9.1 (8.3-10.0)	9.3 (8.1-11.1)	0.270
$paCO_2$ (kPa)	5.3 (4.9-5.9)	5.2 (4.8-5.7)	0.180
Saturation (%)	94 (92-95)	94 (91-97)	0.247
Body composition			
FFM of the arms (kg)	5.1 (3.9-6.5)	4.6 (3.8-6.0)	0.081
FFM of the legs (kg)	15.1 (12.2-17.9)	14.3 (11.3-16.8)	0.061
Waist circumference (cm)	97.8±17.1	96.1±14.9	0.504
T score lumbar spine (L2-L4)	-0.79±1.72	-1.11±1.56	0.198
T score hip (trochanter)	-1.76±1.02	-1.85±1.15	0.522
Physical capacity and exercise tolerance			
6MWT (m)	389 (300-459)	351 (259-428)	0.049
Wmax (W)	59 (43-80)	56 (42-80)	0.694
CWRT TTE (s)	230 (165-334)	184 (151-237)	0.044
Isotonic muscle strength			
Leg press (kg)	70 (50-100)	50 (30-90)	0.027
Leg extension (kg)	28 (20-38)	20 (15-39)	0.053
Upper back (kg)	23 (15-35)	30 (15-35)	0.509
Chest press (kg)	23 (15-33)	25 (13-30)	0.428

Supplemental Table 2. Continued

Patients' characteristics	Included (n=900)	Excluded (n=53)	P-value
Isokinetic muscle strength/endurance			
Peak torque (Nm)	86±33	75±28	0.041
Total work (J)	1487±632	1197±529	0.009
Emotional status			
HADS anxiety (points)	7.5±4.2	8.5±4.5	0.106
HADS depression (points)	7.4±4.0	7.4±3.9	0.952
Short physical performance battery			
Balance tests score	4 (4-4)	4 (3-4)	0.300
4MGS score	4 (4-4)	4 (3-4)	0.001
5STS score	2 (1-3)	1 (1-3)	0.010
SPPB total score	9 (8-10)	8 (7-11)	0.009

Alphabetic characteristics in superscript indicates a sample size deviant from n=953 with the following: a=927 (included=897 and excluded=31), b=952 (included=899 and excluded=53), c=894 (included=844 and excluded=50), d=948 (included=895 and excluded=53), e=910 (included=864 and excluded=46), f=935 (included=884 and excluded 51), g=951 (included=899 and excluded=52), h=881 (included=840 and excluded=41), i=882 (included=841 and excluded=41), j=935 (included=885 and excluded=50), k=949 (included 891 and excluded=50), l=923 (included=874 and excluded=49), m=916 (included=868 and excluded=48), n=916 (included=875 and excluded=41), o=832 (included=796 and excluded=36), p=858 (included=822 and excluded=36), q=909 (included=865 and excluded=44), r= 878 (included=834 and excluded=44), s=825 (included=801 and excluded=24), t=830 (included=794 and excluded=36), u=720 (included=687 and excluded=33), v=892 (included=843 and excluded=49), w=952 (included=900 and excluded=52). Abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CWRT, Constant Work Rate Test; FEV_1, Forced Expiratory Volume in the first second; FFM, Fat-Free Mass; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; mMRC, modified Medical Research Council; $paCO_2$, Partial Pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; O_2, oxygen; SD, standard deviation; SPPB, Short physical performance battery; TTE, time-to-exhaustion; Wmax, maximal workload; 4MGS, 4-meter gait speed; 5STS, 5-repetition sit-to-stand; 6MWT, 6-minute walk test.

Supplemental Table 3. Univariate regression models of patients' characteristics and the SPPB summary score.

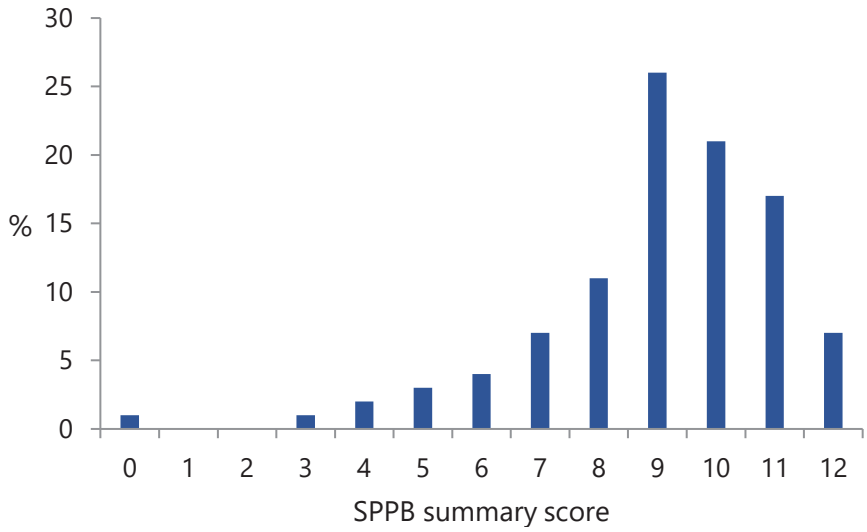
Patients' characteristics	Model	ANOVA		Coefficient		P-value
	Adjusted R^2	F-value	Df	Beta	CI	
Age (y)	0.056	54.415	898	-0.060	-0.076- -0.044	<0.001
Sex (Female/Male)	0.001	2.017	898	-0.196	-0.468- 0.075	0.156
Weight (kg)	-0.001	0.459	895	-0.002	-0.009- 0.005	0.498
BMI (kg/m^2)	0.003	3.928	895	-0.022	-0.044- 0.000	0.048
mMRC (grade)	0.200	225.840	897	-0.920	-1.040- -0.799	<0.001
CAT (points)	0.058	52.603	843	-0.075	-0.095- -0.055	<0.001
Exacerbations in the past 12 months	0.031	29.277	893	-0.207	-0.282- -0.132	<0.001
Hospitalizations in the past 12 months	0.033	31.642	895	-0.300	-0.404- -0.195	<0.001
CCI (points)	0.011	11.262	898	-0.179	-0.283- -0.074	0.001
Long-term O_2 use (yes/no)	0.042	39.922	881	1.047	0.722- 1.372	<0.001
Lung function and arterial blood gases						
FEV_1 (L)	0.026	24.938	898	0.523	0.318-0.729	<0.001
paO_2 (kPa)	0.012	11.482	841	0.160	0.067-0.253	0.001
$paCO_2$ (kPa)	0.046	41.178	841	-0.498	-0.651- -0.346	<0.001
Saturation (%)	0.009	2.111	122	0.096	-0.035-0.226	0.149
Body composition						
FFM of the arms (kg)	0.012	11.815	890	0.142	0.061-0.223	0.001
FFM of the legs (kg)	0.009	9.524	890	0.053	0.019-0.087	0.002
Waist circumference (cm)	0.007	7.152	895	-0.011	-0.019- -0.003	0.008
T score lumbar spine (L2-L4)	0.000	0.643	879	-0.033	-0.112-0.047	0.423
T score hip (trochanter)	0.006	5.973	873	0.167	0.033-0.300	0.015
Physical capacity and exercise tolerance						
6MWT (m)	0.422	653.200	891	0.012	0.011-0.013	<0.001
Wmax (W)	0.097	89.162	820	0.017	0.014-0.021	<0.001
CWRT TTE (s)	0.023	20.127	794	0.001	0.001-0.002	<0.001
Isotonic muscle strength						
Leg press (kg)	0.110	107.639	863	0.016	0.013-0.019	<0.001
Leg extension (kg)	0.114	107.754	832	0.048	0.039-0.057	<0.001
Upper back (kg)	0.075	66.264	799	0.041	0.031-0.051	<0.001
Chest press (kg)	0.061	52.926	792	0.038	0.028-0.048	<0.001
Isokinetic muscle strength/endurance						
Peak torque (Nm)	0.090	69.351	688	0.018	0.014-0.022	<0.001
Total work (J)	0.130	103.696	688	0.001	0.001-0.001	<0.001
Emotional status						
HADS anxiety (points)	0.026	23.885	841	-0.081	-0.113- -0.048	<0.001
HADS depression (points)	0.039	34.742	841	-0.102	-0.136- -0.068	<0.001

Abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CI, Confidence Interval; CWRT, Constant Work Rate Test; DF, Degrees of Freedom; FEV_1, Forced Expiratory Volume in the first second; FFM, fat-free mass; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council; $paCO_2$, Partial Pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; O_2, oxygen; SPPB, Short physical performance battery; TTE, time-to-exhaustion; Wmax, maximal workload; 6MWT, 6-minute walk test.

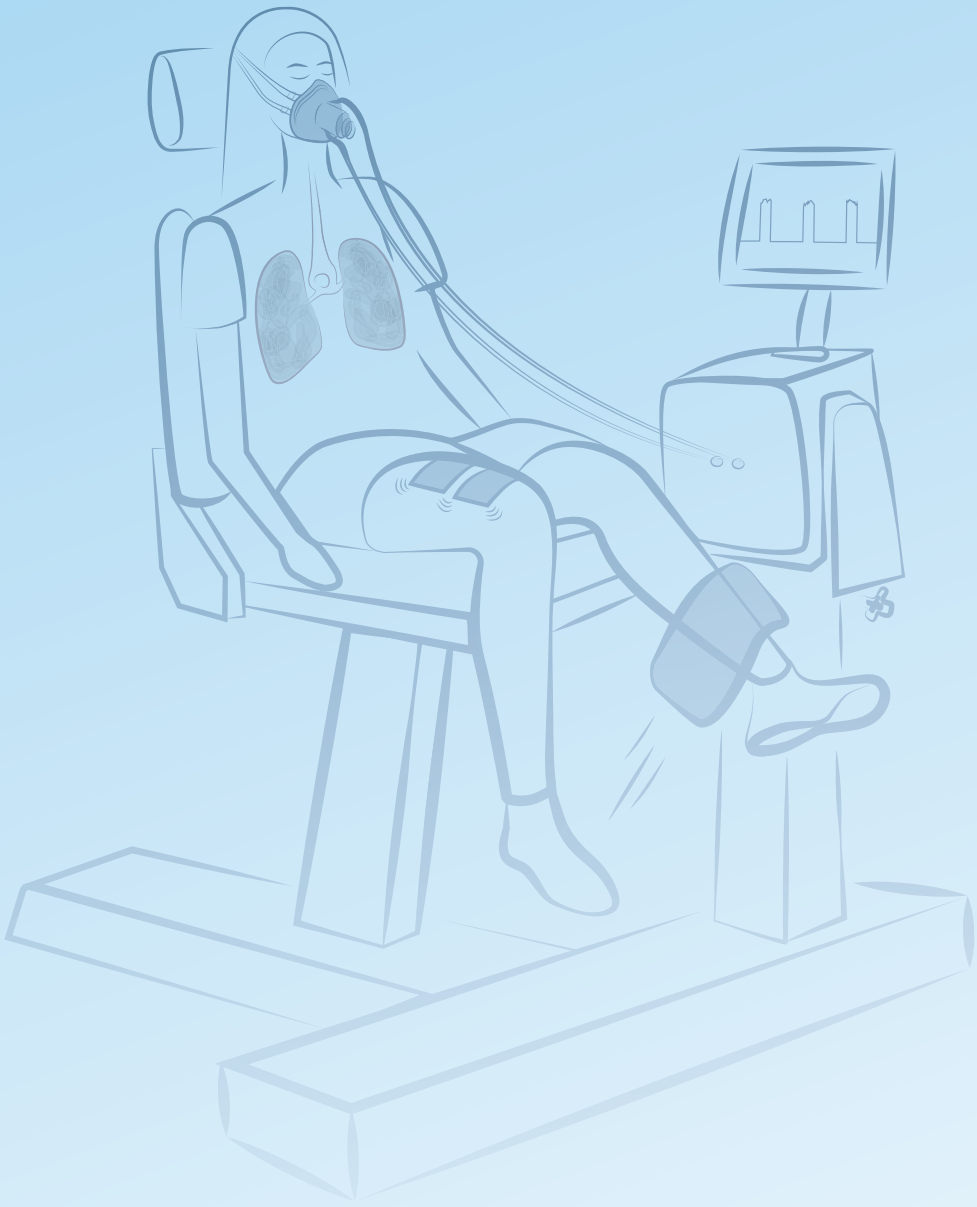
Supplemental Table 4. Multivariate regression model using the ENTER method to predict the SPPB summary score.

Independent variable	Estimate	Standard error	B standardized	P-value	Partial R^2
Age (years)	**-0.016**	**0.008**	**-0.085**	**0.043**	**-0.090**
mMRC (grade)	-0.023	0.075	-0.015	0.757	-0.014
CAT (points)	-0.007	0.010	-0.029	0.519	-0.029
Exacerbations in the past 12 months	0.039	0.039	0.045	0.316	0.045
Hospitalizations in the past 12 months	-0.014	0.060	-0.010	0.810	-0.011
CCI (points)	-0.061	0.049	-0.049	0.212	-0.055
Long-term O_2 use (yes/no)	-0.084	0.168	-0.020	0.617	-0.022
paO_2 (kPa)	-0.004	0.041	-0.004	0.917	-0.005
$paCO_2$ (kPa)	0.045	0.078	0.025	0.563	0.026
Waist circumference (cm)	-0.006	0.004	-0.072	0.141	-0.065
T score hip (trochanter)	-0.066	0.061	-0.045	0.282	-0.048
6MWT (m)	**0.007**	**0.001**	**0.454**	**<0.001**	**0.342**
CWRT TTE (s)	>0.001	0.000	-0.001	0.979	-0.001
Total work (J)	0.000	0.000	0.056	0.292	0.047
HADS depression (points)	-0.019	0.016	-0.048	0.249	-0.051

Abbreviations: B, Beta; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CWRT, Constant Work Rate Test; HADS, Hospital Anxiety and Depression Scale; mMRC, Modified Medical Research Council; $paCO_2$, Partial Pressure of arterial carbon dioxide; paO_2, Partial pressure of arterial oxygen; O_2, oxygen; SPPB, Short Physical Performance Battery; TTE, time-to-exhaustion; 6MWT, 6-minute walk test.



Supplemental Figure 1. The distribution (%) of the SPPB summary score within patients with COPD starting pulmonary rehabilitation.



CHAPTER 3

Short physical performance battery: Response to pulmonary rehabilitation and minimal important difference estimates in patients with chronic obstructive pulmonary disease

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ABSTRACT

Objective: To determine the response to a pulmonary rehabilitation (PR) program and minimal important differences (MIDs) for the short physical performance battery (SPPB) subtests and SPPB summary score in patients with chronic obstructive pulmonary disease (COPD).

Design: Retrospective analysis using distribution- and anchor-based methods.

Setting: PR centre in the Netherlands including a comprehensive 40-session 8-week inpatient or 14-week outpatient program.

Participants: A total of 632 patients with COPD (age, 65±8 years; 50% male; forced expiratory volume in the first second, 43% [interquartile range, 30%-60%] predicted).

Interventions: Not applicable.

Main Outcome Measure: Baseline and post PR results of the SPPB, consisting of 3 balance standing tests, 4-meter gait speed (4MGS), and 5-repetition sit-to-stand (5STS). The chosen anchors were the 6-minute walk test and COPD Assessment Test. Patients were stratified according to their SPPB summary scores into low-performance, moderate-performance, and high-performance groups.

Results: 4MGS (Δ=0.08 [-0.05 to 0.21] m/s), 5STS (Δ=-1.14 [-4.20 to -0.93] s) and SPPB summary score (Δ=1 [0-2] points) improved after PR in patients with COPD. In patients with a low-performance at baseline, balance tandem significantly increased as well. Anchor- and distribution-based MID estimates for the 4MGS ranged between 0.05 and 0.13 m/s, and distribution-based MID estimates ranged between 2.19 and 6.33 seconds for 5STS and 0.83 to 0.96 points for SPPB summary score.

Conclusions: The 4MGS, 5STS, and SPPB summary score are responsive to PR in patients with COPD. The balance tandem test is only responsive to PR in patients with COPD with a low-performance at baseline. Based on distribution-based calculations, an MID estimate of 1 point is recommended for the SPPB summary score.

INTRODUCTION

The short physical performance battery (SPPB) is an easy-to-perform measure for assessment of mobility and balance and its use is intended and recommended for older persons (>65 years).[1] However, there is an increasing interest in SPPB performance for diseased populations, including individuals with chronic obstructive pulmonary disease (COPD). COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as *"a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases"*.[2] Patients with COPD have an increased risk of mortality and readmission and exhibit poorer physical function and health status,[3] which emphasizes the clinical relevance of SPPB performance.

The SPPB summary score has a good interobserver reliability[4] and has been used to classify patients as having low-, moderate- or high-performance in mobility and balance.[5-7] Furthermore, its potential as an alternative to the 6-minute walk test (6MWT) in the BODE index has recently been reported[8] and physical and emotional correlates of the SPPB summary score have been identified.[5, 7] The latter might suggest a positive effect of pulmonary rehabilitation (PR) on the SPPB summary score. To date, the response of the SPPB summary score to PR has only been described in 1 peer-reviewed manuscript,[9] and in 2 congress abstracts,[10, 11] which all reported a significant increase.

Estimated minimal important differences (MIDs) are available for the SPPB subtests 4-meter gait speed (4MGS)[12] and 5-repetition sit-to-stand (5STS) in patients with COPD[13] but are currently lacking for the SPPB summary score. This complicates the evaluation of intervention efficacy using the SPPB.[14, 15] Thus, to improve the interpretation of intervention efficacy at individual and group level, the aims of the present study were: to determine the response to a PR program on the SPPB subtests and summary score in patients with COPD and to estimate MIDs for the SPPB subtests and summary score in patients with COPD.

METHODS

In this observational study, a retrospective analysis was performed on baseline and post PR data of 953 patients between January 2016 and January 2018 in CIRO, a specialized PR centre in the Netherlands.[16] This study was performed in accordance with the principles of Declaration of Helsinki and was approved by the board of directors. The authors were informed by the Medical Ethical Committee of Maastricht University that the Medical Research Involving Human Subjects Act (WMO) does not apply and no official approval was not required (MEC-no. 2018-0541). Therefore, no informed consents from participants were obtained.

The following inclusion criteria were applied: primary diagnosis of COPD according to the GOLD criteria[2] and complete SPPB data (baseline and post PR) available. Participants younger than 40 years old, participation in the PR program more than once, or a baseline SPPB summary score of 12, because of a possible ceiling effect,[9] were excluded from further analyses. Baseline findings have been published previously.[5]

Patients' characteristics

Baseline characteristics including age, sex, weight, body mass index, exacerbation and hospitalization frequency in the last 12 months, Charlson Comorbidity Index, and use of long-term oxygen therapy were systematically collected during an extensive PR assessment. Furthermore, forced expiratory volume in 1 second and its ratio to forced vital capacity were assessed in accordance with the European Respiratory Society recommendations[17] using spirometry (MasterScreen PFT/ Body). The degree of airflow limitation was classified according to GOLD classification.[2]

Short physical performance battery

Baseline and post PR performance of the SPPB was in accordance to the National Institute on Aging protocol.[18] The SPPB includes 3 subtests: the standing balance tests, 4MGS, and 5STS. During the standing balance test the patient was instructed to maintain 3 stances (feet placed side-by-side, semi-tandem, tandem) for 10 seconds. Secondly, the 4MGS was performed in duplicate to obtain the habitual gait speed over 4 meters (normal walking aids were allowed). In the 5STS, the patient was required to perform 5 sit-to-stand manoeuvres as fast as possible with arms folded in front of their chest. Each of the 3 components was scored from 0 (extreme mobility impairment) to 4 points (no mobility impairment), resulting in a SPPB summary score ranging from 0-12 points (Supplemental Table 1). A flowchart of the SPPB subtests and its scoring system was previously reported by Nogueira et al.[19] According to

their baseline SPPB summary score, patients were classified as low-performance (LP; 0-6 points), moderate-performance (MP; 7-9 points) or high-performance (HP; 10-12 points).[20]

Clinical outcomes

Fat-free mass (FFM) was measured using dual energy x-ray absorptiometry (Lunar iDXA).[21] The FFM index was calculated by dividing FFM by height squared. The modified Medical Research Council dyspnoea scale[22] was used to evaluate shortness of breath and a cut-off of ≥2 was used to identify patients with "more breathlessness".[23] The COPD Assessment Test (CAT) assessed the health status of the patients and a threshold of ≥18 points indicated patients who were highly symptomatic.[24] The 6MWT and incremental cardiopulmonary exercise test (Ergoselect) were performed to determine the physical capacity, both in accordance with the corresponding guidelines.[25-27] Exercise tolerance was assessed with the constant work rate test, performed at 75% of the predetermined maximal workload, during which patients cycled until symptom limitation (with a maximum test duration of 20 minutes).[28] Isokinetic quadriceps peak torque and total work of the right leg (or left leg in case of complications with the right leg) were assessed with a computerized dynamometer (Biodex Multi-joint System 3). Patients performed a set of 30 repetitions at an angular speed of 90°/s. Reference values from Borges et al. were used.[29] Symptoms of anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale with a cut-off value of ≥10 points for each domain[30] to classify patients with indications for anxiety or depression.

Pulmonary rehabilitation

The 8-week inpatient and 14-week outpatient PR programs were in line with the American Thoracic Society/European Respiratory Society Statement on PR[31] and consisted of 40 sessions. Patients were supervised by an interdisciplinary team, including a chest physician, respiratory nurse, dietician, occupational therapist, physiotherapist, psychologist, and social worker. The cornerstone of the patient-tailored PR program was physical exercise training consisting mainly of exercises to strengthen muscles of the upper and lower extremities, treadmill walking, stationary cycling, flexibility exercises and daily supervised outdoor walks.[32] Furthermore, the program included (if indicated) nutritional support, psychological counselling, and educational sessions.[32-34] Further description of the PR program was provided by Spruit et al.[34]

Statistical analyses

Statistical analyses were performed using SPSS statistical software (IBM), version 25.0. Data were presented and/or tested as appropriate. Descriptive data are presented as means±SD, medians (interquartile 1-interquartile 3), or percentages. Baseline and delta differences between 2 groups were tested by independent t test or Mann-Whitney U test. Categorical data were tested with Fisher exact test or chi-square test of homogeneity. Differences between baseline and post PR data were tested by paired sample t test or Wilcoxon signed-rank test, and categorical data were tested with McNemar's test or related samples marginal homogeneity test. Differences in deltas between 3 groups were tested by 1-way analysis of variance, Kruskal-Wallis test or chi-square test of homogeneity. When a statistically significant difference was obtained, a pairwise Tukey's post-hoc test was performed and Bonferroni correction was applied for multiple comparisons. Because of the many statistical tests performed in this study, $P \leq 0.01$ was considered significant.

As recommended,[14, 15] both distribution-based and anchor-based techniques were used to determine MID estimates for the SPPB subtests and summary score. Four distribution-based techniques were applied: standard error of the measurement (SEM)=$SD_{baseline} * \sqrt{1\text{-intraclass correlation coefficient}}$; empirical rule effect size=$0.08*6*SD_{delta}$; Cohen's effect size=$0.5*SD_{delta}$; $0.5*SD_{baseline}$.[35] The intraclass correlation coefficients (ICCs) were derived from previous studies [interobserver ICC_{SPPB}=0.81[4] and test-retest ICC_{4MGS}=0.97[12] and ICC_{5STS}=0.97[13]]. The SEM method could not be performed for the standing balance tests because no ICCs have been determined in patients with COPD or in older persons.

To perform anchor-based methods, at least a moderate correlation between the anchors and change in SPPB subtests or summary score ($r \geq 0.3$, $P<0.05$)[14, 15] was required. The chosen anchors were CAT and 6MWT,[36, 37] with known MIDs and expected correlations with the change in SPPB. In the presence of a sufficient correlation, linear regression and receiver operating characteristic analyses were performed between the change in SPPB as the dependent variable and the anchors as independent variables. For the receiver operating characteristic analyses, an area under the curve >0.7 was accepted as a meaningful relationship.[38]

MID estimates of SPPB summary score and SPPB subtests were only determined for tests that are responsive to PR on group level compared with baseline values.

RESULTS

Of the 953 patients with COPD, 632 patients were eligible for analysis. Patients were excluded due to absence of baseline SPPB data (n=1), age younger than 40 years (n=5), and participation in the PR program for the second time (n=20). In addition, 27 patients were excluded because download of the data export showed multiple baseline values for 1 or more attributes. The exclusion of patients corresponds to the baseline study reported by Stoffels et al.[5] Furthermore, patients with missing post PR assessment SPPB data (n=216) and a baseline SPPB summary score of 12 (n=52) were excluded.

A greater number of patients included in the study had a dyspnoea grade ≥2 and a different distribution of GOLD classification (n=632) than excluded patients (n=321; P=0.002 and P=0.008, respectively) (Supplemental Table 2).

Adherence and type of PR program

Adherence to the PR program was high in the included patients (completed sessions=40 (39-40) sessions). There were no differences in adherence between patients in the inpatient and outpatient programs (P=0.209) or between LP, MP and HP groups (P=0.788).

Most patients participated in the inpatient PR program (61%). A larger percentage of these patients were females and experienced more severe symptoms, characterized by higher dyspnoea scores, poorer health status and pulmonary function, larger number of exacerbations and hospitalizations, and more frequent oxygen use compared with patients who participated in the outpatient program (Supplemental Table 3).

Baseline characteristics

The 632 patients with COPD had a severe degree of airflow limitation, an equal male-to-female ratio, and a normal body mass index. After stratification for SPPB summary score in LP (n=69), MP (n=300) and HP (n=263) groups, patients in the LP group were older and experienced higher levels of dyspnoea compared with the MP and HP groups. More clinical characteristics and pulmonary function data are shown in Table 1.

Response to PR in clinical characteristics

Health status, dyspnoea, body composition, symptoms of anxiety and depression, and physical status improved in all patients with COPD who participated in PR (all P-values <0.001) (Supplemental Table 4).

Table 1. Baseline characteristics of all patients with COPD and after stratification for SPPB summary score.

		Short physical performance battery		
	All patients with COPD (n=632)	**Low-performance (n=69)**	**Moderate-performance (n=300)**	**High-performance (n=263)**
Age (years)	65±8 (n=632)	69±8[a,b] (n=69)	66±8 (n=300)	64±8 (n=263)
Gender (male, %)	50 (n=632)	48 (n=69)	50 (n=300)	52 (n=263)
Weight (kg)	72 (60-86) (n=630)	70 (59-90) (n=69)	73 (60-87) (n=298)	70 (60-85) (n=263)
BMI (kg/m^2)	25 (22-30) (n=630)	25 (21-33) (n=69)	26 (22-31) (n=298)	25 (22-29) (n=263)
mMRC score	3 (2-3) (n=631)	4 (3-4)[a,b] (n=69)	3 (2-3)[c] (n=300)	2 (2-3) (n=262)
mMRC ≥2 (% patients)	90 (n=631)	100[b] (n=69)	93[c] (n=300)	83 (n=262)
CAT score	22±6 (n=593)	25±6[a,b] (n=62)	22±6[c] (n=283)	20±6 (n=248)
CAT ≥18 (% patients)	77 (n=593)	92[b] (n=62)	79 (n=283)	71 (n=248)
Exacerbations in the past 12 months: 0/1/2/3/4/>4 (% patients)	18/17/22/14/8/21 (n=627)	7/13/10/22/6/42[a,b] (n=69)	19/18/21/14/9/19 (n=297)	21/17/26/11/7/18 (n=261)
≥2 exacerbations in the past 12 months (% patients)	64 (n=627)	80 (n=69)	63 (n=297)	63 (n=261)
Hospitalizations in the past 12 months: 0/1/2/3/4/>4 (%patients)	53/27/9/6/2/3 (n=630)	37/24/9/16/4/10[a,b] (n=68)	54/27/11/3/1/4 (n=299)	57/27/6/6/3/1 (n=263)
≥1 hospitalization in the past 12 months (% patients)	47 (n=630)	63 (n=68)	47 (n=299)	43 (n=263)
CCI (points)	1 (1-2) (n=632)	2 (1-3) (n=69)	1 (1-2) (n=300)	1 (1-2) (n=263)
CCI ≥2 (% patients)	45 (n=632)	51 (n=69)	45 (n=300)	44 (n=263)
Long-term O_2 use (yes, % patients)	24 (n=620)	42[a,b] (n=69)	24 (n=295)	20 (n=256)
GOLD I/II/III/IV (% patients)	9/28/37/26 (n=632)	3/35/27/35 (n=69)	10/27/38/25 (n=300)	8/29/39/24 (n=263)
GOLD A/B/C/D (% patients)	3/24/7/66 (n=625)	0/15/0/85[b] (n=68)	2/26/5/67 (n=297)	5/24/11/60 (n=260)
FEV_1 (% predicted)	43 (30-62) (n=632)	34 (24-60) (n=69)	42 (30-63) (n=300)	43 (31-63) (n=263)
FEV_1/FVC (%)	35 (27-47) (n=632)	35 (25-48) (n=69)	36 (28-48) (n=300)	35 (27-46) (n=263)
SPPB summary score	9 (7-10) (n=632)	5 (4-6)[a,b] (n=69)	9 (8-9)[c] (n=300)	10 (10-11) (n=263)
Balance side-by-side (s)	10 (10-10) (n=632)	10 (10-10)[a,b] (n=69)	10 (10-10) (n=300)	10 (10-10) (n=263)

Table 1. Continued

	All patients with COPD (n=632)	Short physical performance battery		
		Low-performance (n=69)	Moderate-performance (n=300)	High-performance (n=263)
Balance semi-tandem (s)	10 (10-10) (n=632)	10 (10-10)[a,b] (n=69)	10 (10-10) (n=300)	10 (10-10) (n=263)
Balance tandem (s)	10 (4-10) (n=632)	0 (0-4)[a,b] (n=69)	10 (7-10)[c] (n=300)	10 (10-10) (n=263)
4MGS (m/s)	1.0 (0.9-1.2) (n=632)	0.6 (0.4-0.7)[a,b] (n=69)	1.0 (0.8-1.1)[c] (n=300)	1.2 (1.0-1.3) (n=263)
5STS (s)	17 (14-230) (n=632)	60 (24 – 60)[a,b] (n=69)	19 (17-22)[c] (n=300)	14 (12-15) (n=263)

Data is presented as mean±SD, median (Q1-Q3), or percentages. [a] indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 7-9. [b] indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 0-6 and SPPB scores 10-12. [c] indicates a significant difference after Bonferroni post-hoc correction between SPPB scores 7-9 and SPPB scores 10-12. Abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index; FEV_1, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified Medical Research Council; SPPB, Short physical performance battery; 4MGS, 4-meter gait speed; 5STS, 5-repetition sit-to-stand.

After stratification for baseline SPPB summary score, significant improvements in these clinical characteristics were observed in all 3 SPPB performance groups, except for the anxiety subscale of the Hospital Anxiety and Depression Scale in the LP group, which did not improve after PR (P=0.020). The Δ6MWT was the greatest in the LP group (47±78 m) in comparison to the MP group (24±53 m) and the HP group (12±49 m; P<0.001) (Supplemental Table 5).

Differences in changes in clinical characteristics between patients participating in the inpatient and outpatient programs are depicted in Supplemental Table 6.

Response to PR in SPPB

In contrast to balance tests, the 4MGS (Δ=0.08 [-0.05 to 0.21] m/s) and 5STS (Δ=-1.14 [-4.20 to -0.93] s) were responsive to PR in patients with COPD (all P-values <0.001). Furthermore, SPPB summary score improved significantly from 9 (8-10) to 10 (9-11) points after PR (P<0.001) (Figure 1).

The baseline LP group showed improvements in balance tandem (median Δ=0.00 [0.00-10.00]s and mean Δ=3.36±4.96s), 4MGS (Δ=0.17 [0.06-0.29] m/s), and 5STS (Δ=-6.16 [-35.00 to 0.00]s) subtests of the SPPB after PR (all P-values <0.001). The MP group showed a significant effect of PR on 4MGS (Δ=0.08 [-0.05 to 0.23] m/s) and 5STS (Δ=-2.40 [-6.40 to 0.17]s) subtests (all P-values <0.001). The HP group improved on 4MGS (Δ=0.06 [-0.05 to 0.19] m/s) and 5STS (Δ=-0.74 [-2.40 to 1.00]s) (all P-values

<0.001). Improvements in the LP group were significant larger in contrast to MP and HP groups, which resulted in a larger increase in SPPB summary score for the LP group than the MP and HP groups (Figure 1). A maximum post PR SPPB summary score of 12 was obtained in 23 patients in the MP group and 63 patients in the HP group.

Furthermore, baseline and post PR proportion of patients per performance group were significantly different (P<0.001). The flow and direction of this change in performance group classification is presented in Figure 2.

Because differences in the type of PR program could potentially influence the SPPB response to PR, comparisons between changes in SPPB subtests and summary scores were made for patients participating in inpatient and outpatient PR programs. Changes in SPPB subtests and SPPB summary score were not significantly different between the 2 types of PR programs (Supplemental Table 7).

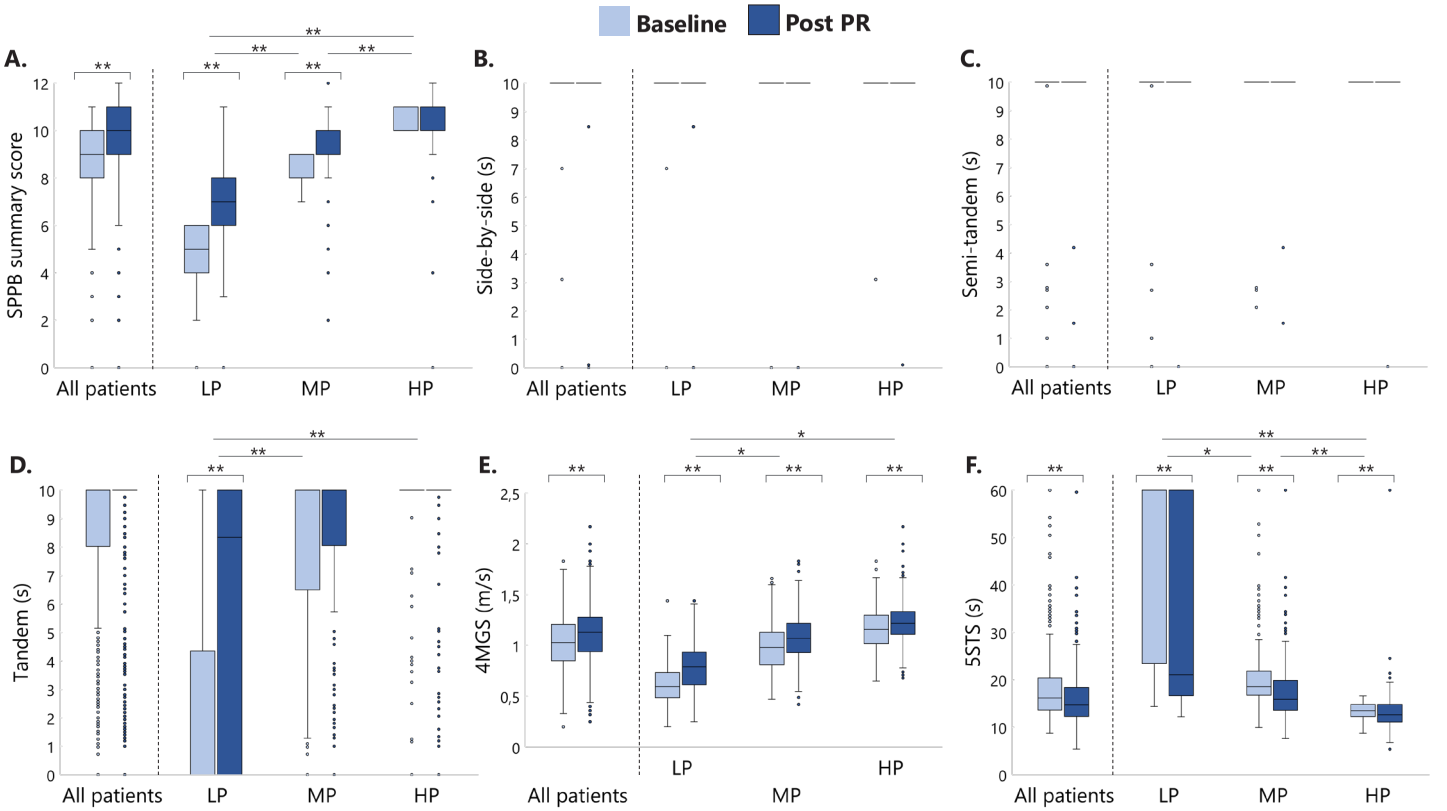

Figure 1. Box plots of the baseline and post PR (**A**) SPPB summary score, (**B**) balance side-by-side, (**C**) semi-tandem, (**D**) tandem, (**E**) 4MGS, and (**F**) 5STS for all patients and the LP, MP, and HP group. *Indicates a significant difference at P<0.01; **Indicates a significant difference at P<0.001. The boxes in (**B**) and (**C**) are displayed as lines at the top because almost all patients maintained the balance side-by-side and semi-tandem positions for the maximum of 10 seconds.

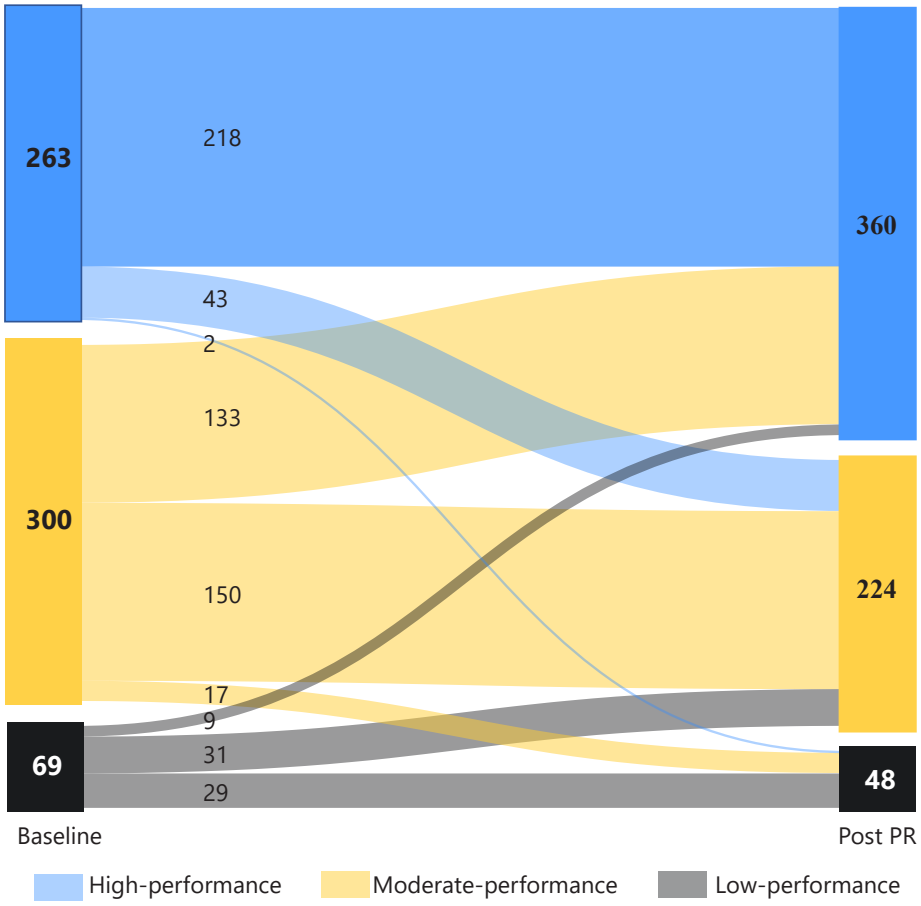

Figure 2. Sankey diagram depicting the flow and distribution of the SPPB summary score for the different performance groups at baseline and post PR.

MID

The MID estimates were determined for the 4MGS, 5STS and SPPB summary score as these tests were responsive to PR, in contrast to the balance tests. Using distribution-based techniques, the MID ranged between 0.05-0.13 m/s for the 4MGS, between 2.19-6.33 seconds for the 5STS, and between 0.83-0.96 points for the SPPB summary score (Table 2). Furthermore, the change in 6MWT and CAT was not correlated or only weakly correlated with the change 5STS and SPPB summary score and could therefore not be used as reliable anchors to determine the MIDs. However, the change in 4MGS did correlate significantly with the change in 6MWT ($r=0.372$, $P<0.001$) and the change in CAT ($r=-0.235$, $P<0.001$) (Supplemental Table 8). As we

aimed to have a significant correlation of ≥0.3, only the change in 6MWT was used to calculate the anchor-based MID. Using linear regression analysis, we obtained a MID for 4MGS of 0.10 (95%CI 0.06-0.11) m/s. It was not possible to compute the MID using the receiver operating characteristic statistics as the obtained area under the curve was below 0.7 (area under the curve=0.687, P<0.001).

Table 2. Distribution-based methods to estimate the minimal important difference in 4MGS, 5STS and SPPB summary score in patients with COPD.

Method	Formula	4MGS (m/s)	5STS (s)	SPPB summary score (Points)
SEM	$SD_{baseline} * \sqrt{1-ICC}$	0.05	2.19	0.83
Empirical rule effect size	$0.08 * 6 * SD_{delta}$	0.10	4.05	0.86
Cohen's effect size	$0.5 * SD_{delta}$	0.10	4.22	0.89
$0.5*SD_{baseline}$	$0.5 * SD_{baseline}$	0.13	6.33	0.96
MID range		0.05-0.13	2.19-6.33	0.83-0.96

Abbreviations: ICC, intraclass correlation coefficient; MID, minimal important difference; N.D., not determined; SD, standard deviation; SEM, standard error of the measurement; 4MGS, 4-meter gait speed; 5STS, 5-repetition sit-to-stand.

DISCUSSION

Generally, the SPPB subtests 4MGS and 5STS, and the SPPB summary score are responsive to PR in patients with COPD. In patients with a low performance at baseline, balance tandem is responsive to PR as well. The MID estimates range between 0.05-0.13 m/s for 4MGS, 2.19-6.33 seconds for 5STS and 0.83-0.96 points for SPPB summary score.

In accordance with previous studies, 4MGS, 5STS and SPPB summary score were responsive to PR in patients with COPD.[9-13] Furthermore, only the LP group improved balance tandem time after PR but had a change of 0 (0-10) seconds (or mean change of 3.36±4.96s), which makes the clinical significance of the improvement questionable. No performance group showed an effect of PR in balance side-by-side or semi-tandem. Although balance impairments are common in patients with COPD,[39] most participants were able to complete the balance tests without difficulty. These results imply that standing balance tests are less useful and effective and perhaps not adequality sensitive in evaluating the effectiveness of PR in patients with COPD, suggesting the use of more complex balance tests like Berg Balance Scale or Balance Evaluation Systems Test.[39] Another possible explanation could be the minor focus on balance issues during PR; Marques et al. highlighted the value of balance training during PR.[40]

The distribution-based and anchor-based MID estimates for 4MGS (0.05-0.13 m/s) are comparable with the MID estimate of Kon et al. (0.11 m/s).[12] The mean 5STS MID estimates (2.19-6.33s) are larger than the MID estimate by Jones et al. (1.7s) in patients with COPD after an 8-week outpatient PR program in the United Kingdom.[13] The current SPPB summary score MID estimates (0.83-0.96 points) are comparable with the study of Perera et al., who reported a small meaningful change of 0.5 points and a substantial change of 1.0 point for SPPB summary scores in older adults.[41] Because the SPPB summary score is reported in whole numbers, it seems reasonable to conclude that an improvement of 1 point on the SPPB summary score can be taken as the MID in patients with COPD after PR. This MID can be interpreted and applied at individual and group levels to determine whether patients improve after PR.

Study limitations

Analyses were performed on a selected population of patients with COPD referred for PR. Including a more diverse group of patients could complicate the interpretation of results and conclusions. These results should be applied with caution in other populations or settings, because differences in interventions, context, and population characteristics are known to influence the response and MID estimates.[39-43] In addition, 86 patients achieved a maximum post PR SPPB score of 12, which could indicate a ceiling effect.

Despite the intent to use anchor- and distribution-based methods to calculate MID estimates, only distribution-based calculations could be performed for the 5STS and the SPPB summary score. Therefore, the obtained MIDs provide no clinical significance but statistical significance only. It is highly recommended that multiple anchor-based approaches be used in future MID estimations, such as incremental shuttle walk test or patient's self-reported improvement, which were used in previous studies.[12, 13, 44]

CONCLUSIONS

The SPPB subtests 4MGS and 5STS, and summary score are responsive to PR in patients with COPD. The balance tandem test is only responsive to PR in patients with COPD with a low performance at baseline. Based on distribution-based calculations, a MID estimate of 1 point for the SPPB summary score is recommended in patients with COPD. Future research is needed to confirm MID estimates for the SPPB in different centres using anchor-based methods as well.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. The scoring system of the standing balance tests, 4-meter gait speed (4MGS) and 5-repetition sit-to-stand (5STS).

Scores	Balance: side-by-side test (s)	Balance: semi-tandem test (s)	Balance: tandem test (s)	4MGS (s)	5STS (s)
4				<4.82	<11.20
3				4.82–6.20	11.20–13.69
2			10.00	6.21–8.70	13.70–16.69
1	10.00	10.00	3.00-9.99	>8.70	16.70–60.00
0	<10.00	<10.00	<3.00	Unable	Unable (>60.00)

Supplemental Table 2. Differences in baseline characteristics between included and excluded patients.

	Included (n=632)	Excluded (n=321)	P-value
Age (years)	65±8 (n=632)	65±9 (n=321)	0.154
Gender (male, %)	50 (n=632)	54 (n=321)	0.373
Weight (kg)	72 (60-86) (n=630)	73 (60-86) (n=298)	0.968
BMI (kg/m^2)	25 (22-30) (n=630)	25 (22-30) (n=298)	0.791
mMRC score	3 (2-3) (n=631)	2 (2-3) (n=321)	0.282
mMRC ≥2 (% patients)	90 (n=631)	82 (n=321)	0.002
CAT score	22±6 (n=593)	21±7 (n=300)	0.383
CAT ≥ 18 (% patients)	77 (n=594)	72 (n=300)	0.100
Exacerbations in the past 12 months (0/1/2/3/4/>4, % patients)	18/17/22/14/8/21 (n=627)	23/16/16/13/8/24 (n=321)	0.258
≥2 exacerbations in the past 12 months (% patients)	64 (n=627)	62 (n=321)	0.434
Hospitalizations in the past 12 months (0/1/2/3/4/>4, % patients)	53/27/9/6/2/3 (n=630)	61/22/9/6/2 (n=299)	0.295
≥1 hospitalization in the past 12 months (% patients)	47 (n=630)	39 (n=299)	0.064
CCI (points)	1 (1-2) (n=632)	1 (1-2) (n=321)	0.280
CCI ≥2 (% patients)	45 (n=632)	42 (n=321)	0.370
Long-term O_2 use (yes, % patients)	24 (n=620)	19 (n=316)	0.115
GOLD I/II/III/IV (% patients)	9/28/37/26 (n=632)	10/27/41/22 (n=320)	0.555
GOLD A/B/C/D (% patients)	3/24/7/66 (n=625)	10/28/8/54 (n=297)	0.008
FEV_1(% predicted)	43 (30-62) (n=632)	43 (32-59) (n=320)	0.691
FEV_1/FVC (%)	35 (27-47) (n=632)	34 (28-48) (n=320)	0.842

Data is presented as mean±SD, median (Q1-Q3), or percentages. Abbreviations: BMI, Body Mass Index; CCI, Charlson Comorbidity Index; FEV_1, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, Modified Medical Research Council.

Supplemental Table 3. Differences in baseline characteristics between patients following an in- and outpatient program.

	Inpatient (n=387)	Outpatient (n=238)	P-value
Age (years)	66±8 (n=387)	65±8 (n=238)	0.252
Gender (male, %)	45 (n=387)	59 (n=238)	0.001
Weight (kg)	71 (59-86) (n=386)	75 (62-88) (n=237)	0.081
BMI (kg/m^2)	25 (21-31) (n=386)	25 (22-30) (n=237)	0.575
mMRC score	3 (2-4) (n=387)	2 (2-3) (n=237)	<0.001
mMRC ≥2 (% patients)	95 (n=387)	80 (n=237)	0.002
CAT score	23±6 (n=364)	19±6 (n=223)	<0.001
CAT ≥18 (% patients)	87 (n=364)	60 (n=223)	0.100
Exacerbations in the past 12 months (0/1/2/3/4/>4, % patients)	14/15/22/15/9/25 (n=385)	26/20/22/11/6/15 (n=235)	<0.001
≥2 exacerbations in the past 12 months (% patients)	71 (n=385)	54 (n=235)	<0.001
Hospitalizations in the past 12 months (0/1/2/3/4/>4, % patients)	48/26/11/7/3/5 (n=386)	63/26/5/3/2/1 (n=237)	<0.001
≥1 hospitalization in the past 12 months (% patients)	52 (n=386)	37 (n=237)	<0.001
CCI (points)	1 (1-2) (n=387)	1 (1-2) (n=238)	0.972
CCI ≥2 (% patients)	45 (n=387)	46 (n=238)	0.741
Long-term O_2 use (yes, % patients)	33 (n=379)	10 (n=234)	<0.001
GOLD I/II/III/IV (% patients)	6/23/39/32 (n=387)	13/37/35/15 (n=238)	<0.001
GOLD A/B/C/D (% patients)	1/21/4/74 (n=384)	8/29/12/51 (n=234)	<0.001
FEV_1 (% predicted)	38 (28-54) (n=387)	51 (38-70) (n=238)	<0.001
FEV_1/FVC (%)	33 (26-47) (n=387)	39 (31-50) (n=238)	<0.001

Data is presented as mean±SD, median (Q1-Q3), or percentages. Abbreviations: BMI, Body Mass Index; mMRC, Modified Medical Research Council; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, Forced Expiratory Volume in the first second; FVC, Forced Vital Capacity.

Supplemental Table 4. Baseline, post and delta (post minus baseline) pulmonary rehabilitation data of all patients with COPD.

	Baseline	Post PR	Delta	P-value
Symptom burden and health status				
mMRC score	3 (2-3) (n=591)	2 (1-2) (n=591)	-1 (-1-0) (n=591)	<0.001
mMRC ≥2 (% patients)	89 (n=591)	64 (n=591)	-25 (n=591)	<0.001
CAT score	22±6 (n=560)	19±7 (n=560)	-3±6 (n=560)	<0.001
CAT ≥18 (% patients)	77 (n=560)	58 (n=560)	-19 (n=560)	<0.001
Body composition				
FFM index	16.5±2.5 (n=620)	17.0±2.4 (n=620)	0.4±0.6 (n=620)	<0.001
FFM legs (kg)	15.1 (12.1 – 17.7) (n=621)	15.5 (12.7 – 18.3) (n=621)	0.5 (0.1-1.1) (n=621)	<0.001
Emotional status				
HADS anxiety score	7 (4-10) (n=557)	6 (3-9) (n=557)	-1 (-3-1) (n=557)	<0.001
HADS anxiety ≥10 (% patients)	28 (n=557)	22 (n=557)	-6 (n=557)	0.001
HADS depression score	7 (4-10) (n=557)	5 (3-8) (n=557)	-1 (-3-0) (n=557)	<0.001
HADS depression ≥10 (% patients)	30 (n=557)	16 (n=557)	-14 (n=557)	<0.001
Physical status				
6MWD (m)	370±109 (n=618)	391±109 (n=618)	22±56 (n=618)	<0.001
CWRT TTE (s)	230 (166-329) (n=546)	328 (215-660) (n=546)	112 (14-347) (n=546)	<0.001
Isokinetic quadriceps peak torque (Nm)	82 (60-105) (n=456)	89 (70-115) (n=456)	9 (2-17) (n=456)	<0.001
Isokinetic quadriceps peak torque (% predicted)	61 (47-72) (n=456)	69 (56-80) (n=456)	7 (2-13) (n=456)	<0.001
Isokinetic quadriceps total work (J)	1389 (994-1836) (n=456)	1676 (1248-2109) (n=456)	247 (107-418) (n=456)	<0.001

Data is presented as mean±SD, median (Q1-Q3), or percentages. Abbreviations: CAT, COPD Assessment Test; CWRT, constant work rate test; FFM, fat-free mass; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council; TTE, Time-To-Exhaustion; 6MWD, 6-Minute Walk Test distance.

Supplemental Table 5. Baseline, post and delta (post minus baseline) pulmonary rehabilitation data of the LP, MP and HP group.

	Low-performance (n=69)		
	Baseline	**Post PR**	**Delta**
Symptom burden and health status			
mMRC score	4 (3-4) (n=63)	2 (2-3)** (n=63)	-1 (-2-0) (n=63)
mMRC ≥2 (% patients)	100 (n=63)	91 (n=63)	-9[a,b] (n=63)
CAT score	25±6 (n=57)	22±6** (n=57)	-3±5 (n=57)
CAT ≥18 (% patients)	91 (n=57)	79 (n=57)	-12 (n=57)
Body composition			
FFM index	16.6±2.7 (n=68)	17.0±2.5* (n=68)	0.4±0.9 (n=68)
FFM legs (kg)	14.4 (11.7-17.5) (n=68)	14.9 (12.2-17.3)* (n=68)	0.5 (-0.0-1.2) (n=68)
Emotional status			
HADS anxiety score	9 (6-13) (n=55)	7 (5-11) (n=55)	-2 (-4-2) (n=55)
HADS anxiety ≥10 (% patients)	47 (n=55)	33 (n=55)	-14 (n=55)
HADS depression score	10 (5-13) (n=55)	8 (4-10)* (n=55)	-2 (-5-1) (n=55)
HADS depression ≥10 (% patients)	56 (n=55)	25** (n=55)	-31[a,b] (n=55)
Physical status			
6MWD (m)	213±84 (n=65)	260±110** (n=65)	47±78[a,b] (n=65)
CWRT TTE (s)	148 (104-260) (n=40)	300 (175-656)** (n=40)	156 (16-383) (n=40)
Isokinetic quadriceps peak torque (Nm)	52 (41-78) (n=38)	63 (52-80)* (n=38)	8 (-1-18) (n=38)
Isokinetic quadriceps peak torque (% predicted)	45 (34-62) (n=38)	52 (44-65)* (n=38)	8 (0-13) (n=38)
Isokinetic quadriceps total work (J)	791 (569-1138) (n=38)	1115 (857-1372)** (n=38)	248 (-26-488) (n=38)

*Data is presented as mean±SD, median (Q1-Q3), or percentages. * indicates a significant difference between baseline and post PR of P<0.01, ** indicates a significant difference between baseline and post PR of P<0.001. [a] indicates a significant difference after Bonferroni post-hoc correction between the delta's SPPB scores 0-6 and SPPB scores 7-9. [b] indicates a significant difference after Bonferroni post-hoc correction between the delta's of SPPB scores 0-6 and SPPB scores 10-12. [c] indicates a significant difference after Bonferroni post-hoc correction between the delta's of SPPB scores 7-9 and SPPB scores 10-12. Abbreviations: CAT, COPD Assessment Test; CWRT, constant work rate test; FFM, fat-free mass; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council; TTE, Time-To-Exhaustion; 6MWD, 6-Minute Walk distance.*

Moderate-performance (n=300)			High-performance (n=263)		
Baseline	**Post PR**	**Delta**	**Baseline**	**Post PR**	**Delta**
3 (2-3)	2 (1-2)**	-1(-1-0)	2 (2-3)	2 (1-2)**	-1 (-1-0)
(n=278)	(n=278)	(n=278)	(n=250)	(n=250)	(n=250)
92	67**	-25[c]	83	54**	-29
(n=278)	(n=278)	(n=278)	(n=250)	(n=250)	(n=250)
22±6	19±7**	-3±6	20±6	18±7**	-2±6
(n=266)	(n=266)	(n=266)	(n=237)	(n=237)	(n=237)
79	60**	-19	70	50**	-20
(n=266)	(n=266)	(n=266)	(n=237)	(n=237)	(n=237)
16.5±2.6	17.0±2.5**	0.5±0.7	16.5±2.4	16.9±2.3**	0.4±0.5
(n=293)	(n=293)	(n=293)	(n=259)	(n=259)	(n=259)
15.0 (12.0-17.7)	15.4 (12.6-18.2)**	0.5 (-0.1-1.1)	15.3 (12.3-17.9)	15.8 (12.8-18.6)**	0.6 (0.2-1.1)
(n=294)	(n=294)	(n=294)	(n=259)	(n=259)	(n=259)
8 (5-10)	6 (4-9)**	-2 (-3-1)	7 (4-9)	5 (3-9)**	-2 (-3-1)
(n=265)	(n=265)	(n=265)	(n=237)	(n=237)	(n=237)
29	23	-6	23	18	-5
(n=265)	(n=265)	(n=265)	(n=237)	(n=237)	(n=237)
7 (5-10)	6 (4-9)**	-1 (-3-1)	6 (4-9)	5 (2-8)**	-1 (-3-0)
(n=265)	(n=265)	(n=265)	(n=237)	(n=237)	(n=237)
29	18**	-11	24	12**	-12
(n=265)	(n=265)	(n=265)	(n=237)	(n=237)	(n=237)
356±91	380±94**	24±53	425±89	437±94**	12±29
(n=294)	(n=294)	(n=294)	(n=259)	(n=259)	(n=259)
217 (159-314)	313 (215-635)**	108 (15-304)	251 (189-344)	390 (230-763)**	112 (6-435)
(n=261)	(n=261)	(n=261)	(n=245)	(n=245)	(n=245)
76 (59-101)	87 (67-114)**	9 (3-17)	88 (69-111)	97 (80-118)**	9 (2-17)
(n=206)	(n=206)	(n=206)	(n=212)	(n=212)	(n=212)
58 (43-70)	65 (52-80)**	7 (2-13)	65 (52-74)	73 (61-82)**	6 (2-13)
(n=206)	(n=206)	(n=206)	(n=212)	(n=212)	(n=212)
1313 (914-1808)	1577 (1156-2016)**	258 (95-433)	1555 (1179-1928)	1789 (1492-2245)**	236 (112-412)
(n=206)	(n=206)	(n=206)	(n=212)	(n=212)	(n=212)

Supplemental Table 6. Baseline, post and delta (post minus baseline) pulmonary rehabilitation data of patient following an in- or outpatient program.

	Inpatient (n=384)		
	Baseline	**Post PR**	**Delta**
Symptom burden and health status			
mMRC score	3 (2-4) (n=363)	2 (1-3)** (n=363)	-1 (-2-0) (n=363)
mMRC ≥2 (% patients)	95 (n=363)	70** (n=363)	-25 (n=363)
CAT score	23±6 (n=347)	20±6** (n=347)	-3±6 (n=347)
CAT ≥18 (% patients)	87 (n=347)	66** (n=347)	-21 (n=347)
Body composition			
FFM index	16.3±2.5 (n=378)	16.8±2.5** (n=378)	0.5±0.7 (n=378)
FFM legs (kg)	14.5 (11.8-17.0) (n=379)	15.0 (12.4-17.4)** (n=379)	0.6 (0.1-1.1) (n=379)
Emotional status			
HADS anxiety score	8 (5-11) (n=345)	6 (4-9)** (n=345)	-1 (-3-1) (n=345)
HADS anxiety ≥10 (% patients)	34 (n=345)	24** (n=345)	-10 (n=345)
HADS depression score	8 (5-11) (n=345)	6 (3-9)** (n=345)	-2 (-4-0) (n=345)
HADS depression ≥10 (% patients)	37 (n=345)	18** (n=345)	-15 (n=345)
Physical status			
6MWD (m)	332±102 (n=377)	358±106** (n=377)	26±59 (n=377)
CWRT TTE (s)	201 (148-300) (n=312)	318 (212-654)** (n=312)	126 (34-398) (n=312)
Isokinetic quadriceps peak torque (Nm)	74 (55-94) (n=268)	84 (65-105)** (n=268)	9 (3-18) (n=268)
Isokinetic quadriceps peak torque (% predicted)	57 (42-69) (n=268)	65 (51-77)** (n=268)	7 (2-13) (n=268)
Isokinetic quadriceps total work (J)	1202 (872-1586) (n=268)	1492 (1108-1889)** (n=268)	250 (92-437) (n=268)

*Data is presented as mean±SD, median (Q1-Q3), or percentages. * indicates a significant difference between baseline and post PR of P<0.01, ** indicates a significant difference between baseline and post PR of P<0.001. Abbreviations: CAT, COPD assessment test; CWRT, constant work rate test; FFM, fat-free mass; HADS, hospital anxiety and depression scale; mMRC, modified Medical Research Council; TTE, Time-To-Exhaustion; 6MWD, 6-Minute Walk Distance.*

	Outpatient (n=238)			Differences in delta's
	Baseline	Post PR	Delta	P-value
	2 (2-3) (n=222)	2 (1-2)** (n=222)	0 (-1-0) (n=222)	<0.001
	79 (n=222)	54** (n=222)	-25 (n=278)	0.805
	19±6 (n=208)	17±7* (n=208)	-1±6 (n=208)	<0.001
	59 (n=208)	45** (n=208)	-14 (n=208)	0.133
	17.0±2.5 (n=235)	17.3±2.5** (n=235)	0.3±0.5 (n=235)	0.004
	16.0 (13.1-18.8) (n=235)	16.4 (13.4-19.3)** (n=235)	0.5 (0-0.9) (n=235)	0.271
	6 (3-8) (n=208)	5 (3-8) (n=208)	-1 (-2-1) (n=208)	0.001
	15 (n=265)	14 (n=265)	-1 (n=208)	0.017
	6 (4-9) (n=208)	5 (3-7)** (n=208)	-1 (-2-1) (n=208)	<0.001
	14 (n=208)	10 (n=208)	-4 (n=208)	<0.001
	432±88 (n=234)	448±92** (n=234)	13±47 (n=234)	0.002
	272 (197-378) (n=227)	349 (217-373)** (n=227)	77 (-24-272) (n=227)	0.001
	92 (73-120) (n=183)	102 (83-129)** (n=183)	8 (2-17) (n=183)	0.729
	67 (55-77) (n=183)	74 (62-83)** (n=183)	6 (1-12) (n=183)	0.284
	1638 (1306-2194) (n=183)	1863 (1530-2402)** (n=183)	234 (119-383) (n=183)	0.764

Supplemental Table 7. Baseline, post PR and delta (post PR minus baseline) data of the SPPB subtests and summary score in patient following an in- or outpatient program.

	Inpatient (n=387)			Outpatient (n=238)			Differences in delta
	Baseline	Post PR	Delta	Baseline	Post PR	Delta	P-value
Side-by-side (s)	10 (10-10)	10 (10-10)	0 (0-0)	10 (10-10)	10 (10-10)	0 (0-0)	0.823
Semi-tandem (s)	10 (10-10)	10 (10-10)	0 (0-0)	10 (10-10)	10 (10-10)	0 (0-0)	0.723
Tandem (s)	10 (7-10)	10 (8-10)	0 (0-0)	10 (10-10)	10 (10-10)*	0 (0-0)	0.144
4MGS (m/s)	1.0 (0.8-1.1)	1.1 (0.9-1.2)**	0.1 (-0.1-0.2)	1.1 (1.0-1.3)	1.2 (1.1-1.4)**	0.1 (-0.1-0.2)	0.988
5STS (s)	17 (14-23)	16 (13-20)**	-1 (-4-1)	15 (13-18)	13 (11-16)**	-1 (-4-0)	0.256
SPPB summary score	9 (8-10)	9 (8-10)**	0 (0-2)	10 (9-11)	10 (9-11)**	1 (0-2)	0.092

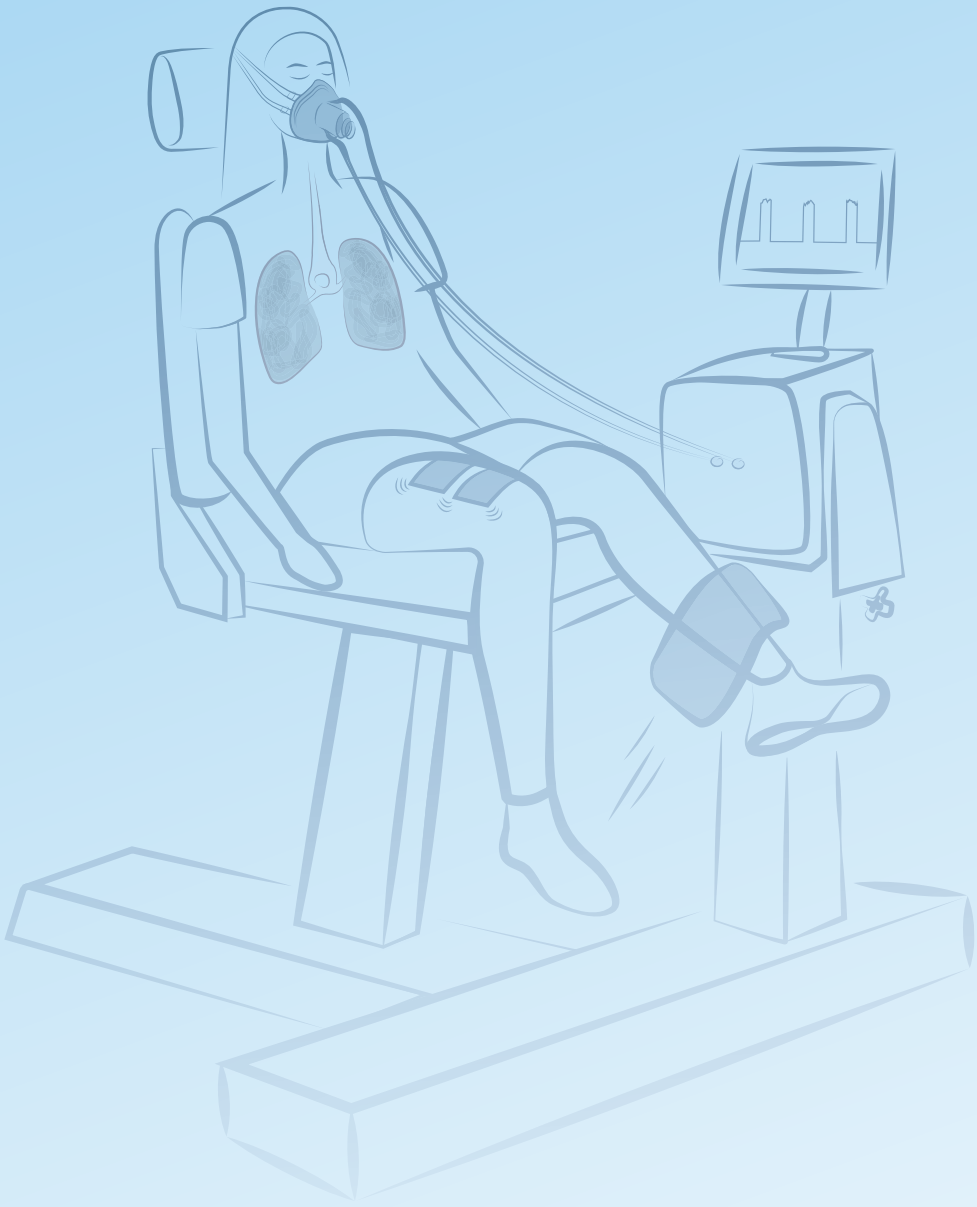
*Data is presented as median (Q1–Q3). * indicates a significant difference between baseline and post PR of P<0.01, ** indicates a significant difference between baseline and post PR of P<0.001. Abbreviations: 4MGS, 4-meter gait speed; 5STS, 5-repetition sit-to-stand; SPPB, Short physical performance battery.*

Supplemental Table 8. Correlations between change in CAT score and 6MWT (m) with the change in 4MGS, 5STS and SPPB summary score for patients with COPD.

	ΔCAT score		Δ6MWT (m)	
	Correlation coefficient	P-value	Correlation coefficient	P-value
4MGS (m/s)	-0.235	<0.001	0.372	<0.001
Δ5STS (s)	0.109	0.010	-0.178	<0.001
ΔSPPB summary score	-0.166	<0.001	0.274	<0.001

Abbreviations: CAT, COPD Assessment Test; SPPB, Short physical performance batter; 4MGS, 4-meter gait speed; 5STS, 5-repetition sit-to-stand; 6MWT, 6-minute walk test.

PART II: EXERCISE CAPACITY AND TOLERANCE



CHAPTER 4

Association between patient-reported outcomes and exercise test outcomes in patients with COPD before and after pulmonary rehabilitation

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ABSTRACT

Background: Over the years, the scope of outcomes assessment in chronic obstructive pulmonary disease (COPD) has broadened, allowing for the evaluation of various patient-reported outcomes (PROs). As it still remains unclear whether and to what extent PROs mirror the exercise performance of patients with COPD, the current study aimed to assess the association between different exercise test outcomes and PROs, before and after pulmonary rehabilitation (PR).

Methods: Correlations between PROs used to describe health-related quality of life (HRQoL), mood status, level of care dependency and dyspnoea in patients with COPD and commonly used laboratory- and field-based exercise test outcomes were evaluated in 518 individuals with COPD attending PR.

Results: Overall, correlations between PROs and exercise test outcomes at baseline were statistically significant. The correlation between modified Medical Research Council (mMRC) dyspnoea score and 6-minute walk distance (6MWD) was strongest (ρ:-0.65; P<0.001). HRQoL related PROs showed weak correlations with exercise outcomes at baseline. Moderate correlations were found between St. George's Respiratory Questionnaire total score and 6MWD (r=-0.53; P<0.001) and maximal workload achieved during cardiopulmonary exercise testing (ρ=-0.48; P<0.001); and between Clinical COPD Questionnaire (CCQ) total score and 6MWD (r=-0.48; P<0.001) and maximal workload (ρ=-0.43; P<0.001). When significant, correlations between changes in exercise test outcomes and changes in PROs after PR were generally very weak or weak. The highest correlation was found between changes in CCQ total score and changes in 6MWD (ρ= -0.36; P<0.001).

Conclusions: PROs and exercise test outcomes, although significantly correlated with each other, assess different disease features in patients with COPD. Individual PROs need to be supported by additional functional measurements whenever possible, in order to get a more detailed insight in the effectiveness of a PR program.

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD), a highly-prevalent chronic lung disease, frequently suffer from symptoms of dyspnoea, exercise intolerance, an impaired mood status and a reduced health status.[1-3] These features are typically weakly related to the degree of lung function impairment.[4] Therefore, the use of additional assessments such as exercise tests and patient-reported outcomes (PROs) has been advocated.[3, 5, 6] Appraisal of these extra-pulmonary features is necessary to better understand the patients' daily needs or problems, to identify possible treatable traits for integrated COPD care programs, and to evaluate its efficacy.[7]

Several laboratory- and field-based exercise tests can be performed to measure exercise performance, which is typically affected in patients with COPD,[3, 8] due to a downward spiral of dyspnoea, disability and physical inactivity.[9] Important aspects from the patient's perspective like health-related quality of life (HRQoL), dyspnoea, anxiety, depression, and the level of care dependency, all of which have a direct impact on daily life,[10] are measured using PROs.

Punekar and colleagues systematically reviewed the strength of the available evidence supporting correlations between the outcomes of different exercise tests and PROs most commonly used to assess HRQoL and dyspnoea.[11] They concluded that only a limited number of studies have focused on the correlations between exercise test outcomes and PROs in patients with COPD. The available evidence indicates a very weak to moderate negative correlation between 6-minute walk distance (6MWD) and HRQoL, measured with the St. George's Respiratory Questionnaire (SGRQ). The relationship between PROs for dyspnoea and 6MWD showed contrasting results, with both moderate to strong positive and negative correlations being reported.[11] So, it still remains unclear whether and to what extent PROs mirror the exercise performance of patients with COPD. It seems reasonable to hypothesize that other exercise test outcomes than 6MWD may be stronger correlated with different PROs. For example, disease-specific questionnaires like the Clinical COPD Questionnaire (CCQ) and the COPD Assessment Test (CAT) focus more on functional impairments and symptoms related to COPD and may therefore be more closely associated with exercise test outcomes in patients with COPD.

Pulmonary rehabilitation (PR) reduces dyspnoea, increases exercise capacity, and improves HRQoL in individuals with COPD.[6] Exercise training is a major component of PR and therefore exercise test outcomes are consistently used to assess the individual patient's response to PR.[12-17] Nevertheless, improvements in exercise performance

after PR do not necessarily lead to a concurrent decrease in symptoms in patients with COPD and vice versa.[18] Therefore, the question remains whether changes in exercise test outcomes after PR translate into changes in disease-specific PROs.

In this observational study, we aimed to assess the association between different exercise test outcomes and PROs most commonly used to describe HRQoL, anxiety, depression and disease-specific symptoms, such as dyspnoea, in patients with COPD before and after PR. *A priori*, we hypothesized that the correlation between PROs for dyspnoea and HRQoL and exercise test outcomes would be statistically significant, but that there would be no strong or very strong association. Furthermore, it was expected that improvements in exercise test outcomes after PR showed weak correlations with changes in PROs in patients with COPD.

METHODS

Study design and participants

The current study is a retrospective analysis of the *'COPD, Health status and Comorbidities'* (Chance) study, Netherlands Trial Register NTR3416.[19] The Medical Ethical Committee of the Maastricht University Medical Centre+ (MEC 11-3-070) approved this trial, which conformed to the 'Declaration of Helsinki' as amended most recently by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.[20] The Medical Research Involving Human Subjects Act (WMO) does not apply for the secondary analysis of the Chance study. Therefore, an additional official approval of this secondary analysis by the Medical Ethical Committee is not required (MEC letter 2019-0987).

Patients with mild to very severe COPD were recruited before the start of a comprehensive PR program at CIRO in Horn, The Netherlands.[21] Patients between the age of 40 and 85 years with a diagnosis of COPD according to GOLD guidelines[22] were eligible. The protocol and part of the results of the Chance study have been published before.[1, 4, 10, 15, 19, 23-26] All patients gave written informed consent prior to inclusion in the study.

PR program

PR took place inpatient (8 weeks, 5 sessions per week; total of 40 sessions) or outpatient (8 weeks, 3 sessions per week, followed by 8 weeks, 2 sessions per week; total of 40 sessions), in line with the 2013 American Thoracic Society & European Respiratory Society Statement.[4] Extensive pre and post PR assessments were performed, as described before.[19]

Measurements

Demographics, body mass index (BMI), body composition (fat-free mass index),[27] and smoking history were assessed, as part of standard care. Lung function was determined with standardized spirometry equipment of Masterlab (CareFusion, Hoechberg, Germany).[28]

To evaluate HRQoL, three disease-specific PROs, the CAT (range 0-40 points),[29] the CCQ (range 0-6 points)[30] and the COPD-specific version of the SGRQ (range 0-100 points)[31] were assessed in all participants. Mood status was measured with the Hospital Anxiety and Depression scale (HADS; range 0-21 points).[32] Higher scores are equivalent to a decreased HRQoL and/or increase in symptoms of anxiety or depression, respectively. The modified Medical Research Council (mMRC) dyspnoea scale was used to establish functional impairment due to dyspnoea.[33] The level of care dependency was determined at baseline with the Care Dependency Scale (CDS; range 15-75 points) with a lower score representing a higher level of care dependency.[34]

The 6-minute walk test (6MWT),[35] cardiopulmonary exercise test (CPET; only at baseline)[36] were used to assess exercise capacity. Exercise tolerance was determined as cycle endurance time (CET) during the constant work rate cycle test (CWRT).[37] Functional mobility was measured with the Timed 'Up and Go' (TUG) test.[15, 17] Isokinetic quadriceps muscle function (i.e., strength and endurance/total work) was determined using a Biodex System 4 Pro (Biodex Medical Systems Inc, New York, USA).[38]

Statistical analyses

Analyses were performed using SPSS software (statistical package for the social sciences) for Windows (version 25.0). Results are presented as mean and standard deviation (SD), median and interquartile range (IQR), and/or proportions, as appropriate. Continuous variables were tested for normality. Differences at baseline between completers and non-completers were analysed using independent samples T-tests or Mann-Whitney U tests. Correlations between PROs and exercise test outcomes were analysed using Scatter plots and Pearson's or Spearman's correlations, as appropriate. The strength of correlations has been classified according to British Medical Journal guidelines, which regard significant correlation coefficients of 0–0.19 as very weak, 0.2–0.39 as weak, 0.4–0.59 as moderate, 0.6–0.79 as strong, and 0.8–1 as very strong.[39] A priori, the level of significance was set at ≤0.01.

RESULTS

A total of 518 patients (55.6% male, age 64.1±9.1 years) volunteered to participate and attended the pre PR assessment. The mean baseline 6MWD was 424±124m, 25.1% of the patients had a 6MWD below 350 meters,[40] and in 74.7% of the patients was the quadriceps muscle strength less than 80% of the predicted value.[41] The PROs showed a high degree of dyspnoea (80.7% with mMRC dyspnoea grade of two or higher),[22] anxiety (34.8% with ≥10 points),[32] depression (33.4% with ≥10 points),[32] care dependency (28.5% with CDS total score of ≤68 points),[25] and an impaired HRQoL (81.9% with a SGRQ total score of ≥44 points; 75.0% with a CAT total score of ≥18 points; 76.7% with a CCQ total score of ≥1.9 points).[22] Baseline characteristics, exercise test outcomes and PROs at baseline are presented in Table 1.

Table 1. Patient characteristics, patient-reported outcomes and exercise test outcomes at baseline.

	Whole group	***n***	**Completers**	***n***	**Non-completers**	***n***
Number, n	**518**		**419**		**99**	
Patient characteristics						
Gender, male (%)	288 (55.6)	518	232 (55.4)	419	56 (56.6)	99
Age, years	64.1±9.1	518	64.3±8.8	419	63.2±10.3	99
Current smoker, n (%)	114 (22.1)	518	79 (18.9)	419	35 (35.4)*	98
Pack years, n	40.0 (30.0-50.0)	518	40.0 (30.0-50.0)	403	40.0 (30.0-51.0)	93
BMI, kg/m^2	26.2±5.8	518	26.2±5.7	419	26.2±6.3	99
FFMI, kg/m^2	17.0±2.5	499	17.0±2.4	405	17.0±2.6	94
FEV_1, L	1.29±0.60	518	1.30±0.60	419	1.26±0.60	99
FEV_1 % predicted	48.6±20.0	518	48.9±20.0	419	47.3±20.1	99
FEV_1 / FVC, %	37.5±12.2	518	37.3±12.1	419	38.4±12.9	99
mMRC-score (0/1/2/3/4), %	2/17/38/25/18	512	2/17/40/22/18	414	0/15/27/36/22	98
GOLD classification (I/II/III/IV), %	7/36/37/20	518	8/36/35/21	419	6/33/43/17	99
GOLD classification (A/B/C/D), % (A/B/C/D)	3/20/5/72	518	2/22/5/71	419	5/12/5/78	99
Oxygen saturation, %	94.6 (92.7-96.0)	510	94.6 (92.8-96.0)	414	94.0 (92.0-96.0)	96
LTOT, n (%)	125 (24.1)	518	104 (24.8)	419	21 (21.2)	96
Patient-reported outcomes						
mMRC score, points	2.4±1.0	512	2.4±1.0	414	2.7±1.0	98
SGRQ-C total score, points	61.1±17.4	504	60.1±17.1	409	65.4±18.1*	95
CAT total score, points	21.5±6.6	505	21.5±6.6	410	21.7±6.9	95
CCQ total score, points	2.6±1.0	502	2.6±1.0	409	2.8±1.1	93
HADS-A score, points	7.8±4.5	500	7.5±4.4	407	9.0±4.9*	93
HADS-D score, points	7.5±4.3	500	7.4±4.2	407	8.0±4.9	93
CDS total score, points	72.0 (68.0-75.0)	480	69.7±7.2	389	68.4±7.9	91

Table 1. Continued

	Whole group	*n*	Completers	*n*	Non-completers	*n*
Number, n	**518**		**419**		**99**	
Exercise test outcomes						
6MWD, meters	424±124	513	431±124	417	393±123*	96
CPET, W_{max} (W)	70.1±34.2	493	70.9±33.7	407	66.6±36.7	86
CPET, VO_{2peak} (ml/min)	1090±414	390	1094±407	316	1071±446	74
CWRT endurance time, seconds	224 (169-327)	477	235 (174-338)	392	199 (149-294)*	85
TUG test time, seconds	9.8 (8.5-11.8)	500	9.6 (8.3-11.6)	408	10.2 (8.7-12.7)	92
Quadriceps peak torque, Nm	94.1±36.4	466	94.4±35.9	383	93.5±39.1	83
Quadriceps total work, J	1627±741	465	1641±724	382	1559±815	83

*Summary variables are presented as n (%) for discrete variables, mean±standard deviation for quantitative variables or median (Interquartile range) for skewed variables, * P<0.01. 'n' represents the total number of sample values per analysis.*

Abbreviations: BMI, body mass index; FFMI, fat-free mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; mMRC, modified Medical Research Council scale; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LTOT, Long Term Oxygen Therapy; mMRC, modified Medical Research Council scale; SGRQ-C, COPD-specific St. George Respiratory Questionnaire score; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; CDS, Care Dependency Scale; 6MWD, 6-minute walk distance, CPET, Cardiopulmonary Exercise Test; Wmax, maximal achieved workload; W, Watts; VO2peak, peak oxygen uptake; ml, milliliter; min, minute; CWRT, Constant Work-Rate Test; TUG, Timed 'Up and Go'; Nm, Newtonmeter; J, Joules.

Correlations between exercise test outcomes and PROs at baseline

Overall, correlations between PROs and exercise test outcomes at baseline were statistically significant (Table 2). Of these, the correlation between mMRC score and 6MWD was the strongest (ρ= -0.65; P<0.001), which is visually presented in Figure 1. A moderate correlation was found between mMRC score and CPET maximum workload (W_{max}; ρ= -0.54; P<0.001), CPET peak oxygen uptake (VO_{2peak}; ρ= -0.40; P<0.001), TUG time (ρ= 0.49; P<0.001), quadriceps total work (ρ= -0.43; P<0.001), respectively.

HRQoL PROs showed weak correlations with exercise outcomes at baseline. Moderate correlations were only found between SGRQ-C and 6MWD (r= -0.53; P<0.001) and CPET maximum workload (ρ= -0.48; P<0.001) and between CCQ and 6MWD (r= -0.48; P<0.001) and CPET maximum workload (ρ= -0.43; P<0.001). See Figure 2 for a scatter plot illustrating the relationship between HRQoL PROs and 6MWD. CDS score was significantly correlated with all exercise test outcomes, with correlations ranging from 0.24 (CWRT cycle endurance time) to 0.50 (6MWD). Both HADS-D and HADS-A showed non-significant or very weak to weak correlations with all exercise test outcomes.

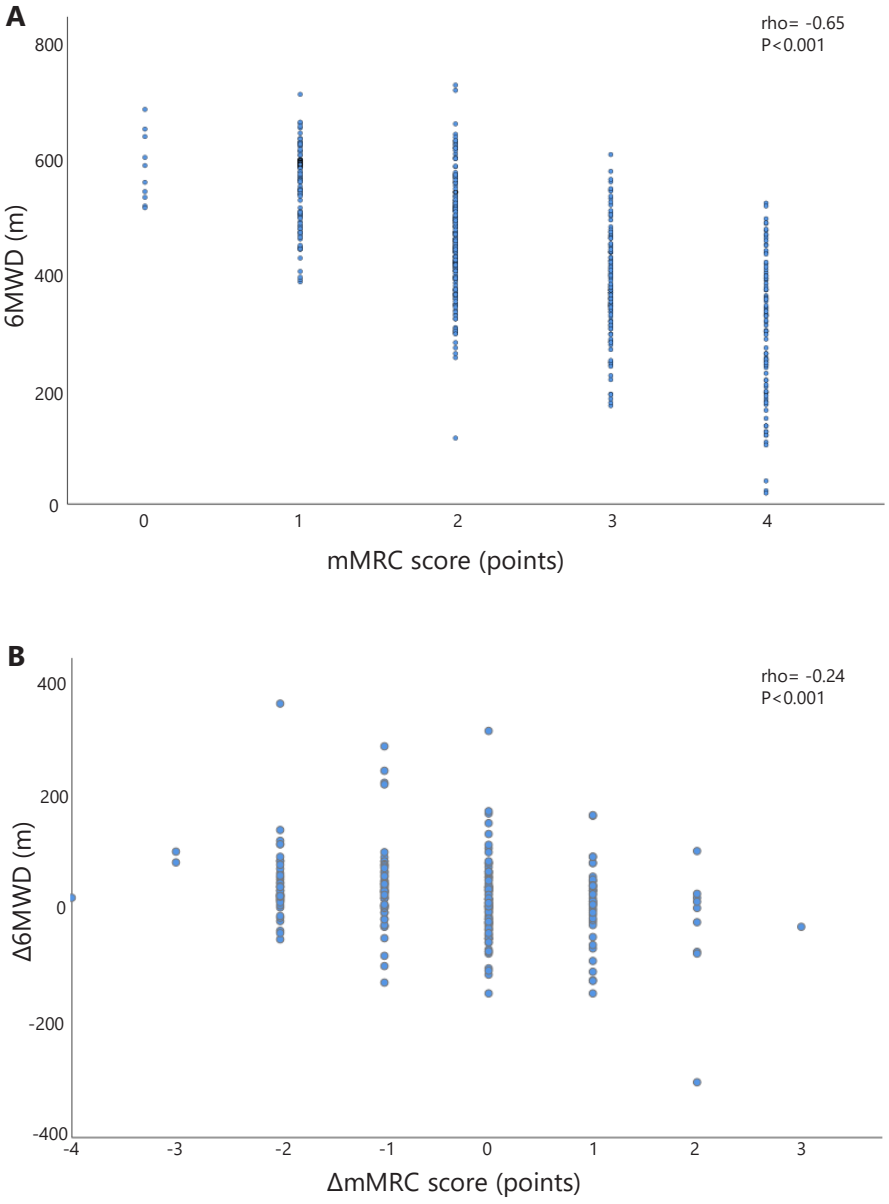


Figure 1. Association between the mMRC score and 6MWD at baseline (**A**) and between changes in mMRC score and changes in 6MWD after PR (**B**).
Abbreviations: mMRC, modified Medical Research Council scale; 6MWD, 6-minute walk distance.

Table 2. Correlations between exercise test outcomes and PROs at baseline

	6MWD (m)	CPET (W_{max})	CPET (VO_{2peak})	CWRT (t)	TUG (t)	Q. Peak torque (Nm)	Q. Total work (J)
mMRC score	-0.65*	-0.54*	-0.40*	-0.39*	0.49*	-0.32*	-0.43*
SGRQ-C total score	-0.53*	-0.48*	-0.31*	-0.35*	0.41*	-0.26*	-0.38*
CAT total score	-0.37*	-0.30*	-0.21*	-0.21*	0.27*	-0.23*	-0.26*
CCQ total score	-0.48*	-0.43*	-0.30*	-0.29*	0.34*	-0.25*	-0.34*
HADS-A score	-0.25*	-0.20*	-0.10	-0.09	0.21*	-0.16*	-0.22*
HADS-D score	-0.27*	-0.22*	-0.06	-0.08	0.26*	-0.11	-0.20*
CDS total score	0.50*	0.40*	0.25*	0.24*	-0.43*	0.28*	0.34*

*Correlations are reported as Pearson's r or, in the case of ordinal and/or skewed variables or variables with significant outliers, as Spearman's ρ; * P<0.001*

Abbreviations: mMRC, modified Medical Research Council scale; SGRQ-C, COPD-specific St. George Respiratory Questionnaire; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; CDS, Care Dependency Scale; 6MWD, 6-minute walk distance, CPET, Cardiopulmonary Exercise Test; Wmax, maximal achieved workload; VO^{2peak}, peak oxygen uptake; t, time; CWRT, Constant Work-Rate Test; TUG, Timed 'Up and Go' test; Q., Quadriceps muscle.

Correlations between changes in exercise test outcomes and changes in PROs after PR

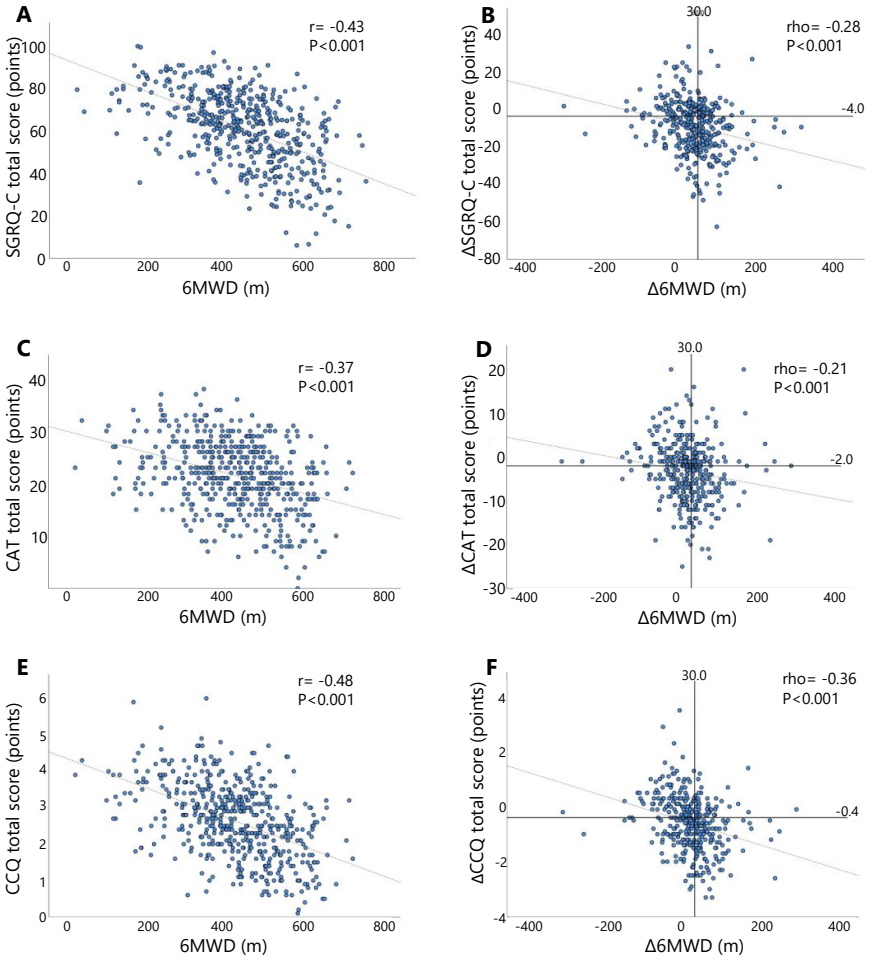
Four hundred nineteen patients completed the PR program. Completers and non-completers were comparable with respect to baseline characteristics (Table 1). Only the number of current smokers was significantly higher in the non-completer group (P<0.001). All PROs and exercise test outcomes changed significantly after PR (Supplemental Table 1). When significant, correlations between changes in exercise test outcomes and changes in PROs were generally very weak or weak. The highest correlation, being classified as weak, was found between ΔCCQ and Δ6MWD (ρ= -0.36; P<0.001; Figure 2). Changes in other HRQoL PROs demonstrated similar association with changes in exercise test outcomes (Table 3). Changes in quadriceps peak muscle strength were not correlated with changes in any of the PROs.

Table 3. Correlations between changes in exercise test outcomes and changes in PROs (pre vs. post PR).

		Δ6MWD (m)	ΔCWRT (t)	ΔTUG (t)	Δ Q. Peak torque (Nm)	Δ Q. Total work (J)
ΔmMRC score	ρ	-0.24*	-0.08	0.19#	-0.08	-0.15
ΔSGRQ-C total score	ρ	-0.28*	-0.29*	0.11	-0.03	-0.10
ΔCAT total score	ρ	-0.21*	-0.24*	0.06	0.03	-0.08
ΔCCQ total score	ρ	-0.36*	-0.33*	0.15#	-0.03	-0.16#
ΔHADS-A score	ρ	-0.19*	-0.17#	0.12	-0.04	-0.07
ΔHADS-D score	ρ	-0.15#	-0.21*	0.16#	0.01	-0.08

*Spearman's ρ is reported since all exercise outcomes changes showed significant outliers; * P<0.001; # P<0.01;*

Abbreviations: mMRC, modified Medical Research Council scale; SGRQ-C, COPD-specific St. George Respiratory Questionnaire score; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; 6MWD, 6-minute walk distance; t, time; CWRT, Constant Work-Rate Test; TUG, Timed 'Up and Go' test; Q., Quadriceps muscle.



< Figure 2. Left: association between the SGRQ-C score (**A**), CAT score (**B**), CCQ score (**C**), and the 6MWD. Right: association between the change in SGRQ-C score (**D**), CAT score (**E**), CCQ score (**F**), and the change in 6MWD after PR. On the X-axis the MCID of 30 m for the 6MWT[42] is marked, on the Y-axis the MCIDs for SGRQ-C (-4.0), CAT (-2.0) and CCQ score (-0.4) are marked.[10, 43]

Abbreviation: MCID, minimal clinically important difference.

DISCUSSION

This study demonstrates that PROs and exercise test outcomes are associated to some extent in patients with mild to very severe COPD, but, in general, these correlations are weak to moderate. A strong relationship was merely found between the severity of dyspnoea (mMRC) and distance covered in the 6MWT at baseline. In the current study, dyspnoea tended to indicate at least moderate negative correlations with exercise test outcomes at baseline, suggesting that exercise performance decreases as dyspnoea scores increase. However, these associations attenuated considerably or even became non-significant once the changes in dyspnoea were correlated with changes in exercise test outcomes following PR, indicating that an improvement in exercise performance after PR does not necessarily imply that self-reported breathlessness decreases concurrently, like shown before.[18] As a side remark, it is important to note that correlations between changes in parameters are always lower than cross-sectional correlations. After all, the measurement error is included twice (pre vs. post) in the analysis, which always results in a weaker signal.[44]

While the mMRC-scale is a unidimensional method to quantify only dyspnoea, there are several multidimensional disease-specific PROs, which assess not only dyspnoea but also other symptoms and perceived HRQoL in COPD.[1] Of these HRQoL PROs (CAT, CCQ, SGRQ), their association with exercise test outcomes was weak to moderate, indicating that no single exercise test accurately reflects HRQoL (or the other way around), proving that HRQoL is indeed a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning. Overall, these results support the findings by Punekar et al.[11] who showed that generally there was a very weak to moderate negative correlation between the 6MWD and the SGRQ.

While guidelines on the diagnosis and treatment of COPD have intensively stated that the assessment of disease severity is substantially improved by using functional criteria,[22] such as exercise capacity, the current study demonstrates that the variance in PROs can only be partially explained by attributes related to exercise performance. So, despite the fact that PROs for HRQoL, dyspnoea, anxiety, depression and the level of care dependency are crucial when evaluating the disease severity and effectiveness of a treatment in COPD, it is justified to conclude that these PROs assess

features not measured by exercise tests. Consequently, if we solely use a few outcome measures (for example, walking distance or HRQoL) to evaluate performance after PR, the clinical complexity and multidimensional aspect of PR in patients with COPD appears to be ignored.[18]

In our study, the 6MWD showed the strongest relationship with important clinical PROs, underlining the fact that the 6MWT indeed seems to play a key role in evaluating *functional* exercise capacity.[14] Since the 6MWT is self-paced, test outcomes are likely to be affected by a patient's mental and emotional status.[3]

Limitations

Patients were solely recruited in a specialized PR centre, resulting in a selected group of COPD patients. This should be considered when applying results to other COPD samples. Furthermore, by quantifying the associated exercise limitation, a mMRC-score of 4 reflects the most disabled COPD patients who are not always able to perform a symptom-limited CPET, as a result of their dyspnoea. In the current study, patients unable to perform a CPET and, concurrently, a CWRT were automatically excluded from the correlation analysis, since they did not present any values for both exercise tests, possibly affecting the correlation coefficients.

CONCLUSIONS

In conclusion, we have found that patient-reported outcomes and exercise test outcomes, although significantly correlated with each other, assess different disease features in patients with COPD. Therefore, it can be stated that relevant features from the patient's perspective like HRQoL, anxiety, depression, and the level of care dependency are not an accurate reflection of a patient's exercise capacity. The only exception to this seems to be dyspnoea, the only PRO that tended to imply at least moderate association with exercise test outcomes. We would like to highlight the complexity of evaluating the effectiveness of a personalized PR program, in which we note that changes in PROs and changes in exercise test outcomes correlate poorly. Indeed, improvements in exercise capacity obtained after PR do not necessarily result in alterations in PROs in patients with COPD. Individual PROs need to be supported by additional functional measurements whenever possible, in order to get a more detailed insight in the effectiveness of a PR program.

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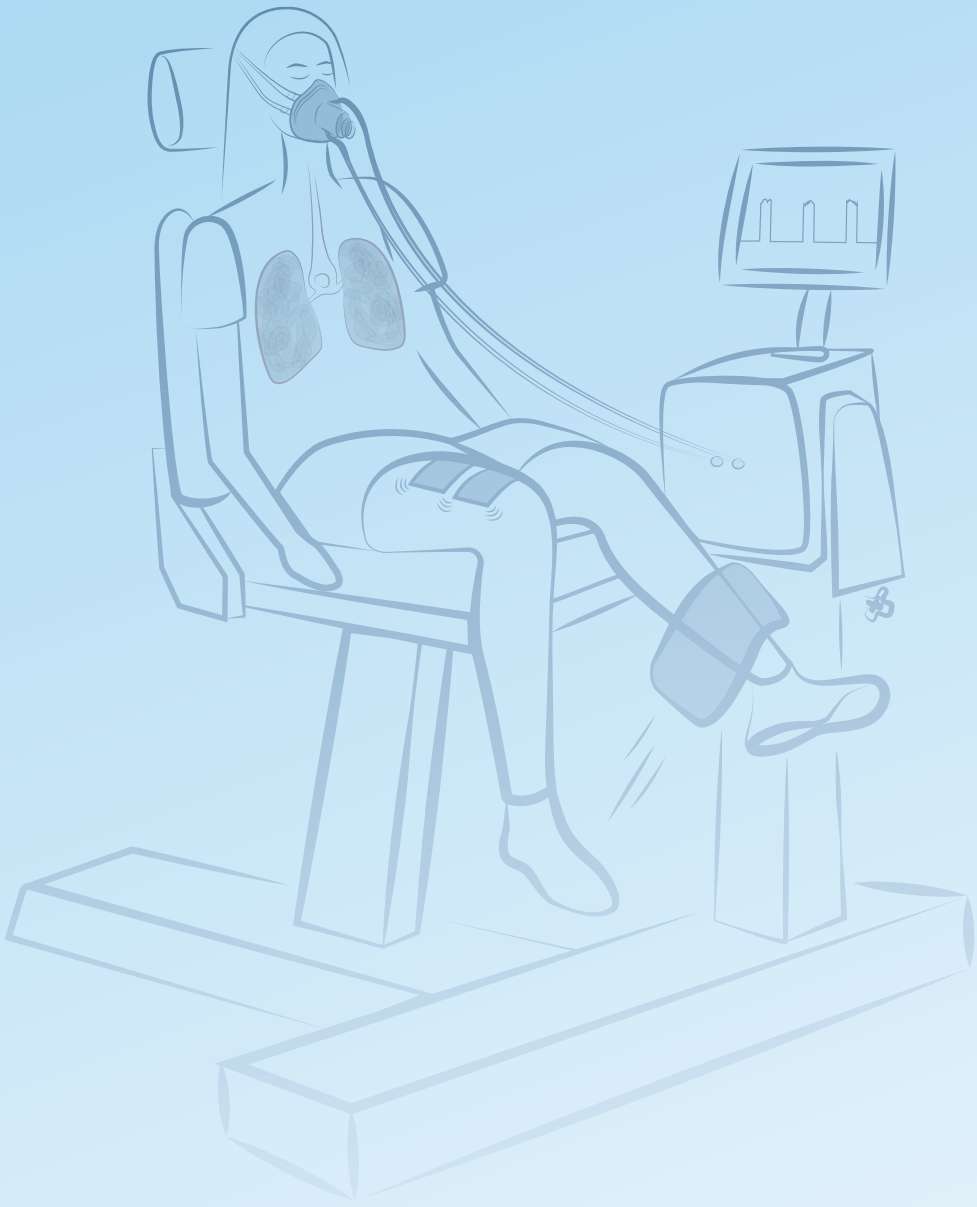
SUPPLEMENTARY MATERIALS

Supplemental Table 1. Changes in PROs and exercise test outcomes after PR.

	Pre	Post	Mean change	*n*
Patient-reported outcomes				
mMRC score, points	2.4±1.0	2.0±1.0[†]	-0.3[*]±1.1	283
SGRQ-C total score, points	60.1±17.1	50.9±17.4	-9.1[*]±14.0	385
CAT total score, points	21.5±6.6	18.5±16.9	-3.0[*]±6.8	389
CCQ total score, points	2.6±1.0	2.0±1.0	-0.6[*]±0.9	377
HADS-A score, points	7.5±4.4	5.8±4.2	-1.7[*]±3.7	372
HADS-D score, points	7.4±4.2	5.3±3.9	-2.1[*]±3.7	372
Exercise test outcomes				
6MWD, meters	431±124	457±122	22.9[*]±66.8	403
CWRT time, seconds	235 (174-338)	377 (210-709)	206.4[*]±305.7	378
TUG test time, seconds	9.6 (8.3-11.6)	9.2 (8.2-11.0)	-0.4[*]±1.8	379
Quadriceps Peak Torque, Nm	94.4±35.8	103.8±38.3	9.2[*]± 14.4	360
Quadriceps Total Work, J	1641±724	1874±769	223.3[*]±357.9	358

*Summary variables are presented as mean±standard deviation for quantitative variables or median (Interquartile range) for skewed variables. Changes were analyzed using paired t tests or Wilcoxon signed rank tests. * P<0.001. [†] out of 419 patients who filled in the mMRC questionnaire before pulmonary rehabilitation, 136 patients did not fill in the questionnaire after the intervention.*

Abbreviations: mMRC, modified Medical Research Council scale; SGRQ-C, COPD-specific St. George Respiratory Questionnaire score; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; HADS-A, Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale, Depression subscale; 6MWD, 6-minute walk distance; CWRT, Constant Work-Rate Test; TUG, Timed 'Up and Go'; Nm, Newtonmeter; J, Joules.



CHAPTER 5

Correlates of variability in endurance shuttle walk test time in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: The endurance shuttle walk test (ESWT) is used to evaluate exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). The recommended pre-intervention tolerated duration (Tlim) is between 3-8 minutes for optimal interpretation of treatment effects. However, this window may be exceeded and factors determining ESWT Tlim are not completely understood. Therefore, we aimed to determine whether pulmonary function, physical and incremental shuttle walk test (ISWT) performance measures are associated with ESWT Tlim in COPD patients.

Methods: Assessment data from patients eligible for pulmonary rehabilitation was retrospectively analysed. Inclusion criteria were: diagnosis of COPD and complete data availability regarding ESWT and ISWT. Patients performed an ESWT at 85% of ISWT speed and were divided into three groups (ESWT Tlim: <3 minutes, 3-8 minutes, >8 minutes). Subject characteristics, severity of complaints, pulmonary function, physical capacity and activity, exercise tolerance and quadriceps muscle strength were evaluated.

Results: 245 COPD patients (FEV_1 38 (29-52)% predicted) were included. Median ESWT Tlim was 6.0 (3.7-10.3) minutes, 41 (17%) patients walked <3 minutes and 80 (33%) patients walked >8 minutes. Body mass index, maximal oxygen consumption, Tlim on constant work rate cycle test, physical activity level, maximal ISWT speed, dyspnoea Borg score at rest and increase of leg fatigue Borg score during ISWT independently predicted Tlim in multivariate regression analysis (R^2=0.297, P<0.001).

Conclusions: This study reported a large variability in ESWT Tlim in COPD patients. Secondly, these results demonstrated that next to maximal ISWT speed, other ISWT performance measures as well as clinical measures of pulmonary function, physical capacity and physical activity were independent determinants of ESWT Tlim. Nevertheless, as these determinants only explained ~30% of the variability, future studies are needed to establish whether additional factors can be used to better adjust individual ESWT pace in order to reduce ESWT Tlim variability.

INTRODUCTION

The endurance shuttle walk test (ESWT) is commonly used to evaluate effects of interventions on exercise tolerance in patients with chronic obstructive pulmonary disease (COPD)[1, 2] in both research and clinical settings.[3] This accessible and low-cost field walking test is performed at an imposed constant pace and is therefore better controlled than other field walking tests, like the 6- and 12-minute walk tests.[4-6] Furthermore, the tolerated duration (Tlim) of the ESWT is considered to be highly responsive to interventions, especially in comparison to maximal walking tests[1, 7] and the change in ESWT Tlim has been associated with change in exercise capacity and quality of life.[8, 9]

However, the potential effect size of interventions on Tlim of constant load tests is strongly determined by the load on which the test is performed.[10] Since Tlim has a negative hyperbolical relation with the relative load of the test, testing at higher relative loads will yield less potential improvement on Tlim.[10-12] Accordingly, ESWT load, i.e., pace, is set at a fixed percentage (usually 85%) of the maximum walking pace, pre-determined by an incremental shuttle walk test (ISWT).[6] Despite this fixed pace, considerable variability in ESWT Tlim was recently observed in patients with COPD (ESWT Tlim=353 seconds, 95% CI [299-407]).[13] Because effects sizes of interventions on ESWT Tlim depend on pre-intervention ESWT Tlim, a large variability in pre-intervention ESWT Tlim complicates statistical analysis of intervention efficacy and increases the number of participants required in clinical studies.[12, 14] Accordingly, a pre-intervention Tlim between 3 and 8 minutes has been recommended for constant load exercise tests, like the ESWT.[15]

It is currently not completely understood why Tlim of some patients falls outside the recommended timeframe of 3-8 minutes. However, we do know that causes of exercise intolerance are multifactorial and heterogenous in patients with COPD.[16] Next to the severity of pulmonary dysfunction, extrapulmonary features, like muscle weakness and psychological status are known to determine tolerance to exercise.[10, 16, 17] Furthermore, the variability of endurance time on a constant work rate cycle exercise test (CWRT) with equal relative loads for all COPD patients was only partly explained by peak exercise capacity and maximal quadriceps strength,[18] suggesting that variability of endurance time is determined by additional clinical variables. Whether these factors influence ESWT Tlim as well has not yet been determined. Lastly, procedural factors can also play a role in ESWT Tlim variability. For example, over- and underestimation of the maximal speed obtained from ISWT can lead to ESWT performance at an intensity not truly representing 85% of the

peak capacity. Hence, a performance of the ISWT in accordance with the European Respiratory Society/American Thoracic Society Technical Standards is important,[19] as well as maximal effort of the patient.

Collectively, considering that despite protocolized execution of ISWT and ESWT substantial heterogeneity is observed in ESWT Tlim in patients with COPD, hampering clinical evaluation of interventions, there is a need to better understand determinants of ESWT Tlim variation. Therefore, our primary aim was to determine whether pulmonary function, physical and ISWT performance variables are associated with ESWT Tlim in patients with COPD. A priori, we hypothesized that parameters of pulmonary function and physical performance are independent determinants of ESWT Tlim and can partly explain the high variability of ESWT Tlim in patients with COPD.

MATERIALS AND METHODS

Retrospective analyses were performed on an anonymized dataset from 306 patients that attended a comprehensive pulmonary rehabilitation (PR) program in Dekkerswald – Radboudumc (Nijmegen, The Netherlands) between September 2016 and December 2019. The data was collected during baseline assessment as part of standard care of the PR program. Inclusion criteria for the analyses were a primary diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease criteria[20] and complete data availability regarding ISWT speed and ESWT speed and time. These criteria were met by 245 patients. A flowchart of in- and exclusion of patients is depicted in Figure 1.

This study was in accordance with the principles of the Declaration of Helsinki. The local ethical board Arnhem/Nijmegen, The Netherlands, informed the authors that the Medical Research Involving Human Subject Act (WMO) did not apply to this retrospective study (2020-6621).

Measurements

Subject characteristics and severity of complaints as age, gender, weight, body mass index (BMI), Charlson Comorbidity Index,[21] fat-free mass index, modified Medical Research Council (mMRC),[22] COPD Assessment Test,[23] Hospital Anxiety and Depression Scale[24] and Checklist Individual Strength Fatigue[25] were systemically assessed.

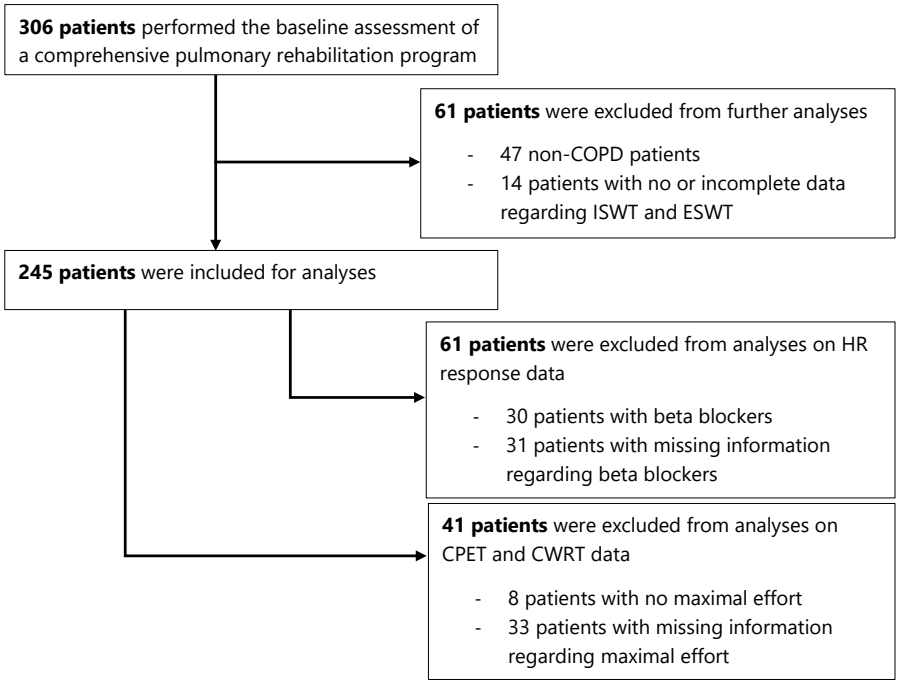

Figure 1. Flowchart of in- and exclusion of patients for analysis

Abbreviations: COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise test; CWRT, constant work rate test; HR, heartrate; ISWT, incremental shuttle walk test; ESWT, endurance shuttle walk test.

Pulmonary function tests

Post-bronchodilator pulmonary function tests including spirometry (forced expiratory volume in one second, FEV_1; Tiffeneau index, FEV_1/vital capacity), static lung volumes (residual volume, RV; functional residual capacity, FRC; total lung capacity, TLC) and diffusion capacity for carbon monoxide (DL_{CO}) by single-breath method (MasterScreen PFT/Body; Jaeger, Würzburg, Germany) were executed according to the European Respiratory Society Recommendations[26] and related to predicted normal values.[27, 28]

Physical performance tests

The ISWT required the patients to walk around two markers set nine meters apart (10 meters course) at a speed which increases every minute indicated by a pre-recorded audio signal. The patients were instructed to walk for as long as possible.[29] The ESWT was performed at 85% of the maximal ISWT speed and used the same course and auditory signal method. In contrast to the ISWT, the patients were

required to walk at a constant speed throughout the test for as long as possible. The ESWT had a maximum test duration of 20 minutes for practical reasons.[6] Both tests were performed according to standardized protocols[6, 29] with on average one week in-between. The following ISWT and ESWT parameters were recorded: Tlim, walking distance, speed, resting and maximal values of transcutaneous peripheral oxygen saturation (SpO_2), heartrate (HR) and Borg scores (dyspnoea and leg fatigue). Furthermore, the ISWT distance in meters was calculated as percentage of predicted.[30] Patients with beta blockers (n=30) or missing information regarding beta blockers (n=31) were excluded from analyses on HR responses to exercise during both shuttle walk tests (Figure 1).

A symptom-limited ramp maximal cardiopulmonary exercise test (CPET) was performed on an electromagnetically braked cycle ergometer (Ergoselect, Ergoline, Bitz, Germany) according to the recommended guidelines[31] to determine the maximal workload (Wmax) and oxygen uptake (VO_2max). Furthermore, the maximal HR was recorded in order to determine the maximal HR during the ISWT relative to the maximal HR during the CPET ($HRmax_{ISWT}$/$HRmax_{CPET}$). The CWRT was performed at 65% of Wmax on the same cycle ergometer as the CPET. Patients cycled until symptom limitation or until pedalling rate decreased under 60 rotations per minute, with a maximum of 20 minutes. Only data of patients that performed CPET with maximal effort, as based on the European Respiratory Society and American Thoracic Society/ American College of Chest Physicians statements on CPET, were included in analysis of CPET and CWRT variables (n=204)[31, 32] (Figure 1).

Isometric quadriceps strength (maximal voluntary contraction) was assessed with a computerized dynamometer (Biodex System 4 Pro, Biodex Medical Systems, Inc., New York, USA). Participants performed 3 maximal unilateral isometric knee extensions for 5 seconds at a knee angle of 60°, interspersed with 15 seconds of rest. The maximal voluntary contraction was defined as the highest peak torque (Nm)[33] and was both expressed as absolute value as well as related to predicted normal values.[34]

Physical activity was measured using the Dynaport MoveMonitor (McRoberts BV, The Hague, The Netherlands) for a duration of 7 (with a minimum of at least 5) consecutive days and defined as steps per day and average physical activity level (PAL).[35, 36]

Statistical analysis

Statistical analyses were performed using SPSS statistical software program (IBM, New York, USA), version 25.0. Descriptive data were presented as mean±SD, median (interquartile range 25-75%) or number of patients (percentage), as appropriate.

Based on the ESWT Tlim, the subjects were divided into three groups (group 1: <3 minutes, group 2: 3-8 minutes, group 3: >8 minutes). These cut-off points were chosen to reflect the desirable ESWT duration of 3 to 8 minutes.[15] Accordingly, in the results section we focussed on differences in groups 1 and 3 compared to group 2.

Between-groups comparisons for continuous variables were tested by one-way analysis of variance (ANOVA) or Kruskal-Wallis test, as appropriate. Categorical variables were tested with a Chi-square test. When a statistically significant difference was obtained, a pairwise post-hoc test was performed and Bonferroni post-hoc testing was applied to correct for multiple comparisons. A P-value of <0.05 was considered significant.

Univariate and multivariate linear regression models were used to evaluate the association of pulmonary function, physical and ISWT performance variables with the ESWT Tlim. Univariate linear regression models were built using the ENTER method. Explanatory variables with a P-value <0.20 and not strongly correlated (r <0.8) with another variable of interest were used to build a multivariate linear regression model, using the backward method. Variables with a P-value <0.05 in the multivariate linear regression model were considered as independent predictors of ESWT Tlim.

RESULTS

The included patients had a mean age of 61.4±7.8 years, a mean BMI of 25.8±5.7 kg/m^2, a median FEV_1 of 38 (29-52)% predicted and 47% were male (Table 1). The median ESWT Tlim was 6.0 (3.7-10.3) minutes. A total of 41 (17%) patients walked <3 minutes (group 1), 124 (50%) patients walked between 3-8 minutes (group 2) and 80 (33%) patients walked >8 minutes (group 3). Furthermore, 42 (17%) patients reached the maximum test duration of 20 minutes. The distribution of patients according to the ESWT Tlim is depicted per minute in Figure 2.

Subgroup characteristics

Gender, BMI, fat-free mass index and Charlson Comorbidity Index were similar between groups. Patients in group 3 were younger (59.4±8.6 years) than patients in group 2 (62.4±7.2 years, P=0.021). The severity of dyspnoea sensation, as reflected by the mMRC score, was lower in patients from group 3 (median 2(1-3) and mean 1.8±1.2) than group 2 (median 2(1-3) and mean 2.2±1.2, P=0.006). There were no differences in severity of complaints, COPD Assessment Test, Hospital Anxiety and Depression Scale and Checklist Individual Strength Fatigue scores, between the groups (Table 1).

Table 1. Subject characteristics, severity of complaints and parameters of pulmonary function and physical performance of the whole group and the three subgroups based on tolerated duration during the ESWT.

	All patients with COPD (n=245)	Group 1 (n=41)	Group 2 (n=124)	Group 3 (n=80)	
Variables		**Tlim <3 min**	**Tlim = 3-8 min**	**Tlim >8 min**	**P-value**
Gender (male, %)	114 (47)	17 (42)	61 (49)	36 (45)	0.653
Age (years)	61.4±7.8	61.9±7.1	62.4±7.2	59.4±8.6	0.021[†]
BMI (kg/m^2)	26±6	26±7	26±5	25±6	0.195
CCI [a]	1 (1-2)	1 (1-3)	1 (1-2)	1 (1-2)	0.853
FFMI [b]	16.9±2.5	16.8±3.1	17.2±2.3	16.6±2.5	0.296
Severity of complaints					
mMRC score [c]	2 (1-3)	2 (2-3)	2 (1-3)	2 (1-3)	0.006[#,†]
CAT score [d]	17.2±7.0	17.3±6.5	16.9±7.4	17.7±6.7	0.784
HADS anxiety score [e]	8.5±4.2	8.7±5.0	8.3±4.0	8.6±4.1	0.852
HADS depression score [e]	8.6±3.8	8.6±4.3	8.2±3.7	9.1±3.6	0.349
CIS fatigue score [f]	48 (43-53)	48 (42-52)	48 (44-53)	49 (44-54)	0.836
Pulmonary function parameters					
FEV_1 (L) [g]	1.1 (0.8-1.5)	0.9 (0.7-1.2)	1.0 (0.8-1.5)	1.2 (0.9-1.8)	<0.001[*,#]
FEV_1 (% predicted) [g]	38 (29-52)	31 (27-42)	37 (29-49)	44 (33-56)	0.001[#]
Tiffeneau index (%) [g]	34.5 (28.0-45.5)	31.7 (26.7-38.6)	33.5 (26.9-43.7)	37.8 (30.8-50.2)	0.005[#]
FRC (% predicted) [h]	163±38	169±37	165±38	156±39	0.158
RV (% predicted) [i]	191±53	201±52	191±54	186±53	0.394
TLC (% predicted) [i]	123±19	125±20	124±19	122±18	0.591
FRC/TLC (%) [h]	70±9	72±9	70±9	67±10	0.009[#]
RV/TLC (%) [i]	56±10	60±9	56±10	54±10	0.026[#]
DL_{CO} (mL/mmHg/min) [j]	3.6±1.6	3.0±1.4	3.6±1.5	3.9±1.8	0.011[#]
DL_{CO} (% predicted) [j]	42±16	36±15	42±15	45±18	0.021[#]
Physical performance parameters					
Wmax (Watts) [k]	70±34	53±25	68±34	82±34	<0.001[#,†]
VO_2Max (ml/min/kg) [l]	13.8 (11.8-16.8)	12.5 (10.7-13.7)	13.4 (11.8-16.1)	16.1 (13.6-18.3)	<0.001[#,†]
VO_2Max (% predicted) [l]	58 (48-67)	52 (45-63)	57 (47-66)	61 (50-74)	0.008[#]
CWRT time (s) [m]	300 (187-495)	224 (165-290)	294 (180-433)	327 (218-600)	0.028[#]
MVC (Nm) [n]	117±38	113±30	120±42	114±37	0.414
MVC (% predicted) [n]	63±15	64±14	64±16	62±13	0.445
Physical activity (steps/day) [o]	3480 (2386-5168)	2651 (1517–3923)	3228 (2388-4752)	4732 (2934-6097)	<0.001[#,†]
Physical activity (average PAL) [p]	1.34 (1.29-1.42)	1.30 (1.26-1.35)	1.34 (1.29-1.41)	1.38 (1.31-1.48)	<0.001[#,†]

*Data is presented as mean±SD, median (IQR 25-75%) or number of patients (percentage), as appropriate. * indicates a significant difference after Bonferroni post-hoc correction between group 1 and group 2, # indicates a significant difference after Bonferroni post-hoc correction between group 1 and group 3, † indicates a significant difference after Bonferroni post-hoc correction between group 2 and group 3. Alphabetic characters in superscript indicate a sample size deviant from n=245 (group 1: 41, group 2: 124, group 3: 80) with the following: a. n=226 (37, 116, 73), b. n=209 (37, 101, 71), c. n= 222 (39, 112, 71), d. n=214 (37, 106, 71), e. n=221 (39, 111, 71), f. n=223 (39, 112, 72), g. n=240 (41, 121, 78), h. n=235 (39, 120, 76), i. n=236 (39, 121, 76), j. n=228 (39, 114, 75), k. n=203 (33, 104, 66), l. n=194 (33, 97, 64), m. n=154 (21, 78, 55), n. n=226 (40, 112, 74), o. n=242 (40, 123, 79), p. n=241 (40, 122, 79). Definitions of abbreviations: BMI, Body Mass Index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; CIS, Checklist Individual Strength; CWRT, constant work rate cycle test; DL_{CO}, single-breath carbon monoxide diffusion capacity; FEV_1,*

forced expiratory volume in 1 second; FFMI, fat-free mass index; FRC, functional residual capacity; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council; MVC, maximal voluntary contraction; PAL, physical activity level; TLC, total lung capacity: Tlim, tolerated duration; RV, residual volume; VO_2max, maximal oxygen uptake; Wmax, maximal workload.

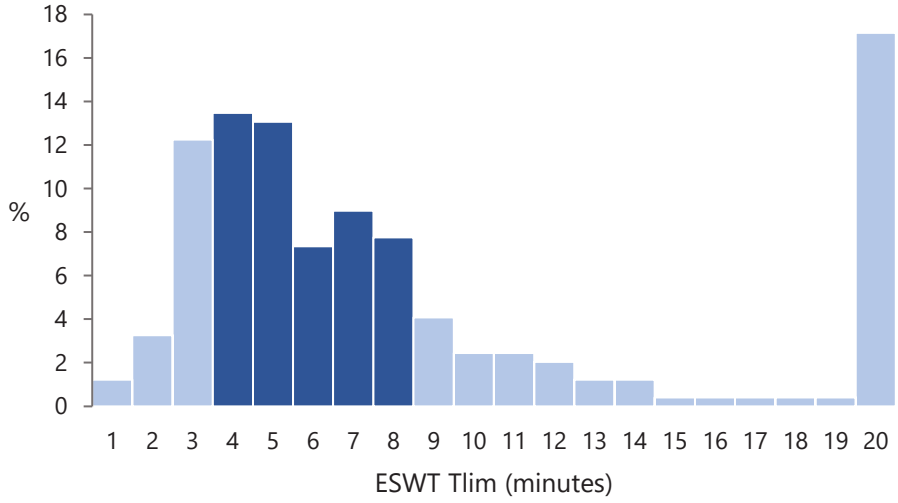

Figure 2. The distribution of patients according to the ESWT Tlim per minute.

Pulmonary function and physical performance parameters

Pulmonary function of patients in group 2 were similar to patients in group 1 and 3, except for a lower FEV_1 (L) in group 1 than group 2 (P<0.001). Measures of physical performance, like maximal exercise capacity, muscle strength and physical activity were comparable between patient in group 1 and 2. Patients in group 3 had a better physical capacity (Wmax and VO_2max) and were more physically active (steps/day and average PAL) in comparison to group 2 (all P-values <0.001) (Table 1).

ISWT performance parameters

The median ISWT distance of all patients was 280 (200-390) meters. Group 1, 2 and 3 walked 205 (173-328) meters, 285 (200-380) meters and 320 (213-438) meters, respectively. Patients in group 1 desaturated more during the ISWT than group 2 (all P-values <0.001). Furthermore, these patients had a higher rest and maximal dyspnoea Borg score in comparison to group 2 (P<0.001, P=0.011, respectively). Although the HR before and at the end of the ISWT was comparable between the three groups, the maximal HR during ISWT in ratio to the maximal HR reached during CPET ($HRmax_{ISWT}$/$HRmax_{CPET}$) was lower in patients from group 3 than in patients from group 2 (P=0.002). Other ISWT performance parameters were not significantly different for group 1 and 3 in comparison to group 2 (Table 2).

ESWT performance parameters

Patients with an ESWT Tlim >8 minutes had a higher maximal oxygen saturation and higher resting and maximal dyspnoea Borg score during the ESWT than patients from group 2 (all P-values <0.001). Besides speed and time, other ESWT performance parameters of patients from group 1 and 3 were comparable to group 2 (Supplemental Table 1).

Table 2. ISWT performance parameters of the whole group and the three subgroups based on tolerated duration during the ESWT.

	All patients with COPD (n=245)	Group 1 (n=41)	Group 2 (n=124)	Group 3 (n=80)	
Variables		**Tlim <3 min**	**Tlim = 3-8 min**	**Tlim >8 min**	**P-value**
Distance (m) [a]	280 (200-390)	205 (173-328)	285 (200-380)	320 (213-438)	0.004[#]
Distance (% predicted) [b]	45 (30-58)	33 (25-49)	47 (29-58)	47 (34-64)	0.015[#]
Speed (km/h)	4.8 (4.2-5.4)	4.2 (3.6-5.1)	4.8 (4.2-5.4)	4.8 (4.2-6.0)	0.029[#]
SpO_2 rest (%)	96 (94-97)	95 (93-96)	96 (94-97)	96 (94-98)	0.146
SpO_2 at max (%)	89 (85-94)	85 (82-91)	90 (85-94)	90 (87-94)	0.001[*,#]
SpO_2 delta (max-rest, %)	-7 (-11- -2)	-9 (-13- -6)	-6 (-11- -2)	-5 (-9- -1)	0.002[*,#]
HR rest (bpm) [c]	84±12	86±12	84±13	83±10	0.632
HR at max (bpm) [c]	113±19	114±16	114±21	110±17	0.507
$HRmax_{ISWT}/HRmax_{CPET}$ [d]	92±14	97±10	94±17	87±11	0.002[#,†]
HR delta (max-rest, bpm) [c]	29±15	27±11	30±17	27±15	0.379
Borg score dyspnoea rest	2 (1-3)	2 (1-3)	2 (1-3)	1 (0-2)	0.058
Borg score dyspnoea max	5 (4-7)	7 (5-7)	5 (4-7)	5 (3-7)	<0.001[*,#]
Borg score dyspnoea delta	3 (2-5)	5 (3-6)	3 (2-5)	3 (2-5)	0.011[*,#]
Borg score fatigue rest	2 (1-3)	3 (1-5)	2 (1-3)	2 (1-4)	0.221
Borg score leg fatigue max	5 (3-7)	5 (3-7)	5 (3-7)	4 (3-6)	0.238
Borg score leg fatigue delta	2 (1-4)	3 (1-5)	2 (1-4)	2 (0-3)	0.065

*Data is presented as mean±SD or median (IQR 25-75%), as appropriate. * indicates a significant difference after Bonferroni post-hoc correction between group 1 and group 2, # indicates a significant difference after Bonferroni post-hoc correction between group 1 and group 3, † indicates a significant difference after Bonferroni post-hoc correction between group 2 and group 3. Alphabetic characters in superscript indicate a sample size deviant from n=245 (group 1: 41, group 2: 124, group 3: 80) with the following: a. n=242 (40, 122, 80), b. n=243 (40, 123, 80), c. n=184 (27, 91, 66), d. n=167 (25, 80, 62). Definitions of abbreviations: HR, heartrate; $HRmax_{ISWT}/HRmax_{CPET}$, maximal HR of the incremental shuttle walk test relative to the maximal HR during the cardiopulmonary exercise test; SpO_2, peripheral capillary oxygen saturation; Tlim, tolerated duration.*

Predictors of ESWT time

Univariate linear regression models that were used to explain ESWT Tlim variability are documented in Supplemental Tables 2 and 3. Age, BMI, mMRC and several variables of pulmonary function (FEV_1, Tiffeneau index, FRC, FRC/TLC, RV/TLC and DL_{CO}), physical performance (Wmax, VO_2max, CWRT time, steps/day and average PAL) and ISWT performance (distance, speed, SpO_2, $HRmax_{ISWT}/HRmax_{CPET}$ and Borg scores for dyspnoea and leg fatigue) were significant explanatory variables of ESWT Tlim in univariate analyses.

In a multivariate linear regression model, BMI, VO_2max, CWRT time, average PAL, ISWT speed, dyspnoea Borg score at rest and increase of leg fatigue Borg score during ISWT were independent predictors of ESWT Tlim (Supplemental Table 4). This model explained ~30% of the variability in ESWT Tlim (R^2=0.297, P<0.001).

DISCUSSION

The current study confirmed that patients with COPD display a large variability in ESWT Tlim, even though ESWT was performed at a fixed percentage of pre-determined maximal walking speed. To our knowledge, this is the first study that determined possible predictors of ESWT Tlim in patients with COPD. We found that BMI, VO_2max, CWRT time, average PAL, ISWT speed, dyspnoea Borg score at rest and increase of leg fatigue Borg score during ISWT are independent predictors of ESWT Tlim. However, collectively these determinants can only explain ~30% of ESWT Tlim variability.

ESWT Tlim highly variable

A large interindividual variability in ESWT Tlim was illustrated by the notion that half of the patients with COPD performed the ESWT outside the desired duration of 3-8 minutes. Furthermore, a required termination of the test was needed in 17% of the patients as they reached the maximum test duration of 20 minutes, but probably could have walked even longer. This large interindividual variability is in accordance with a recent study of Maltais et al., who investigated the responsiveness of the ESWT to bronchodilation.[13] In their analysis the authors were urged to exclude patients that had a baseline ESWT Tlim of more than 15 minutes to allow measurable room for improvement on a post-intervention ESWT. So, high interindividual variability in ESWT Tlim requires a larger number of participants in clinical studies to detect an effect of interventions. The interpretation of intervention efficacy is even more complicated as the potential effect size (i.e., post- – pre-intervention) of ESWT Tlim depends on the pre-intervention ESWT Tlim due to the hyperbolic nature of the load-duration relationship.[12] Therefore, in a population with a high interindividual variability in ESWT Tlim, individual effects of interventions are difficult to compare.[12, 14, 15] The best solution to reduce this variability is to determine the load-duration relationship in every individual. However, this is clinically impractical because it requires the completion of several ESWT tests at various intensities. Another possibility is to perform a second ESWT at an adjusted pace in patients with an ESWT Tlim <3 or >8 minutes. However, the size of the adjustment in pace has not been determined yet and a second ESWT is not always possible due to practical reasons like time constraints. Therefore, it is important to search for other

possibilities to reduce the variability in ESWT Tlim. One option would be to better predict the ESWT Tlim prior to its performance in order to individually adjust the ESWT pace with clinical available measures. Therefore, this study further investigated correlates of ESWT Tlim variability.

Pulmonary function and physical performance parameters

Patients performing the ESWT longer than 8 minutes had a higher physical capacity and activity in comparison to group 2. In addition, exercise tolerance obtained by CWRT was also positively related to the ESWT Tlim. On the other hand, patients that could not sustain the ESWT for at least 3 minutes, were characterized by a lower FEV_1 (L) than patients in group 2 and several pulmonary function measures were negatively associated with ESWT Tlim. Pulmonary dysfunction is a well-known contributor to exercise intolerance in patients with COPD.[10, 11] In short, ventilatory capacity is limited by airflow obstruction and hyperinflation, which may even exacerbate during exercise. On the other hand, ventilatory demand in patients with COPD may be increased as a result of abnormal pulmonary gas exchange, increased work of the respiratory muscles and early lactate production in the peripheral muscles.[16, 37-40] This leads to increased sensations of dyspnoea during exercise and explains why the severity of pulmonary dysfunction is related to the ability to sustain a certain exercise load.[37, 38] However, it should be stressed that the load of the ESWT is normalized for maximal exercise capacity, as ESWT pace is individually set at 85% of maximal ISWT pace. Despite this normalization, pulmonary function, physical capacity and physical activity are still related to the time patients can sustain this individually assessed pace. This suggests that the load-duration relationship is affected by these measures. The load-duration relation is described by two parameters; the critical load and the curvature constant.[10-12] Neder et al. previously reported that both parameters are reduced in patients with COPD in comparison to healthy controls.[11] The results of the current study suggest that even within the COPD population, critical load and the curvature constant might be influenced by pulmonary function, physical capacity and physical activity.

Thus, the current findings suggest that, in addition to maximal ISWT pace, measures of pulmonary function, physical capacity and physical activity, if clinically available, might be helpful to more adequately set ESWT pace. It appears that patients with more severe airway obstruction should be set at paces slower than 85% of maximal pace and patients with higher physical capacity and activity levels at paces faster than 85% of maximal pace. However, exact cut-off values and sizes of adjustment should be explored in future studies.

ISWT performance parameters

Because ESWT pace is based on maximal ISWT speed, it is essential that the ISWT is performed with maximal effort and using a standardized operating procedure. Therefore, we investigated performance measures obtained during ISWT. In contrast to healthy individuals, the exercise capacity of most patients with COPD is not limited by cardiac output.[37] So maximum HR during ISWT cannot be used to establish maximal effort in patient with COPD. Accordingly, we examined ISWT HR in ratio to the maximum HR obtained during CPET, i.e., $HRmax_{ISWT}/HRmax_{CPET}$. We found that this ratio was significantly lower in patients that displayed an ESWT Tlim >8 minutes (group 3). Furthermore, the ratio was negatively associated with ESWT Tlim. This indicates that some patients with an ESWT time >8 minutes might have performed submaximally on their ISWT. A longer ESWT Tlim was also associated with a reduced increase of perceived leg fatigue during ISWT. Although this is a subjective measure, it is in line with a submaximal effort during the ISWT. A more objective indication of maximal effort can be provided by additional physiological measures like minute ventilation, oxygen consumption and/or blood lactate values,[31] but these would make the ISWT less accessible and more expensive. Our data suggest that if maximal attained HR during CPET is available it can be used together with simple non-invasive measurement of HR during ISWT to provide an estimation of ISWT effort.

Additionally, patients with a shorter ESWT Tlim desaturated more during the ISWT than patients with a longer ESWT Tlim, which was also reported during the ESWT. This might suggest that patients who desaturate more during the ISWT should perform the ESWT at a lower relative load than 85%.

Predicting ESWT

Because our data showed that several clinically obtained measures significantly correlated with ESWT Tlim, we further investigated if a model could be built to predict ESWT Tlim. Based on a multivariate linear regression model, BMI, VO_2max, CWRT time, physical activity, ISWT speed, dyspnoea Borg score at rest and delta leg fatigue Borg score during ISWT were identified as independent predictors of ESWT Tlim. Although each of these parameters significantly contributes to ESWT Tlim variability, the total explained variance is only ~30%. Therefore, it is important to evaluate additional factors that might be associated with ESWT Tlim. For example, dynamic hyperinflation and reduced leg muscle endurance are known to frequently occur in patients with COPD and affect exercise tolerance independent of the severity of pulmonary dysfunction.[2, 39, 41-43] Further research is necessary to assess if these or other factors could improve the accuracy of predicting ESWT Tlim. Eventually, a proper prediction model with clinical available measures might help clinicians

to identify patients that are expected to reach an ESWT Tlim outside the desired timeframe of 3-8 minutes[44] and to decide if ESWT pace should be set a different level than 85% of maximal ISWT pace.

Study limitations

In our design ESWT pace was based on patients' maximal pace obtained from one ISWT. Because Dyer et al. reported a learning effect in a second ISWT,[45] two ISWT tests are recommended when the ISWT is used to measure change over time or interventions.[19] However, when ISWT is only used to set ESWT pace, one test has been postulated to be sufficient.[46] Although we expect that performing two ISWT's prior to ESWT might reduce the interindividual variability, it does not necessarily eliminate the need of a second ESWT in all patients. Furthermore, two ISWT's would increase the amount of tests in all patients, while our data show that with one ISWT half of the patients perform their ESWT within the desired duration of 3-8 minutes.

CONCLUSIONS

This study confirmed a large interindividual variability in ESWT Tlim in patients with COPD, as only half of the patients reached an ESWT Tlim within the desired duration of 3-8 minutes. Our data showed that next to maximal ISWT speed, other ISWT performance measures as well as clinically available measures of pulmonary function, physical capacity and physical activity were independent determinants of ESWT Tlim. Nevertheless, these determinants could only explain ~30% of its variability. Therefore, future studies are needed to establish whether these and additional factors can be used to better adjust individual ESWT pace in order to reduce ESWT Tlim variability.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. ESWT parameters of the whole group and the three subgroups based on tolerated duration during the ESWT.

	All patients with COPD (n=245)	Group 1 (n=41)	Group 2 (n=124)	Group 3 (n=80)	
Variables		**Tlim <3 min**	**Tlim = 3-8 min**	**Tlim >8 min**	**P-value**
Speed (km/h)	4.1 (3.6-4.6)	3.6 (3.1-4.4)	4.1 (3.6-4.6)	4.1 (3.7-5.1)	0.007[#]
Time (s)	360 (221-617)	147 (118-165)	291 (239-383)	1200 (623-1200)	<0.001[*,#,†]
SpO_2 rest (%) [a]	96 (94-97)	95 (94-97)	96 (94-97)	96 (95-98)	0.106
SpO_2 at max (%) [b]	90 (85-94)	87 (84-91)	89 (84-94)	92 (89-95)	<0.001[#,†]
SpO_2 delta (max-rest, %) [c]	-5 (-10- -2)	-8 (-12- -5)	-5 (-11- -2)	-3 (-8- -1)	<0.001[#,†]
HR rest (bpm) [d]	83 (73-91)	86 (78-92)	82 (73-90)	83 (72-92	0.351
HR at max (bpm) [e]	113 (100-122)	108 (100-120)	115 (100-122)	113 (100-125)	0.574
$HRmax_{ESWT}/HRmax_{ISWT}$ (%) [e]	99 (93-106)	97 (89-103)	98 (92-104)	103 (96-111)	0.027
HR delta (max-rest, bpm) [f]	29 (20-39)	26 (18-33)	29 (19-40)	31 (23-40)	0.188
Borg score dyspnoea rest [g]	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-2)	<0.001[#,†]
Borg score dyspnoea max [h]	5 (4-7)	6 (5-8)	5 (4-7)	4 (3-6)	<0.001[#,†]
Borg score dyspnoea delta [g]	3 (2-5)	4 (3-5)	4 (2-5)	3 (2-5)	0.140
Borg score leg fatigue rest [g]	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	0.127
Borg score leg fatigue max [h]	5 (3-6)	5 (4-7)	5 (3-6)	4 (3-5)	0.119
Borg score leg fatigue delta [g]	3 (1-4)	3 (2-4)	2 (1-4)	3 (1-4)	0.285

*Data is presented as median (IQR 25-75%). * indicates a significant difference after Bonferroni post-hoc correction between group 1 and group 2, # indicates a significant difference after Bonferroni post-hoc correction between group 1 and group 3, † indicates a significant difference after Bonferroni post-hoc correction between group 2 and group 3. Alphabetic characters in superscript indicate a sample size deviant from n=245 (group 1: 41, group 2: 124, group 3: 80) with the following: a. n=236 (41, 123, 72), b. n=236 (41, 122, 73), c. n=235 (41, 122, 72), d. n=182 (27, 90, 65), e. n=181 (27, 88, 66), f. n=180 (27, 88, 65), g. n=237 (41, 123, 73), h. n=238 (41, 124, 73). Abbreviations: HR, heartrate; $HRmax_{ESWT}/HRmax_{ISWT}$, maximal HR of the endurance shuttle walk test relative to the maximal HR during the incremental shuttle walk test; SpO_2, peripheral capillary oxygen saturation; Tlim, tolerated duration.*

Supplemental Table 2. Univariate linear regression models for the subject characteristics, severity of complaints, pulmonary function and physical performance with the tolerated duration on the ESWT.

Variables	R^2	Df	Beta	CI	P-value
Gender (male (%))	0.003	243	37.847	-55.732- 131.426	0.426
Age (years)	0.030	243	-8.296	-14.235- -2.358	0.006
BMI (kg/m^2)	0.021	243	-9.499	-17.639- -1.359	0.022
CCI	0.001	225	7.599	-32.123- 47.321	0.707
FFMI	0.019	207	-20.585	-40.896- -0.275	0.047
Severity of complaints					
mMRC score	0.054	220	-73.405	-114.311- -32.499	<0.001
CAT score	0.000	212	-0.250	-7.503- 7.004	0.946
HADS anxiety score	0.000	219	-0.597	-12.280- 11.086	0.920
HADS depression score	0.001	219	2.357	-10.608- 15.322	0.720
CIS fatigue score	0.000	221	0.246	-6.511- 7.003	0.943
Pulmonary parameters					
FEV_1 (L)	0.019	238	94.852	8.328- 181.376	0.032
FEV_1 (% predicted)	0.020	238	3.361	0.377- 6.345	0.027
Tiffeneau index (%)	0.020	238	4.487	0.510- 8.464	0.027
FRC (% predicted)	0.007	233	-0.830	-2.067- 0.408	0.188
RV (% predicted)	0.001	234	-0.264	-1.152- 0.623	0.558
TLC (% predicted)	0.002	234	-0.831	-3.385- 1.723	0.522
FRC/TLC (%)	0.018	233	-5.319	-10.373- -0.265	0.039
RV/TLC (%)	0.011	234	-3.826	-8.489- 0.837	0.107
DL_{CO} (mL/mmHg/min)	0.009	226	22.554	-7.964- 53.071	0.147
DL_{CO} (% predicted)	0.011	226	2.404	-0.624- 5.432	0.119
Physical parameters					
Wmax (Watt)	0.054	201	2.534	1.066- 4.003	0.001
VO_2Max (ml/min/kg)	0.120	192	32.856	20.162- 45.551	<0.001
VO_2Max (% predicted)	0.076	192	6.765	3.411- 10.118	<0.001
CWRT time (s)	0.034	171	0.238	0.046- 0.430	0.015
MVC (Nm)	0.004	224	-0.645	-1.914- 0.624	0.317
MVC (% predicted)	0.001	224	-0.803	-4.170- 2.564	0.639
Physical activity (steps/day)	0.059	240	0.037	0.018- 0.056	<0.001
Physical activity (average PAL)	0.060	239	813.292	401.348- 1225.235	<0.001

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CCI, Charlson Comorbidity Index; CI, confidence interval; CIS, checklist individual strength; CWRT, constant work rate cycle test; Df, degrees of freedom; DL_{CO}, single-breath carbon monoxide diffusion capacity; FEV_1, forced expiratory volume in 1 second; FFMI, fat-free mass index; FRC, functional residual capacity; HADS, hospital anxiety and depression scale; mMRC, modified medical research council; MVC, maximal voluntary contraction; PAL, physical activity level; TLC, total lung capacity; RV, residual volume; VO_2max, maximal oxygen uptake; Wmax, maximal workload.

Supplemental Table 3. Univariate linear regression models for the ISWT parameters with the tolerated duration on the ESWT.

Variables	R^2	Df	Beta	CI	P-value
Distance (m)	0.029	240	0.449	0.121-0.778	0.008
Distance (% predicted)	0.033	241	1.814	0.561- 3.067	0.005
Speed (km/h)	0.022	243	53.959	8.110-99.808	0.021
SpO_2 rest (%)	0.009	243	15.188	-5.355- 35.731	0.147
SpO_2 max (%)	0.022	243	8.207	1.253-15.161	0.021
SpO_2 delta (max-rest, %)	0.017	243	8.396	0.440-16.353	0.039
HR rest (bpm)	0.003	182	-1.781	-6.555-2.992	0.463
HR max (bpm)	0.009	182	-1.910	-4.857-1.038	0.203
$HRmax_{ISWT}/HRmax_{CPET}$	0.066	165	-6.862	-10.835- -2.889	0.001
HR delta (max-rest, bpm)	0.005	182	-1.821	-5.420-1.777	0.319
Borg score dyspnoea rest	0.021	243	-37.866	-70.270- -5.462	0.022
Borg score dyspnoea max	0.051	243	-40.123	-62.053- -18.192	<0.001
Borg score dyspnoea delta	0.014	243	-20.618	-42.132- 0.897	0.060
Borg score fatigue rest	0.002	243	8.860	-16.147-33.867	0.486
Borg score leg fatigue max	0.019	243	-23.227	-44.285- -2.168	0.031
Borg score leg fatigue delta	0.029	243	-27.962	-48.317- -7.607	0.007

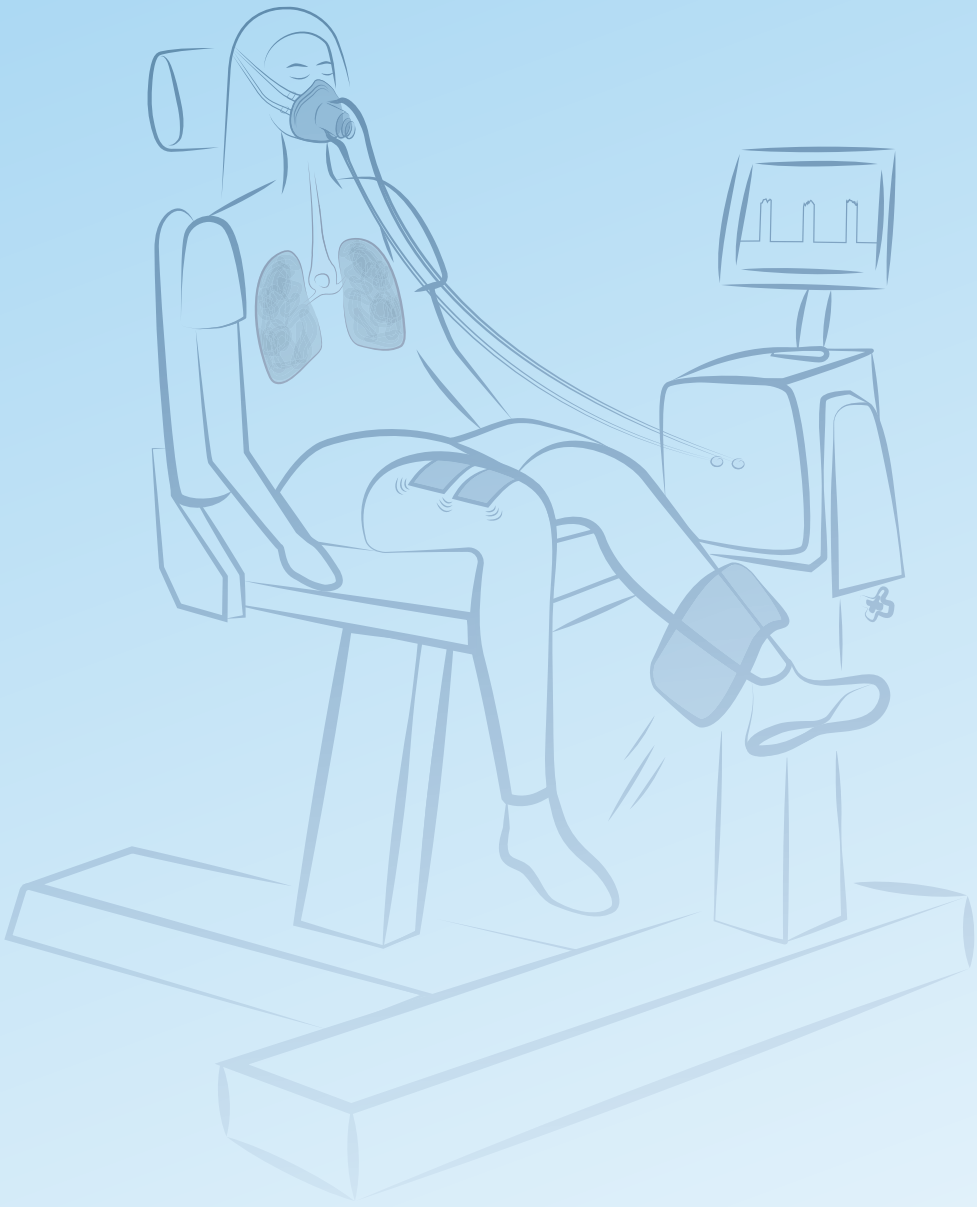
Abbreviations: CI, confidence interval; Df, degrees of freedom; HR, heartrate; $HRmax_{ISWT}/HRmax_{CPET}$, maximal HR of the incremental shuttle walk test relative to the maximal HR during the cardiopulmonary exercise test; SpO_2, peripheral capillary oxygen saturation.

Supplemental Table 4. Multivariate linear regression analysis to predict tolerated duration on the ESWT.

Variables	Unstandardized B	95% CI for B	P-value
(Constant)	160.235	-601.759-922.226	0.678
BMI (kg/m^2)	-12.312	-23.225- -1.339	0.027
VO_2max (ml/min/kg)	34.907	16.077-53.737	<0.001
CWRT time (s)	0.219	0.018-0.420	0.033
Physical activity (average PAL)	576.920	38.403-1115.436	0.036
ISWT speed	-105.806	-182.810- -28.802	0.007
ISWT Borg score rest dyspnoe	-65.736	-113.438- -18.033	0.007
ISWT Borg score delta leg fatigue	-32.033	-57.387- -6.680	0.014

Abbreviations: B, beta; BMI, body mass index; CI, confidence interval; CWRT, constant work rate cycle test; ISWT, incremental shuttle walk test; PAL, physical activity level; VO_2max, maximal oxygen uptake.

PART III: PERIPHERAL MUSCLE FUNCTION



CHAPTER 6

Isokinetic testing of quadriceps function in COPD: Feasibility, responsiveness, and minimal important differences in patients undergoing pulmonary rehabilitation

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ABSTRACT

Background: Isokinetic testing of peripheral muscle function is valid and reliable in patients with chronic obstructive pulmonary disease (COPD).

Objective: To evaluate whether and to what extent isokinetic testing of quadriceps function meets pre-defined test criteria in patients with COPD; to determine the response to pulmonary rehabilitation (PR), and to calculate minimal important differences (MIDs) of isokinetic quadriceps function.

Methods: Retrospective analysis of 2033 patients with COPD (age: 65±9 years, body mass index: 26±6 kg/m^2, FEV_1: 49±22% predicted) who followed a comprehensive PR program. Pre and post PR isokinetic quadriceps function was assessed with 30 maximal extension-flexion contractions at an angular speed of 90°/s on a computerized dynamometer. The chosen anchors were 6-minute walk test and COPD assessment test.

Results: Pre PR, 27% of the patients performed the isokinetic test incorrectly. In male and female patients with a correct pre and post PR isokinetic test, peak torque (Δ=10±13 Nm or 9% and Δ=7±9 Nm or 10%, respectively) and total work (Δ=263±270 J or 14% and Δ=198±190 J or 15%, respectively) improved significantly. There was no change in work fatigue index following PR. Using distribution-based calculations, MID estimates for peak torque and total work ranged between 6-7 Nm and 97-135 J in males and between 4-5 Nm and 62-99 J in females.

Conclusions: Based on the current test criteria, 3 in 4 patients with COPD performed the isokinetic quadriceps test correctly during baseline PR assessment. Furthermore, peak torque and total work, but not work fatigue index, were responsive to PR and sex-specific MIDs were established.

INTRODUCTION

Peripheral muscle dysfunction is a prominent component of physical impairment and disability[1] and has been associated with impaired health status, increased utilization of healthcare resources, and mortality in patients with chronic obstructive pulmonary disease (COPD).[2-4] Besides muscle strength, it seems reasonable to evaluate additional muscular features to obtain a more comprehensive overview of skeletal muscle function. One of these aspects is muscle endurance, which represents the muscle's ability to sustain a given task over time.[5] Quadriceps endurance is more impaired in patients with COPD than quadriceps strength.[6, 7] This impairment cannot be predicted based on the degree of airflow limitation or maximal muscle strength[8] and seems to be more closely related to exercise capacity and daily activities than muscle strength.[9, 10] In addition, recent studies reported significant correlations between muscle endurance and muscle oxidative profile.[11, 12] This provides a strong rationale for an in-depth assessment of quadriceps endurance in patients with COPD.

Isokinetic, isometric, and isotonic approaches are available to volitionally assess quadriceps endurance in patients with COPD,[2, 7, 13] amongst which isokinetic testing is most common.[13] Advantages of isokinetic methods are the dynamic evaluation of muscle function while controlling for angular velocities, amplitude, and duration of movement, and its high reliability.[14, 15] This latter especially applies when using a computerized dynamometer, provided that 3 pre-defined criteria of correct test performance are met: completion of all (mostly 30) repetitions, peak torque reached within the first 5 repetitions, and presence of work fatigue.[15, 16] However, in patients with COPD, these test criteria have only been validated in relatively small studies and it remains unclear whether and to what extent these criteria are met in clinical settings. In addition, differences in clinical characteristics between patients with and without a correct test performance are unknown.

Pulmonary rehabilitation (PR) is an effective therapy for patients with COPD.[17] But studies regarding the responsiveness of isokinetic quadriceps endurance and minimal important differences (MIDs) of isokinetic quadriceps strength and endurance following PR are still lacking. Hence, an extensive evaluation regarding isokinetic quadriceps test performance in a PR centre is essential.[18]

Therefore, the main objectives of the current study were: 1) to evaluate whether and to what extent the isokinetic testing of quadriceps function meets the pre-defined test criteria (i.e., feasibility) in patients with COPD assessed pre and post PR; 2) to assess differences in clinical characteristics between patients with a correct

and incorrect isokinetic test performance; 3) to determine the response to PR and calculate MIDs of isokinetic quadriceps function.

METHODS

A retrospective analysis was performed on pseudonymized clinical data of 3152 patients with a diagnosis of COPD.[19] These patients were referred for a comprehensive PR program by a chest physician in CIRO (Horn, the Netherlands)[20] between June 2013 and August 2019. Data during the PR program were systematically collected as part of standard care. At the start of the PR program, patients received a brochure entitled 'Privacy regulations CIRO'. One of the paragraphs stated that their information could be used (pseudonymized) for scientific research and statistics and that signing informed consent was not necessary. However, patients had the opportunity to fill in a form when they objected. The information of patients who did not object was entered into a large database.

For this study, individuals younger than 40 years of age were excluded and only data from the first PR program were used when participating on multiple occasions over time. The medical ethical committee informed the authors that the Medical Research Involving Human Subjects Act (WMO) does not apply to this retrospective study and approved the use of data for this study (METC 2019-1384). The Board of Directors of CIRO approved the use of pseudonymized patient records.

Isokinetic quadriceps testing

The isokinetic quadriceps tests were performed on a computerized dynamometer (System 3, Biodex Inc., Shirley, NY, USA) at baseline (pre PR) and post PR. The patients were positioned on the dynamometer chair with hip and knee placed at a 90° angle and the lever arm attached as described by Frykholm et al.[16] Extraneous movement during the test was reduced with the use of straps across the chest, waist, thigh, and ankle of the tested leg, and range of motion (ROM) was full knee extension to 90° flexion. Furthermore, participants were instructed to keep their arms crossed over their chest. A warm-up protocol was used in which the patient performed 5 isokinetic contractions with a progressively higher force production, followed by 2 minutes of rest. The isokinetic protocol consisted of 30 contractions at an angular velocity of 90°/s with maximal effort during extension and passive (submaximal) flexion. Strong verbal encouragement was provided during all repetitions.[16] The main outcomes were: peak torque in newton-meter (Nm) and as percentage of predicted values (based on reference values of Borges et al.[21]), total work of all completed

repetitions reported in Joules (J), and work fatigue index$_{10}$ and index$_5$ as percentages ($(\frac{\text{work first 5 or 10 repetitions} - \text{work last 5 or 10 repetitions}}{\text{work first 5 or 10 repetitions}}) * 100\%$, respectively; Supplemental Figure 1).[15] The following criteria for correct execution of isokinetic quadriceps testing were applied: completion of all 30 repetitions, peak torque within the first 5 repetitions, and presence of work fatigue (positive work fatigue index$_{10}$).[15, 16]

Other assessments

All clinical characteristics were evaluated during a comprehensive baseline assessment at the start of PR. Demographic data consisted of age, sex, body mass index (BMI), smoking status (pack-years), and use of long-term oxygen therapy. Additionally, pulmonary function was determined using spirometry, static lung volume measurement, and transfer factor for carbon monoxide (MasterScreen PFT/Body; Jaeger, Würzburg, Germany) following the European Respiratory Society (ERS) guidelines.[22, 23] Disease severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[19] and modified Medical Research Council dyspnoea scores were obtained with a cut-off value of ≥2 to classify patients as highly symptomatic.[24] Dual-energy x-ray absorptiometry (Lunar iDXA; DEXAtech Benelux BV, Ridderkerk, the Netherlands) was performed to assess fat-free mass and to calculate the fat-free mass index (fat-free mass divided by height squared).[25] Symptoms of anxiety and depression were determined using the Hospital Anxiety and Depression Scale with a cut-off value of ≥10 points.[26] Respiratory muscle strength was obtained using maximal inspiratory and expiratory pressures.[27] The constant work rate cycle test was performed on an ergometer (Ergoselect; Ergoline, Bitz, Germany) at 75% of the maximal workload (obtained by an incremental cardiopulmonary exercise test[28]) to determine exercise tolerance.[29] Isotonic peripheral muscle strength was evaluated using 1-repetition maximum leg press and leg extension on standard training apparatus.

Exercise capacity (6-minute walk distance; 6MWD) and health status (COPD Assessment Test; CAT) were determined at baseline and post PR. The 6MWD was performed in duplicate at baseline and once during post PR assessment, following the American Thoracic Society (ATS) guidelines[30, 31] and using the reference values from Troosters et al.[32] on a 30-meter course. [33] A threshold of ≥18 points was used for the CAT[34] to identify patients as highly symptomatic.

Pulmonary rehabilitation

Patients followed a comprehensive inpatient PR program at CIRO (Horn, the Netherlands) or outpatient PR program within the CIRO+ rehabilitation network based on the latest PR statement of ATS/ERS.[20] The patient-tailored program

consisted of 40 sessions and was supervised by an interdisciplinary team consisting of a chest physician, respiratory nurses, dieticians, occupational therapists, physical therapists, psychologists, and social workers. The cornerstone of the PR program was physical exercise training including resistance training, aerobic training, flexibility exercises, unsupported arm exercises, and daily supervised 30-minute outdoor walks. Additionally, occupational therapy, guidance in medication uses and adherence, psychosocial counselling, nutritional advice, education, and/or exacerbation management were provided to the patients if indicated.

Resistance training was performed once per day to improve peripheral muscle strength. Patients performed 3 to 4 exercises per training focusing on either upper or lower extremity (varying per day). The initial load of the exercises was individually set at 60% of 1-repetition maximum and was aimed to increase progressively by 3-5% each week. A total of 4 sets with 8 repetitions were performed for each exercise with a 2-minute rest period between sets.

Aerobic training included 1 morning session of treadmill walking and 1 afternoon session of stationary cycling (or reversed). The initial intensity of walking and cycling was individually based on 6MWD and maximum workload obtained during the incremental cardiopulmonary exercise test, respectively. Borg scores for dyspnoea and fatigue (target score of 4-6) were used to make weekly adjustments to the intensity. The type of aerobic training sessions was either (intensive or extensive) interval session or endurance/recovery (both performed once per day). The intensity, duration, rest period, and progression varied for each of these types and are described in the supplementary material (Supplemental Table 1). Patients who were unable to perform aerobic training received lower-limb high-frequency neuromuscular electrical stimulation (NMES) twice per day. If patients could only perform one aerobic training session per day, they received 1 interval training and 1 NMES session per day.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, USA). Descriptive data were presented as mean±SD unless stated otherwise. A priori, the level of significance was set at $P<0.05$.

Between-group differences were tested using an unpaired t-test for continuous variables and a chi-square test for categorical variables, as appropriate. Responsiveness of isokinetic quadriceps function to PR was tested using a paired sample t-test. MID estimates for isokinetic quadriceps function variables that were

responsive to PR were determined using a combination of distribution-based and anchor-based techniques.[35] Three distribution-based techniques were applied: standard error of measurement (SEM)=$SD_{baseline}$ * $\sqrt{1 - \text{intraclass correlation coefficient}}$; empirical rule effect size=0.08 * 6 * SD_{delta}; Cohen's effect size=0.5 * $SD_{delta.}$[36] Test-retest intraclass correlation coefficients were derived from previous studies in patients with COPD (ICCs: peak torque (Nm)=0.97,[15] total work (J)=0.98,[15, 16] and work fatigue $index_{10}$ (%)=0.64-0.92).[15] To perform the anchor-based method, a minimal correlation of 0.3 between the change in pre-determined anchors (CAT and 6MWD) and the change in muscle function was required to subsequently perform a linear regression and receiver operating characteristic (ROC) analysis.[35, 37] For the ROC analysis, an area under the curve of more than 0.7 was accepted as meaningful.[35, 37] Furthermore, the data were stratified for sex as several studies have reported the influence of sex on muscle function.[38, 39]

RESULTS

Characteristics

A flowchart illustrating how many patients performed the isokinetic quadriceps test and which criteria were assessed in terms of a correct performance at baseline is shown in Figure 1. Pre-rehabilitation isokinetic muscle test data were available from 2033 of the 3152 patients and used for further analyses. These patients were 65±9 years old, had a BMI of 26±6 kg/m^2, and forced expiratory volume in one second of 49±22% predicted (Supplemental Table 2).

Test performance criteria pre PR

Of all 2033 patients who performed the isokinetic quadriceps test at baseline and had complete data available, 193 patients (10%) were not able to complete all 30 repetitions due to various reasons (i.e., dyspnoea, fatigue; Figure 1). The second criterion, to reach the maximal torque value within the first 5 repetitions, was not observed in 328 patients (16%). Seventy percent of these patients obtained their peak torque between repetition 6 and 10, while 5% produced their peak torque between repetition 20 and 30. The third criterion, work fatigue (less work in the last 10 repetitions compared to the first 10 repetitions), was not present in 18 patients (1%). Thus, in total 539 patients (27%) did not fulfil at least one of three test performance criteria (Figure 1).

Male and female patients who incorrectly performed the isokinetic quadriceps test at baseline had a significantly lower exercise capacity, and a lower isotonic peripheral and respiratory muscle strength than male and female patients who performed

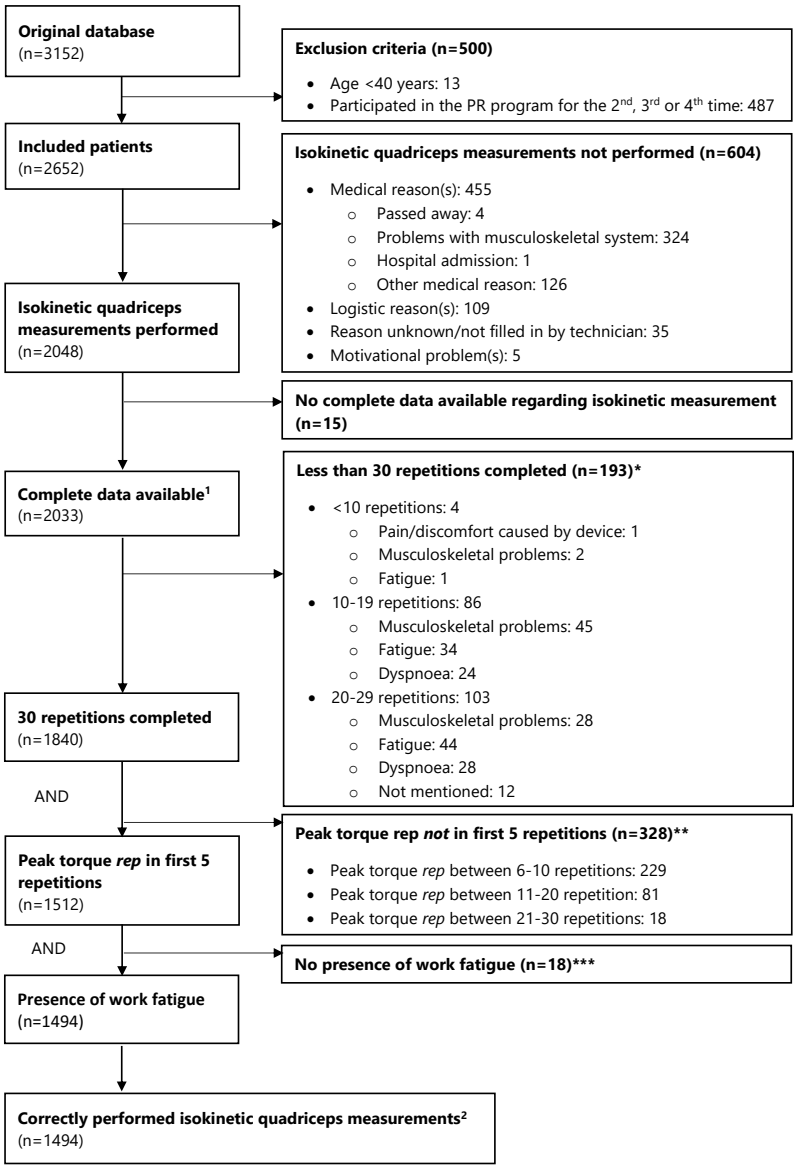

Figure 1. Flowchart of patients who performed the baseline isokinetic quadriceps measurement correctly according to the following three criteria: 30 repetitions completed, peak torque within first 5 repetitions, and presence of work fatigue.

**Some patients reported multiple reasons for early test termination. **30 patients with the highest peak torque not in the first 5 repetitions were already excluded due to the fact that they performed less than 30 repetitions. ***50 patients with no presence of work fatigue were already excluded due to the fact that their peak torque was not within first 5 repetitions. [1] indicates the group of patients used to evaluate the feasibility of isokinetic test performance at baseline. [2] indicates the group of patients used to evaluate the feasibility of isokinetic test performance post PR (Figure 2, Supplementary materials).*

the test correctly (all P-values <0.05). In males, an incorrect measurement was also related to higher dyspnoea severity and anxiety scores. Age, pulmonary function, body composition, and disease severity (GOLD) did not differ between patients who correctly and incorrectly performed the isokinetic quadriceps test (Table 1).

Table 1. Differences between patients with a correct and incorrect isokinetic quadriceps measurement, stratified for sex.

	Male patients		Female patients	
	Incorrect	**Correct**	**Incorrect**	**Correct**
Number	312	745	227	749
Age, years	66±8	67±8	63±9	63±8
BMI, kg/m^2	26.7±5.4	26.5±5.2	26.1±7.3	25.6±6.4
FFMI, kg/m^2	17.8±2.2	17.8±2.2	15.4±2.1	15.3±2.0
FEV_1, L	1.48±0.73	1.49±0.71	1.06±0.52	1.05±0.50
FEV_1, % predicted	49±23	50±22	49±22	47±21
FEV_1/FVC, %	41±16	40±15	42±15	39±13§
RV/TLC, %	51±12	49±11§	56±12	55±11
TL_{CO}, % predicted	50±19	52±18	49±15	48±16
Smoking, packs per year	47±25	45±25	41±21	40±22
LTOT, n (%)	62 (20)	132 (18)	50 (22)	160 (22)
GOLD (1/2/3/4), %	11/34/31/24	11/31/37/20	11/29/39/21	8/30/40/22
GOLD (A/B/C/D), %	8/29/7/56	11/26/9/54	5/18/5/72	6/23/8/63
mMRC ≥2, n (%)	266 (86)	594 (81)§	203 (90)	643 (86)
CAT total ≥18 points, n (%)	205 (71)	490 (70)	172 (79)	553 (77)
HADS-Anxiety ≥10 points, n (%)	88 (31)	167 (24)§	86 (39)	254 (36)
HADS-Depression ≥10 points, n (%)	85 (30)	176 (25)	82 (38)	222 (31)
PImax, kPa	7.1±2.1	7.5±2.1*	5.9±1.8	6.2±1.9§
PImax, % predicted	68±20	72±19*	84±25	88±26§
PEmax, kPa	11.0±3.7	11.8±3.4*	8.5±2.9	9.1±3.0*
PEmax, % predicted	56±19	60±17*	63±21	68±22*
6MWD, m	386±124	423±112†	348±116	395±108†
6MWD, % predicted	58±18	64±16†	59±18	66±17†
CWRT time to exhaustion, s	304±252	296±207	225±146	248±165
1RM Leg press, kg	91±44	101±46*	53±31	60±30*
1RM Leg extension, kg	34±13	38±14†	21±10	25±10†

*Abbreviations: BMI, body mass index; FFMI, Fat-Free Mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; T_{LCO}, transfer capacity for carbon monoxide; LTOT, long-term oxygen therapy; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; HADS, Hospital Anxiety and Depression Scale; PImax, maximal inspiratory mouth pressure; PEmax, maximal expiratory mouth pressure; 6MWD, 6-Minute Walk Distance; CWRT, constant work rate cycle test; 1RM, 1-repetition maximum. § indicates a significant difference of P<0.05; * indicates a significant difference of P<0.01; † indicates a significant difference of P<0.001.*

Test performance criteria post PR

Of the 1494 patients who performed the baseline isokinetic quadriceps test correctly, 1106 patients also had complete post PR data. Thirty-five patients (3%) did not complete all 30 repetitions post PR; 82 patients (8%) did not obtain a peak torque within the first 5 repetitions; work fatigue was not present in two patients (0.2%). Thus, a total of 987 patients (89%) performed the post PR assessment correctly (Figure 2, Supplementary material).

Responsiveness and MID estimates

Responsiveness and MID estimates were determined for male and female patients with a correct baseline and post PR isokinetic test performance (n=987). Baseline characteristics for these patients are illustrated in the supplementary material (Supplemental Table 3). Following PR, male and female patients improved their isokinetic quadriceps peak torque by 10±13 Nm and 7±9 Nm and total work by 263±270 J and 198±190 J, respectively (all P-values <0.05). Both work fatigue indexes did not change after PR (Table 2). The mean quadriceps work in J per repetition of the baseline and post PR isokinetic tests for males and females are depicted in Figure 2, demonstrating an overall increase in mean work per repetition following PR. In addition, CAT and 6MWD improved significantly in male and female patients (ΔCAT= -3±6 points and -4±6 points, Δ6MWD=19±62 m and 19±57 m, respectively; all P-values <0.001).

Table 2. Changes in isokinetic quadriceps function after PR in male and female patients with COPD with a correct baseline and post PR isokinetic test.

	Male patients (n=474)			Female patients (n=513)		
	Baseline	**Post PR**	**Delta**	**Baseline**	**Post PR**	**Delta**
Peak torque (Nm)	112±35	122±36†	10±13	73±22	80±22†	7±9
Peak torque (% predicted)	67±19	73±19†	6±8	64±18	70±18†	6±8
Total work (J)	1947±688	2210±727†	263±270	1283±437	1481±453†	198±190
Work Fatigue index$_{10}$ (%)	43±14	43±11	0±12	45±13	44±10	-1±12
Work Fatigue index$_{5}$ (%)	49±14	50±13	1±15	52±14	51±11	-1±13

*§ indicates a significant difference between baseline and post PR of P<0.05; * indicates a significant difference between baseline and post PR of P<0.01; † indicates a significant difference between baseline and post PR of P<0.001. Abbreviations: COPD, chronic obstructive pulmonary disease; PR, pulmonary rehabilitation.*

MID estimates were calculated for peak torque and total work, both in absolute values and as percentage change from baseline, as these outcomes turned out to be responsive to PR. Unfortunately, MID estimates could not be calculated using both anchor-based methods (linear regression and ROC analyses) as all correlation coefficients between changes in isokinetic function and changes in 6MWD and

CAT score were <0.3 (Supplemental Table 4). Using distribution-based calculations, MID estimates for peak torque ranged between 6-7 Nm or 8% change in males and 4–5 Nm or 8% change in females. For total work, MIDs ranged between 97–135 J or 24-25% change in males and between 62–99 J or 13-14% change in females (Table 3).

Table 3. Distribution-based estimates of the minimal important difference (MID) in isokinetic quadriceps function for male and female patients with COPD.

	Males (n=474)				Females (n=513)			
Method	**SEM**	**Empirical rule effect size**	**Cohen's effect size**	**MID estimates**	**SEM**	**Empirical rule effect size**	**Cohen's effect size**	**MID estimates**
Peak torque (Nm)	6	6	7	6-7	4	4	5	4-5
Peak torque (% change)	NA	8	8	8	NA	8	8	8
Total work (J)	97	129	135	97-135	62	95	99	62 – 99
Total work (% change)	NA	24	25	24-25	NA	13	14	13-14

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not applicable; SEM, standard error of measurement.

Isokinetic test performance criteria

The two most prevalent reasons for an incorrect isokinetic test performance in patients with COPD were a peak torque between repetition 6 and 10 (PT_{6-10}, n=229) and premature test termination between repetition 20 and 29 (REP_{20-29}, n=103). At baseline, patients with PT_{6-10} were characterized with lower peak torque and smaller work fatigue index (all P-values <0.05) compared to patients with a correct test performance. Patients with REP_{20-29} reported a lower peak torque percentage predicted and smaller total work and work fatigue $index_5$ than patients with a correct test performance (all P-values <0.05) (Supplemental Table 5). Furthermore, the responsiveness to PR was different between patients with PT_{6-10} and REP_{20-29} compared to patients with a correct test performance. Both groups reported a significant increase in work fatigue $index_5$ (PT_{6-10}: 4±23 % and REP_{20-29}: 13±36 %, both P-values <0.05), while patients with a correct test performance had no change following PR. In addition, peak torque as percentage predicted improved more in patients with PT_{6-10} (8±9 %) than in patients with a correct test performance (6±8 %) (Supplemental Table 6).

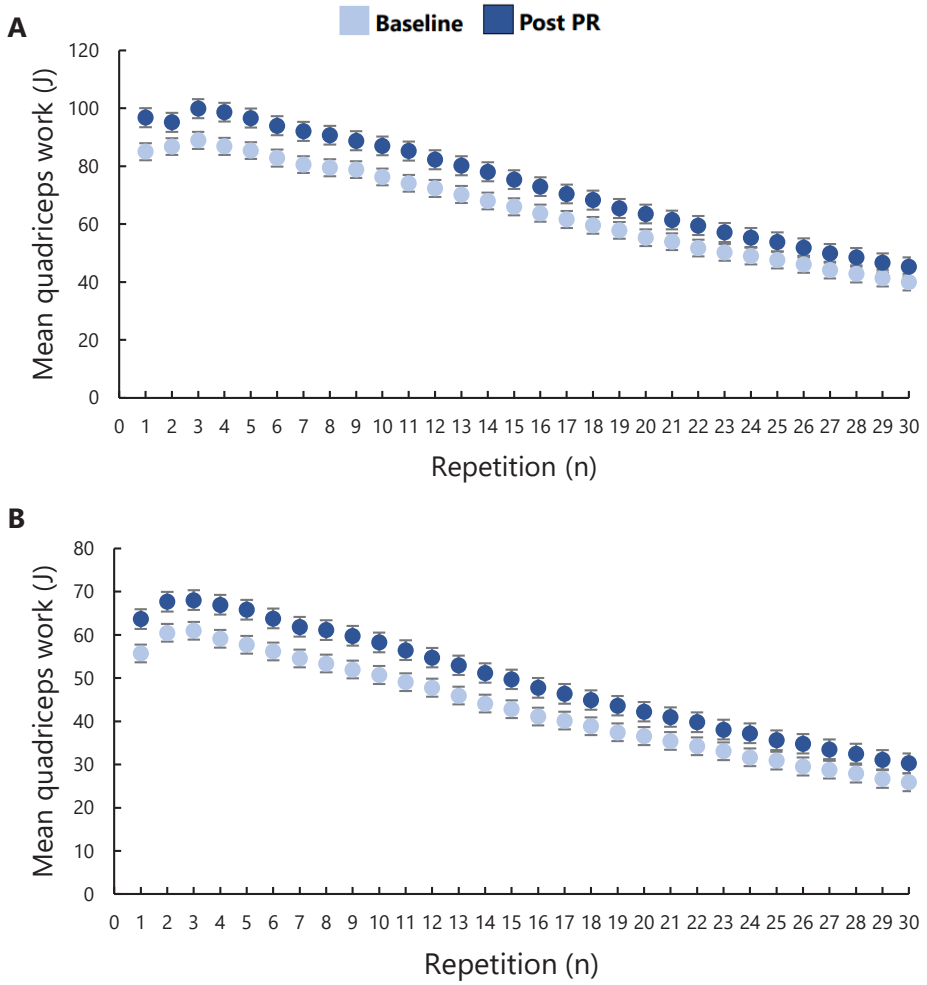

Figure 2. Baseline and post pulmonary rehabilitation mean quadriceps work (J) per repetition with standard error for male (**A**) and female (**B**) patients with chronic obstructive pulmonary disease.

DISCUSSION

The present study is the first to provide an extensive overview of the rate of patients with positive test performance criteria, responsiveness, and MID estimates of isokinetic evaluation of quadriceps function in male and female patients with COPD following PR. At baseline, 1 in 4 patients was not able to perform the test correctly according to the pre-defined test criteria. Generally, quadriceps peak torque (strength) and total work (endurance) improved in male and female patients following PR. The MID estimates were 6–7 Nm and 97–135 J for males and 4–5 Nm and 62–99 J for females, respectively.

Rate of patients with positive test performance criteria

Even though Frykholm et al. reported great feasibility of the isokinetic quadriceps test in terms of test duration,[16] the current study found that 1 in 4 patients in a clinical setting was not able to perform the test correctly. The 2 most common reasons were premature test termination between repetition 20 and 29 (instead of 30), and peak torque reached between repetition 6 and 10 (instead of within the first 5 repetitions). These male and female patients with an incorrect test performance at baseline were weaker and had a lower exercise capacity. In addition, patients with an incorrect test performance report lower values for total work and work fatigue index, which is expected to reflect the difference in test performance rather than a reduced quadriceps endurance. A familiarization session may increase the rate of patients with a correct test performance based on the pre-defined criteria.[15, 16] However, due to time and personnel constraints, this will not always be possible in clinical practice.

Responsiveness

In patients with COPD and a correct baseline and post PR isokinetic test, peak torque and total work were responsive following PR as they improved with 9% and 14% in males and 10% and 15% in females, respectively. The improvement in peak torque is in accordance with prior studies.[40-43] In addition, there is a moderate-to-high correlation between the change in peak torque and total work ($r=0.723$, $P<0.001$), highlighting the influence of muscle strength on total work. Previous literature regarding the responsiveness of isokinetic quadriceps endurance identified positive effects of different exercise interventions on quadriceps endurance in patients with COPD.[44] However, these studies used different testing protocols, interventions, or outcome measures.[44] This study did not find an improvement in work fatigue index following PR. The exercise-based interventions of the current PR program did not specifically focus on the fatigability of the quadriceps, which may explain the lack of change. Therefore, it is recommended to monitor the training intervention more extensively in future research.

MID estimates

The current study shows that MIDs for males and females were different. Therefore, sex-specific MIDs are recommended to be applied to obtain a more accurate interpretation of the efficacy of specific interventions, and can be used to determine the 'number needed to treat' for future intervention studies.[45] It is important to note that the MID estimates only apply for patients with a correct baseline and post PR isokinetic test. The changes in the 6MWD and the CAT showed only weak correlations with the changes in peak torque and total work. Whether changes in other outcomes (such as the Short physical performance battery or the endurance shuttle walk test) can be used as anchors, remains to be determined.

Methodological limitations

The high correlation between peak torque and total work reflects the influence of muscle strength on total work, which is expected based on its formula 'work=force*distance'. This raises the question of whether total work is an appropriate outcome measure of quadriceps endurance. In addition, weak and similar correlations were seen between peak torque (strength) and total work (endurance) with 6MWD. This might indicate that the applied outcome measures for muscle strength and endurance partly represent associated aspects of muscle function. However, recent studies have demonstrated that peak torque and total work are two different aspects of quadriceps function which independently correlate to exercise capacity.[10, 46] Future research should determine the optimal protocol and outcome measures for evaluating quadriceps endurance. For now, it is important to make a clear distinction between quadriceps endurance and total work and not use both terms interchangeably.

In addition, the exercise training is not identical for all patients due to the patient-tailored nature of the PR program. Unfortunately, we were not able to retain the performed exercise training parameters per individual due to the retrospective design of this study. In general, the main goal of the prescribed resistance training in this study was to improve muscle strength rather than muscle endurance. Therefore, potentially greater improvements in quadriceps muscle endurance could be achieved if combining aerobic training[1] with low-load/high-repetition resistance training.[47] For future studies, it is recommended to extensively monitor and report the training parameters.

Finally, data were obtained from 1 location and included only a selected group of patients with COPD, specifically those who were more severe and dyspnoeic. This should be noted when interpreting the results as it reduces generalizability.

Clinical implications

Based on the results of this study, we recommend using the pre-defined test criteria for isokinetic test performance in clinical practice. Furthermore, the test can be used to evaluate PR efficacy on peak torque and total work in individual patients with COPD. Whether this isokinetic protocol is suitable to determine changes in work fatigue index following PR has to be investigated in future studies using exercise interventions focussing on improving fatigability.

We are aware that a computerized dynamometer is a complex and expensive equipment and is not available in all settings. However, this study is relevant for the centres that already use a computerized dynamometer or have the opportunity to purchase one. Furthermore, it is of great importance to create a standardized operating procedure for isokinetic quadriceps testing and determine reference values regarding quadriceps endurance.

CONCLUSIONS

Based on the current test criteria, 3 in 4 patients with COPD performed the isokinetic quadriceps test correctly during baseline PR assessment. These patients were stronger and had a higher exercise capacity than patients with an incorrect test performance. Furthermore, peak torque and total work, but not work fatigue index, were responsive to PR and sex-specific MIDs were established. However, future studies are needed to determine prediction equations and/or normal values to improve the interpretation of isokinetic quadriceps endurance.

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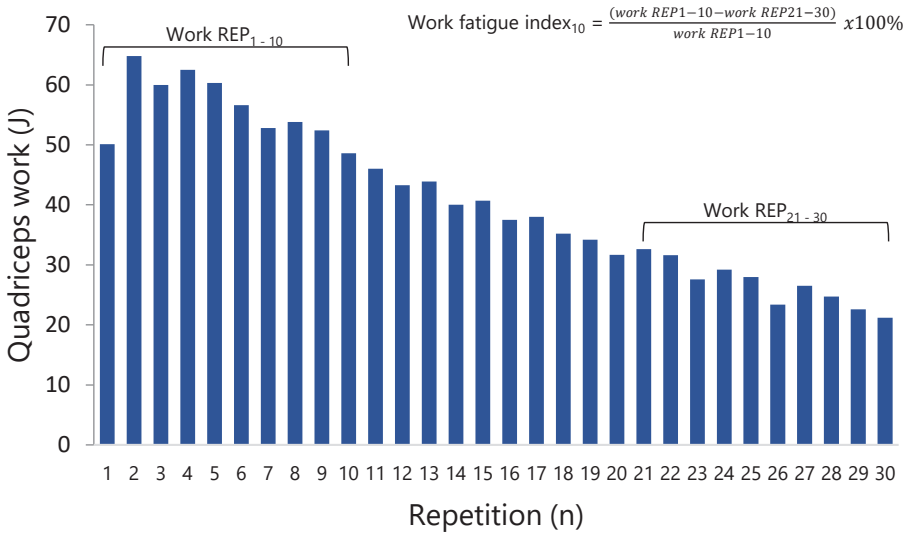
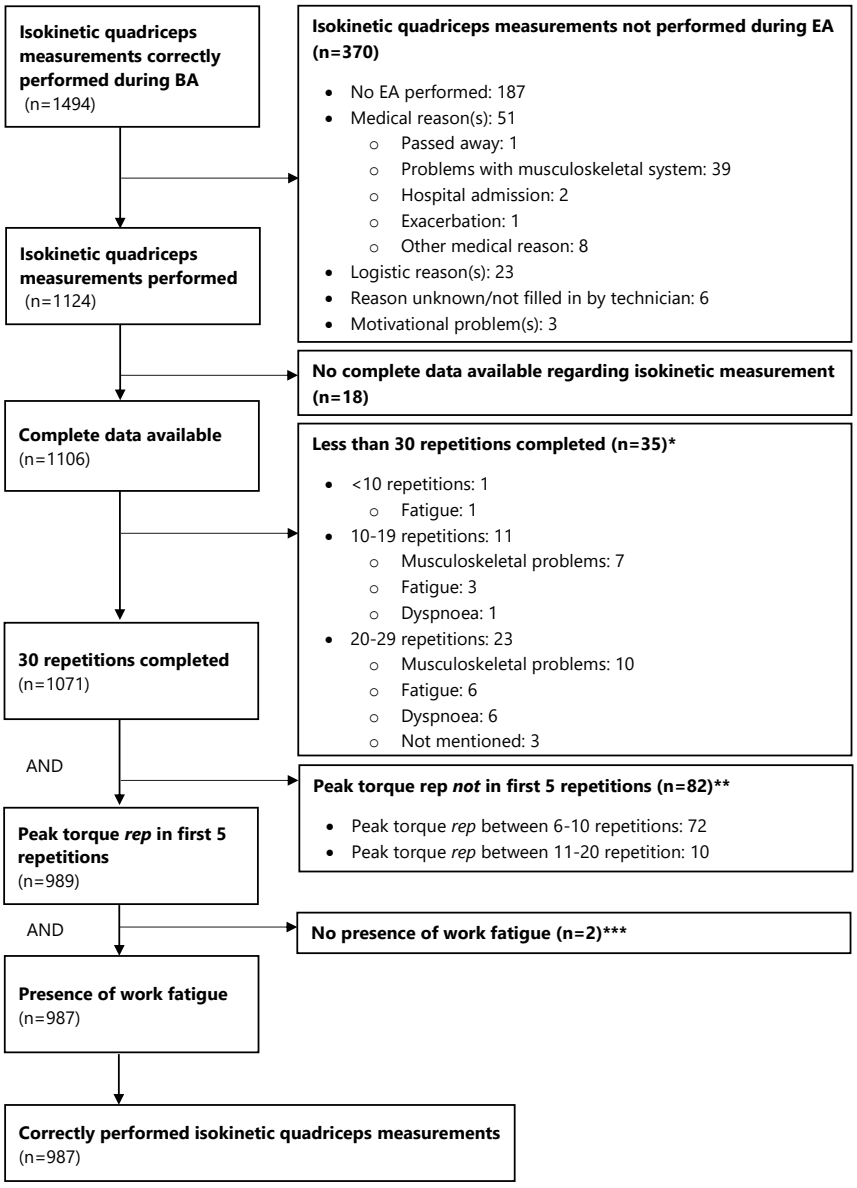
SUPPLEMENTARY MATERIALS



Supplemental Figure 1. Quadriceps work (J) per repetition of one patient to visualize the work fatigue index$_{10}$.
Abbreviations: REP, repetition.



Supplemental Figure 2. Flowchart of patients that performed the post PR isokinetic quadriceps measurement correctly according to the following three criteria: 30 repetitions completed, peak torque within first 5 repetitions and presence of work fatigue.

*Abbreviations: BA, baseline assessment; PR, pulmonary rehabilitation; rep, repetition. *Some patients reported multiple reasons for early test termination. **5 patients with the highest peak torque not in the first 5 repetitions were already excluded due to the fact that they performed less than 30 repetitions. ***7 patients with no presence of work fatigue were already excluded due to the fact that their peak torque was not in the first 5 repetitions.*

Supplemental Table 1. Training parameters for the different types of cycling and walking training.

Modality	Type	Intensity	Duration	Rest	Progression
Cycling	Endurance/recovery	40% Wmax	1 x 20 min		5% each 2 weeks
Cycling	Extensive interval	60% Wmax	8 x 2 min	1 min	5% each week
Cycling	Intensive interval	80% Wmax	12 x 1 min	1 min	10% each 2 weeks
Walking	Endurance/recovery	60% 6MWD	1 x 20 min		5% each week
Walking	Extensive interval	75% 6MWD	4 x 5 min	1 min	10% each week (first 4 weeks), 10% each 2 weeks (second 4 weeks)
Walking	Intensive interval	100% 6MWD	12 x 1 min	1 min	10% each 2 weeks

Abbreviations: Wmax, maximal workload; 6MWD, 6-Minute Walk Distance.

Supplementary Table 2. Baseline characteristics of all patients.

	Mean±SD	N
Age, years	65±9	2033
BMI, kg/m^2	26.2±6.0	2033
FFMI, kg/m^2	16.6±2.5	1993
FEV_1, L	1.28±0.66	2030
FEV_1, % predicted	49±22	2030
FEV_1/FVC, %	40±14	2030
RV/TLC, %	52±12	1964
TL_{CO}, % predicted	50±17	1885
Smoking, packs per year	44±24	1891
LTOT, n (%)	404 (20)	1988
GOLD (1/2/3/4), %	10/31/37/22	2030
GOLD (A/B/C/D), %	8/24/8/60	2011
mMRC ≥2, n (%)	1706 (85)	2014
CAT total ≥18, n (%)	1420 (74)	1927
HADS-Anxiety ≥10, n (%)	595 (31)	1919
HADS-Depression ≥10, n (%)	565 (29)	1919
PImax, kPa	6.8±2.1	2012
PImax, % predicted	79±24	2008
PEmax, kPa	10.3±3.5	1865
PEmax, % predicted	63±20	1861
6MWD, m	399±115	2019
CWRT time to exhaustion, s	272±196	1851
1RM Leg press, kg	79±44	1973
1RM Leg extension, kg	31±14	1942

Abbreviations: BMI, body mass index; FFMI, Fat-Free Mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; TLCO, transfer capacity for carbon monoxide; LTOT, long-term oxygen therapy; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; HADS, Hospital Anxiety and Depression Scale; PImax, maximal inspiratory mouth pressure; PEmax, maximal expiratory mouth pressure; 6MWD, 6-Minute Walk Distance; CWRT, constant work rate cycle test; 1RM, 1-repetition maximum.

Supplemental Table 3. Baseline characteristics of male and female patients with COPD with a correct baseline and post PR isokinetic test performance.

	Male patients (n=474)		Female patients (n=513)	
	Mean±SD	n	Mean±SD	n
Age, years	67±9	474	63±8	513
BMI, kg/m^2	26±5	474	26±6	513
FFMI, kg/m^2	18±2	467	15±2	506
FEV_1, L	1.50±0.71	473	1.06±0.49	513
FEV_1, % predicted	50±22	473	48±20	513
FEV_1/FVC, %	39±15	473	29±13	513
RV/TLC, %	49±11	465	55±11	496
T_{LCO}, % predicted	52±18	461	48±15	475
Smoking, packs per year	45±24	437	41±23	495
LTOT, n (%)	82 (18)	468	115 (23)	501
GOLD (1/2/3/4), %	11/30/39/20	473	8/30/42/20	513
GOLD (A/B/C/D), %	12/24/10/54	467	6/25/7/62	509
mMRC ≥2, n (%)	367 (79)	467	444 (87)	510
CAT total ≥18, n (%)	315 (70)	448	386 (78)	493
HADS-Anxiety ≥10, n (%)	98 (22)	448	166 (34)	493
HADS-Depression ≥10, n (%)	111 (25)	448	155 (31)	493
PImax, kPa	7.6±2.1	471	6.4±1.9	510
PImax, % predicted	73±19	471	91±26	509
PEmax, kPa	11.8±3.3	425	9.4±3.0	491
PEmax, % predicted	61± 17	425	70±22	490
6MWD, m	435±111	470	401±108	512
CWRT time, s	302±206	453	253±167	484
1RM Leg press, kg	103±45	462	62±31	501
1RM Leg extension, kg	39±14	453	25±10	500

Abbreviations: BMI, body mass index; FFMI, Fat-Free Mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; T_{LCO}, transfer capacity for carbon monoxide; LTOT, long-term oxygen therapy; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; HADS, Hospital Anxiety and Depression Scale; PImax, maximal inspiratory mouth pressure; PEmax, maximal expiratory mouth pressure; 6MWD, 6-Minute Walk Distance; CWRT, constant work rate cycle test; 1RM, 1-repetition maximum.

Supplemental Table 4. Pearson correlations between change in isokinetic quadriceps function and change in anchors 6MWD and CAT in male and female patients with COPD.

	Male patients (n=474)				Female patients (n=513)			
	Δ6MWD		ΔCAT		Δ6MWD		ΔCAT	
	R	N	R	N	R	N	R	N
ΔPeak torque (Nm)	0.151*	466	-0.073	423	0.171*	507	-0.101*	478
ΔPeak torque (% change)	0.189*	466	-0.082	423	0.197*	507	-0.076	478
ΔTotal work (J)	0.193*	466	0.015	423	0.227*	507	-0.159*	478
ΔTotal work (% change)	0.196*	466	-0.076	423	0.233*	507	-0.096*	478

*Abbreviations: 6MWD, 6-Minute Walk Distance; CAT, COPD Assessment Test. * indicates a P<0.05.*

Supplemental Table 5. Baseline isokinetic quadriceps function of patients with an incorrect isokinetic test performance (based solely on peak torque between repetition 6 and 10 and premature test termination between repetition 20 and 29) and the reference group of patients with a correct baseline isokinetic test performance.

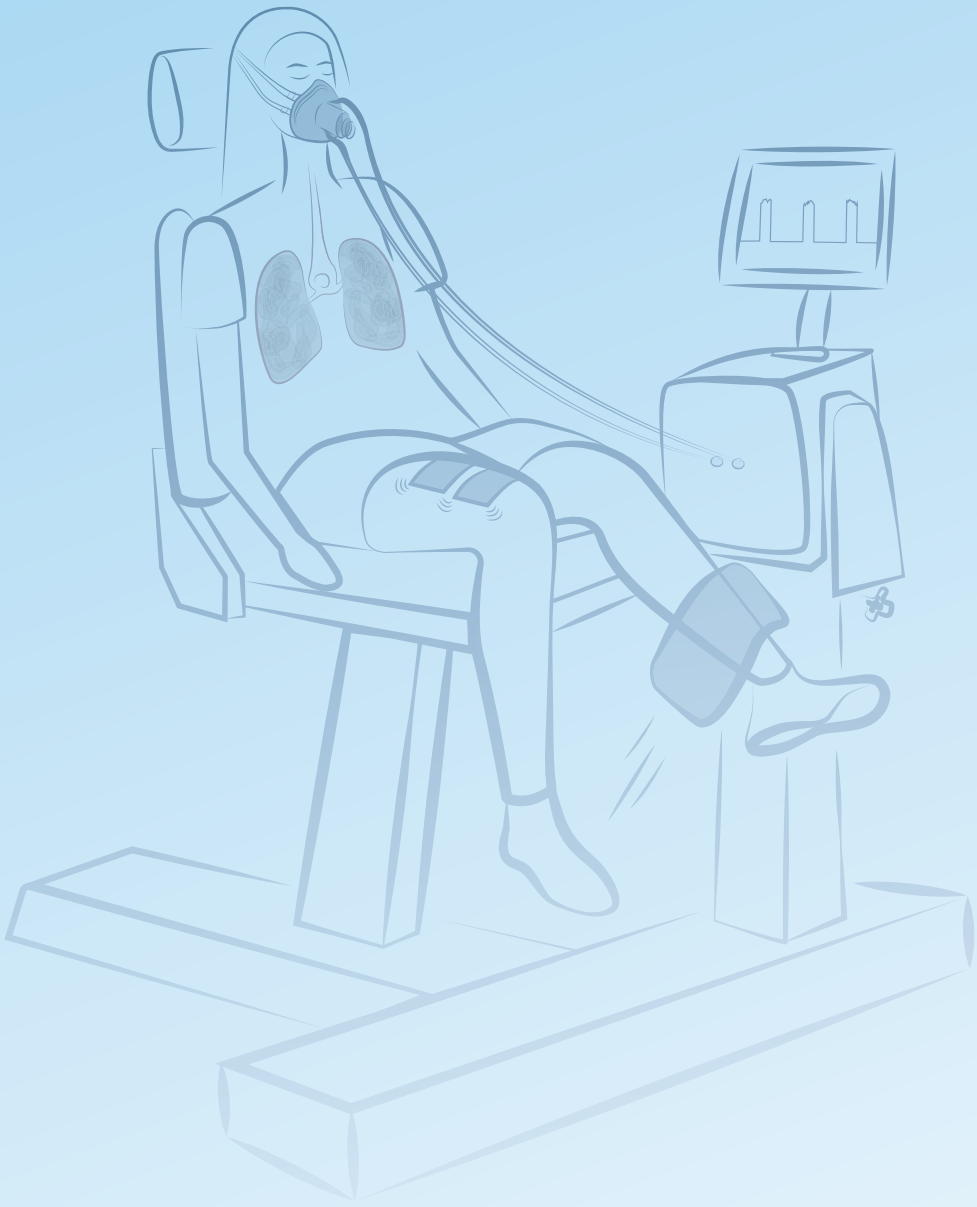
	Reference group (n=1494)	**Peak torque between repetition 6–10 (n=217)**	**Number of repetitions between 20–29 (n=83)**
Peak torque (Nm)	90±35	83±33*	87±35
Peak torque (% predicted)	64±19	58±18**	58±19*
Total work (J)	1573±669	1513±682	1206±536**
Work Fatigue index$_{10}$ (%)	44±13	32±15**	39±48
Work Fatigue index$_{5}$ (%)	50±15	30±21**	45±20*

** indicates a significant difference of P<0.05, ** indicates a significant difference of P<0.001.*

Supplemental Table 6. Baseline, post PR and delta (post PR – baseline) isokinetic quadriceps function of patients with an incorrect isokinetic test performance at baseline and/or post PR (based solely on peak torque between repetition 6 and 10 and premature test termination between repetition 20 and 29) and the reference group of patients with a correct baseline and post PR isokinetic test performance.

	Reference group (n=987)			Peak torque between repetition 6–10 (n=211)			Number of repetitions between 20–29 (n=74)		
	Baseline	**Post PR**	**Delta**	**Pre**	**Post PR**	**Delta**	**Pre**	**Post PR**	**Delta**
Peak torque (Nm)	91±35	100±36**	8±12	88±34	99±35**	10±14	89±35	99±35**	10±15
Peak torque (% predicted)	65±19	72±19**	6±8	60±18	68±18**	8±9$	59±18	66±16**	7±10
Total work (J)	1602±661	1831±702**	229±234	1607±669	1870±686**	263±265	1376±553	1482±640	106±904
Work Fatigue index$_{10}$ (%)	44±13	44±11	0±12	34±15	34±14	0±16	51±35	51±25	0±47
Work Fatigue index$_{5}$ (%)	50±15	50±12	0±14	35±20	39±17*	4±23$	46±18	59±26*	13±36$

** indicates a significant difference between baseline and post PR of P<0.05, ** indicates a significant difference between baseline and post PR of P<0.001, $ indicates a significant difference between deltas in comparison to the reference group of P<0.05, $$ indicates a significant difference between deltas in comparison to the reference group of P<0.001.*



CHAPTER 7

Relationship between volitional and non-volitional quadriceps muscle endurance in patients with chronic obstructive pulmonary disease

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CHAPTER 8

Summary and general discussion

Patients with chronic obstructive pulmonary disease (COPD) frequently experience limitations in their physical performance, which can be characterized by a reduction in functional performance, exercise capacity, exercise tolerance, and/or peripheral muscle function.[1-4] Timely and extensive evaluation of a patient's physical performance is essential to identify the severity and specific domain of the impairment in order to prescribe a personalized intervention. Therefore, tests that evaluate physical performance measures must be feasible, valid, reliable, and, in case of interventions, responsive. The purpose of this thesis was to expand the existing knowledge regarding the feasibility, validity, and responsiveness of physical performance outcome measures in patients with COPD. In this chapter, the main findings will be discussed in depth according to their physical performance domain.

FUNCTIONAL PERFORMANCE

The short physical performance battery (SPPB) is a functional performance measure that evaluates mobility and balance.[5] In **Chapter 2,** univariate regression analyses were performed in a large sample of patients with COPD (n=900) to assess the validity of the SPPB in regards to, amongst others, the 6-minute walk distance, maximal workload on a symptom-limited cardiopulmonary cycle exercise test, time-to-exhaustion on a constant work rate cycle test, and isotonic and isokinetic lower-limb muscle function. Our data revealed significant correlations between the SPPB summary score and patient's exercise capacity, exercise tolerance, and peripheral muscle function. This is in line with previously reported relations between the SPPB and exercise capacity and peripheral muscle function in patients with COPD.[6, 7] However, in **Chapter 2** a multivariate linear regression analysis explained only 29% of the variance in SPPB summary score, of which the largest contribution came from the 6-minute walk distance. This finding demonstrates that only a small portion of the SPPB summary score is determined by exercise capacity, exercise tolerance, and peripheral muscle function. Thus, this emphasizes the additional value of implementation of functional tests in complement to exercise tests that assess exercise capacity, exercise tolerance, or peripheral muscle function in order to obtain an extensive overview of the patient's physical performance. Furthermore, it is important to note that the standing balance, 4-meter gait speed (4MGS), and 5-repetition sit-to-stand (5STS) subtests of the SPPB contribute independently to the SPPB summary score. These 3 subtests are related to different outcome measures. The standing balance subtest is not or to a lesser extent related to exercise capacity and exercise tolerance than the other 2 subtests, as maintenance of balance requires complex integration and coordination of musculoskeletal and neural systems.[6, 8] The 4MGS is associated with exercise capacity

and psychological factors and is an excellent screening measure for exercise capacity and frailty.[6, 9] The 5STS is the only subtest that correlates with health-related quality of life in patients with COPD and thus has additional value in evaluating the impact of COPD on the patient's life.[6, 10] In addition, Bernabeau-Mora et al. determined the clinical validity of the SPPB summary score and its 3 components for identifying mobility limitations in patients with COPD.[11] They revealed that only the 5STS and the SPPB summary score showed a good discriminative capability for self-reported mobility limitations. Taken together with the notion that the greatest variation in scores was reported for the 5STS in **Chapter 2** and previously by Mohan et al.,[7] it is suggested that the 5STS has the highest discriminative power among the subtests of the SPPB to identify functional limitation in patients with COPD. Furthermore, additional analyses with data from **Chapter 3** (not reported) revealed only weak correlations between balance, 4MGS, and 5STS scores at baseline (ρ=0.142-0.329, all P-values <0.001) and no significant correlations between the changes following a pulmonary rehabilitation (PR) program. Again, this substantiates that each of the 3 SPPB subtests provides distinct information regarding the patient's mobility and balance. Therefore, it is recommended to perform all 3 SPPB subtests in patients with COPD, especially considering the great feasibility due to the simplicity of the test in terms of test duration and required equipment.

To date, functional performance outcome measures such as the SPPB are often incorporated in pre- and post-intervention assessments. Therefore, it is important to ensure the responsiveness and determine minimal important differences (MIDs) of the SPPB. **Chapter 3** evaluated the effect of a comprehensive PR program on the SPPB and determined MIDs in patients with COPD. Our data reported improvements in 4MGS, 5STS, and SPPB summary scores following the PR program, but no change was observed in balance standing test scores. This is consistent with recent studies evaluating the effect of PR programs on SPPB summary scores and/or SPPB subtests.[10, 12-16] These findings might indicate that improvements in SPPB summary scores following PR are predominantly caused by changes in 4MGS and 5STS and perhaps not, or to a lesser extent, by changes in balance standing tests. The latter can be the result of a ceiling effect as 85% of the patients in **Chapter 2** obtained the maximal standing balance score of 4. Subsequently, 15% of these moderate-to-severe patients with COPD report balance impairments at the start of the PR program. An additional analysis revealed that 74% of these patients with balance impairments did show improvements of at least 1 point in balance standing score following the PR program (data not reported). Thus, it seems that the balance standing subtest is clinically relevant to perform in patients with moderate-to-severe COPD. However, the incidence of patients with balance impairments observed in **Chapter 2** is

lower than the 20% to 45% described by previous studies.[17] Furthermore, 40% of patients with COPD, and with comparable baseline characteristics as the patients in **Chapter 2**, reported falls within the previous 12 months.[18] This might indicate that the balance standing subtest of the SPPB alone can perhaps only identify patients with extreme balance impairments, and is not adequately sensitive in patients with milder balance deficits. Therefore, more comprehensive tests such as the (mini-) Balance Evaluation Systems Test or Berg Balance Scale may be more useful in patients with COPD.[19]

In addition, **Chapter 3** reported a distribution-based MID estimate of 0.83-0.96 points (1 point as the SPPB summary score is reported in whole numbers) for the SPPB summary score. This indicates that an improvement of ≥1 point following a PR intervention can be considered a statistically significant improvement, which is consistent with the study of Perera et al. who reported a substantial change of 1.0 point for SPPB summary scores in older adults.[20] For the 4MGS, a MID range of 0.05-0.13 m/s was obtained using distribution- and anchor-based (6-minute walk distance as anchor) methods in **Chapter 3**. This is in line with the MID estimate of Kon et al. (0.11 m/s).[13] Finally, a distribution-based MID range of 2.19-6.33 seconds was observed for the 5STS in **Chapter 3**. These MID estimates are larger than the anchor-based MID estimate by Jones et al. of 1.7 seconds in patients with COPD after an 8-week outpatient PR program in the United Kingdom.[10] The discrepancy between both MID estimates can be explained by the different methods used to calculate the MIDs. Distribution-based MIDs indicate a statistically significant difference and anchor-based MIDs describe a clinically meaningful difference. In **Chapter 3** only distribution-based MID estimates for the 5STS could be determined because no significant moderate or strong correlations were present between the 5STS and both anchors (i.e., COPD Assessment Test and 6-minute walk test). Jones et al. used a 5-point Likert scale (ranging from 1 'feeling much better' to 5 'feeling much worse') to calculate anchor-based MIDs and did not report distribution-based MIDs.[10] With the reported standard deviation for the baseline 5STS time (SD=6.5 s),[10] 2 distribution-based calculations can be performed ($SD_{baseline}$*√(1-intraclass correlation coefficient)=1.1 s and 0.5*$SD_{baseline}$=3.3 s). The latter MID is more comparable to the MID estimates obtained in **Chapter 3**. However, it is also important to note that differences in for example study population and intervention might explain the discrepancy between the MIDs. The choice for an appropriate MID is therefore dependent on the study population, intervention, and method used to estimate the MID.

EXERCISE CAPACITY AND TOLERANCE

To date, it is still unclear whether and to what extent patient-reported outcomes (PROs) mirror the physical performance of patients with COPD, especially for exercise tests other than the 6-minute walk test.[21] Therefore, **Chapter 4** used univariate correlations to evaluate the validity of exercise capacity (6-minute walk distance and cardiopulmonary exercise test), exercise tolerance (constant work rate cycle test), functional performance (timed 'Up and Go' test), and peripheral muscle function (isokinetic peak torque and total work of the quadriceps) in comparison to patient-reported health-related quality of life, mood status, dyspnoea, and care dependency. This study revealed weak-to-moderate correlations and demonstrated that physical performance exercise tests and PROs assess different aspects in patients with COPD. These findings are recently confirmed by Quadflieg et al. who concluded that exercise tests are generally poorly related to PROs during a severe exacerbation of COPD.[22] Furthermore, recent studies in other populations demonstrated predominantly weak correlations between PROs and performance-based measures as well.[23-26] Therefore, additional assessment of health-related quality of life, anxiety, depression, and/or the level of care dependency is recommended in addition to exercise tests.

As already mentioned, exercise tests used to evaluate the effect of interventions must be able to pick up the improvements following the intervention. Therefore, **Chapter 4** assessed the responsiveness of exercise capacity (6-minute walk distance), exercise tolerance (constant work rate cycle test), functional performance (Timed 'Up and Go' test), and peripheral muscle function (isokinetic peak torque and total work of the quadriceps during a fatigue protocol) to a comprehensive PR program and reported a significant improvement for all outcome measures. In addition, univariate correlations between changes in exercise capacity, exercise tolerance, functional performance, and peripheral muscle function with changes in patient-reported health-related quality of life, mood status, dyspnoea, and care dependency were obtained. Our data revealed only very weak-to-weak correlations between changes in exercise tests and changes in PROs following a PR program. Again, this highlights that physical performance outcomes need to be supported by PROs to get a more comprehensive insight into the effectiveness of a PR program. It should be noted that the specific goals and the content of the PR program are personalized and a patient is thus not expected to improve in all aspects. Therefore, outcome measures used to evaluate the responsiveness of the intervention should match the patient's goals.

The endurance shuttle walk test (ESWT) is a feasible, valid, reliable, and responsive measure to evaluate exercise tolerance in patients with COPD.[27-36] Unfortunately,

there is a large interindividual variability in tolerated duration (Tlim) of the ESWT,[33, 37-39] which was confirmed in **Chapter 5** as half of the patients had a test duration exceeding the desired 3-8 minutes. This large variability in ESWT Tlim complicates the interpretation of intervention efficacy and increases the required number of patients in clinical studies. An option to reduce the variability would be to perform a second ESWT at an adapted pace in patients with an ESWT Tlim exceeding the desired duration of 3-8 minutes. However, this is not always feasible due to logistic constraints. Thus, it is important to evaluate determinants of the ESWT Tlim in patients with COPD (i.e., validity) to better understand this large variation and possibly even adapt the ESWT pace prior to the ESWT test in order to reduce variability. Univariate regression analyses in **Chapter 5** revealed significant correlations between ESWT Tlim and pulmonary function, physical performance, physical activity, and incremental shuttle walk test (ISWT) performance measures, and not with isometric quadriceps muscle strength, in patients with moderate-to-severe COPD. This emphasizes that exercise capacity, exercise tolerance, and peripheral muscle function are not completely independent and distinctive components of physical performance but are somehow interrelated. However, it is still important to evaluate multiple, if not all, components of physical performance to obtain an extensive and complete overview of the patient's physical performance. Furthermore, a multivariate regression model showed that next to maximal ISWT speed, other ISWT performance measures as well as clinical measures of pulmonary function, exercise capacity, and physical activity were independent determinants of ESWT Tlim. Nevertheless, these determinants only explained ~30% of the variability in ESWT Tlim, indicating that the variance is predominantly related to other outcome measures than those assessed in **Chapter 5**. Furthermore, this makes it currently difficult to individualize the ESWT pace more accurately before the ESWT itself in order to reduce the large variability. To date, others have also tried to reduce the interindividual variability in ESWT Tlim. Dolmage et al. suggested the use of predetermined usual and fast walk speeds to provide a simple, quick, and inexpensive method for clinicians to set an acceptable endurance walk speed.[40] In addition, Hill et al. found that participants with milder symptoms of dyspnoea (Borg score <4) and leg fatigue (Borg score <2) on completion of baseline 6MWT and ISWT may achieve a longer ESWT Tlim. They recommended repeating the ESWT at a higher walking speed to achieve an ESWT Tlim between the desired duration.[41] Thus, no accurate prediction formula is available yet to determine the individual ESWT pace that will result in a desired pre-intervention ESWT Tlim. Therefore, the performance of a second ESWT would be preferable when the pre-intervention ESWT Tlim exceeds the desired duration of 3-8 minutes. Future studies with additional outcome measures like dynamic hyperinflation and peripheral muscle endurance are necessary in order to obtain such a prediction formula.

PERIPHERAL MUSCLE FUNCTION

Peripheral muscle endurance is more severely reduced than muscle strength in patients with COPD and requires different training strategies.[42-44] This highlights the clinical relevance of the assessment of peripheral muscle endurance in these patients. Peripheral muscle endurance is most commonly assessed using isokinetic contractions in patients with COPD.[45] Recent studies already reported good reliability and feasibility in those patients but were only performed in research settings.[42] Therefore, **Chapter 6** assessed the feasibility of isokinetic evaluation of quadriceps muscle endurance in patients with COPD in a PR centre. The findings revealed that 3 out of 4 patients with COPD performed the isokinetic quadriceps test correctly during baseline PR assessment. The main reasons for an invalid test performance were premature test termination (i.e., not completing 30 repetitions) and not reaching peak torque within the first 5 repetitions. Furthermore, **Chapter 7** reported that 4 out of 26 patients (15%) performed the isokinetic test incorrectly. Those patients with an invalid test performance at baseline in **Chapter 6** were characterized by a lower exercise capacity and a lower isotonic peripheral and respiratory muscle strength than patients with a valid test. However, it is unclear whether repeating the baseline test will improve the feasibility in those patients with an invalid test, or whether these patients are just not capable of performing the test correctly for other unknown reasons. Therefore, further research should reveal whether a second endurance test at baseline is beneficial in patients with an invalid test. As it might not always be feasible to repeat the isokinetic endurance test in research or clinical settings, a second option would be to perform a different quadriceps endurance test. Hence, it is important to determine the feasibility of isotonic and isometric quadriceps endurance tests in clinical settings as well. **Chapter 7** showed already promising results regarding the feasibility of the isometric quadriceps endurance test as all 26 patients with COPD performed the isometric endurance test correctly.

To date, it is still unknown whether isokinetic evaluation of quadriceps muscle endurance can pick up improvements following a PR program. In addition, MIDs are currently lacking, which complicates the interpretation of intervention efficacy. Therefore, **Chapter 6** evaluated the response of isokinetic quadriceps muscle endurance following PR and determined MIDs. Our data demonstrated that isokinetic muscle strength (i.e., peak torque) and total work improved following PR, but no change was observed for work fatigue index. The improvement in isokinetic total work was also observed following a low-load/high-repetition resistance training in patients with COPD.[46, 47] The lack of change in work fatigue index following PR might be explained by the low test-retest intraclass correlation coefficient[48] or the fact that

the current program did not specifically focus on the fatiguability of the quadriceps muscle. Unfortunately, no other study has evaluated the effect of an exercise training intervention on work fatigue index yet. Therefore, additional studies are needed to evaluate the responsiveness of the work fatigue index following an intervention that focuses on the fatiguability of the quadriceps muscle. In addition, sex-specific MIDs were calculated as differences between peak torque, total work, and work fatigue index were observed between healthy males and females.[49] **Chapter 6** revealed distribution-based MIDs for peak torque ranging between 6-7 Nm or 8% change for males, and 4-5 Nm or 7% change for females. For total work, the distribution-based MIDs ranged between 97-135 J or 24-25% change for males, and between 62-99 J or 13-14% change for females. Furthermore, it is important to note that these MIDs only apply to patients who perform a valid baseline and post PR test. Lastly, it should be emphasized that there was a strong relation observed in **Chapter 6** between isokinetic peak torque (i.e., muscle strength) and total work at baseline and following a PR intervention. This might question whether total work is the most appropriate outcome measure to evaluate peripheral muscle endurance. In addition, it should be highlighted that a computerized dynamometer is expensive and requires trained personnel, and not all centres have a computerized dynamometer available. In these cases, isotonic protocols might be an alternative as these tests require simpler equipment like elastic bands, exercise platforms or benches, or a pully system. These protocols are performed with a constant external load and standardized range of motion and speed and have a great reliability and feasibility in patients with COPD.[48] Furthermore, isotonic peripheral muscle endurance is correlated with functional performance and exercise capacity and is better associated with daily physical activity than isokinetic and isometric peripheral muscle endurance.[50, 51]

There is still no consensus yet on the best protocol to evaluate peripheral muscle endurance in patients with COPD. Therefore, **Chapter 7** evaluated the validity of volitional isometric and isokinetic quadriceps endurance tests by assessing its relation to non-volitional electrically stimulated isometric quadriceps endurance in patients with COPD. The study reported that outcome measures of the 2 volitional endurance tests correlate significantly and strongly. So, these 2 protocols evaluate a great amount of similarity in quadriceps endurance despite the difference in contraction type. However, neither of those volitional tests showed a significant correlation with non-volitionally assessed quadriceps muscle endurance. This might imply that volitional and non-volitional tests evaluate different constructs of quadriceps muscle endurance in patients with COPD. Recent studies have already reported that volitional isometric and isokinetic endurance exercises are related to the oxidative metabolism of the active muscle.[52-54] However, the severity

of dyspnoea and central fatigue (i.e., the deficient drive of motor cortical output attenuating performance or even stopping the activity)[55] is expected to intervene to a greater extent in volitional tests than non-volitional tests. Therefore, the preferred protocol for quadriceps endurance assessment is dependent on the aim of the measurement. Non-volitional tests are less influenced by the severity of dyspnoea and the motivation and cooperation of the patient and are presumably a truer reflection of fatigue mechanisms within the peripheral muscle. However, these tests are less practical because they require more time and trained personnel and are not always tolerated by patients. This latter is supported by **Chapter 7** in which 5 of the 21 patients (24%) had an invalid non-volitional endurance test. Furthermore, the purpose of muscle function tests in clinical settings is also to prescribe an individualized exercise training. Dyspnoea and central fatigue intervene in the performance of these endurance training exercises, and thus may volitional tests perhaps be more suitable in a clinical setting.

CONCLUSIONS

Taken together, this thesis underpins the evidence that functional performance, exercise capacity, exercise tolerance, and peripheral muscle function are 4 distinctive, but partly related, domains of physical performance. All 4 domains should be evaluated to identify appropriate targets for an effective and individualized exercise intervention.

The present thesis demonstrates that the SPPB is a valid and responsive outcome measure for functional performance in patients with moderate-to-severe COPD. Furthermore, the performance of all 3 SPPB subtests is advisable in current clinical practice because they provide distinct information about the patient's mobility and frailty. Nevertheless, it should be noted that the balance standing subtest might not be adequately sensitive to pick up mild balance deficits in these patients. This knowledge will help clinicians to screen for a reduced mobility and balance in patients with COPD and therefore supports them to establish an effective treatment strategy.

PROs and exercise test outcomes establish different disease-related aspects in patients with COPD. Thus, it is recommended that exercise tests are supported by PROs to obtain a comprehensive overview of the patient and provide a more detailed insight in the efficacy of interventions. Moreover, this thesis substantiates a large interindividual variability in the outcome measure of the ESWT exercise test

(Tlim), which complicates the interpretation of intervention efficacy. Unfortunately, the current findings are largely not able to explain this variability. So, until a more specific prediction formula is available, a second ESWT is recommended when Tlim exceeds 3-8 minutes.

This thesis shows that an improvement of >7% or >8% in volitional isokinetic quadriceps muscle strength following a PR program can be considered as a true effect in female and male patients with COPD respectively. The effectiveness of a PR program on volitional isokinetic quadriceps muscle endurance depends on the outcome measures of endurance that are being applied. Nevertheless, the current thesis also indicates that a great extent of similarity in quadriceps muscle endurance can be assessed using either volitional isometric or isokinetic contractions. However, volitional and non-volitional outcome measures evaluate partly different aspects of quadriceps muscle endurance in patients with COPD. Accordingly, volitional and non-volitional outcome measures of quadriceps endurance should not be used interchangeably. Finally, this thesis reports a greater feasibility, in terms of percentage patients with a valid test performance, for the volitional isometric protocol than the volitional isokinetic and non-volitional isometric protocols. A better understanding of these protocols will guide clinicians and researchers to make an informed decision about which protocol is most suitable to perform in their specific context.

FUTURE DIRECTIONS

Even though this thesis has brought new insights into the feasibility, validity, and responsiveness of physical performance measures in patients with COPD, some aspects need to be addressed in the future. Firstly, validation of the established MID for 5STS in **Chapter 3** is needed to help clinicians and researchers interpret intervention efficacy, ideally using both anchor-based and distribution-based methods. Furthermore, additional studies on determinants of ESWT Tlim are necessary to develop an accurate prediction formula for ESWT pace to reduce the ESWT Tlim variability. As previously mentioned, this will improve the interpretation of intervention efficacy and, in turn, lead to the development of more optimal endurance training programs. Lastly, the fatiguability of the quadriceps muscles is known to be greatly reduced in patients with COPD but only limited studies have focused on the effectiveness of appropriate exercise interventions on the fatiguability of peripheral muscles in these patients. Thus, future research is needed to assess the effectiveness of exercise interventions targeting the fatiguability of the quadriceps muscle in patients with COPD. Accordingly, it is important to evaluate which quadriceps muscle endurance outcomes can be used to optimize effective individualized exercise programs.

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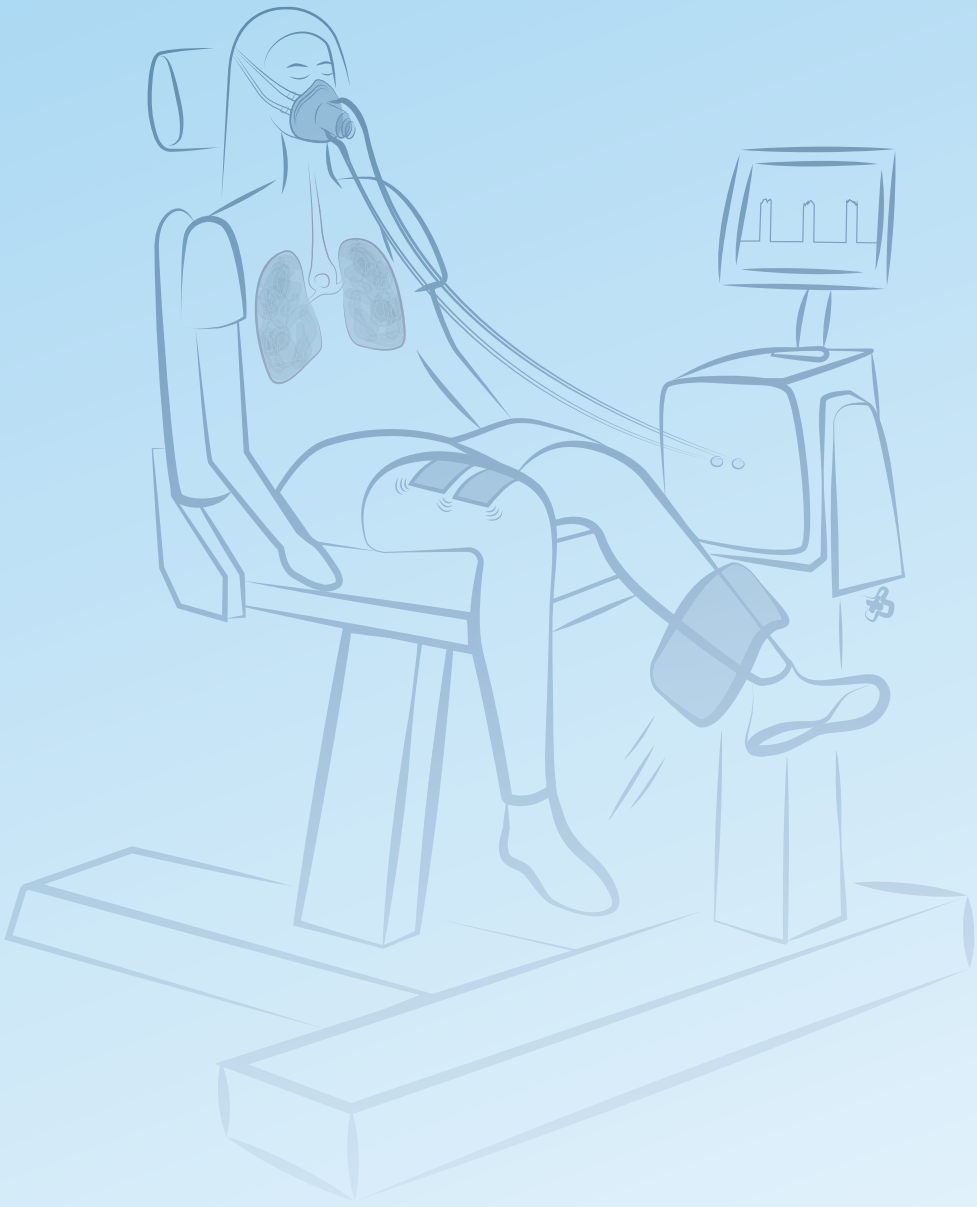

Addenda

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SAMENVATTING

Beperkingen in fysieke prestaties komen veel voor bij patiënten met chronische obstructieve longziekten (COPD). De consequenties zijn ingrijpend en omvatten, onder andere, een verminderde kwaliteit van leven, verhoogde kans op ziekenhuisopname, en zelfs een vergroot risico op overlijden. De onderliggende mechanismen van de achteruitgang in fysieke prestaties zijn multifactorieel en variëren per patiënt. Daarom is het klinisch relevant om de beperkingen van fysieke prestaties uitgebreid en tijdig in kaart te brengen, zodat een gepersonaliseerde en gerichte (trainings-)interventie voorgeschreven kan worden. Het doel van dit proefschrift is om de kennis van de uitvoerbaarheid, validiteit, en responsiviteit van fysieke prestatie metingen bij patiënten met COPD uit te breiden. In dit proefschrift is fysieke prestatie onderverdeeld in functionele prestatie (Deel I), inspanningscapaciteit en -tolerantie (Deel II), en perifere spierfunctie (Deel III) (**Hoofdstuk 1**).

Deel I – Functionele prestatie

De short physical performance battery (SPPB) wordt gebruikt om beperkingen in mobiliteit en balans (d.w.z. functionele prestatie) in kaart te brengen bij patiënten met COPD. Deze test bestaat uit drie onderdelen: balans test, 4 meter looptest, en herhaalde zit-staan test. In **Hoofdstuk 2** is de validiteit van de SPPB onderzocht bij een grote groep patiënten met COPD (n=900). Aan de hand van univariate en multivariate regressieanalyses is gebleken dat de SPPB-totaalscore correleert met uitkomstmaten van de drie overige domeinen van fysieke prestatie, te weten inspanningscapaciteit, -tolerantie, en perifere spierfunctie. In andere woorden, patiënten met een slechtere mobiliteit en balans hebben over het algemeen een verminderde inspanningscapaciteit, inspanningstolerantie, en perifere spierfunctie. Echter kunnen patiënten met een behouden mobiliteit en balans ook beperkingen ervaren in (een van) de drie overige domeinen van fysieke prestatie, waardoor de SPPB niet gebruikt kan worden om limitaties in inspanningscapaciteit, en -tolerantie, en perifere spierfunctie aan te tonen. Daarbij komt uit **Hoofdstuk 2** naar voren dat slechts 29% van de totale variatie in SPPB-totaalscore door deze maten van fysieke prestatie bepaald wordt. Dit benadrukt de toegevoegde waarde van het implementeren van functionele prestatie metingen bij patiënten met COPD in combinatie met andere fysieke testen. Daarnaast is de SPPB niet geschikt om patiënten te identificeren in behoeven van longrevalidatie. **Hoofdstuk 3** beschrijft de responsiviteit en minimaal klinisch significant verschil van de SPPB na het volgen van een longrevalidatie programma. De data tonen aan dat de 4 meter looptest, herhaalde zit-staan test, en de SPPB-totaalscore responsief zijn voor longrevalidatie.

Een minimaal klinisch significant verschil voor de SPPB-totaalscore is 1 punt, voor de 4 meter looptest 0.05–0.13 m/s en voor de herhaalde zit-staan test 2.19–6.33 seconden. Met name het minimaal klinisch significante verschil voor de SPPB-totaalscore kan in de praktijk gebruikt worden om aan te tonen of de mobiliteit en balans van een (groep) patiënt(en) met COPD verbeterd is na het volgen van een longrevalidatie programma in Nederland. Aanvullend onderzoek naar de klinisch relevante verschillen van de twee subtesten van de SPPB is gewenst voordat deze toegepast worden in de praktijk.

Deel II – Inspanningscapaciteit en -tolerantie

Patiënt-gerapporteerde uitkomsten (PROs) geven inzicht in het perspectief van de patiënt over de impact van de ziekte op zijn dagelijkse leven (bv. in kader van gezondheid, kwaliteit van leven, fysieke prestatie), en kunnen vastgesteld worden door vragenlijsten. Doordat deze methode makkelijker uitvoerbaar is dan het afnemen van inspanningstesten, is het klinisch relevant om inzicht te krijgen in het verband tussen PROs en uitkomsten van inspanningstesten. In **Hoofdstuk 4** is de relatie onderzocht tussen verschillende PROs en uitkomsten van inspanningstesten in kader van fysieke prestatie. Hieruit is gebleken dat er geen-tot-zwakke correlaties zijn tussen PROs en uitkomsten van deze inspanningstesten. Dit benadrukt dat PROs het perspectief van de patiënt over de impact van COPD op zijn dagelijkse leven en/of zijn gezondheid in kaart brengen dat niet bepaald wordt door inspanningstesten. Aan de andere kant geven PROs geen objectief en accuraat inzicht in de fysieke prestatie van een patiënt. Hierdoor dienen PROs en uitkomsten van inspanningstesten elkaar aan te vullen en niet elkaar te vervangen.

De endurance shuttle walk tes (ESWT) wordt gebruikt bij patiënten met COPD om de inspanningstolerantie in kaart te brengen. De (getolereerde) duur waarop ze de sub-maximale loopsnelheid, bepaald op basis van de incremental shuttle walk test, kunnen volhouden, wordt als maat gebruikt voor de inspanningstolerantie. Desondanks rapporteren veel recente studies een grote variabiliteit in de getolereerde duur van de ESWT. Dit compliceert de interpretatie van interventie effectiviteit en resulteert in een groter aantal patiënten dat nodig is om effecten aan te tonen in klinische studies. Om te zoeken naar verklaringen voor deze grote variabiliteit is in **Hoofdstuk 5** gekeken naar correlaties tussen verschillende klinische maten, zoals longfunctie, inspanningscapaciteit, inspanningstolerantie, en spiersterkte, met de getolereerde duur op de ESWT. Significante univariate correlaties tussen de maximale zuurstofopname, getolereerde duur op de fietsduurtest, maximale loopsnelheid, en de getolereerde duur van de ESWT tonen aan dat inspanningscapaciteit en -tolerantie niet geheel onafhankelijke componenten zijn van fysieke prestatie.

De resultaten beschreven in **Hoofdstuk 5** onderbouwen daarmee het belang van het meten van de verschillende fysieke prestatie componenten bij patiënten met COPD. Een multivariate regressie model toont aan dat ~30% van de variatie in de getolereerde duur op de ESWT verklaard kan worden door de klinische maten die in **Hoofdstuk 5** zijn bestudeerd. Dit maakt het momenteel lastig om de grote variatie in getolereerde duur te verklaren en vervolgens te verkleinen. Een mogelijke optie voor het verkleinen van de variabiliteit is het afnemen van een tweede ESWT als de getoleerde duur van de eerste ESWT buiten 3-8 minuten valt.

Deel III – Perifere spierfunctie

Naast een verslechtering van de longfunctie, ervaren patiënten met COPD doorgaans een afname in het functioneren van hun perifere spieren. Het duurvermogen van de perifere spieren lijkt meer aangedaan dan de maximale spiersterkte. Bovendien dienen deze twee separate aspecten van spierfunctie op verschillende manieren getraind te worden. Als gevolg hiervan is het klinisch relevant om onderzoek uit te voeren naar zowel de maximale sterkte als het duurvermogen van de perifere spieren bij patiënten met COPD. In **Hoofdstuk 6** is gekeken naar de uitvoerbaarheid, responsiviteit, en minimaal klinisch significante verschillen van een isokinetisch protocol om het duurvermogen van de quadricepsspier te bepalen bij patiënten met COPD tijdens een longrevalidatie programma. Hieruit blijkt dat 3 van de 4 patiënten aan het begin van de longrevalidatie de test correct (d.w.z. op basis van vooraf bepaalde criteria) uitvoert. Patiënten die de test correct uitvoeren zijn sterker en hebben een betere inspanningscapaciteit dan patiënten die deze test niet correct uitvoeren. Patiënten met een correct uitgevoerde test aan het begin én einde van het longrevalidatie programma laten een verbetering zien in de peak torque en total work, maar niet in de work fatigue index. De minimaal klinisch significante verschillen voor mannelijke en vrouwelijke patiënten waren respectievelijk 6–7 Nm en 4–5 Nm voor peak torque en 97–135 J en 62–99 J voor total work. Toekomstige studies zullen de klinische relevantie van deze verschillen moeten uitwijzen door gebruik te maken van ankermethodes. Eventuele aanbevelingen voor ankers zijn de getolereerde duur op de ESWT en SPPB-totaalscore.

Tot op heden is er geen consensus over de meest effectieve en geschikte methode om het duurvermogen van de perifere spieren in kaart te brengen bij patiënten met COPD. **Hoofdstuk 6** toont aan dat een kwart van de patiënten met COPD de duurtest op basis van vrijwillige spiercontracties niet correct uitvoert. In **Hoofdstuk 7** is de relatie onderzocht tussen het duurvermogen van de quadricepsspier op basis van vrijwillige isometrische en isokinetische spiercontracties ten opzichte van elektrische geïnduceerde spiercontracties. De resultaten indiceren geen significante

correlatie tussen het duurvermogen van de quadricepsspier bepaald door middel van vrijwillige en gestimuleerde spiercontracties. Dit suggereert dat deze protocollen verschillende aspecten van het duurvermogen van de quadricepsspier in kaart brengen en dus niet als vervanging van elkaar gebruikt kunnen worden.

Hoofdstuk 8 bevat een samenvatting en discussie van de belangrijkste bevindingen van dit proefschrift, evenals een algehele conclusie en aanbevelingen voor toekomstig onderzoek. De voornaamste boodschap van dit proefschrift is dat functionele prestatie, inspanningscapaciteit en -tolerantie, en perifere spierfunctie vier verschillende, maar gedeeltelijk gerelateerde, domeinen zijn van fysieke prestatie. Daarom is het van belang om alle vier deze domeinen uitgebreid en tijdig in kaart te brengen bij patiënten met COPD om zo patiënt-specifieke aangrijppunten te identificeren voor effectieve en geïndividualiseerde behandelingen. Daarnaast brengt deze thesis een aantal suggesties voort voor toekomstige studies, waaronder: 1) validatie van het minimaal klinisch significant verschil voor de herhaalde zit-staan test en spierfunctietesten in patiënten met COPD d.m.v. ankermethodes; 2) bepalen van determinanten van de getolereerde duur op de ESWT bij patiënten met COPD om vervolgens een predictie formule op te stellen; en 3) het onderzoeken van de effectiviteit van inspanningsinterventies op de vermoeidheid van de perifere spieren bij patiënten met COPD.

IMPACT PARAGRAPH

The findings presented in this thesis contribute to a more profound understanding of physical performance outcome measures in patients with chronic obstructive pulmonary disease (COPD). This impact paragraph offers a thoughtful analysis of the scientific and social implications of these findings. It does so by addressing four key questions: 1) What is the main objective of the research described in the thesis and what are the most important results and conclusions? 2) What is the (potential) contribution of the results from this research to science and social sectors? 3) To whom and why are the research results relevant? and 4) How can these target groups be involved in and informed about the research results, so that the knowledge gained can be used in the future?

Main objective, results, and conclusions

Patients with COPD frequently experience limitations in their physical performance, which have a major clinical impact on the patient's daily life. The underlying mechanisms are multifactorial and widely diverse between patients. There are effective (exercise) interventions available that are known to improve the patient's physical performance. Therefore, timely and adequate assessment of physical performance is highly relevant. The main objective of this thesis was to expand the existing knowledge on the feasibility, validity, and responsiveness of commonly used physical performance outcome measures in patients with COPD.

The first part of this thesis demonstrates that the Short physical performance battery (SPPB) is a valid and responsive outcome measure for functional performance in patients with moderate-to-severe COPD following a pulmonary rehabilitation (PR) program. Furthermore, the performance of all three SPPB subtests is advisable in current clinical practice because they provide dissimilar information about the patient's mobility and balance. The second part of this thesis confirms that patient reported outcomes (PROs) establish different disease-related aspects in patients with COPD than objective physical performance exercise tests. Therefore, PROs should be performed in complement to exercise tests to acquire the patient's perspective on the impact of COPD on their daily life in addition to the obtjectively assessed physical performance. Furthermore, this thesis adds to the existing evidence that a large variability in the tolerated duration of the endurance shuttle walk test is present. However, this large variability cannot be explained by other clinical measures that were assessed in this thesis. The last part of this thesis reports that three in four patients with COPD who are eligible for PR performed the volitional isokinetic quadriceps muscle endurance test correctly. A superior feasibility was

found for isometrically assessed muscle endurance. Furthermore, the isokinetic protocol is able to pick up improvements following a PR program, but this does not apply for all outcome measures of the test. Both the isometric and isokinetic protocols evaluate to a great extent similar aspects of quadriceps muscle endurance, which is not the case when using a non-volitional protocol with repetitive electrical stimulations. Therefore, these findings suggest that volitional and non-volitional outcome measures evaluate partly different aspects of quadriceps muscle endurance in patients with COPD.

Taken together, this thesis underpins the evidence that functional performance, exercise capacity, exercise tolerance, and peripheral muscle function are four distinct yet interconnected domains of physical performance. Therefore, this thesis recommends evaluating these four domains to obtain a comprehensive overview of the patient and prescribe an effective and patient-tailored (exercise) intervention.

Potential contribution to science and social sectors

Timely identification of impaired physical performance in patients with COPD is clinically relevant, as poor physical performance can result in an increased risk of hospitalization, poor quality of life, and even premature mortality. To date, several (exercise) interventions are available to counteract these limitations in physical performance. The results of this thesis demonstrate that functional performance, exercise capacity, exercise tolerance, and peripheral muscle function are four dissimilar domains of physical performance. Therefore, this thesis highlights the importance of assessing multiple, if not all, domains of physical performance in patients with COPD using valid, feasible, reliable, and responsive outcome measures. The obtained results of multiple exercise tests in combination with PROs will provide healthcare professionals with an extensive overview of the patient's physical performance and the patient's perspective on the impact of COPD on their daily life. Information regarding the severity and specific domain of the impairment can be used by healthcare professionals to prescribe a more effective (exercise) intervention. In turn, this is expected to result in greater improvements in physical performance in patients with COPD, which might eventually lead to greater improvements in quality of life, and greater reductions in mortality rate and hospital admissions.

Furthermore, chapter 7 demonstrates that volitional and non-volitional outcome measures of quadriceps muscle endurance are not related. These results raise awareness among healthcare professionals and researchers that those outcome measures should not be used interchangeably.

In addition, this thesis provides minimal important differences for the SPPB and the volitional isokinetic quadriceps muscle test. This knowledge will help healthcare professionals, clinicians, and researchers interpret the effectiveness of interventions in individuals and groups of patients with COPD following a PR program in the Netherlands.

Target group

The research results of this thesis are relevant to multiple target groups, like healthcare professionals, researchers, and patients. First, it raises awareness among healthcare professionals of the need to assess physical performance routinely and extensively in patients with COPD. Furthermore, the obtained knowledge will help healthcare professionals and researchers adequately select, perform, and interpret exercise tests. In turn, this will hopefully lead to an improved and even more patient-tailored prescription of (exercise) interventions to counteract the limitations in physical performance. Therefore, patients will indirectly benefit from the results of this thesis, as the improved screening of physical performance and even more patient-tailored prescription of exercise interventions are expected to improve their quality of life and decrease the risk of hospitalization and mortality. At last, the research results are relevant for other researchers as they provide more insight into the assessment of physical performance in patients with COPD and bring forth novel leads for future research.

Activities

Several steps have been undertaken to engage and inform the target groups of the research results with the aim that the gained knowledge is effectively used in the future. The results of this thesis have been or will be published in international, peer-reviewed journals and have been presented at national and international congresses and meetings, and within multiple PR centres. This is an effective strategy to inform other researchers and healthcare professionals about our novel findings.

A

DANKWOORD

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CURRICULUM VITAE

Anouk Stoffels was born on November 15th, 1994 in Venlo, the Netherlands. She completed her secondary school (VWO) at Den Hulster in Venlo in 2012. Subsequently, she started her bachelor Biomedical Sciences with a focus on Human Movement Sciences at Maastricht University. She completed an internship at the Orthopedics department of Zuyderland in Heerlen. The topic of her internship was *physical activity of patients with spinal stenosis*. Following the completion of her bachelor's degree in 2016, she began her master's program in Biomedical Sciences at Radboud University in Nijmegen. Given her keen interest in human physiology, she decided to specialize in Human Movement Sciences with a focus on consultancy. She completed her consultancy internship at the Koninklijk Nederlands Korfbalverbond (KNKV) in Zeist, where she wrote an advisory report on *the optimal pathways for playing korfball at a professional level.* She executed her research internship at the Physiology department of Radboudumc in Nijmegen. During this period she investigated *the effect of physical training on the peripheral muscle function in statin users with and without muscle complaints*. She obtained her master's degree (cum laude) in 2018.

In 2019, she started her PhD project at Merem in Hilversum, in close collaboration with CIRO in Horn, and the Research Institute of Nutrition and Translational Research in Metabolism (NUTRIM) in Maastricht. She aimed to investigate the *effect of beta-alanine supplementation in combination with non-linear periodized exercise training in patients with chronic obstructive pulmonary disease*. As a result of various unexpected factors, her PhD project took a different direction, focusing on *physical performance measures in patients with chronic obstructive pulmonary disease*. Additionally, the project was relocated to the department of Pulmonary Diseases at the Radboudumc in Nijmegen. Throughout this period, she concurrently provided education activities at the Radboud University in Nijmegen and she achieved her Basis Kwalificatie Onderwijs (BKO) certificate. The findings of her thesis have been published in international, peer-reviewed journals and have been presented at national and international congresses and meetings.

Currently, Anouk holds the position of senior researcher for the municipality of Venlo.

A

LIST OF PUBLICATIONS

Scientific articles in international journals

Meys R, Sillen MJ, Franssen FME, **Stoffels AAF,** Wouters EFM, van Hees HWH, van den Borst B, Klijn PH, Spruit MA; BASES-consortium. Impact of mild-to-moderate exacerbations on outcomes of neuromuscular electrical stimulation (NMES) in patients with COPD. Respir Med. 2020 Jan;161:105851. doi: 10.1016/j.rmed.2019.105851. Epub 2019 Nov 28. PMID: 32056725.

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Conference contributions

Stoffels AAF. Beta-alanine supplementation in patients with COPD receiving NLPE. 2019. Oral presentation. PhD Introduction days, Maastricht, the Netherlands

Stoffels AAF. BASE-TRAIN trial – effects of beta-alanine supplementation in COPD patients receiving exercise training – rationale and study design. 2019. Oral presentation. Netherlands Respiratory Society (NRS) Young Investigator Symposium, Amsterdam, the Netherlands

Stoffels AAF, Meys R, De Brandt J, van Hees HWH, Franssen FME, Sillen MJH, Burtin C, Klijn P, van den Borst B, Otker JM, Donkers J, Derave W, Spruit MA. Beta-alanine supplementation in COPD patients receiving non-linear periodized exercise (NLPE) training or neuromuscular electrical stimulation (NMES): protocol of two randomized, double-blind, placebo-controlled trials. 2020. Poster presentation. Symposium: Recent advances in rehabilitation of cardiorespiratory and internal diseases, Hasselt, Belgium

Stoffels AAF, van den Borst B, Donders ART, Peters JB, Klaassen MP, van Helvoort HAC, Meys R, Klijn P, Burtin C, Derave W, Franssen FME, van 't Hul AJ, Spruit MA, van Hees HWH. Correlates of variability in endurance shuttle walk test time in patients with COPD. 2020. Poster presentation. European Respiratory Society (ERS) International Congress, virtual congress.

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