2014•2015
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de revalidatiewetenschappen en de kinesitherapie

Masterproef

Relations between cardiopulmonary function during exercise and exercise tolerance in patients with COPD

Promotor :
Prof. dr. Dominique HANSEN

Maarten Cuypers , Tine Vos
Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie

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Acknowledgement

Sincere thanks go to all the persons who contributed to this master thesis. First of all, we would like to thank our promotor, Prof. Dr. Dominique Hansen. Without his advice, arrangement of the study design and guidance in the writing process, we would not have been able to complete this research. Second of all, our thanks go out to the staff of the Rehabilitation- and Health centre (ReGo) of the Jessa Hospital in Hasselt. They supervised the cardiopulmonary exercise tests and rehabilitation program of the patients with chronic obstructive pulmonary disease. A grateful mention goes out to the personnel, nurses and doctors of the Jessa Hospital in Hasselt. They supervised the spirometry and cardiopulmonary exercise tests. Last but not least, we would like to thank our mothers and father for the mental support during the processing of this master thesis.

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Research context

Master students in Rehabilitation Sciences and Physiotherapy of the faculty Medicine and Life Sciences at Hasselt University have to write a master project in the first and second master year. This master project is not part of ongoing research, but data were collected from the subjects that participated in an exercise program in Rehabilitation- and Health centre (ReGo) of the Jessa Hospital in Hasselt. They were redirected with the diagnosis of chronic obstructive pulmonary disease (COPD) and performed a lung function test during rest and a cardiopulmonary exercise test.

This study about the cardiopulmonary function during exercise in chronic obstructive pulmonary disease (COPD) is situated in the research field of the rehabilitation of internal diseases. COPD is an important cause of morbidity and mortality worldwide[1]. Characteristics of obstructive lung disease are dyspnea, coughing and excessive sputum production. COPD patients also experience exercise intolerance. Ventilatory constraints, pulmonary gas exchange abnormalities, peripheral muscle dysfunction, cardiac dysfunction, or any combination of these anomalies are potential determinants of exercise intolerance[2]. Previous studies about predictors of exercise intolerance in COPD patients reported conflicting findings. We hypothesize that the cardiopulmonary parameters during exercise determine peak oxygen consumption and peak workload.

Master project two is part of a duo master study. Both students did not have participated in the elaboration of the study design and the methods used, but they both collected data of the participants and the tests performed in Jessa Hospital and ReGo. The statistical analysis was performed by Tine Vos with the help of promotor Prof. Dr. Hansen. The introduction was written by Maarten Cuypers, materials and methods and results were written by Tine Vos. The students debated with Prof. Dr. Hansen about the results that were found and Maarten Cuypers and Tine Vos wrote the discussion together.

Reference list research context

1. Pocket Guide To COPD Diagnosis, Management, And Prevention. 2014, 2014.
2. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med.* 2013;188(8):e13-64.

Abbreviation list

BF: Breathing frequency, number of breaths taken in one minute

BMI: Body mass index, an indicator of body density as determined by the relationship of body weight to body height (weight in kg/height in m^2)

CO_2: Carbon dioxide

COPD: Chronic obstructive pulmonary disease, a disease of chronic diffuse irreversible airflow obstruction

CPET: Cardiopulmonary exercise testing, controlled physical activity which is performed in order to allow assessment of physiological functions, particularly cardiovascular and pulmonary, but also aerobic capacity

DLco: Diffusing capacity for the lungs measured using carbon monoxide

DLco/VA: Diffusing capacity for carbon monoxide per unit of alveolar volume

$EqCO_2$: Carbon dioxide output equivalent (VE/VCO_2), the amount of air which is necessary in order to exhale one liter of carbon dioxide

EqO_2: Oxygen uptake equivalent (VE/VO_2), the amount of air which is necessary in order to inhale one liter of oxygen

FEV_1: Forced expiratory volume in one second, measure of the maximum amount of air that can be expelled in one second during a forced vital capacity maneuver

FEV_1 %pred: The ratio of FEV_1 to the predicted value of FEV_1

FEV_1/FVC: Tiffeneau index

FVC: Forced vital capacity, the maximal volume of air exhaled with maximally forced effort from a maximal inspiration

FVC %pred: The ratio of FVC to the predicted value of FVC

HR: Heart rate, number of heartbeats per minute

MIP: Maximal inspiratory pressure, the maximal pressure that can be produced by the patient trying to inhale through a blocked mouthpiece

MVV: Maximal voluntary ventilation, maximum amount of air that can be inhaled and exhaled within one minute

O_2/HR: Oxygen pulse, oxygen uptake divided by the heart rate

$PETCO_2$: End-tidal CO_2 pressure

$PETO_2$: End-tidal oxygen pressure, reflection of the alveolar oxygen tension

$P_{0,1}$: Airway occlusion pressure

ReGo: Rehabilitation- and health centre at Hasselt

RER: Respiratory exchange ratio (VCO_2/VO_2), the ratio between CO_2 output and O_2 uptake per unit of time

Ti: Inspiratory time, total time of one inspiration

Ti/Ttot: Inspiratory time/total respiratory cycle time

TLC: Total lung capacity, the volume of air contained in the lungs at the end of a maximal inspiration, the sum of vital capacity and residual volume

TLC %pred: Total lung capacity in relation to predicted value of total lung capacity

T-tot: Total respiratory cycle time, total time of one breath

T-ex: Time of expiration, total time of one expiration

VA: Alveolar ventilation, the volume of gas per unit time that reaches the alveoli

Vde: Dead space ventilation, the volume of gas per unit time that does not reach the alveoli, but instead remains in the airways

VE: Minute ventilation, volume of expired air exhaled from the lungs in one minute

VCO_2: Carbon dioxide output, volume of carbon dioxide that you breathe out after transporting oxygen through your body

VO_2: Oxygen uptake, volume of O_2 extracted from inspired air in a given period of time

VO_2peak: Peak oxygen uptake, the peak volume of oxygen that can be utilized in one minute during maximal or exhaustive exercise

VO_2peak %pred: VO_2peak in relation to predicted value of VO_2peak

Vt: Tidal volume, the volume of air inspired or expired during each respiratory cycle

Vtin: Inspiratory tidal volume, the volume of air inspired during each respiratory cycle

Vtex: Expiratory tidal volume, the volume of air expired during each respiratory cycle

Wpeak: Peak workload, the highest amount of work performed by an individual during an exercise test

Abstract

Background: Exercise intolerance in chronic obstructive pulmonary disease (COPD) could be caused by ventilatory anomalies, peripheral muscle dysfunction and cardiac dysfunction. Previous studies reported conflicting findings concerning the cardiopulmonary factors determining peak oxygen uptake (VO_2peak) and peak workload (Wpeak) in COPD patients. The purpose of this study was to investigate which factors determine exercise tolerance in COPD and whether changes in these determinants explain changes in exercise tolerance during follow-up.

Methods: In part 1, a cross-sectional study took place. Sixty COPD patients performed a spirometry and a cardiopulmonary exercise test (CPET). Predictors of exercise tolerance were examined. In part 2, a longitudinal observational study took place. Twelve COPD patients completed an exercise training intervention. A study on relations between changes in cardiopulmonary function and changes in exercise tolerance was performed.

Results: Significant predictors of VO_2peak are peak carbon dioxide output (VCO_2peak), peak respiratory exchange ratio (RERpeak), peak oxygen pulse (O_2/HRpeak), peak heart rate (HRpeak) and total lung capacity %predicted (TLC %pred). Significant predictors of Wpeak are VCO_2peak and body mass index (BMI). Significant predictors of ΔVO_2peak during follow-up are the change in peak inspiratory tidal volume (ΔVtinpeak) and the change in peak inspiratory time/total respiratory cycle time (ΔTi/Ttot). Significant predictors of ΔWpeak are ΔO_2/HRpeak and ΔRERpeak.

Conclusions: Resting lung function test has a limited predictability on exercise capacity, but certain CPET variables are predictive of (changes in) exercise tolerance in COPD patients. Physicians and physical therapists should strive for an optimization of pulmonary, muscle and cardiac function to enhance exercise tolerance in COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) is a severe, progressive inflammatory lung disease[1]. In a recent study[2] it was described that the overall COPD prevalence ranged from seven to twelve percent based on data from twelve countries across the world. The incidence of COPD was higher in men than in women (with a relative risk of one and a half fold higher in men). With an increase in age, a higher prevalence of COPD follows[3].

Patients with COPD suffer from an irreversible airflow limitation. Other characteristics of this disease are mucus hypersecretion and coughing[1]. COPD patients are typically divided in two phenotypes: emphysema and chronic bronchitis. COPD is not limited to the lungs but has an impact on the whole body. It is a systemic disease associated with cardiovascular anomalies, osteoporosis, skeletal muscle dysfunction and exercise intolerance[4].

Exercise intolerance is an often observed consequence of COPD. Previous studies have examined the causes of such exercise intolerance in COPD. It was considered that ventilatory constraints, pulmonary gas exchange abnormalities, peripheral muscle dysfunction, cardiac dysfunction, or any combination are decisive determinants of exercise intolerance[4].

Previous studies have tried to examine predictors of peak oxygen uptake (VO_2peak)[5-9]. These studies reported that maximal voluntary ventilation (MVV), forced expiratory flow, body surface area, diffusing capacity for the lungs measured using carbon monoxide (DLco), forced vital capacity (FVC), maximal inspiratory pressure (MIP), dead space volume/tidal volume (Vd/Vt), forced expiratory volume in one second (FEV_1), resting minute ventilation (VE), weight, age, ratings of perceived exertion and six minute walking distance (6MWT) predicted VO_2peak. Age, body weight, Tiffeneau index (FEV_1/VC), MIP and airway occlusion pressure/tidal volume/inspiratory time ($P_{0,1}$/Vt/Ti) predicted the peak workload (Wpeak). However, there were significant differences in outcomes between these studies. Moreover, only one study used cardiopulmonary exercise test (CPET) parameters during exercise to predict exercise tolerance in COPD[10].

Exercise testing is essential for patients with COPD suffering from an exercise limitation. This is due to the fact that airway obstruction alone accounts for 16 to 36% of the variance in exercise performance. This means that there are others factors contributing to exercise limitation[11].

An important additional contributor to exercise intolerance in COPD are dysfunctional lower limb muscles. COPD patients suffer from muscle weakness due to muscle atrophy, increased muscle fatigue and impaired energy production[12]. But also ventilatory constraints, pulmonary gas exchange abnormalities and cardiac dysfunction that emerge during exercise could have a profound impact on exercise tolerance in COPD[4].

The purpose of this study was to investigate which factors determine exercise tolerance in COPD, and whether changes in these determinants explain changes in exercise tolerance. We hypothesized that

pulmonary function parameters are not highly predictive for VO_2peak and Wpeak. Instead, we assumed that cardiopulmonary function during exercise has a better predictive value for VO_2peak and Wpeak.

Materials and Methods

Design and ethical approval

This study was a combination of a retrospective cross-sectional study (part 1) and a retrospective longitudinal observational study (part 2). In part 1, baseline tests consisted of a pulmonary function test and a maximal CPET. In part 2, CPET was re-executed after an exercise program for 24 weeks. All subjects gave permission prior to collection of their test results. The flowchart of this study is shown in figure 1.

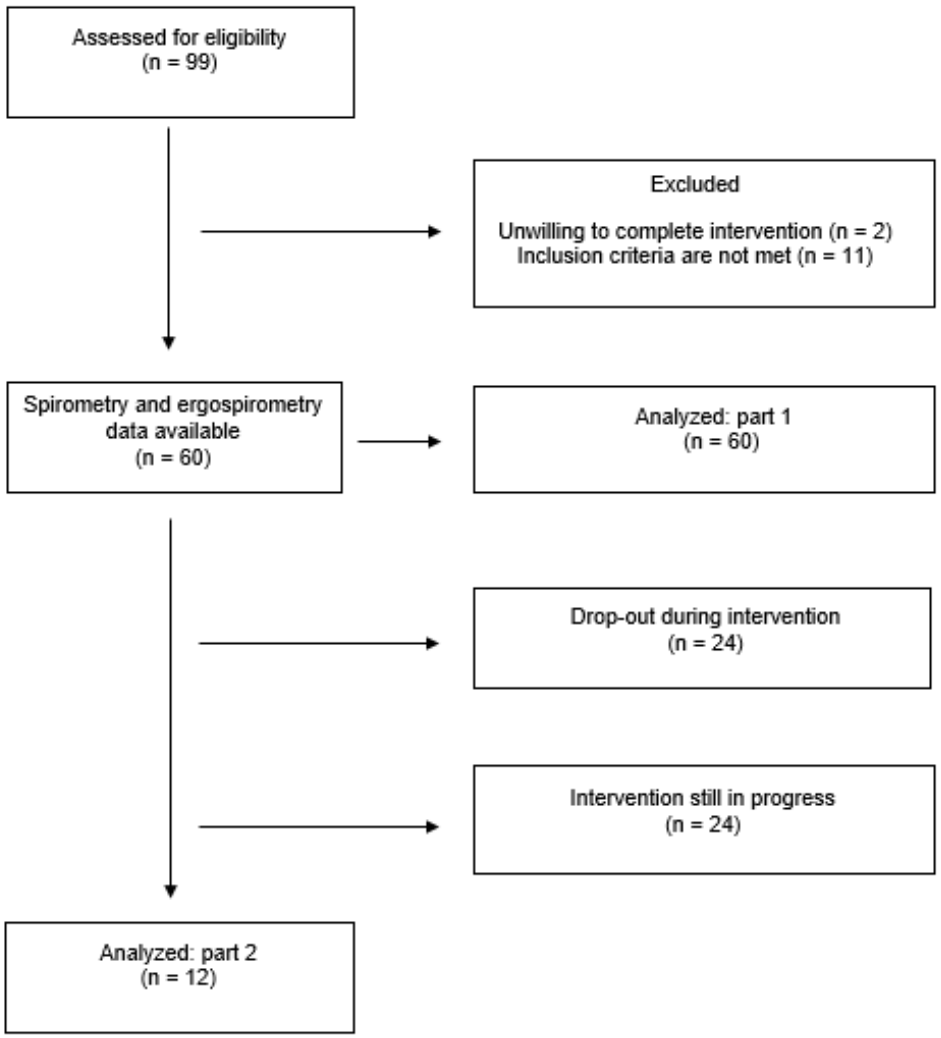

Figure 1 Study flow chart

Setting and participants

Part 1

Ninety-nine patients with diagnosis of COPD were redirected to Rehabilitation- and Health centre (ReGo) of Jessa Hospital at Hasselt for ambulatory pulmonary rehabilitation. These patients underwent a baseline spirometry and ergospirometry test. To be allowed to this study, spirometry test (with a post bronchodilator) Tiffeneau index had to be lower than 70%[13]. Patients unwilling or unable to complete the tests were excluded. The spirometry and ergospirometry data were available in sixty COPD patients with a mean age of 67.9 ± 7.7 years.

Table 1 Description of the sample in part 1 (n = 60)

General characteristics	Mean	SD
Sex (M:F)	36:24	
Smoker (Active: non active)	13:47	
Age (y)	67.9	7.7
Body length (cm)	167	9
Body weight (kg)	66	17
BMI (kg/m^2)	23.75	5.11
FEV_1 (L)	1.00	0.46
FEV_1 pred (%)	39.1	14.6
TLC (L)	6.4	1.4
TLC pred (%)	112	24
FVC (L)	2.3	0.8
FVC pred (%)	73.2	19.8
DLco/VA (mmol/min/kPa/L)	0.85	0.36
DLco/VA pred (%)	62	27
Tiffeneau (%)	42.4	10.3

SD: standard deviation, M: male, F: female, y: years, BMI: body mass index, FEV_1: forced expiratory volume in one second, FEV_1 pred: FEV_1 in relation to the predicted FEV_1 , TLC: total lung capacity, TLC pred: TLC in relation to the predicted TLC, FVC: forced vital capacity, FVC pred: FVC in relation to the predicted FVC, DLco/VA: diffusing capacity for carbon monoxide divided by the alveolar volume, DLco/VA pred: DLco/VA in relation to the predicted DLco/VA, Tiffeneau: FEV_1/FVC

Table 2 Medication use of subjects in part 1 (n = 60)

Medication	COPD patients
Bronchodilatator (n)	59
Mucolytics (n)	7
Vasodilator (n)	35
Antiplatelet (n)	17
Beta-blocker (n)	40
Diuretics (n)	9
Anti-inflammatory drug (n)	15
Corticosteroids (n)	54
Antibiotics (n)	12
Analgesic (n)	7
Anti-Allergic (n)	5
Blood glucose lowering (n)	3
Statin (n)	19
Sleeping drug (n)	7
Anti-depressant (n)	12
Benzodiazepine (n)	9
Thyroid hormone replacement drug (n)	2
Anti-psychotics (n)	1
Insulin (n)	3
Proton pump inhibitor (n)	21
Supplementary oxygen (n)	17
Osteoporotic treatment (n)	5

Part 2

The same sixty COPD patients followed an exercise program for 24 weeks. There was a drop out of 24 subjects due to different reasons and 24 subjects were not finished yet. Of twelve subjects, ergospirometry data after exercise training of 24 weeks were available in April 2015. Subject characteristics are summarized in table 3. Medication use is described in table 4.

Table 3 Description of the sample in part 2 (n = 12)

General characteristics	Mean	SD
Sex (M:F)	7:5	
Smoker (active: non active)	1:11	
Age (y)	68.1	5.1
Body length (cm)	167.0	10
Body weight (kg)	65	17
BMI (kg/m^2)	23.08	5.04
FEV_1 (L)	0.84	0.35
FEV_1 pred (%)	29.9	5.3
TLC (L)	6.7	1.6
TLC pred (%)	119	27
FVC (L)	2.2	0.7
FVC pred (%)	65.7	9.8
DLco/VA (mmol/min/KPa/L)	0.74	0.31
DLco/VA pred (%)	53	21
Tiffeneau index (%)	39.5	10.3

SD: standard deviation, M: male, F: female, y: years, BMI: body mass index, FEV_1: forced expiratory volume in one second, FEV_1 pred: FEV_1 in relation to the predicted FEV_1 , TLC: total lung capacity, TLC pred: TLC in relation to the predicted TLC, FVC: forced vital capacity, FVC pred: FVC in relation to the predicted FVC, DLco/VA: diffusing capacity for carbon monoxide divided by the alveolar volume, DLco/VA pred: DLco/VA in relation to the predicted DLco/VA, Tiffeneau: FEV_1/FVC

Table 4 Medication use in part 2 (n = 12)

Medication	COPD patients
Bronchodilatator (n)	12
Mucolytics (n)	0
Vasodilator (n)	7
Antiplatelet (n)	1
Beta-blocker (n)	0
Diuretics (n)	1
Anti-inflammatory drug (n)	2
Corticosteroids (n)	12
Antibiotics (n)	1
Analgesic (n)	1
Anti-allergic (n)	0
Blood glucose lowering (n)	1
Statin (n)	2
Anti-depressant (n)	2
Benzodiazepine (n)	2
Thyroid hormone replacement drug (n)	0
Anti-psychotics (n)	0
Sleeping drug (n)	2
Insulin (n)	0
Proton pump inhibitor (n)	2
Supplemental oxygen (n)	4
Osteoporotic treatment (n)	0

Measurements

Primary outcome measures were VO_2peak and Wpeak. Secondary outcome measures were parameters of ventilatory and cardiac function during exercise: peak carbon dioxide output (peakVCO_2, ml/min), peak breathing frequency (BFpeak, breaths/min), VEpeak (L/min), peak respiratory gas exchange ratio (RERpeak = VCO_2/VO_2), peak oxygen uptake equivalent (EqO_2peak = VE/VO_2), peak carbon dioxide output equivalent ($EqCO_2$peak = VE/VCO_2), peak expiratory tidal volume (Vtex peak, L), peak inspiratory tidal volume (Vtin peak, L), peak total time of one breath (t-tot peak, s), peak time of expiration (t-ex peak, s), peak dead space ventilation (Vde peak, ml), peak end-tidal oxygen pressure ($PETO_2$peak, mmHg), peak end-tidal carbon dioxide pressure ($PETCO_2$peak, mmHg), the peak relative proportion of inspiratory to total respiratory cycle time (Ti/Ttot peak, %), peak heart rate (HR peak, beats/minute), peak oxygen pulse (O_2/HRpeak, ml).

Spirometry

At baseline, long function tests were assessed in sixty subjects with a body plethysmograph or MasterScreen™ PFT system (CareFusion Corporation, Hoechberg, Germany) at Jessa Hospital at Hasselt. The spirometer was calibrated each morning and the ambient temperature was monitored between 19°C and 21°C. The test was performed following the ATS/ETS Task Force on lung function testing. The specialized respiratory nurse practitioner of Jessa Hospital gave the patient instructions about the test and demonstrated the test to the subject. The subject sat in a correct posture with the head slightly deviated. A nose clip was attached and the lips were closed around the mouthpiece. The subject inhaled maximally and then exhaled with maximal force until no more air can be expelled while maintaining an upright posture. This was repeated for a minimum of three maneuvers. More maneuvers were performed if necessary. The best attempt was saved. FEV_1 (L), FEV_1 %pred, total lung capacity (TLC, L), TLC %pred, FVC (L), FVC %pred, the diffusing capacity for carbon monoxide per unit of alveolar volume (DLco/VA, mmol/min/kPa/L) and DLco/VA %pred were measured. The Tiffeneau index was calculated from FEV_1 and FVC.

Ergospirometry

A maximal incremental cycle ergometer test was performed by sixty subjects following the statement of ATS/ACCP on cardiopulmonary exercise testing on an electrically braked cycle ergometer (Ergoline GmbH, Germany) at baseline (part 1) and after the 24-week intervention (part 2). The ergospirometer was calibrated every morning and ambient temperature was monitored between 19°C and 21°C. The patients were asked to abstain from smoking for at least eight hours. The morning of the test, patients were asked not to exercise and to take a light meal no less than two hours before the test. The test started with three minutes of resting. Then, participants cycled for three minutes without load. This was followed by an incremental phase of exercise every minute. The load rose five watt every minute till the patient reached complete exhaustion. The patient tried to achieve 70 revolutions per minute. Pulmonary gas exchange (Vmask™, Hans Rudolph inc, Kansas, USA) was measured continuously breath-by-breath and averaged every ten seconds. Heart rate was constantly monitored by a 12-lead ECG device. Wpeak, VO_2peak,

VCO_2peak, BFpeak, VEpeak, RERpeak, EqO_2peak, $EqCO_2$peak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETO_2$peak, $PETCO_2$peak, Ti/Ttot peak, HRpeak, O_2/HRpeak were measured during exercise. Length (cm) and body weight (kg) were assessed at baseline. Body mass index (BMI) was calculated from body weight and length assessment. Prediction of VO_2peak was calculated by the following formulae[14] Women predicted VO_2peak = 0,207-(0,027*age) + (0,0158*length) + (0,00899*weight). Men predicted VO_2peak = -0,332 - (0,031*age) + (0,023*length) + (0,0117*weight). Prediction of Wpeak was calculated by the following formulae[15]: Women predicted Wpeak = (age*-1,19) + (0,96*length) + 28,1. Men predicted Wpeak = (age*-1,78) + (0,65*weight) + (1,36*length) - 45,4.

Intervention

Twelve participants followed a supervised exercise program of sixty sessions. Frequency of the training sessions was three times per week, for approximately ninety minutes each session. The session consisted of strength, endurance and breathing exercises. Resistance exercises for the chest, shoulders, legs and abdominal muscles were performed. The exercises were performed for one minute with a maximum of three sets, depending on the fatigue of the patient. The patients chose the resistance themselves, they should be able to sustain this intensity for one minute. Endurance capacity was trained on a cycle ergometer and/or a treadmill. The patients started with an endurance time of ten minutes. Training load was calculated for each individual by the physician, in accordance with the first ventilatory threshold (aerobic threshold). The load was built up progressively during the exercise program and the patients trained at moderate intensity, using the Borg scale. After every training session, the training load and duration was noted. The breathing exercises consisted of exercise in chest breathing, abdominal breathing and flank breathing combined with huffing and autogenous drainage. Inhalation was performed through the nose and exhalation was performed through the mouth.

Statistical analysis

Statistical analyses were performed by using SPSS Statistics version 22.0 (IBM Corporation, Chicago, USA). Normality was tested with the Shapiro-Wilk test, which indicated that most data in part 1 were not normally distributed ($p < 0,05$). Therefore, non-parametric tests were applied. Spearman correlations were evaluated and a forward stepwise multivariate regression model was constructed to explore the relation between VO_2peak and ventilatory and cardiac parameters at rest and during peak exercise at baseline. Parameters examined on non-parametric correlations with VO_2peak %pred were age, gender, length, weight, BMI, FEV_1, FEV_1 %pred, TLC, TLC %pred, FVC, FVC %pred, DLco/VA, DLco/VA %pred, Tiffeneau, time, Wpeak, HRpeak, CO_2peak, BFpeak, VEpeak, RERpeak, $EqCO_2$peak, EqO_2peak, O_2/HRpeak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETCO_2$peak, $PETO_2$peak and Ti/Ttot peak. Parameters examined to be a predictor of VO_2peak were the patient characteristics (age, gender, length, weight and BMI), spirometry data (FEV_1, FEV %pred, TLC, TLC %pred, FVC, FVC %pred, DLco/VA, DLco/VA %pred and Tiffeneau) and ergospirometry data (HRpeak, VCO_2peak, BFpeak, VEpeak, RERpeak, $EqCO_2$peak, EqO_2peak, O_2/HRpeak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETCO_2$peak, $PETO_2$peak

and Ti/Ttot peak). Likewise, Spearman correlations and a forward stepwise multivariate regression model were made between Wpeak and ventilatory and cardiac parameters at rest and during peak exercise at baseline. Parameters examined on non-parametric correlations with Wpeak %pred were age, gender, length, weight, BMI, FEV_1, FEV %pred, TLC, TLC %pred, FVC, FVC %pred, DLco/VA, DLco/VA %pred, Tiffeneau, time, HRpeak, VCO_2peak, VO_2peak, BFpeak, VEpeak, RERpeak, $EqCO_2$peak, EqO_2peak, O_2/HRpeak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETCO_2$peak, $PETO_2$peak and Ti/Ttot peak. Parameters examined to be a predictor of Wpeak were age, gender, length, weight, BMI, FEV_1, FEV %pred, TLC, TLC %pred, FVC, FVC %pred, DLco/VA, DLco/VA %pred, Tiffeneau, HRpeak, VCO_2peak, BFpeak, VEpeak, RERpeak, $EqCO_2$peak, EqO_2peak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETCO_2$peak, $PETO_2$peak and Ti/Ttot peak.

Normality was tested again with the Shapiro-Wilk test, which indicated that most data in part 2 were not normally distributed ($p < 0,05$). Therefore, non-parametric tests were applied. Changes in ventilatory and cardiac parameters during exercise after intervention program were analysed by Wilcoxon signed ranks tests. Parameters examined were Wpeak, HRpeak, time, VCO_2peak, VO_2peak, BFpeak, VEpeak, RERpeak, EqO_2peak, $EqCO_2$peak, O_2/HRpeak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETCO_2$peak, $PETO_2$peak and Ti/Ttot peak. Next, a forward stepwise multivariate regression model was developed to examine predictors of changes in VO_2peak and Wpeak after an exercise program. Parameters examined to be a predictor of change in VO_2peak after the intervention were ΔHRpeak, ΔVCO_2peak, ΔBFpeak, ΔVEpeak, ΔRERpeak, $\Delta EqCO_2$peak, ΔEqO_2peak, ΔO_2/HRpeak, ΔVtin peak, ΔVtex peak, Δt-tot peak, Δt-ex peak, $\Delta PETCO_2$peak, $\Delta PETO_2$peak, ΔVde peak and ΔTi/Ttot peak. Parameters examined to be a predictor of change in Wpeak after the intervention were ΔHRpeak, ΔVCO_2peak, ΔBFpeak, ΔVEpeak, ΔRERpeak, $\Delta EqCO_2$peak, ΔEqO_2peak, ΔO_2/HRpeak, ΔVtin peak, ΔVtex peak, Δt-tot peak, Δt-ex peak, $\Delta PETCO_2$peak, $\Delta PETO_2$peak, ΔVde peak and ΔTi/Ttot peak. Overall, statistical significance was set at $p<0,05$ (2-tailed).

Results

Part 1

Univariate correlations between VO_2peak, Wpeak and subject characteristics/exercise tolerance parameters

Univariate correlations between VO_2peak %pred and ventilatory parameters during rest and exercise were examined. Significant correlations were found between VO_2peak %pred and following resting ventilatory parameters: FEV_1 %pred, FVC_1 %pred, DLco/VA and DLco/VA %pred. Significant correlations were found between VO_2peak %pred and following ventilatory and cardiac parameters during exercise: Wpeak, HRpeak, VCO_2peak, VEpeak, $EqCO_2$peak, O_2/HRpeak, Vtex peak, Vtin peak, t-tot peak and t-ex peak. R-values and p-values of Spearman rho's correlations are mentioned in table 5.

Univariate correlations between Wpeak %pred and ventilatory and cardiac parameters during rest and exercise were examined. Significant correlations between Wpeak %pred and following patient characteristics were found: age, gender, length and weight. Significant correlations were found between Wpeak %pred and following ventilatory parameters during rest: FEV_1, FEV_1 %pred, TLC %pred, FVC, FVC %pred, DLco/VA, DLco %pred and Tiffeneau index. Significant correlations were found between Wpeak %pred and following ventilatory and cardiovascular parameters during exercise: HRpeak, VCO_2peak, VO_2peak, BFpeak, VEpeak, RERpeak, EqO_2peak, VO_2/kg peak, O_2/HRpeak, Vtex peak, Vtin peak, t-tot peak, t-ex peak, Vde peak, $PETO_2$peak and Ti/Ttot peak. R-values and p-values of Spearman rho's correlations are mentioned in table 6.

Table 5 Correlations with VO_2peak %pred

	R-value	P-value
Age	0.119	0.369
Gender	-0.126	0.343
Body length	-0.159	0.228
Body weight	0.162	0.221
BMI	0.190	0.149
FEV_1	0.181	0.169
FEV_1 %pred	0.390**	0.002
TLC	-0.260	0.65
TLC %pred	-0.217	0.127
FVC	0.083	0.530

FVC %pred	0.305*	0.019
DLco/VA	0.444**	0.002
DLco/VA %pred	0.406**	0.004
Tiffeneau	0.242	0.065
Wpeak	0.404**	0.001
HRpeak	0.335**	0.010
VCO_2peak	0.496**	0.000
BFpeak	0.251	0.212
VEpeak	0.387**	0.002
RERpeak	0.102	0.441
$EqCO_2$peak	-0.357**	0.006
EqO_2peak	-0.174	0.187
O_2/HRpeak	0.394**	0.002
Vtex peak	0.296*	0.023
Vtin peak	0.272*	0.038
T-tot peak	-0.290*	0.027
T-ex peak	-0.311*	0.018
Vde peak	-0.127	0.338
$PETCO_2$peak	0.099	0.457
$PETO_2$peak	-0.095	0.487
Ti/Ttot peak	0.208	0.113

** Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

BMI: body mass Index, FEV_1: forced expiratory volume in one second, FEV_1 pred: FEV_1 in relation to the predicted FEV_1 , TLC: total lung capacity, TLC pred: TLC in relation to the predicted TLC, FVC: forced vital capacity, FVC pred: FVC in relation to the predicted FVC, DLco/VA: diffusing capacity for carbon monoxide divided by the alveolar volume, DLco/VA pred: DLco/VA in relation to the predicted DLco/VA, HR: heart rate, VCO_2: carbon dioxide output, BF: breathing frequency, VE: minute ventilation, RER: respiratory exchange ratio, $EqCO_2$: carbon dioxide equivalent, EqO_2: oxygen equivalent, O_2/HR: oxygen pulse, Vtex: tidal volume during expiration, Vtin: tidal volume during inspiration, t-tot: total respiratory cycle time, t-ex: time of expiration, Vde: dead space ventilation, $PETCO_2$: end-tidal CO_2 pressure, $PETO_2$: end-tidal oxygen pressure, Ti/Ttot: inspiratory time/total respiratory cycle time

Table 6 Correlations with Wpeak %pred

	R-value	P-value
Age	0.258*	0.046
Gender	0.462**	0.000
Body length	0.334**	0.009
Body weight	0.287*	0.026
BMI	0.042	0.753
FEV_1	0.650**	0.000
FEV_1 %pred	0.531**	0.000
TLC	0.047	0.743
TLC %pred	-0.361**	0.009
FVC	0.456**	0.000
FVC %pred	0.269*	0.038
DLco/VA	0.338*	0.019
DLco/VA %pred	0.402**	0.005
Tiffeneau	0.456**	0.000
HRpeak	0.295*	0.022
VCO_2peak	0.766**	0.000
VO_2peak	0.666**	0.000
BFpeak	0.0357**	0.005
VEpeak	0.714**	0.000
RERpeak	0.538**	0.000
$EqCO_2$peak	-0.091	0.493
EqO_2peak	0.264*	0.044
VO_2/kg peak	0.586**	0.000
O_2/HRpeak	0.530**	0.000
Vtex peak	0.657**	0.000

Vtin peak	0.675**	0.000
T-tot peak	-0.351**	0.006
T-ex peak	-0.462**	0.000
Vde peak	0.314*	0.015
$PETCO_2$peak	-0.184	0.160
$PETO_2$peak	0.320*	0.015
Ti/Ttot peak	0.424**	0.001

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

BMI: body mass Index, FEV_1: forced expiratory volume in one second, FEV_1 pred: FEV_1 in relation to the predicted FEV_1, TLC: total lung capacity, TLC pred: TLC in relation to the predicted TLC, FVC: forced vital capacity, FVC pred: FVC in relation to the predicted FVC, DLco/VA: diffusing capacity for carbon monoxide divided by the alveolar volume, DLco/VA pred: DLco/VA in relation to the predicted DLco/VA, HR: heart rate, VCO_2: carbon dioxide output, VO_2: oxygen uptake, BF: breathing frequency, VE: minute ventilation, RER: respiratory exchange ratio, $EqCO_2$: carbon dioxide equivalent, EqO_2: oxygen equivalent, O_2/HR: oxygen pulse, Vtex: tidal volume during expiration, Vtin: tidal volume during inspiration, t-tot: total respiratory cycle time, t-ex: time of expiration, Vde: dead space ventilation, $PETCO_2$: end-tidal CO_2 pressure, $PETO_2$: end-tidal oxygen pressure, Ti/Ttot: inspiratory time/total respiratory cycle time

Predictors for VO_2peak and Wpeak

VO_2peak can be predicted (model adjusted $r^2 = 0.994$, $p < 0.001$) in patients with COPD with a forward stepwise multivariate regression model. Significant predictors of VO_2peak were VCO_2peak (standardized coefficient $\beta = 0.675$, $p < 0.001$), RERpeak (SC $\beta = -566.293$, $p < 0.001$), O_2/HRpeak (SC $\beta = 33.707$, $p < 0.001$), HRpeak (SC $\beta = 2.375$, $p < 0.001$) and TLC %pred (SC $\beta = 0.452$, $p = 0.005$).

Wpeak can be predicted (model adjusted $r^2 = 0.731$, $p < 0.001$) in patients with COPD with a forward stepwise multivariate regression model. Significant predictors of Wpeak were VCO_2peak (SC $\beta = 0.054$, $p < 0.001$) and BMI (SC $\beta = -1.005$, $p = 0.004$).

Part 2

Effect of rehabilitation

The combined exercise program had no effect on cardiopulmonary function during exercise (table 7). Figure 2 and figure 3 show the effect of rehabilitation on VO_2peak and Wpeak for every subject.

Table 7 Impact of exercise training on ventilatory and cardiac function during exercise

	Initial test (mean ± SD)	Test after intervention (mean ± SD)	P-value
Wpeak (W)	48 ± 20	44 ± 25	0.754
HRpeak (bpm)	116 ± 17	117 ± 20	0.636
VCO_2peak (ml/min)	847 ± 361	859 ± 380	0.433
VO_2peak (ml/min)	799 ± 249	828 ± 351	0.638
BFpeak (bpm)	31 ± 6	30 ± 6	0.395
VEpeak (L/min)	32.8 ± 11.6	33.3 ± 13.7	0.766
RERpeak	1.03 ± 0.15	1.00 ± 0.09	0.266
$EqCO_2$peak	37.3 ± 5.7	37.3 ± 7.7	0.701
EqO_2peak	38.2 ± 6.4	38.2 ± 9.1	1.000
VO_2/kg peak (ml/min/kg)	12.1 ± 2.6	12.5 ± 3.4	0.463
O_2/HRpeak (ml)	7.1 ± 2.5	6.7 ± 2.5	0.410
Vtex peak (L)	1.05 ± 0.31	1.15 ± 0.50	0.272
Vtin peak (L)	1.10 ± 0.33	1.20 ± 0.41	0.139
T-tot peak (s)	1.9 ± 0.3	2.0 ± 0.3	0.260
T-ex peak (s)	1.2 ± 0.3	1.2 ± 0.1	0.314
Vde peak (ml)	314 ± 103	316 ± 122	0.646
$PETCO_2$peak (mmHg)	34.9 ± 5.4	35.3 ± 7.2	0.646
$PETO_2$peak (mmHg)	115.0 ± 7.5	113.5 ± 9.8	0.401
Ti/Ttot peak (%)	35.5 ± 4.9	37.0 ± 4.8	0.592
Wpeak %pred	42.5 ± 13.2	39.5 ± 19.8	0.695
VO_2peak %pred	41.3 ± 7.5	41.9 ± 10.2	0.814

HR: heart rate, VCO_2: carbon dioxide output, VO_2: oxygen uptake, BF: breathing frequency, VE: minute ventilation, RER: respiratory exchange ratio, $EqCO_2$: carbon dioxide equivalent, EqO_2: oxygen equivalent, O_2/HR: oxygen pulse, Vtex: tidal volume during expiration, Vtin: tidal volume during inspiration, t-tot: total respiratory cycle time, t-ex: time of expiration, Vde: dead space ventilation, $PETCO_2$: end-tidal CO_2 pressure, $PETO_2$: end-tidal oxygen pressure, Ti/Ttot: inspiratory time/total respiratory cycle time, Wpeak %pred: peak workload in relation to predicted peak workload, VO_2peak %pred: oxygen uptake in relation to predicted oxygen uptake

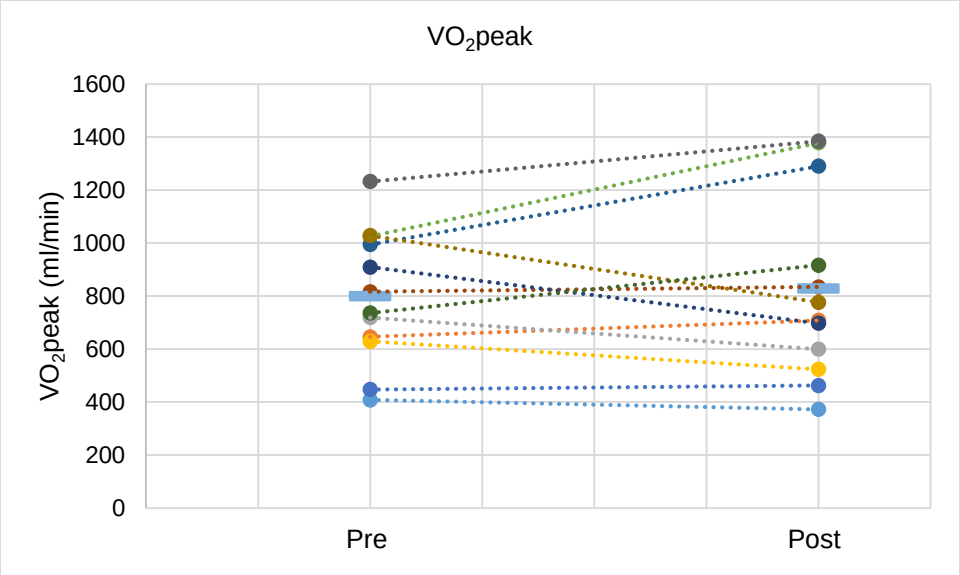

Figure 2 Effect of rehabilitation on VO_2peak

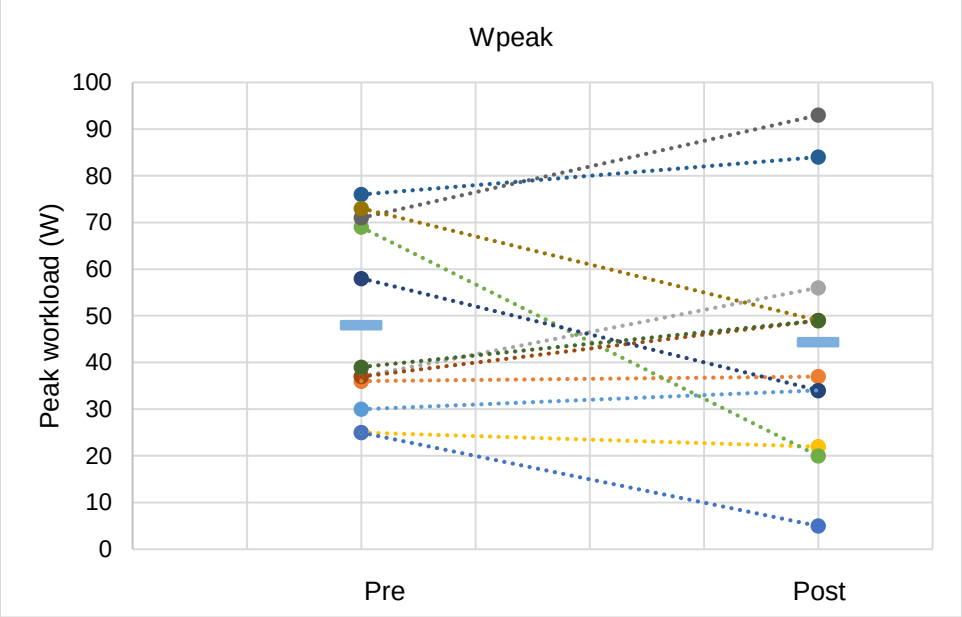

Figure 3 Effect of rehabilitation on Wpeak

Predictors ΔVO_2peak and ΔWpeak

The change in VO_2peak after an exercise program can be predicted (model adjusted $r^2 = 0.91$, $p < 0.001$) in patients with COPD with a forward stepwise regression model. Significant predictors of the change in VO_2peak were the change the change in Vtin peak (SC $\beta = 2372.694$, $p < 0.001$) and the change in Ti/Ttot peak (SC $\beta = -36.249$, $p = 0.003$).

The change in Wpeak after an exercise program can be predicted (model adjusted $r^2 = 0.776$, $p < 0.001$) in patients with COPD with a forward stepwise regression model. Significant predictors of the change in Wpeak after exercise were the change in O_2/HRpeak (SC $\beta = 10.498$, $p = 0.006$) and the change in RERpeak (SC $\beta = 75.459$, $p = 0.010$).

Discussion

Predictors of VO_2peak in COPD patients were VCO_2peak, RERpeak, O_2/HRpeak, HRpeak and TLC %pred. Predictors of Wpeak were VCO_2peak and BMI. Predictors of the change in VO_2peak after exercise intervention were the change in Vtin peak and change in Ti/Ttot peak. Significant predictors of the change in Wpeak after exercise intervention were the change in O_2/HRpeak and change in RERpeak.

Previous studies have examined predictors for exercise tolerance in COPD patients. From those studies, it was found that MVV, forced expiratory flow, body surface area, DLco, FVC, MIP, Vd/Vt, FEV_1, MIP, resting VE, weight, age, ratings of perceived exertion and six minute walking distance (6MWT) predicted VO_2peak[5-9] and that age, body weight, FEV_1/VC, MIP, and $P_{0,1}$/Vt/Ti predicted Wpeak[10]. Limitations of those studies were however small sample sizes[5,6], submaximal CPET to measure exercise capacity[5], use of non-exercise variables only[6,9,10] and use of 6MWT to measure exercise capacity[7].

As opposed to previous studies considerably more cardiopulmonary parameters during exercise were used in the present study to predict VO_2peak and Wpeak in a COPD population. We also had a large sample of COPD patients available in this study and evaluated predictors for changes in VO_2peak and Wpeak over time after completion of an exercise intervention. We performed this study to get a better understanding of the cardiopulmonary determinants of exercise tolerance in patients with COPD. If this gets clarified, this could lead to improved exercise prescription and rehabilitation programs for patients with COPD.

VCO_2peak is the most predictive parameter for VO_2peak and Wpeak in patients with COPD. A high VCO_2peak predicts a high VO_2peak and Wpeak. A study about quadriceps metabolism during constant work rate cycling exercise in COPD suggested that impaired oxidative capacity due to a decreased mitochondrial function can be a factor in the accumulation of lactate in COPD[16]. In COPD, the concentration of lactate in the muscle is increased during exercise as a result of a faster activation of glycolysis with an excessive lactate production[22]. They already develop a lactic acidosis during exercise at a low intensity[23]. The production of CO_2 is the result of buffering of lactate with a bicarbonate buffer[24-28]. CO_2 will be exhaled, so it will not accumulate in tissues. Greater exhalation of CO_2 leads to greater in VCO_2peak[29]. So in conclusion, we hypothesize that a greater VCO_2peak could indicate an increase in lactate buffering in the muscle and hereby postpone lactate production.

In addition, RERpeak is a negative coefficient estimate of VO_2peak in COPD. The higher the RERpeak, the lower the VO_2peak in COPD patients. A greater RER implicates a higher production of CO_2 due to elevation of carbohydrate oxidation during exercise. COPD patients show an impaired lipolysis due to a decreased availability of free fatty acids. Therefore, COPD patients are more dependent on glucose as a source of energy[16,17]. Normal function of the mitochondria is needed for a normal muscle function and exercise tolerance[18]. This may also be true for COPD patients because the mitochondrial oxidative capacity is correlated with muscle endurance capacity[19]. COPD is associated with a decreased mitochondrial density and mitochondrial respiration capacity[18]. The beta-oxidation is controlled in the mitochondria[20]. In the vastus

lateralis muscle of patients with COPD, there are problems with oxidative phosphorylation and beta oxidation while the glycolytic potential is normal or elevated[21]. Patients with COPD will have shifts of muscle fiber type I to II[20]. So in conclusion, we hypothesize that a lower RERpeak, which is indicative for enhanced fat oxidation is linked with mitochondrial function and thus with exercise tolerance.

The cardiovascular parameters O_2/HRpeak and HRpeak are positively related to VO_2peak. The higher O_2/HRpeak and HRpeak, the higher the VO_2peak in COPD. O_2/HR reflects the capacity of the heart to deliver oxygen to the active tissues per heartbeat. COPD patients with greater thoracic hyperinflation (inspiratory capacity/TLC) have a lower O_2/HR, a lower increase in O_2/HR during exercise and a reduction in exercise tolerance compared to individuals with less hyperinflation[30,31]. Dynamic hyperinflation leads to reduced cardiac function due to decreased venous return or tension on the left ventricle as a result of intra thoracic pressure fluctuations. Patients with severe COPD have a lower end-diastolic volume of the left and right ventricles at rest[30,32]. Hyperinflation can hereby result in a reduced cardiac output. VO_2peak is primary limited by cardiac output and there is a linear relationship between VO_2peak and cardiac output, at least in healthy subjects[33]. Maximal stroke volume is the most important factor in order to explain differences between subjects in maximal cardiac output. In addition, beta-blocker intake results in a reduction of maximal cardiac output and blood flow in the legs, which causes a decline in VO_2peak[33]. A higher cardiovascular capacity (higher stroke volume) and a lower hyperinflation can result in a higher O_2/HR. A higher HR results in increased cardiac output, this leads to a higher oxygen delivery to the muscles during exercise. This results in a higher exercise tolerance. So in conclusion, we hypothesize that the relation between VO_2peak, O_2/HRpeak and HRpeak is influenced by beta-blocker intake and hyperinflation.

The higher the TLC %pred, the higher VO_2peak will be in COPD. Significant loss in elastic recoil and a significant increase in TLC are present in early stages of emphysema[34]. In chronic bronchitis, TLC is often normal. COPD patients however, have a mixture of both phenotypes which implicates that most patients have an increased TLC. A reduced elastic recoil of the lungs combined with an expiratory flow limitation results in lung hyperinflation[34]. During exercise, the expiration time is shortened. Previous studies show that an increase in TLC leads to a decrease in exercise tolerance[35-37]. However, we found the opposite. We think that this result is influenced by 17 restricted COPD patients with a TLC% pred lower than 100%. We expect a parabolic relation between TLC% pred and VO_2peak. This hypothesis remains however to be verified.

BMI is a negative coefficient estimate of Wpeak. The higher the BMI, the lower the Wpeak in COPD. However, a previous study found the opposite[38]. They observed a significantly greater exercise capacity in obese COPD patients compared with normal-weight COPD patients. However, they excluded emphysema patients and the patients in their sample were younger, had a higher FEV_1 and a higher Tiffeneau index than the patients in our sample. In addition, they did not mention use of corticosteroids. Almost every patient in our sample used corticosteroids. Long-term corticosteroid intake results in clinically significant weight gain: they have an obesogenic effect[39]. Glucocorticoid use is also associated with muscle weakness[40]. A

possible consequence of this muscle weakness is a lower Wpeak. Another potential explanation is that a high BMI results from a sedentary lifestyle[41,42], with a lower Wpeak as a consequence.

We also examined the changes in VO_2peak and Wpeak after an exercise program. Significant predictors of the change in VO_2peak were the change in Vtin peak and the change in Ti/Ttot peak. Significant predictors of the change in Wpeak after exercise intervention were the change in O_2/HRpeak and the change in RERpeak. To date, nobody examined this. Previous studies[43,44] examined the effect of an exercise program on ventilatory parameters, but did not search for predictors of changes in exercise tolerance in COPD.

The exercise program in part 2 of the study had no effect on Wpeak and VO_2peak and no significant changes were found in respiratory and cardiac parameters during exercise. Change in VO_2peak after an exercise program can be predicted by changes in Vtin peak and changes in Ti/Ttot peak. The change in Vtin peak after the intervention is the most important predictor of a change in VO_2peak. The greater the increase in Vtin peak after rehabilitation, the greater the increase in VO_2peak after intervention in COPD. We assume that an increase in Vtin peak leads to an increase in alveolar ventilation (VA)[45]. This may have a positive effect on exercise capacity due to an increase in oxygen supply in the blood and CO_2 elimination from the blood. When Ti/Ttot peak decreases after rehabilitation there will be an increase in VO_2peak. We expected this relation in opposite direction. Because of an expiratory flow limitation in patients with COPD the Ti/Ttot peak will be decreased. When the inspiration time is prolonged relative to total time of respiration cycle, there will be an increase in Ti/Ttot peak. We assumed that a higher Ti/Ttot peak would lead to a greater increase in VO_2peak due to a longer inspiration time, resulting in a higher VA. We do not have an adequate explanation for this result.

The change in O_2/HRpeak is the most important predictor of change in Wpeak after an exercise intervention. The greater the change in O_2/HRpeak after the intervention, the greater the change in Wpeak. A higher cardiovascular capacity and a lower hyperinflation can result in a higher O_2/HRpeak, as previously hypothesized. The greater the change in RERpeak, the higher the change in peak workload after intervention. A higher RERpeak is indicative for enhanced carbohydrate oxidation and is linked with exercise tolerance.

The most important clinical implication of this study is that cardiac parameters during exercise, ventilatory parameters during exercise and lung function parameters at rest are all influencing exercise tolerance in COPD patients. COPD is a systemic disease and does not solely affect the respiratory system. The lung function test at rest has a limited predictability on exercise capacity. CPET is therefore very important in the clinical evaluation of patients with COPD. The focus, when predicting exercise tolerance in COPD, should be shifted from lung function tests at rest to cardiopulmonary exercise tests. Physicians and physical therapists should strive for an optimization of pulmonary function, cardiac function and muscle function to enhance exercise tolerance in COPD patients. On the one hand, physicians could play a role by adjusting

medication use. On the other hand, physical therapists should establish exercise programs to improve pulmonary function, cardiac function and muscle function.

Limitations of this study were the lack of a control group, we did the cross-sectional part only with COPD patients. The inclusion of healthy controls would have been better. This way, we could have compared the predictors of exercise tolerance between healthy controls and patients with COPD and whether which effects the exercise program could have had on healthy persons. We do not know if all patients reached their maximal capacity during ergospirometry test. The rehabilitation intervention had no impact on exercise tolerance, this is in conflict with results of previous studies[4]. Part two of this study had a small sample of twelve patients.

Conclusion

Cardiopulmonary parameters during exercise and lung function parameters at rest are all influencing exercise tolerance in COPD patients. The lung function test at rest has a limited predictability of exercise capacity, but CPET is very important in the clinical evaluation of patients with COPD. The focus, when predicting exercise tolerance in COPD, should be shifted from lung function tests at rest to cardiopulmonary exercise tests. Physicians and physical therapists should strive for an optimization of cardiopulmonary function and muscle function to enhance exercise tolerance in COPD patients.

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Relations between cardiopulmonary function during exercise and exercise tolerance in patients with COPD

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen**
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Voor akkoord,

Cuypers, Maarten **Vos, Tine**