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Submaximal Spiroergometric Parameters Are Unaffected by Severity of Chronic Obstructive Pulmonary Diseases

JOACHIM SCHNEIDER and MELANIE FUNK

Institute and Outpatient Clinic of Occupational and Social Medicine, University Giessen, Giessen, Germany

Abstract. *Background/Aim: The Global initiative for chronic obstructive lung diseases (GOLD) reports a staging system for chronic obstructive pulmonary disease (COPD) based on airflow limitations at rest. Cardiopulmonary exercise testing (CPET) is used in surveys to determine the remaining working capacity concerning the degree of disability and the disability benefit payment after rehabilitation in patients with COPD. The aim of the present study was to examine if sub-maximal exercise levels also correlate with COPD disease stage. Patients and Methods: A total of 63 consecutive male patients with COPD and 24 elderly healthy volunteers underwent pulmonary functional tests including CPET. Work capacity, oxygen uptake, ventilation volume, carbon dioxide production and arterial blood gases were measured. Results: Exercise capacity, oxygen uptake, ventilation volume, oxygen pulse, carbon dioxide output and arterial oxygen pressure decreased significantly ($p<0.001$) with advancing GOLD stage. Significant positive correlations ($p<0.001$) to GOLD stage were seen for the alveolar-arterial differences for oxygen pressure and arterial carbon dioxide pressure. Weight-related exercise capacity ($p<0.001$), oxygen uptake ($p<0.01$) and lactate concentrations ($p<0.05$) were significantly lower in patients with COPD. Reduction of (weight-related) oxygen uptake, ventilation volume, oxygen pulse or carbon dioxide output at identical sub-maximal workload was not detected according to GOLD stage, not in comparison of patients with healthy individuals. Conclusion: The GOLD staging system correlates with maximal CPET. At identical workload, discrimination between patients with different GOLD stages and healthy individuals was not possible. For the detection of exercise impairment, maximal CPET is recommended.*

Correspondence to: Professor Dr. Joachim Schneider, Institut und Poliklinik für Arbeits- und Sozialmedizin am Universitätsklinikum, Aulweg 129/III, D-35385 Giessen, Germany. Tel: +49 6419941300, Fax: +49 6419941309, e-mail: Joachim.Schneider@ arbmed.med.uni-giessen.de

Key Words: COPD, respiratory function tests, exercise tests, pulmonary ventilation.

Determination of functional impairment in individuals with chronic obstructive pulmonary disease (COPD) is necessary before an invalidity pension-based on the degree of disability can be rendered. Cardiopulmonary exercise testing (CPET) is used in surveys to determine the remaining working capacity concerning the degree of disability and thus the disability benefit payment after rehabilitation in patients with COPD. Objective measured exercise impairment assessed by a reduction in walking distance or during incremental exercise testing is an indicator of health status impairment and a predictor of prognosis in COPD (1). Pace-shuttled walk tests and unpaced 6-minute walk are recommended by the Global initiative for chronic obstructive lung diseases (GOLD). Ergometry can identify alternative conditions (2). Although symptoms may be mild at the onset, limitation of physical activity is the most disabling and distressing consequence of COPD for the majority of patients. At an early stage of a disease, limitations mostly manifest during physical stress. Cardiopulmonary exercise testing is a valuable tool not only for the determination of medical fitness but also for the assessment of patients with cardiac or pulmonary dysfunctions. Spiroergometry provides additional parameters in the determination of cardiopulmonary performance in comparison to basic ergometry. In patients with COPD, peak oxygen uptake during exercise has been considered to reflect the given limitations better than pulmonary function tests at rest (1). Thus not only is the maximal power an index of exercise tolerance but so is the peak oxygen uptake (2). Therefore measurements of ventilation and gas exchange should also be included in diagnosis.

Spiroergometric parameters (peak oxygen uptake, oxygen pulse, maximum:voluntary ventilation and gas exchanges) at maximum work power were correlated with COPD disease status (2). However, multi-morbid elderly persons often did not reach cardiopulmonal limits. Spiro *et al*. claimed that there is no need to stress a patient with COPD to the limit of their effort tolerance to demonstrate major disturbances in cardiopulmonary function.

The aim of this study was to examine if weight-related oxygen uptake, ventilation volume, oxygen pulse, carbon dioxide output at sub-maximal exercise levels also correlate with COPD disease stage. Spiroergometric parameters have mostly been reported for younger adults; however patients with COPD are predominantly of an older age. Therefore we compared the patients with COPD with an elderly healthy control group.

Patients and Methods

Study population. A total of 63 consecutive male patients with stable COPD rendering an invalidity pension, without exacerbation in previous six weeks before enrolment and not participating in a pulmonary rehabilitation program within the previous six months, were included in this study. All patients underwent examination for occupational airway disease. Patients with asthma, defined as a long history of dyspnoea and reversible airflow obstruction dating from childhood, with persistent airflow obstruction later on were excluded. Depending on the spirometric results [as recommended by GOLD (2)] they were grouped into the following four stages of COPD severity [forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio ≤0.7 for all stages]: stage 1, FEV1 ≥80% predicted; stage 2, FEV1 <80% and ≥50% predicted; stage 3, FEV1<50% and ≥30% predicted; and stage 4, FEV1 <30% predicted. Additionally, all included patients had body plethysmographically elevated airway resistances (R_{aw}) exceeding 0.35 kPa/l/s before and after exercise testing.

Patients with COPD were compared to a male group of 24 healthy well-defined individuals (4). These were recruited from the local population and examined for the purpose of finding reference values for elderly persons. Persons suffering from respiratory disorders or other diseases potentially limiting the exercise test were excluded from the control group.

All participants underwent a clinical examination by a physician. Competing left-sided heart failure potentially limiting CPET identified by echocardiography proved to be an exclusion criterion. Informed consent was obtained from all participants. The study was approved by the Ethics Committee of the Justus-Liebig University in Giessen (Az.: 251/11).

Pulmonary function testing. All pulmonary function tests were performed by trained technicians using a MasterLab (Erich Jaeger, Würzburg, Germany) according to the guidelines adjusted for body temperature and pressure-saturated with water vapour. Measurements in which the two best attempts fulfilled the American Thoracic Society (ATS) (5) criteria for reproducibility (an agreement within 5%) were included in the analysis. The flow volume curve was formed with the envelope method from curves obtained from at least three successive forced expiratory breathing manoeuvres by using the standards of the ATS (5). Standard parameters were measured and FEV1 and the FEV1/FVC ratio were relevant for this study. Airway resistance (R_{aw}) was measured by body plethysmography (Erich Jaeger). For grading of the pulmonary function, FEV1 was also expressed as a percentage of the predicted value in the reference population as recommended by the guidelines (6).

CPET. All participants performed an incremental maximal CPET, according to the criteria of the ATS (7). Seated individuals rode an electrically-braked cycle ergometer (Masterlab; Jaeger) at a pedaling rate of 60 rotations per minute, while breathing room air. After unloaded pedaling for three minutes, the workload was started at 25 W and increased by 25 W every three minutes.

During exercise, ventilation volume, oxygen uptake and carbon dioxide output were collected with Oxycon Alpha (Jaeger) measured breath by breath. Using spiroergometry the respiratory rate, the minute ventilation and the respiratory exchange ratio (RER) were determined. The main objectives were peak performance (W), maximal weight specific performance (W/kg), maximal oxygen consumption (ml/min), weight-specific maximal oxygen consumption (ml/kg/min), carbon dioxide output (ml/min) and oxygenpulse (ml/beat). In addition, blood samples were obtained from a vasodilated ear lobe for measuring of arterial oxygen pressure and carbon dioxide pressure before and during CPET. In the same manner, blood lactate concentrations at different workloads were determined. The alveolar-arterial difference for oxygen pressure was calculated. 12-Lead electrocardiography was conducted and blood pressure was measured at rest, during exercise, and until 5 min into the recovery phase.

Symptom-limited exercise testing was terminated when the participant reached exhaustion or if defined criteria for stopping according to the ATS were met (7).

Statistical analysis. Statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

The Shapiro-Wilk test was used to analyze the distribution of the lung function parameters. Since a non-normal distribution was found in all groups, the statistical comparisons between the groups were carried out using the non-parametric Wilcoxon test. All *p*-values were obtained by using a two-sided test. Boxplots were created. Correlations between lung function parameters and the stage of disease were calculated by Pearson's correlation coefficients. A *p*-value <0.05 was considered as statistically significant.

Results

The severity of disease in patients with stable COPD was classified as stage I (mild) in six persons, stage II (moderate) in 29, stage III (severe) in 25 and stage IV (very severe) in three persons according to the spirometric classification of GOLD (2). The clinical characteristics of patients and healthy control subjects are given in Table I.

The healthy control group was older than the patients suffering from COPD. Weight and nutrition status by Broca [weight (in kg) should equal height (in cm) – 100] decreased with severity of COPD. FEV1 was significantly lower ($p<0.001$) in patients with COPD and was negatively correlated with GOLD stage ($r=-0.945$, $p<0.001$). As expected, the R_{aw} was significantly higher ($p<0.001$) in patients than in healthy adults.

The pulmonary function data under physical exercise are summarized in Table II. Exercise capacity and ventilation volume decreased at peak exercise as the stage of COPD increased from 1 to 4, as seen in Figures 1 and 2. Corresponding data were recorded for oxygen uptake, oxygen pulse and carbon dioxide output in each case. The severity of GOLD was significantly associated with reduced maximal exercise capacity ($r=-0.687$, $p<0.001$), maximal oxygen uptake ($r=-0.647$, $p<0.001$), oxygen pulse ($r=-0.537$, $p<0.001$), carbon dioxide output ($r=-0.624$, $p<0.001$) and

Table I. *Anthropometric and baseline pulmonary function data in male patients with chronic obstructive pulmonary disease (COPD) according the stages of the global initiative for chronic obstructive lung diseases (GOLD) and healthy individuals. Values are presented as the mean±standard deviation (significant results in bold).*

Variable	Healthy males	GOLD stage			
		1	2	3	4
No.	24	6	29	25	3
Age (years)	67.9±5.3	**52.3±7.6*** **	**54.6±11.6*** **	**58.5±5.8*** **	**58.1±2.5*** **
Weight (kg)	81.8±10.3	**106.7±10.7*** **	**93.1±21.4* **	**84.4±14.7**	**60.3±11.7** **
Broca (%)	111.2±15.1	**136.8±10.5*** **	**125.1±25.7* **	113.1±13.3	91.7±21.0
FEV1 (l)	3.4±0.48	3.2±0.42	**2.2±0.43*** **	**1.4±0.27*** **	**0.76±0.11*** **
FEV1% pred.	111.5±15.1	**87.2±4.8*** **	**64.4±8.8*** **	**41.4±5.5*** **	**25.3±2.1*** **
R_{aw} (kPa/l/s)	0.18±0.06	**0.48±0.10*** **	**0.48±0.13*** **	**0.52±0.11*** **	**0.84±0.26** **

pred.: Predicted; Broca: weight (in kg) should equal height (in cm) – 100; FEV_1: forced expiratory volume in 1 s; R_{aw}: airways resistance.*$p<0.05$, **$p<0.01$; ***$p<0.001$ compared to the healthy individuals

Table II. *Cardiopulmonary exercise testing values for male patients with chronic obstructive pulmonary disease (COPD) according the stages of the global initiative for chronic obstructive lung diseases (GOLD) and healthy individuals. Values are presented as the mean±standard deviation (significant results in bold).*

Variable	Healthy males	GOLD stage			
		1	2	3	4
No.	24	6	29	25	3
Exercise power (W)	149±32	**117±34* **	**98±36*** **	**80±24*** **	**50±25*** **
Weight related exercise power (W/kg)	1.9±0.50	**1.1±0.25*** **	**1.1±0.50*** **	**0.95±0.25*** **	**0.80±0.32** **
RER max	1.0±0.15	1.1±0.06	1.0±0.09	1.0±0.12	1.0±0.07
Blood lactate (mmol/l)	6.4±2.7	**4.0±1.7* **	**3.3±1.5*** **	**3.3±1.0*** **	**3.5±0.85** **
VO_2 max (ml/min)	2221±340	1851±539	**1692±514*** **	**1404±311*** **	**931±385*** **
Weight related VO_2 max (ml/min/kg)	27.5±5.5	**17.2±3.9 *** **	**18.8±7.2*** **	**16.8±3.8*** **	**14.9±4.0** **
O_2 pulse max (ml/beat)	15.9±2.4	14.7±5.3	**13.2±3.1** **	**11.6±2.8*** **	**8.3±4.5** **
VCO_2 max (ml/min)	2316±414	1967±537	**1720±562*** **	**1464±389*** **	**908±398*** **
Breathing rate (breath/min)	30.3±9.3	28.1±8.2	29.5±7.7	30.6±5.1	28±3.6
Ventilation volume (l/min)	77.5±21.0	**56.9±12.5* **	**54.0±14.5*** **	**48.8±10.5*** **	**31.4±12.1** **
$AaDO_2$ (kPa)	2.13±1.07	2.29±0.67	**3.40±1.23** **	**4.15±1.32*** **	**4.76±0.99** **
pO_2 at rest (kPa)	11.33±1.25	10.51±1.68	**10.20±1.31** **	**8.91±0.89*** **	**8.87±0.37** **
pO_2 at max (kPa)	13.07±1.37	12.28±0,79	**11.24±1.31*** **	**10.09±1.81*** **	**8.81±1.23*** **
pCO_2 at rest (kPa)	4.64±0.43	4.93±0.43	**4.96±0.48* **	**5.09±0.63** **	**5.49±0.45** **
pCO_2 at max (kPa)	4.12±0.56	**4.75±0.36** **	**4.72±0.61*** **	**5.11±0.71*** **	**5.37±0.53** **

RER: Respiratory exchange ratio; VO_2: oxygen uptake; VCO_2: carbon dioxide output; $AaDO_2$: alveolar-arterial difference for oxygen pressure; pO_2: arterial oxygen tension, pCO_2: arterial carbon dioxide tension. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared to the healthy males.

ventilation volume (r=–0.620, $p<0.001$). At rest and at peak exercise, arterial oxygen pressure decreased with advancing GOLD stage, while the arterial carbon dioxide pressure increased (Table II). Statistically significant negative correlations were observed for arterial oxygen pressure at rest (r=–0.612, $p<0.001$) and during exercise (r=–0.656, $p<0.001$) with ascending GOLD stage. In contrast, the alveolar arterial difference in oxygen pressure at anaerobic threshold increased and was significantly positively correlated with advanced stage of COPD (r=0.581, $p<0.001$). We also found significantly positive correlations for arterial carbon dioxide pressure at rest (r=0.366, p=0.001) and during exercise (r=0.656, $p<0.001$) with GOLD stage. Significantly lower exercise capacity in relation to body weight ($p<0.001$), oxygen uptake in relation to body weight ($p<0.01$) and maximal lactate concentrations ($p<0.05$) were also recorded in patients with COPD in comparison with healthy individuals but this proved to be independent of COPD severity (Table II). Only the respiratory exchange ratio (RER) and the breathing rate were similar in all groups.

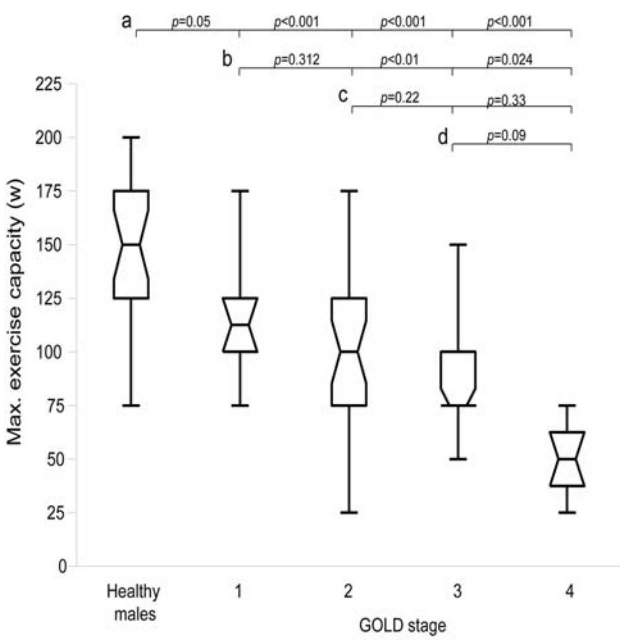

Figure 1. *Maximal exercise capacity in healthy male and patients with chronic obstructive pulmonary disease (COPD) grouped according the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum, the boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The centers of the notches indicate the median. The width of the notches is proportional to the IQR (±1.58×IQR) and inversely proportional to the square root of the size of the sample. p-Values were calculated by the Mann-Whitney Test compared to a) healthy controls, b) patients with COPD GOLD 1, c) patients with COPD GOLD 2, d) patients with COPD GOLD 3.*

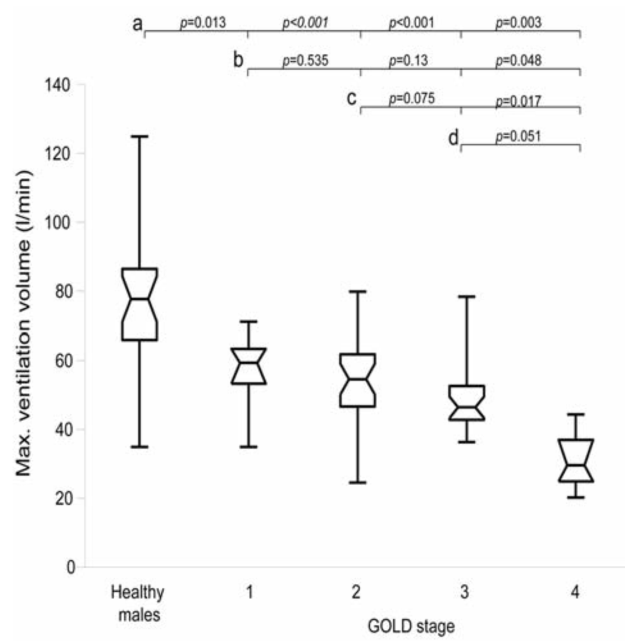

Figure 2. *Maximal ventilation volume in healthy male and patients with chronic obstructive pulmonary disease (COPD) grouped according the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum, the boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The centers of the notches indicate the median. The width of the notches is proportional to the IQR (±1.58×IQR) and inversely proportional to the square root of the size of the sample. p-Values were calculated by the Mann-Whitney Test compared to a) healthy controls, b) patients with COPD GOLD 1, c) patients with COPD GOLD 2, d) patients with COPD GOLD 3.*

In addition sub-maximal ventilation parameters were analyzed. Oxygen uptake, weight-related oxygen uptake, oxygen pulse, carbon dioxide output and ventilation volume at the end of each workload step were measured until reaching individual peak exercise power. As can be seen from Figures 3 to 6, there were no significant differences in the ventilated volume, oxygen uptake, weight-related oxygen uptake or oxygen pulse at the identical workloads between healthy individuals and all stages of COPD; this was also true for the carbon dioxide output (Figure 7).

Oxygen pulse in patients with advanced stages of COPD tended to be lower, but the differences were not significant (Figure 6).

Discussion

The COPD assessment test correlates with health status impairment in COPD (2). The future risk of exacerbations are described by symptoms, exacerbation history and airflow limitations. Spirometric assessment is based on the easily-measured FEV1 and FEV1/FVC, as well as FEV1%pred. Because it was not the primary goal of this study to calculate the future risk of hospital admission, we classified the severity of COPD based on the commonly used spirometric parameters, which allows for easy comparisons with literature (1, 8). However exercise intolerance is a typical sign of COPD. The 6-minute walk reflects limitations expected in normal life. A significant relationship between walking distances and FEV1 and FVC was reported (9). The estimated exercise performance at peak work capacity (10-12) or peak oxygen uptake (13-16) either on a treadmill or cycle ergometer, were shown to be reduced in patients with COPD. This was also described for the maximal values of oxygen uptake (17, 18), carbon dioxide output (18), oxygen saturation and minute ventilation, as well as for voluntary volume (2). In our study, we analyzed all relevant spiroergometric parameters in patients with different severity of COPD in comparison to healthy elderly persons. Exercise capacity, oxygen uptake, ventilation volume, oxygen pulse and carbon dioxide output decreased as the stages of the COPD patients increased from 1 to 4.

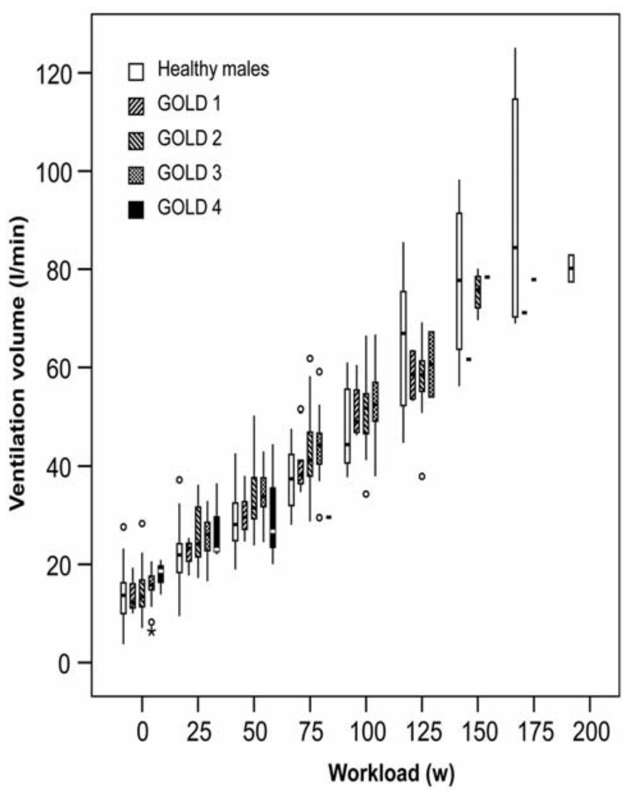

Figure 3. *Ventilation volume at each workload step in healthy males and in patients with chronic obstructive pulmonary disease (COPD) stages 1 to 4 according to the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum values. The boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The center of the notch indicates the median. Dots and stars indicate outliers more than 1.5 resp. 3 times the IQR from either end of the box.*

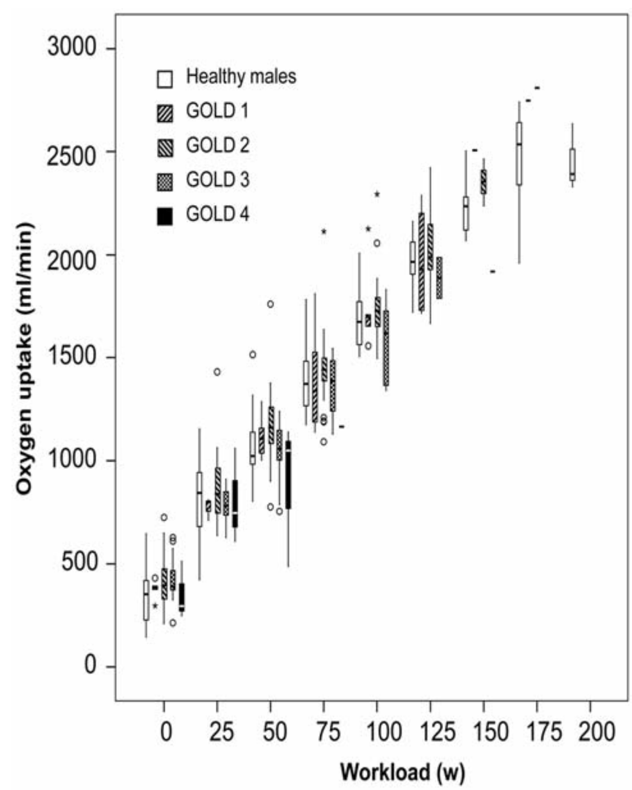

Figure 4. *Oxygen uptake at each workload step in healthy males and in patients with chronic obstructive pulmonary disease (COPD) stages 1 to 4 according to the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum values. The boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The center of the notch indicates the median. Dots and stars indicate outliers more than 1.5 resp. 3 times the IQR from either end of the box.*

We detected a significant negative correlation of peak exercise capacity with GOLD stage, revealing a reduced functional capacity which showed impairment in patients with COPD. We also demonstrated that maximal oxygen uptake, maximal oxygen pulse and maximal ventilation volume were highly significantly correlated ($p<0.001$) with advanced stages of COPD. The reduction in exercise capacity for patients at every stage of COPD was similarly described by Pinto-Plata *et al*. (19). Our determined values of maximal weight-related oxygen uptake in relation to the GOLD classification are in accordance with the previously published data (20). In healthy individuals significantly higher lactate concentrations were observed. Due to impaired exercise tolerance, the values for lactate in patients with COPD cannot be regarded as appropriate (21). Blood lactate concentrations were low and did not limit exercise performance (3).

In our study advanced COPD stage correlated with reduced arterial oxygen and carbon dioxide pressures at rest and under exercise. The measured concentrations of arterial blood gases were reported at the same level by Verhage *et al*. (22) and Pinto-Plata *et al*. (19). Significant correlations of arterial oxygen pressure with moderate and severe COPD were also described by Yazici *et al*. (23). Age and arterial oxygen slope was found to be independent prognostic factors closely associated with survival time in patients with COPD (24). In accordance with Wang *et al*. (18), we observed an increase of alveolar arterial difference and oxygen pressure during exercise in patients with COPD; this was significantly positively correlated with the severity of COPD ($r=0.581$, $p<0.001$).

The current study confirmed that the GOLD staging system reflects a patient's exercise capacity in stages 1 to 4 concerning the maximal work capacity, maximal oxygen uptake, maximal ventilation volume, maximal oxygen pulse, carbon dioxide output, maximal alveolar-arterial oxygen difference and the arterial blood gases at rest and at peak exercise.

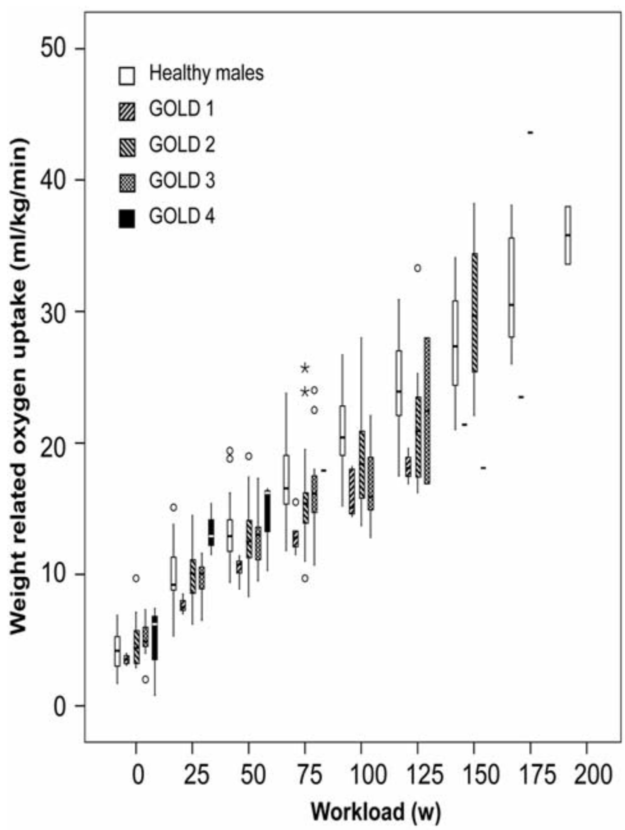

Figure 5. *Weight-related oxygen uptake at each workload step in healthy males and in patients with chronic obstructive pulmonary disease (COPD) stages 1 to 4 according to the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum values. The boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The center of the notch indicates the median. Dots and stars indicate outliers more than 1.5 resp. 3 times the IQR from either end of the box.*

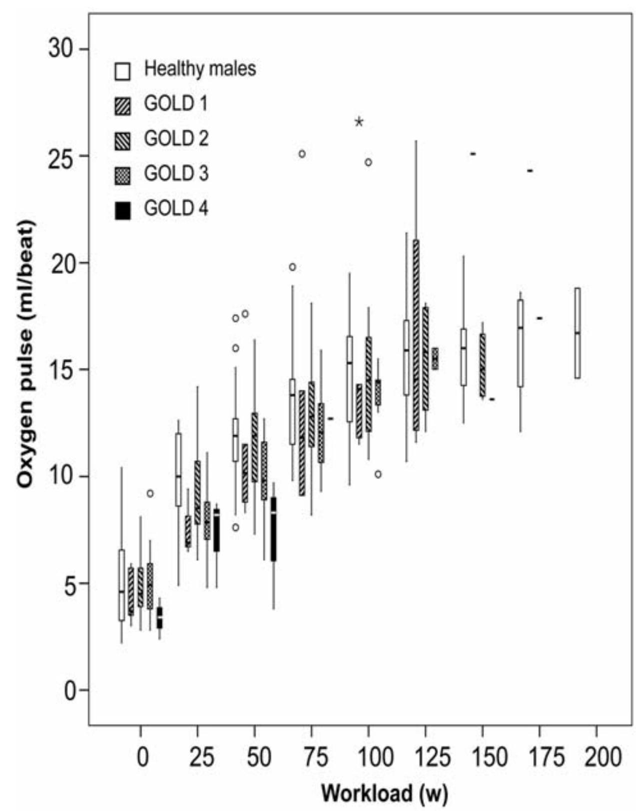

Figure 6. *Oxygen pulse at each workload step in healthy males and in patients with chronic obstructive pulmonary disease (COPD) stages 1 to 4 according to the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum values. The boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The center of the notch indicates the median. Dots and stars indicate outliers more than 1.5 resp. 3 times the IQR from either end of the box.*

In all the mentioned studies the maximal exercise capacity was reported as an indicator of health status in patients with COPD (22). Spiro *et al*. claimed that there is no need to stress a patient with COPD to the limit of their effort tolerance in order to demonstrate major disturbances in cardiopulmonary function (3). Sub-maximal exercise tests and the common 6-minute walk are used to identify performance limitations in normal life. Therefore we also looked at sub-maximal ventilation parameters and analyzed weight-related oxygen uptake, oxygen pulse, carbon dioxide output and ventilation volume at the end of each workload step until peak exercise was achieved. At sub-maximal effort, we did not observe a relevant difference in ventilation volume, oxygen uptake, weight-related oxygen uptake, oxygenpulse or carbon dioxide output, (Figures 3-7) at identical workload between the GOLD categories or in comparison to healthy controls. Because we observed highly significant differences at maximal workload, even in relatively small patient groups suffering from COPD of GOLD stages 1 and 4, we do not believe that inability to detect significant differences between controls and COPD patients is ascribed to an under-powered study population.

Unexpectedly, despite relevant obstructive ventilation patterns, there were no differences in ventilation volume, weight-related oxygen uptake, oxygen pulse and carbon dioxide output between patients with COPD even with high GOLD stage, and the healthy control group at the same workload.

Using sub-maximal CEPT, discrimination between patients with COPD of different GOLD stages is not possible. Limitations in work capacity at different stages of COPD become evident only by maximal CEPT. Moreover unequivocal differentiation from healthy individuals is only possible at maximal exercise performance. For the detection

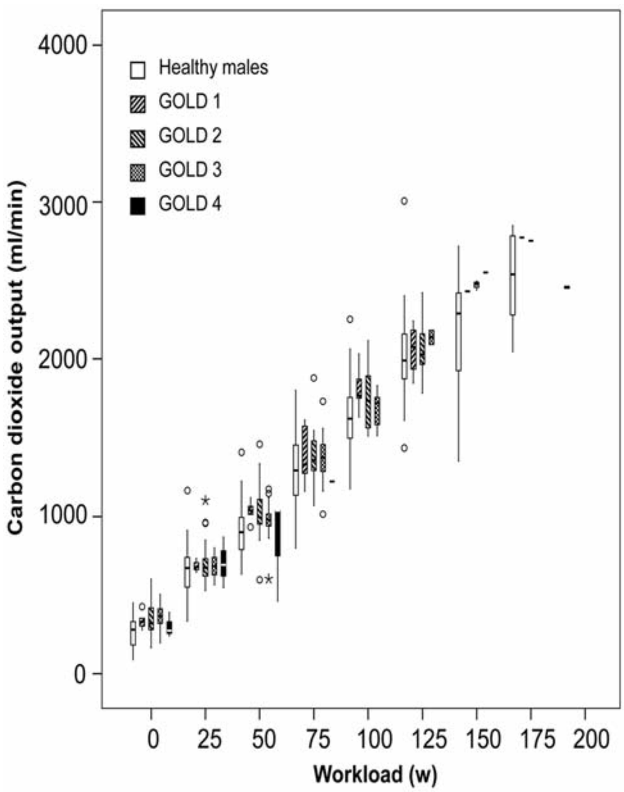

Figure 7. *Carbon dioxide output at each workload step in healthy males and in patients with chronic obstructive pulmonary disease (COPD) stages 1 to 4 according to the global initiative for chronic obstructive lung diseases (GOLD) classification. The whiskers of the boxplots indicate the minimum and maximum values. The boxes indicate the 25th and 75th percentile (=interquartile range or IQR). The center of the notch indicates the median. Dots and stars indicate outliers more than 1.5 resp. 3-times the IQR from either end of the box.*

of exercise impairment in patients with COPD seeking compensation or reintegration into working life, symptom-limited maximal CPET aims to detect pulmonary dysfunctions.

Conflicts of Interest

All Authors declare no financial conflicts. There was no commercial funder. All Authors are employees of the Federal University in Giessen.

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