## 46. Skeletal muscle weakness in COPD: physical (in)activity and biological markers

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**Validation of the current equations to estimate peak work load based on 6-min walk distance and general demographics in COPD patients entering pulmonary rehabilitation**

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**Background:** Due to limited resources it is not possible to conduct a cardiopulmonary exercise test (CPET) in all COPD patients entering pulmonary rehabilitation (PR). Therefore regression equations were developed to estimate peak work load (Wpeak) by using 6MWD in combination with gender, age, height, weight and/or fat free mass. The aim of this study was to validate these equations in a large cohort of COPD patients entering PR.
**Methods:** In 3000 patients with COPD (53% men, age: 63±9 yrs; $FEV_1$: 44±18% pred), referred to 4 specialized pulmonary rehabilitation centres in the Netherlands, the estimated Wpeak using 6 different regression equations (table) was compared to actual Wpeak obtained during CPET.
**Results:** Patients had poor peak (60±33 watts) and functional exercise capacity (6MWD: 399±120 m). Mean difference between actual Wpeak and estimated Wpeak ranged between 0 to 42 Watts. Moreover, only 6 to 24% of the estimated Wpeak differed less than 5 watts (±) compared to actual Wpeak.

Table 1. Wpeak regression equations

| Authors | Regression equations | % Patients between –5 and +5 watts | Actual-predicted Wpeak (watts) |
|---|---|---|---|
| Hill 1 | (0.122∗6MWD) + (72.683∗height) – 117.109 | 22 | 6.8 (26.5) |
| Hill 2 | 17.393 + (1.442∗6MWW) | 12 | 0.32 (37.7) |
| Luxton | 103.217 + (30.50∗gender) + (–1.613∗age) + (0.002∗6MWW) | 6 | 42.1 (32.1 |
| Cavalheri | –27.9717 + 3.7792∗(6MWD∗FFM) | 24 | 18.6 (40.5) |
| Kozu 1 | (0.168∗6MWD) – 4.085 | 18 | –3.1 (24.7) |
| Kozu 2 | (2.310∗6MWW) + 8.820 | 13 | –16.4 (22.5) |

**Conclusion:** Current regression equations to estimate Wpeak based on 6MWD in COPD are inaccurate in COPD. So, estimated Wpeak cannot be used to target training intensity during PR in individuals with COPD.

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**Divergent effects of obesity on weight bearing versus non-weight bearing exercise testing in patients with COPD**

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**Introduction:** Obesity is common in patients with COPD and may impact on disease severity. However, obesity was not associated with diminished exercise capacity or greater dyspnea during non-weight bearing exercise (e.g. stationary cycling) in COPD[1]. Aim of this study was to investigate the impact of obesity during weight bearing exercise (e.g. six-minute walk test, 6MWT) in patients with severe COPD.
**Methods:** Data obtained during pre-rehabilitation assessment of 44 male obese COPD patients (OB) (age 58±4y, $FEV_1$41±5%, BMI 34.1±3.8 kg $m^{-2}$) were compared with those of 44 matched male normal weight COPD patients (NW) (age 58±5y, $FEV_1$39±6%, BMI 23.0±1.2 kg $m^{-2}$). 6MWT and progressive cycle ergometry (CPET) were performed, BORG scores for dyspnea and leg fatigue were recorded at the end of both tests.
**Results:** Distance of 6MWT was significantly reduced in OB (452±101 m) compared with NW (497±82 m, $p<0.05$), while peak cycling exercise load was comparable (OB 90±31W, NW 85±24W, ns). Dyspnea (5.9±2.0 vs. 4.9±2.0, $p<0.05$) and leg fatigue (4.8±2.4 vs. 3.4±2.2, $p<0.05$) sensations after 6MWT were significantly increased in OB compared to NW, while these were comparable after CPET (dyspnea: OB 7.6±1.8 vs. NW 7.4±2.0, ns; leg fatigue: OB 6.1±2.3 vs. NW 6.3±2.3, ns).
**Conclusion:** In contrast to non-weight bearing exercise, obesity has a negative impact on weight bearing exercise capacity and exercise-related symptoms in male patients with severe COPD. Obese COPD patients may prefer cycling instead of treatmill walking as training modality during rehabilitation.
[1] Ora J et al, Combined effects of obesity and COPD on dyspnea and exercise tolerance, Am J Respir Crit Care Med 2009

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**Investigating circulating microRNAs as potential biomarkers of quadriceps weakness in COPD**

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**Introduction:** Non-invasive biomarkers of quadriceps phenotype in COPD are needed. MicroRNAs (mirs) are small non-coding RNA that modulate gene expression. They circulate in blood as exosomes and are promising biomarkers. We hypothesised that muscle specific mir-499, which controls slow myosin expression, would be differentially expressed and correlate with physiological parameters.
**Methods:** We studied 101 COPD patients and 24 controls. Mir-499 was quantified in stored plasma samples using q-RT PCR[1]. Mir-16 and mir-122 were quantified as negative controls. Results were normalised to a spiked-in control. All subjects had paired quadriceps biopsy samples.
**Results:** Characteristics as mean (SD); COPD patients: 66 M: 35 F, age= 66 (8), FEV1% pred= 44 (19), six-minute walk (6MW)= 394 (121). Controls: 14 M: 10 F, age 66 (8), FEV1% pred= 112 (13), 6MW= 616 (83).
Plasma mir-499 was significantly elevated in COPD patients, p= 0.0036. There was no difference in mir-16 and mir-122.
Mir-499 levels negatively correlated with total fibre cross sectional area (P= 0.03 $R^2$= 0.04) and in the patients there was a weak positive correlation with 6MW (p=0.047 $R^2$= 0.0016). Patients with no quadriceps muscle fibre type shift (defined from the control samples) had higher mir-499 (p= 0.02).
**Conclusion:** We have demonstrated a difference in plasma mir-499 levels between COPD patients and controls. Higher mir-499 in patients with no fibre type shift is consistent with its proposed role of maintaining a high endurance skeletal myofibre phenotype. Our results may reflect higher protein turnover in COPD and contribute towards developing a blood-borne biomarker to stratify treatment.
[1]Kroh, Methods 50 (2010)298–301

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**Biomarkers of systemic inflammation after two resistance training protocols in moderate clinically stable COPD**

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Systemic inflammation is an important factor in skeletal muscle dysfunction (SMD) in chronic obstructive pulmonary disease (COPD) patients. The SMD can be reversed partially by physical training; however, the response is dependent of type, intensity and duration of exercise. This study evaluated the inflammatory response, muscle strength and fat-free mass outcomes in COPD patients comparing two protocols of resistance training. COPD (n=34) were assigned to conventional resistance training (CRT) or elastic tubing training (ETT) groups (n=17 each, $FEV_1$= 1,23±0,46% and 1,24±0,54% predicted; aged 64,94±7,62 and 65,11±9 years, respectively). CRT group were trained at moderate intensity (3×10 RM) and ETT group were trained at 2-7 sets of repetitions determined individually by resistance to fatigue test. TNF-α, citokines 1L-1β and IL-10 on plasma by ELISA, peripheral muscle strength and fat-free mass were obtained at baseline (D0) and after the 8-weeks training intervention (D2). Citokines also were measured acutely immediately after the first (D1) and the last training session (D3). TNF-α, IL-1β and IL-10 increased in CRT group after 8 weeks compared to baseline ($p<0.001$, $p<0.05$ and $p<0.001$, respectively). IL-1β and IL-10 levels also increased in response to acute exercise (D1) and IL-10 measured acutely after 8 weeks training (D4) was reduced ($p<0.01$, compared to D3). No changes in cytokines levels in plasma were observed in the ETT group. Muscle strength increased in both groups, but only the ETT protocol increased the fat-free mass after 8 weeks. These findings suggest that structural and functional gains were obtained from a lower systemic cost in the ETT group.

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**Early peripheral muscle structural and metabolic impairment in chronic obstructive pulmonary disease (COPD) patients cannot be considered as a consequence of sedentarity**

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Peripheral muscle dysfunction in COPD patients has been related to a muscle/fiber atrophy and oxidative metabolism reduction, which mimicks a severe disuse. Thus, we investigated the structure and mitochondrial function in skeletal muscle biopsies from patients with COPD and sedentary healthy subjects (SHS).
24 stage I-III (according to the GOLD classification) COPD patients and 21 age-matched SHS (<150m/W of moderate-vigorous PA) had accelerometry recording, quadriceps function and muscle mass (impedancemetry) assessment. All subjects had a biopsy of the quadriceps, allowing assessment of the respiratory parameters and mitochondrial ATP synthesis, and of the muscle morphology (immunohistochemistry). Results are presented in mean ± SD or median [inter-quartile range]. COPD patient and PA level-matched SHS (activity counts/day: 133±70 vs 135±48; p=0,9), had the same muscle mass and fiber cross-sectional areas. However, there was a reduction of the quadriceps endurance and of the type I fiber proportion (35% [28-49] vs 41% [38-53]; $p<0,05$). While the maximal ADP-stimulated respiration (state 3) with pyruvate substrate was comparable in COPD and SHS, the ATP/O value (ratio between ATP synthesis and oxygen consumption) was significantly reduced in COPD (0,96±0,4 vs 2,6±0,8; $p<0,001$), and observed in early stages. This study showed an early impairment of the muscle oxidative metabolism (type I fibers and mitochondrial efficiency), unexplained by the PA reduction in COPD patients and suggest that the oxidative phosphorylation alteration (OXPHOS pathway) occurs in the PHOS part, i.e. the ATP synthesis rate.

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**Effects of a new walking aid on 6MWD in COPD patients**

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COPD patients often experience walking as a problematic daily activity. Although a rollator can improve mobility, many patients feel ashamed to use it. Therefore, other walking aids may be worthwhile to consider. We aimed to determine whether a new walking aid (fig1a) has similar direct effects on 6MWD as a rollator (fig1b) in COPD patients.

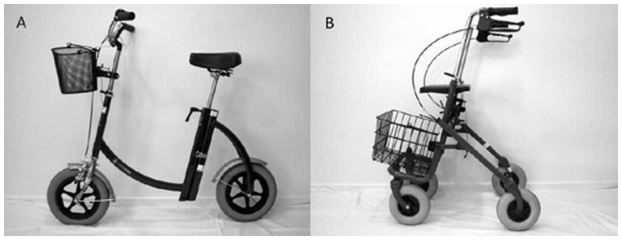


Figure 1. A: Walking frame "City", B: rollator.

21 COPD patients (52% men; age: 64±10yrs; $FEV_1$: 42±15% pred) performed 2 6MWTs during pre-rehabilitation assessment (mean best 6MWD: 369±88 m). In addition, 2 extra 6MWTs were randomly performed on 2 consecutive days: 1x with rollator and 1x with walking frame. Walking pattern (n=21) was determined using an accelerometer and metabolic demands (n=10) were assessed using a mobile oxycon.

Using walking frame resulted in a higher mean 6MWD (466±189 vs. 383±85 m) and fewer steps (491±122 vs. 601±98) compared to a rollator (all $p<0.05$). Oxygen uptake, ventilation, heart rate, oxygen saturation and Borg symptom scores were comparable. 19% felt ashamed using rollator compared to 10% using walking frame.

Functional exercise performance can be improved using walking aids in COPD patients. Moreover, using walking frame led to a significant improvement in 6MWD compared to using rollator, with the same metabolic demands. Therefore, the new walking aid may be a good alternative for a rollator in COPD patients.

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**Combining physical activity monitoring and cardiac output during exercise in COPD patients with GOLD stages II-IV**

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**Background:** Daily physical activity recorded by activity monitors, is an important clinical outcome in COPD patients. However, it is unknown whether changes in physical activity data are related to changes in hemodynamic responses during exercise.

**Aim:** To investigate whether changes in estimated energy expenditure (EE) by activity monitoring are associated with changes in cardiac output (CO) during exercise.

**Methods:** 30 COPD patients (10 for each GOLD stage:II,III,IV) undertook a standardized treadmill test including breath-by-breath gas exchange measurements. Cardiac haemodynamics was assessed by impedance cardiography. The SenseWear armband (SW) and the DynaPort Minimod (MM) were used to estimate EE. All patients exercised at 4 different velocities increasing by 0.7-0.8 km/h every 3 min. Minimum and maximum speeds were 1.4±0.3 km/h and 3.7±0.4 km/h, respectively. Minute-by-minute data were acquired and aligned for each patient.

**Results:** CO was linearly increased with increasing speeds (r=0.97). Median and interquartile range of the correlation between CO and EE by SW and MM are shown below. The level of correlation between CO and EE was not different across GOLD stages and between the two activity monitors.

Median and interquartile range of the correlation between CO & EE

| AM | All (N=30) | GOLD II | GOLD III | GOLD IV |
|---|---|---|---|---|
| SW (min-by-min) | 0,69 (0,46–0,79) | 0,62 (0,19–0,86) | 0,75 (0,53–0,87) | 0,64 (0,34–0,73) |
| MM (min-by-min) | 0,9 (0,81–0,94) | 0,9 (0,81–0,96) | 0,91 (0,66–0,93) | 0,91 (0,85–0,93) |

**Conclusion:** Hemodynamic variations during incremental treadmill exercise in COPD were reliably reflected by changes in EE as those were recorded by the SenseWear armband and the Dynaport Minimod. Supported by IMI-JU Proactive#115011.