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Title: Fat Free Mass Depletion is Associated to Poor Exercise Capacity Irrespective of Dynamic Hyperinflation in COPD Patients

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Short title: Low Fat Free Mass and Response to Exercise in COPD Patients

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ABSTRACT

BACKGROUND: In patients with COPD, we investigated the effect of the fat-free mass (FFM) on maximal exercise capacity and the relationship with changes in operational lung volumes during exercise. METHODS: In a cross-sectional study fifty-seven patients (16 females; age 65 ± 8 yrs) were consecutively assessed by resting lung function, symptom-limited cardiopulmonary exercise test, and body composition by means of bioelectrical impedance analysis to measure the FFM index (FFMI, kg/m^2). RESULTS: Patients were categorized as depleted (n = 14) or non depleted (n = 43) according to FFMI. No significant difference in gender, age and in resting lung function was found between depleted and non depleted patients. When compared with non depleted, the depleted COPD patients had a significantly lower O_2 uptake at peak of exercise and at anaerobic threshold as well as peak O_2 pulse, O_2 uptake efficiency slope (OUES) and heart rate recovery (HRR) ($p < 0.05$ for all comparisons), but similar inspiratory capacity/total lung capacity ratio at peak of exercise. Moreover, they also reported significantly higher leg fatigue ($p < 0.05$), but not dyspnea on exertion. In all patients, significant correlations ($p < 0.01$) were found between FFMI and peak O_2Pulse, OUES, HRR and leg fatigue. CONCLUSIONS: This study shows that FFM depletion *per se* plays a part in the reduction of exercise capacity of COPD patients, regardless of dynamic hyperinflation, and is strictly associated to poor cardiovascular response to exercise and to leg fatigue, but not to dyspnoea.

Abstract word count: 243

Key Words: Fat-free Mass, Dynamic hyperinflation, Exercise, Cardiac function, COPD

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ABBREVIATIONS

AT: anaerobic threshold

BMI: body mass index

COPD: chronic obstructive pulmonary disease

CPET: cardiopulmonary exercise test

FEF_{50}: forced expiratory flow measured at 50% of FVC

FEV_1: forced expiratory volume in 1st second

FIF_{50}: forced inspiratory flow measured at 50% of FVC

FFM: fat-free mass

FVC: forced vital capacity

HR: heart rate

HRR: heart rate recovery

IC: inspiratory capacity

O_2Pulse: oxygen pulse

OUES: oxygen uptake efficiency slope

SD: standard deviation

TLC: total lung capacity

TLco: lung diffusion capacity for carbon monoxide

VAS: visual analogue scale

VC : Vital Capacity

VCO_2: carbon dioxide production

VE: minute ventilation

VO_2: oxygen uptake

V_T: tidal volume

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INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) commonly exhibit impaired exercise capacity. In these patients, the decreased physical activity does not seem to depend merely on resting lung function. The relationship between the forced expiratory volume in 1st second (FEV_1) and daily physical activities in COPD is very modest (1) and other factors are considered important in contributing to stagnation. On the one hand, the development of dynamic hyperinflation plays an important role in limiting exercise capacity (2) and may explain the reduction in the patient's daily physical activities, regardless of the severity of the COPD (3). Indeed, these subjects breathe in before achieving a full exhalation and, as a consequence, trap air within the lungs with each further breath with serious mechanical and sensory repercussions (4). Furthermore, the ventilatory constraints occurring during exercise have the potential for significant negative effects on the cardiovascular function (5,6).

Additionally, a fat free mass (FFM) depletion commonly occurs in COPD patients, resulting from several factors, such as systemic inflammatory mediators, disuse atrophy, poor nutrition and oral corticosteroid medication (7). Importantly, the reduction in FFM may also contribute to impairment of exercise capacity in these patients. Earlier studies have reported a significant correlation between body weight and maximal exercise capacity in COPD patients (8-10). Notably, the FFM was found to be strictly related both to submaximal (11) and maximal (12) exercise performance in these patients.

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

As compared with non depleted patients, a blunted ventilatory response at maximal exercise was found in depleted COPD patients (10,12), thereby suggesting a greater degree of dynamic hyperinflation in these patients. However, in these studies (10,12) the end-expiratory lung volume was not measured during exercise and thus the involvement of dynamic hyperinflation in the ventilatory constraints was only speculative.

We hypothesized that the depletion of lean body mass may *per se* reduce exercise capacity independent of dynamic hyperinflation during exertion. Therefore, the purpose of this study was to investigate in a cohort of patients with COPD the effect of the FFM on maximal exercise capacity and the relationship with changes in operational lung volumes during maximal effort.

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

METHODS

Patients

We enrolled patients affected by COPD, as defined according to the GOLD criteria (13), who were consecutively admitted to a pulmonary rehabilitation program. Eligibility criteria were: 1) stable clinical condition (exacerbation free for at least 4 weeks); 2) no oxygen therapy; 3) absence of any comorbidity affecting exercise performance (anaemia, neuromuscular disorders, chronic cardiac failure, malignancies or obesity); 4) ability to perform a symptom-limited cycle ergometry cardio pulmonary test (CPET) with a peak of respiratory exchange ratio (RER) $\geq$ 1.05 in order to exclude poor motivation; 5) CPET stopped for muscle fatigue and/or dyspnoea. All the procedures and their risks were explained to the patients, who gave their written informed consent to enter the study. The protocol was approved by the ethical committee of the University Hospital of Parma (Clinical Trial Registration Number: 36215; Nov, 12th 2010). All participants' data were analysed and reported anonymously. No extramural funding was used to support the study.

Lung function

Pulmonary function tests were performed according to international recommendations (14,15). A flow-sensing spirometer and a body plethysmograph connected to a computer for data analysis (Vmax 22 and 6200, Sensor Medics, Yorba Linda, U.S.A.) were used for the measurements. Vital Capacity (VC), Forced Expiratory Volume at 1st Second (FEV_1), Forced Expiratory Flow measured at 50% of Forced Vital Capacity

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(FVC) (FEF_{50} in L/s) and Forced Inspiratory Flow measured at 50% of FVC (FIF_{50} in L/s) were recorded. FEV_1/VC and FEF_{50}/FIF_{50} ratios were taken as indices of airway obstruction and airway collapsibility, respectively.

Thoracic Gas Volume (TGV) was measured by body plethysmography with the subject panting against a closed shutter at a frequency slightly < 1 Hz and their cheeks supported by their hands. Total Lung Capacity (TLC) was obtained as the sum of TGV and linked Inspiratory Capacity (IC). IC/TLC ratio was taken as index of hyperinflation of the lung. At least three measurements were made for each spirometry and lung volume variable to ensure reproducibility and the highest value was used in subsequent calculations. The flow-sensor was calibrated before each test using a three-litre syringe.

Lung diffusion capacity for carbon monoxide (TLco) was measured by the single breath method using a mixture of carbon monoxide and methane; this measurement was done at least in duplicate. TLC, VC, IC, FEV_1 and TLco were expressed as a percentage of the predicted values, which were obtained from regression equations by Quanjer et al (16) and Cotes et al (17).

Cardiopulmonary exercise test

CPET was performed according to a standardized procedure (18). After calibrating the oxygen and carbon dioxide analyzers and flow mass sensor, patients were asked to sit on an electromagnetically braked cycle ergometer (Corival PB, Lobe Bv, Groningen, The Netherlands) and the saddle was adjusted properly to avoid the maximal extension

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of the knee. The exercise protocol involved an initial 3 minutes of rest, followed by unloaded cycling for another 3 minutes with an increment every minute of 5 to 15 W, according to the patient's anthropometry and degree of functional impairment, in order to achieve an exercise time in between 8-12 min. Patients were asked to maintain a pedalling frequency of 60 rpm indicated by a digital display placed on the monitor of the ergometer. Breath-by-breath oxygen uptake (VO_2 in L/min), carbon dioxide production (VCO_2 in L/min), tidal volume (V_T in L) and minute ventilation (VE in L/min) were collected during the test (CPX/D; Med Graphics, St Paul, MN, U.S.A.). Patients were continuously monitored by a 12-lead electrocardiogram (Welch Allyn CardioPerfect, Delft, the Nederlands) and a pulse oximeter (Pulse Oximeter 8600, Nonin Medical Inc, MPLS, Mn U.S.A.). Blood pressure was measured at 2 min intervals. Stopping criteria consisted of symptoms such as unsustainable dyspnoea or leg fatigue, chest pain, ECG significant ST-segment depression, a drop in systolic blood pressure or oxygen saturation (SaO_2) $\leq 84\%$.

Peak workload and peak VO_2 were recorded as the mean value of watts and VO_2 during the last 20 sec of the test. Peak VO_2 was expressed as absolute value in mL/min. Anaerobic threshold (AT) was non-invasively determined by both V-slope and ventilatory equivalents methods ("dual method approach"), as the respiratory exchange ratio approximated 1.0 (18), and was expressed as absolute value in mL/min. Ventilatory response to exercise was calculated as a linear regression function by plotting VE against VCO_2 obtained every 10 seconds during exercise (VE/VCO_2 slope).

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

Changes in operational lung volumes were assessed every two min during exercise and at peak exercise, taking the IC measured at rest, as the baseline. After a full explanation to each patient of the procedure, satisfactory technique and reproducibility of IC manoeuvres were established during an initial practice session at rest. Assuming that TLC remains constant during exercise in COPD (19), changes in IC reflect changes in end-expiratory lung volume. Accordingly, dynamic hyperinflation can be defined as a decline in the IC greater than zero (20).

The exercise's cardiovascular response was expressed by the following parameters: oxygen pulse (O_2Pulse), oxygen uptake efficiency slope (OUES) and heart rate recovery (HRR). O_2Pulse (mL/bpm) was calculated by dividing instantaneous oxygen uptake by the heart rate (18) and was recorded at peak of exercise. The OUES describes the relationship between VO_2 and VE during incremental exercise, via a log transformation of VE and was expressed in L/min as the gradient of the linear relationship of $\log_{10}$VE to VO_2 (21). OUES thus represents the absolute rate of increase in oxygen uptake per 10-fold increase of minute ventilation. HRR in bpm was defined as the reduction of the heart rate at the exercise peak level compared to the rate one minute after the cessation of exercise (22).

Dyspnoea and muscle fatigue

Daily living activity-related dyspnoea was evaluated with the Italian version of five-point MRC scale modified by the ATS (23). Dyspnoea and muscle fatigue induced by CPET were measured at the end of the incremental exercise by a visual analogue scale

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

(VAS). The VAS scale consisted of a 100-mm horizontal line with the word "*none*" placed at the left end of the scale and the word "*very severe*" placed at the right of the scale. The VAS scored from 0 to 100, but the subjects were unaware of the numbers. Dyspnoea and muscle fatigue ratings were then divided by the maximal workload (VAS_{dys} and VAS_{fat}, respectively in mm/watts) (24).

Body Composition

Body height and weight were measured anthropometrically. Body composition was assessed by a bioelectrical impedance analysis (BIA) method, that is based on the conductance of an electrical sinusoidal alternating current through body fluids. BIA measures the impedance or resistance to the signal as it travels through the water that is found in muscle and fat. Foot-to-foot BIA was measured using a SC-331S Body Composition analyzer (TANITA CO., Tokyo, Japan). Patients were measured in standing position with bare feet on the analyzer footpads. The algorithms used to estimate lean body mass from impedance are those given by Segal et al (25). The fat-free mass (FFM) was standardized for height similar to BMI: FFM index (FFMI: $FFM/height^2$, kg/m^2).

Statistical analysis

This is a pilot, cross-sectional study. Due to the explorative nature of the study no formal sample size calculation was performed. Data are reported as mean ± standard deviation (SD), unless otherwise specified. The distribution of variables was assessed by means of Kolmogorov-Smirnov Goodness-of-Fit test. Relationships between

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

variables were assessed by the Pearson's correlation coefficient (r) and linear regression analysis. Comparisons between variables were determined by unpaired t test and χ^2 test, when appropriate.

For analysis purposes, population sample was divided into **depleted** and **non depleted** patients, according to the FFMI value. The cut-off values were 14.6 kg/m^2 and 16.7 kg/m^2 for women and men, respectively (26). According to IC/TLC ratio at peak of exercise and to peak O_2pulse value, patients of both groups were also divided in two categories: patients with IC/TLC $\leq$ 0.25 or > 0.25, and patients with peak O_2pulse < 10 mL/bpm or $\geq$ 10 mL/bpm, respectively. The patients with the IC/TLC ratio at the peak of exercise $\leq$ 0.25 may be defined as "heavy hyperinflators" (5,6). On the basis of the age of our population sample, a value of 10 mL/kg/min may be considered as a threshold value of normality for the peak oxygen pulse (27).

A p value of less than 0.05 was taken as significant.

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

RESULTS

Seventy-four consecutive stable COPD patients (19 females), aged between 42 and 75 years were screened. Seventeen patients were excluded because of their BMI > 30 kg/m^2. Demographic and clinical characteristics of the 57 patients included in the study are shown in Table 1. At study entry, patients were receiving regular therapy with inhaled steroids (65%), long-acting $beta_2$-agonists (63%) and Tiotropium (51%). All of them were ex-smokers. Among them a wide range of airflow obstruction (FEV_1/VC from 30 to 69%), lung hyperinflation (IC/TLC from 0.10 to 0.56), airway collapsibility (FEF_{50}/FIF_{50} ratio 0.07 to 0.93), diffusing capacity (TL_{CO} from 21 to 106 %) and daily living activity-related dyspnoea (MRC from 0 to 4) were found.

Thirty-one (8 females) out of 57 patients (54%) suffered from arterial hypertension and were taking diuretics (42%), ACE-inhibitors (30%), beta-blockers (25%), Ca-antagonists (14%), and sartans (5%). The prevalence of arterial hypertension was not different between **depleted** and **non depleted** patients (50% vs 56%). Additionally, the percentage of patients on beta-blockers was not different between depleted and non depleted patients (29% vs 23%).

Body composition varied consistently (FFMI range from 12.9 to 21.3 kg/m^2) and, as expected, females had significantly significantly lower FFMI (15.1 ± 1.6 kg/m^2 vs 18.3 ± 1.7 kg/m^2; $p < 0.001$). According to the FFMI, 14 (24.5%) out of 57 patients were categorized as **depleted** (mean±SD FFMI: 15.0 ± 1.4 kg/m^2), whereas 43 were **non depleted** (mean±SD FFMI: 18.1 ± 1.8 kg/m^2). No significant differences in gender, age,

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

and any lung function parameter at rest were recorded between the two groups (Table 1).

All the included patients completed the exercise test without any complication. Mean peak workload and peak VO_2 values were 83 ± 38 watt and 1,150 ± 397 mL/min, respectively. Exercise data are summarised in Table 2. The two groups of patients significantly differed ($p < 0.05$) in terms of peak VO_2 and AT and in terms of cardiovascular, but not ventilatory parameters during exercise. Notably, IC/TLC at peak of exercise was 0.24 ± 0.1 and 0.26 ± 0.1 in **depleted** and in **non depleted** patients, respectively ($p = 0.496$) (Figure 1), being ≤ 0.25 in 9 out of 14 (64%) **depleted** and in 23 out of 43 (53%) **non depleted** patients (chi square = 0.500; p = 0.479) (Figure 2). On the other hand, peak O_2Pulse was 7.6 ± 2.4 and 10.1 ± 3.0 mL/bpm in **depleted** and in **non depleted** patients, respectively ($p = 0.006$), being ≥ 10 mL/bpm in 3 out of 14 (21%) **depleted** and in 23 out of 43 (53%) **non depleted** patients (*chi square* = 4.376; $p = 0.036$) (Figure 2). The two categories of patients were different in VAS_{fat}, but not in VAS_{dys}.

Ten (mean age: 66 ± 9 years, 3 females) out of the 14 **depleted** patients and thirty-six (mean age: 65 ± 8 years, 10 females) out of the 43 **non depleted** patients developed dynamic hyperinflation (decline in IC greater than zero). When hyperinflators were considered, again **depleted** and **non depleted** patients were not different in resting airflow obstruction (FEV_1/VC: 50 % ± 8 vs 50% ± 11; p = 0.952), lung hyperinflation (IC/TLC: 0.28 ± 0.12 vs 0.33 ± 0.09; p = 0.166) and airway collapsibility (FEF_{50}/FIF_{50}:

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

0.26 ± 0.11 vs 0.31 ± 0.20; p = 0.432) as well as in dynamic hyperinflation during exercise (peak IC/TLC: 0.22 ± 0.09 vs 0.26 ± 0.09; p = 0.221) and in VAS_{dys} (1.51 mm/watts ± 1.4 vs 1.16 mm/watts ± 0.56; p = 0.227). On the other hand, they significantly differed in peak VO_2 (897 mL/min ± 213 vs 1,182 mL/min ± 356; p= 0.027), in peak O_2Pulse (7.3 mL/bpm ± 2.1 vs 9.8 mL/bpn ± 2.7; p= 0.009), OUES (1,033 mL/min ± 334 vs 1,519 mL/min ± 512; p= 0.007), HRR (7.5 bpm ± 5.1 vs 15.0 ± 11.0; p= 0.043) and in VAS_{fat} (1.55 mm/watts ± 0.8 vs 0.99 mm/watts ± 0.44; p= 0.005).

In all patients, significant correlations were found between FFMI and peak O_2Pulse (r = 0.643, p = 0.001), peak VO_2 (r = 0.587, p = 0.001), OUES (r = 0.527, p = 0.001), peak workload (r = 0.507, p = 0.001), and VAS_{fat} (r = -0.438, p = 0.001) (Figure 3).

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

DISCUSSION

The main finding of this study is that COPD patients with low fat-free mass, as compared to non depleted patients, may show significant lower exercise tolerance for a given and similar levels of resting and dynamic lung hyperinflation on exertion. This finding supports the view that FFM depletion significantly plays a part in the reduction of exercise capacity, irrespective of ventilatory constraints in COPD population. In addition, the FFM depletion is strictly associated with poor cardiovascular response to exercise and to leg fatigue but not to dyspnoea on exertion.

In the present study, we found that a fourth of COPD patients across GOLD stages and in stable clinical condition presents depletion of lean body mass. Malnutrition is a common finding in COPD patients and the estimate of its prevalence may vary depending on the characteristics of the study population. In a large cohort of COPD patients, Schols et al (28) showed that depletion of body weight was present in 40 to 50% of patients suffering from chronic hypoxemia or with severe airflow obstruction and in 25% of patients with moderate airflow limitation. More recently, the prevalence of low BMI as well as low FFMI was found to be significantly higher in female than in male COPD patients, whereas no differences in FEV_1, dyspnoea score and health status were observed between depleted and non-depleted COPD patients (29). The reduction in body weight and in FFM in COPD is mainly ascribed to a disturbed energy balance, since it has been shown that these patients may exhibit an increased daily energy expenditure, as compared to healthy subjects (30). It is not yet clear whether malnutrition in people with COPD is the cause of their deterioration or just part of the

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

progress of the disease (31), in any case it may be only partially reversed by nutritional supplementation (32).

The results of this study are in line with previous reports showing that body weight depletion is related to a decreased exercise performance in COPD patients (8-12). Our patients with low FFM showed a significant reduction in aerobic capacity both at peak of exercise and at anaerobic threshold. In our study, **depleted** and **non depleted** patients did not differ both in resting spirometry and lung volume measurements and in operational volumes measured during maximal exercise. The two groups of patients were also not different in breathlessness perception, but they differed in leg fatigue at peak of exercise. It is conceivable to assume that the same degree of dynamic hyperinflation and the lower FFM may explain on the one hand the same degree of exertional dyspnea and on the other hand the greater leg fatigue in the depleted patients, as compared to non depleted patients.

Differently from our results, earlier studies reported a blunted ventilatory response at maximal exercise in depleted patients with COPD (10,12). Notably, Palange et al (10) showed that patients with a lower body weight had higher dead space to tidal volume ratio when cycling. Moreover, Baarends et al (12) showed that patients with low FFM had an impaired ability to increase the tidal volume during exercise. These findings were explained by a greater degree of dynamic hyperinflation on exertion that would have been likely borne by the malnourished COPD patients, though in none of these studies the operational volumes during exercise were assessed. It is noteworthy that in

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

these two studies (10,12), the **depleted** patients differed in resting lung function and that a blunted response of tidal volume at peak of exercise could have been also explained by the weakness of respiratory muscle, as it can be found in malnourished COPD patients (33,34). This was not the case in our study population.

In our study, a poor cardiovascular response to exercise was strictly associated to the FFM below the cut-off values. A poor cardiovascular response to exercise was related to dynamic hyperinflation on exertion in severe COPD patients (5), and this finding has been recently confirmed and extended by our group in patients with a wide range of airflow obstruction (6). In the present series, the **depleted** patients, as compared to **non depleted**, significantly differed in cardiovascular response to exercise, for a given level of hyperinflation at rest and on exertion, indicating that a low FFM may independently affect the cardiovascular function. Indeed, both resting and peak O_2Pulse values were significantly lower in **depleted** patients, as compared to **non depleted**, whereas peak O_2Pulse strongly related to FFM in the whole population. The O_2Pulse may be considered as a reliable surrogate marker of the stroke volume (19). In healthy subjects, exercise stroke volume may be estimated simply as five times the slope of the linear oxygen uptake-heart rate relationship (35).

We also found that **depleted** and **non depleted** patients differed in two other non invasive parameters of cardiovascular response to exercise, such as OUES and HRR. OUES values were significantly lower in depleted patients and strongly related to FFM in all patients. The OUES represents the rate of increase of oxygen uptake in response to

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

a given minute ventilation during incremental exercise, indicating how effectively oxygen is extracted and taken into the body (36) and it is considered as an objective measure of cardiorespiratory and muscular fitness (37). Last, HRR, a marker of the cardiac autonomic function and a powerful predictor of mortality in the general population (22), was significantly lower in our depleted patients, being as on average 8.7 bpm. It is of note that a value of 12 bpm or less is considered as abnormal (22) and a low HRR was associated with a decreased survival even in the COPD population (38).

It is conventionally assumed that the skeletal muscle pump is crucial in the local and systemic circulatory effects following exercise (39). By expulsing the peripheral venous blood volume during exercise, the muscle pump may enhance venous return, central venous pressure, end-diastolic volume and thus stoke volume and cardiac output (39). In this way, the muscle pump makes also more blood flow available to be diverted to active muscle and thereby indirectly inducing muscle hyperemia (39). Muscle blood vessels are in turn tethered to the surrounding muscle, thereby ensuring that muscle mechanical factors are transmitted to the vasculature (40). Accordingly, a skeletal muscle depletion may negatively affect the cardiovascular response to exercise. The present study further strengthens this conclusion.

In summary, low fat-free mass is one important determinant of exercise tolerance by impairing the cardiovascular response in patients with COPD, irrespective of ventilatory constraints on exertion. This finding may have some indirect clinical implications. It is

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

conceivable that during rehabilitation course, malnourished COPD patients might present an impaired cardiovascular response to exercise, thereby having a worsen impact on their disability. Further studies should be able to address this matter and to find possible solutions.

CONTRIBUTOSHIP STATEMENT

ET served as the primary author. She developed the study protocol, participated in the patients recruitment and statistical analysis and drafted the manuscript and she is the guarantor of the entire manuscript. PT, MA, SR and FA participated in the design of the study and helped to patients recruitment. EM participated in the coordination of the study. EC participated in the design of the study and helped to draft the manuscript. AC developed the study protocol, interpreted study data, contributed to and reviewed drafts of the manuscript. All authors read and approved the final manuscript.

DISCLOSURE

The authors declare no conflicts of interest in this work.

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

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RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

Legends for figures

Figure 1. Mean and standard deviation values of IC/TLC (*upper panel*) and O_2 Pulse (*lower panel*) in relation to the corresponding rest and peak VO2 values in depleted and non depleted COPD patients. No difference was found between depleted and non depleted patients when IC/TLC values were considered both at rest and at peak of VO_2 values. O_2 Pulse values were significantly lower both at rest ($p = 0.004$) and at peak ($p = 0.006$) of VO_2 values in depleted as compared to non depleted patients.

Figure 2. Percentage of COPD patients categorized by FFMI and by IC/TLC (*upper panel*) and by FFMI and Peak O_2 Pulse (*lower panel*). The ratio between the number of patients with IC/TLC ≤ 0.25 and that of patients with IC/TLC > 0.25 was not different in depleted patients, as compared to non depleted (9/14 *vs* 23/20; $\chi^2 = 0.500$, $p = 0.479$). On the contrary, the ratio between the number of patients with Peak O2Pulse ≥ 10 mL/bpm and that of patients with Peak O2Pulse < 10 mL/bpm was significantly lower in in depleted patients, as compared to non depleted (3/11 *vs* 23/20; $\chi^2 = 4.376$, $p = 0.036$).

Figure 3. Relationship between fat-free mass index and peak O_2 pulse (*upper panel*), oxygen uptake efficiency slope (*middle panel*) and leg fatigue (*lower panel*) in 57 COPD patients.

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

Table 1. Demographic and baseline characteristics of COPD patients.

	All Patients (n = 57)	Depleted (n = 14)	Non Depleted (n = 43)	*p value**
Age (years)	65 ± 8	67 ± 8	65 ± 8	0.443
Females/Males	16/41	6/8	10/33	0.156
BMI (Kg/m^2)	25 ± 3	21 ± 2	26 ± 3	0.001
MRC (0-4)	1 (0-4)	1 (0-4)	1 (0-4)	0.990
TLC (% pred)	120 ± 24	119 ± 21	120 ± 25	0.890
FEV_1 (% pred)	51 ± 16	48 ± 16	52 ± 16	0.394
FEV_1/VC (%)	52 ± 11	54 ± 9	51 ± 11	0.391
IC/TLC	0.31 ± 0.09	0.28 ± 0.11	0.32 ± 0.09	0.180
FEF_{50}/FIF_{50}	0.33 ± 0.21	0.33 ± 0.21	0.32 ± 0.22	0.894
TL_{CO} (% pred)	60 ± 19	52 ± 17	63 ± 20	0.089

**p value*: depleted patients *vs* non depleted patients

Values are expressed as mean ± SD, median (range) or ratio

RESPIRATORY CARE Paper in Press. Published on October 29, 2013 as DOI: 10.4187/respcare.02709

Table 2. Exercise characteristics of COPD patients.

	All Patients (n = 57)	Depleted (n = 14)	Non Depleted (n = 43)	*p value**
Peak VO_2 (mL/min)	1,150 ± 397	942 ± 258	1,218 ± 413	0.023
AT (mL/min)	819 ± 258	667 ± 151	868 ± 268	0.003
Peak Workload (watts)	83 ± 38	68 ± 30	88 ± 39	0.084
VE (mL/min)	42 ± 14	38 ± 12	43 ± 14	0.227
VE/VCO_2 (L)	31 ± 9	32 ± 9	31 ± 9	0.768
Peak IC/TLC	0.25 ± 0.1	0.24 ± 0.1	0.26 ± 0.1	0.496
Rest O_2Pulse (mL/bpm)	3.6 ± 1.3	2. 74 ± 1.3	3.89 ± 0.8	0.004
Peak O_2Pulse (mL/bpm)	9.5 ± 3.1	7.6 ± 2.4	10.1 ± 3.0	0.006
OUES (mL/min)	1,421 ± 516	1,065 ± 323	1,537 ± 516	0.002
HRR (bpm)	12.9 ± 10	8.7 ± 6	14.4 ± 11	0.018
VAS_{dys} (mm/watts)	1.22 ± 0.79	1.46 ± 1.2	1.14 ± 0.62	0.198
VAS_{fat} (mm/watts)	1.16 ± 0.62	1.59 ± 0.83	1.01 ± 0.47	0.025

**p value*: depleted patients *vs* non depleted patients

Values are expressed as mean ± SD

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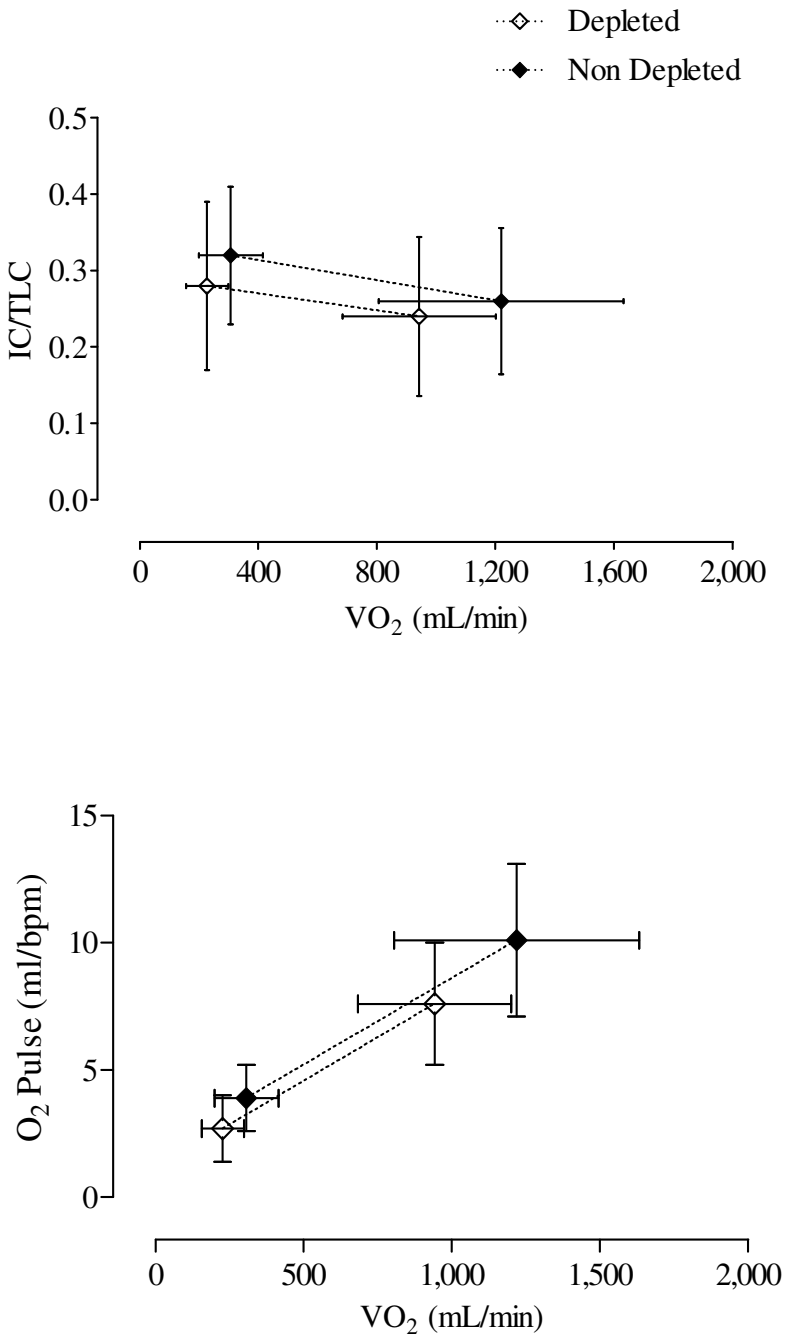

Figure 1

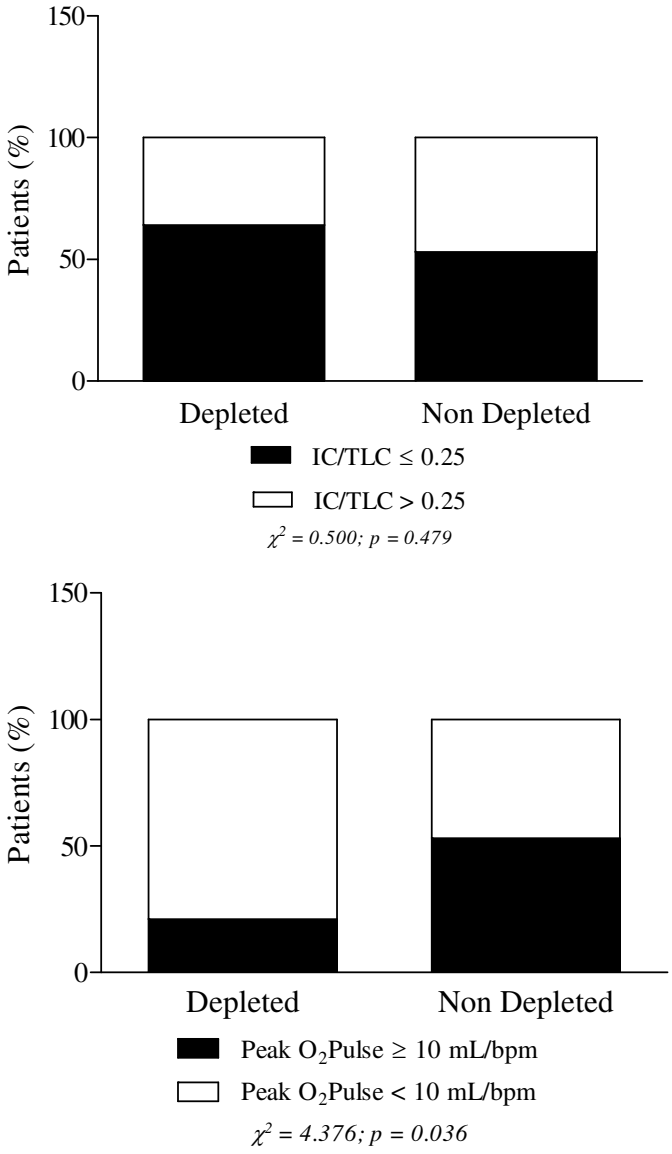

Figure 2

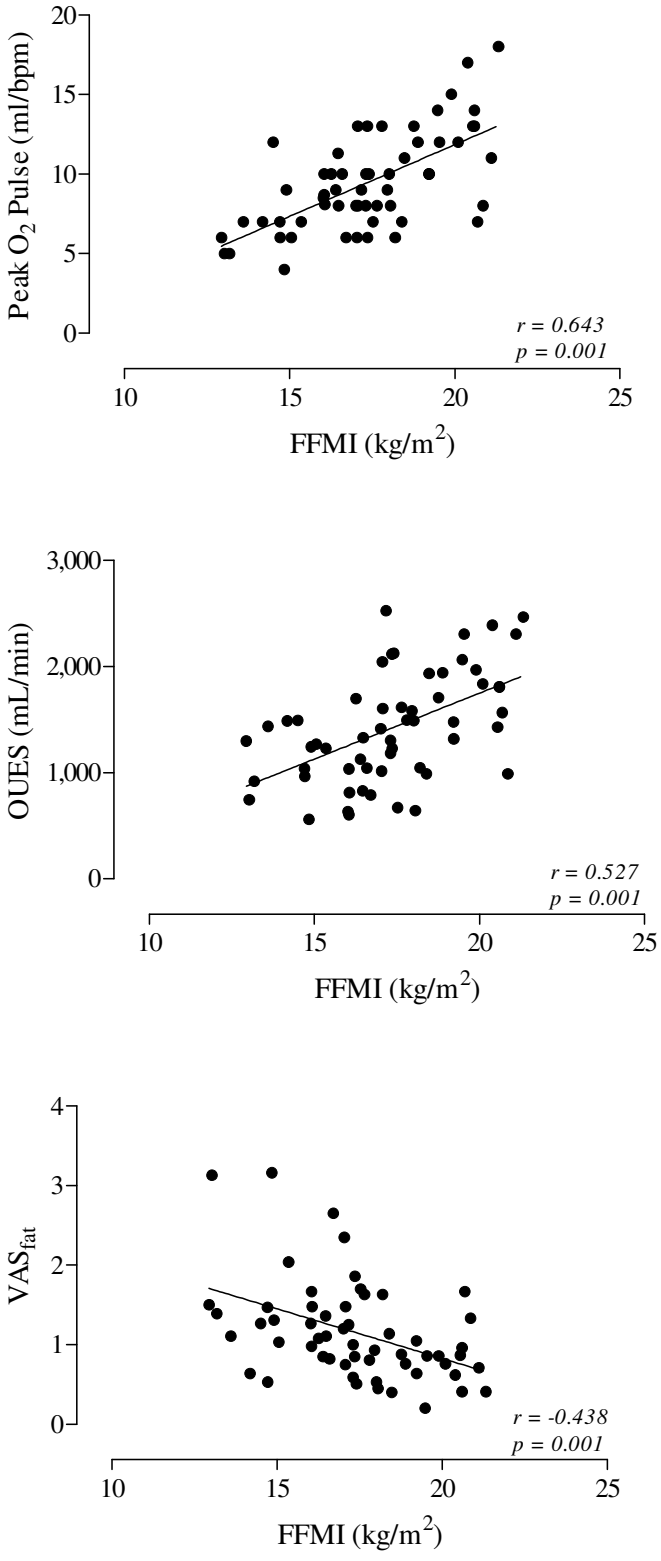

Figure 3