

## ORIGINAL RESEARCH ARTICLE

## The role of phenotype on ventilation and exercise capacity in patients affected by COPD: a retrospective study

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## ABSTRACT

**Background:** The idea of phenotype in chronic obstructive pulmonary disease (COPD) has evolved in the last decades, and the importance of peculiar treatment strategies has now been acknowledged. Although dyspnea and exercise limitation are hallmarks of COPD, this aspect has never been fully explored in literature in terms of disease phenotype. The aim of the present study was to explore the relevance of clinical COPD phenotypes on exercise ventilation and maximal capacity.

**Methods:** In this observational cohort retrospective study we analyzed the data of 50 COPD patients who underwent cardiopulmonary exercise test, categorized as emphysematous (n=29), and non-emphysematous (n=21) according to a previously validated model.

**Results:** We found a significant difference in terms of VE/VCO<sub>2</sub> slope (median values 32.4 vs 28.0,  $p=0.015$ ) and VE/VCO<sub>2</sub> ratio at nadir (median values 37 vs. 33,  $p=0.004$ ), which resulted higher in emphysematous patients, who also presented lower P<sub>ET</sub>CO<sub>2</sub> values (median values 32.6 vs 35.6,  $p=0.008$ ). In a subgroup of 31 tests which met the maximality criteria, emphysematous patients presented a significantly lower work rate at peak (median value 51 vs 72% predicted,  $p=0.016$ ), and showed a lower peak oxygen consumption, although at the limit of significance (median values of 63 vs 85 % predicted,  $p=0.051$ ).

**Conclusions:** This study extends our knowledge about the characterization of the COPD phenotypical expression of disease, showing that patients affected by emphysema are more prone to ventilatory inefficiency during exercise, and that this is likely to be an important cause of their overall reduced exercise capacity.

**Key words:** COPD; cardiopulmonary exercise test; ventilation; exercise capacity; phenotype; emphysema.

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## Introduction

The idea of phenotype in chronic obstructive pulmonary disease (COPD) has evolved in the last decades starting from a mere morphological and functional description, as in Burrows and colleagues pivotal works [1], coming to assume a wider meaning. In fact, many efforts have been spent to identify subgroups with key characteristics including the many aspects that concur to the wide variability of presentation in these patients: clinical features, physiology, imaging, response to therapy, decline in lung function, and survival. Although research is also relentlessly focused on defining the determinants of COPD in terms of genetics, many data are still lacking to clearly delineate a role for this aspect in the management of patients [2], underlining the importance of the clinical nature of phenotypization. The main aim becomes then to describe “clinical phenotypes”, that include all the variables that the advances made in the study of the disease in terms of imaging technology, molecular biology, therapeutic targets and clinical outcomes [3] offer, highlighting the need to overcome FEV<sub>1</sub> as the only physiological variable involved in diagnosis and treatment of the COPD population [4]. The importance of stratifying these patients and treat them differently has been acknowledged by the committees of several national statements and guidelines since the beginning of the current decade [5], suggesting that the management of patients with COPD can also be addressed in the light of the clinical phenotype. Although dyspnea and exercise capacity limitation are hallmarks of COPD [6], this aspect has never been fully explored in literature in terms of disease phenotype.

Various papers focused on exercise capacity in selected groups of patients defined by phenotypical characteristics (particularly emphysema) can be found in literature [7-10]. Although, to our knowledge, there is only one paper by Marquez-Martin and colleagues [11] reporting only a few data on peak exercise capacity measured through the gold standard, which is the cardiopulmonary exercise test (CPET) [12], comparing directly two groups of patients affected by COPD with different phenotypical expression (emphysematous and non-emphysematous). It is still an open question how much difference phenotype influence has on exercise capacity and in particular on ventilation [13]. It is then the purpose of the present study to explore the relevance of clinical COPD phenotypes in terms of maximal exercise capacity and ventilation, as measured thorough CPET.

## Methods

### Protocol and study population

This is an observational cohort retrospective analysis involving outpatients affected by COPD, who underwent CPET for clinical reasons or as part of observational studies as control group at our exercise laboratory at San Paolo Hospital in Milan (Italy) between March 2012 and May 2018. Local ethics committee approved the study. In our tertiary center all patients affected by COPD are evaluated routinely with body plethysmography, and diffusing capacity of the lung for carbon monoxide (DL<sub>CO</sub>). Patients had an established diagnosis of COPD (*i.e.* post-bronchodilator FEV<sub>1</sub>/FVC < LLN, and history of exposure to tobacco smoke with no evidence of asthma or any other lung disease) [14]. Spirometric severity was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [15]. All the patients met the criteria for the phenotype evaluation (see below). All the clinical data were obtained from medical records of the subjects, including medical history evaluation, and symptoms assessment.

Specifically, dyspnea was estimated using the Italian version of the modified Medical Research Council dyspnea scale (mMRC). Comorbidities were evaluated by Charlson comorbidity index, in which a higher score indicates greater coexisting conditions.

### Exercise and pulmonary function tests

Symptom-limited, incremental, exercise testing was performed on an electronically braked cycle ergometer using the Vmax Spectra Cardiopulmonary Exercise Testing System (SensorMedics, Yorba Linda, USA) [12]. The rate of work rate increment (W/min) was identified on an individual basis according to expected exercise tolerance, and resting functional data. Ventilation (VE, L/min), oxygen uptake (VO<sub>2</sub>, L/min), carbon dioxide output (VCO<sub>2</sub>, L/min) end-tidal carbon dioxide tension (P<sub>ET</sub>CO<sub>2</sub>, mmHg), respiratory frequency (fR, breaths/min), and tidal volume (VT, L) were averaged at 30 s intervals. Arterial oxygen saturation was measured by pulse oximetry (SpO<sub>2</sub>, %) non-invasively. Nadir VE/VCO<sub>2</sub> ratio was the lowest 30-s average data point. We also collected the values of the slope and intercept of VE plotted *versus* CO<sub>2</sub> output (VCO<sub>2</sub>) during exercise, excluding data above the ventilatory compensation point [16]. Peak VE response was expressed as percentage of the estimated maximal voluntary ventilation (MVV, L/min), which was equal to FEV<sub>1</sub> × 35. Breathing reserve (BR, %) was computed as MVV - VE<sub>peak</sub> and expressed as percentage of MVV. We considered as maximal a test meeting at least one of the following: i) respiratory exchange ratio (RER) at peak ≥ 1.15; ii) breathing reserve < 15%; iii) heart rate reserve < 15% with no evidence of heart rhythm disorders [12]. Spirometry, body plethysmography and lung diffusion test were performed according to ATS/ERS statements (Med Graphics Elite spirometer, USA) [17-19].

### Evaluation of phenotype

We used the CT score, published by Camiciottoli *et al.* [20], to evaluate the disease phenotype of our patients. This model, validated against the morphological gold standard that is the CT scan, is based on DL<sub>CO</sub> (% predicted), TLC (% predicted), and the presence of purulent sputum to identify three kind of prevalent involvement: emphysema, airway disease, and intermediate. We then grouped our patients in two groups for our final analysis: prevalent emphysema and non-emphysematous (including patients with prevalent airway disease and intermediate phenotype).

### Statistical analysis

We decided to present all the quantitative data as median and interquartile range as the normality was not confirmed for all the variables, as assessed through the Wilk-Shapiro test. We used the Mann-Whitney U-test and the *Chi*-square test to compare respectively quantitative and qualitative data. Spearman's correlation was used to examine the association between variables. We calculated that a sample size of at least 15 patients per group was needed assuming that a difference of at least a standard deviation would exist if a phenotype was less efficient in terms of exercise ventilation, starting from the literature where a VE/VCO<sub>2</sub> slope value of 33 ± 3 was found in a group of mild-to-moderate emphysematous COPD patients [21]. A *p* < 0.05 was considered statistically significant. Statistical tests were performed using the Statistical Package for Social Sciences (SPSS, Chicago IL, USA), ver. 23.0.

## Results

We included in our analysis 50 patients (29 in the emphysema group, and 21 in the non-emphysema group). The main reason for undergoing CPET was pre-operative evaluation, followed by par-

participation to research protocols, and dyspnea of unknown origin. Table 1 illustrates patient characteristics according to phenotype. We found a difference in  $DL_{CO}$  that can be accounted as this being one of the variables determining the phenotype in the CT score. Moreover, we found a significant difference in BMI ( $p=0.039$ ), with, as expected, lower values for emphysematous patients.

### Overall ventilatory response during exercise

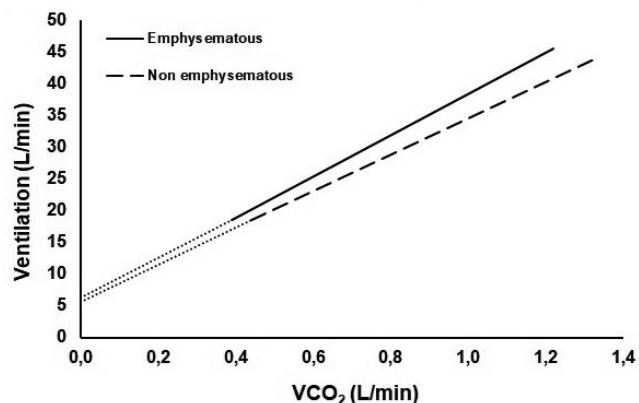
The analysis of the whole sample of 50 patients are summarized in Table 2. There was a significant difference in terms of  $VE/VCO_2$  slope, an effort-independent parameter of ventilatory efficiency, that resulted higher in emphysematous patients (Figure 1).  $P_{ET}CO_2$  was confirmed to be lower in this group (Figure 2), while  $VE/VCO_2$  at nadir was higher. No difference was found in breathing reserve, tidal volume at peak or at rest, or in breathing frequency.

### Maximal exercise capacity

Thirty-one tests met the maximality criteria, as previously described. Table 3 illustrates the effort-dependent variables, from maximal tests. Emphysematous patients presented a significantly lower work rate at peak (as percentage of predicted). This group also showed a lower peak oxygen consumption (percentage of predicted), although at the limit of significance ( $p=0.051$ ). We did not find differences in the other cardiovascular or metabolic variables. In terms of ventilatory response emphysematous patients featured a higher value of  $VE/VCO_2$  at nadir, as well as a significantly lower end tidal pressure for carbon dioxide.  $VE/VCO_2$  ratio at nadir showed a marked correlation with maximal oxygen consumption at peak (Figure 3; Spearman's  $r = -0.658$ ,  $p < 0.01$ , 43% of the variation explained).

## Discussion

Two major findings come from our study: i) emphysematous patients show less ventilatory efficiency during exercise than the non-emphysematous; ii) emphysematous patients have an overall lower exercise capacity than the non-emphysematous.



**Figure 1.** Graphical representation of the median values of  $VE/VCO_2$  slope and intercept in the two groups during cardiopulmonary exercise test.  $VCO_2$ , Carbon dioxide output;  $VE/VCO_2$  slope median values and interquartile range: emphysematous 32.4 (29.4-35.3), non-emphysematous 28.0 (26.1-33.2);  $p=0.015$ .  $VE/VCO_2$  intercept median values and interquartile range: emphysematous 6.3 (3.7-7.6), non-emphysematous 5.6 (4.2-6.4);  $p=0.536$ .

**Table 1.** Baseline characteristics of all patients according to phenotype.

	Emphysematous (n=29)	Non-emphysematous (n=21)	p
Male, n (percentage)	25 (86%)	17 (81%)	0.706
BMI, kg/m <sup>2</sup>	24.5 (21.9-27.4)	27.1 (24.9-28.1)	0.039*
Age, years	70 (61-74)	71 (64-75)	0.345
FEV <sub>1</sub> , %predicted	56 (41-60)	60 (53-67)	0.077
FVC, %predicted	86 (68-94)	76 (65-95)	0.529
TLC, %predicted	108 (101-121)	102 (89-121)	0.325
RV, %predicted	159 (131-189)	146 (124-175)	0.350
$DL_{CO}$ , %predicted	50 (40-63)	75 (65-92)	0.000*
mMRC <sup>o</sup>	1 (1-2)	1 (1-1)	0.976
mMRC (0/1/2/3/4) <sup>o</sup>	1/7/6/1/0	1/8/2/0/0	0.473
Charlson Index	2 (1-4)	3 (1-3)	0.217
Ischemic heart disease	3	1	0.632
Arrhythmia	1	0	0.578
Heart failure	2	0	0.504
Systemic arterial hypertension	12	5	0.235
Diabetes	6	2	0.440
Chronic kidney disease	2	0	0.509
GOLD obstruction grade (1/2/3/4)	2/18/6/3	2/15/4/0	0.483
Reason for test (dyspnea/pre-operative/research)	2/17/10	0/9/12	0.137
Reason for stopping (dyspnea/muscular fatigue/discomfort)	10/16/2	4/10/6	0.093

<sup>o</sup>Available for 26 patients; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume;  $DL_{CO}$ , diffusing capacity of the lung for carbon monoxide; mMRC, modified medical research council scale for dyspnea; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease. \* $p < 0.05$ .

The relationship between the increase in VE and in CO<sub>2</sub> output during exercise is of pivotal importance to explore the mechanisms of exercise intolerance in COPD; nevertheless, it requires a careful interpretation across the spectrum of severity of the disease, especially in terms of VE/VCO<sub>2</sub> slope and value of VE/VCO<sub>2</sub> ratio at nadir [13]. As a matter of fact, the relevance of the VE/VCO<sub>2</sub> slope as indicator of ventilatory efficiency per se, is matter of debate in literature [22]. Patients typically showing ventilatory inefficiency during exercise, but with a preserved ventilatory pump function such as in chronic heart failure, pulmonary arterial hypertension

and chronic thromboembolic disease [23-26], display an increasing tendency to hyperventilation (expressed as higher values of VE/VCO<sub>2</sub> slope) as the disease progresses. This paradigm was found not to be so true in COPD [22], as in the majority of patients, the progression of the disease is accompanied by an increasing impairment in the capacity of producing ventilation in response to a stimulus, due to a reduced ventilatory mechanical capacity [10]. In more impaired patients the values of VE/VCO<sub>2</sub> are reduced (comparable to those of healthy subjects), meaning a mechanical constraint that prevents patients from increasing their ventilation.

**Table 2. Overall ventilatory response during exercise in COPD patients according to phenotype.**

	Emphysematous (n=29)	Non-emphysematous (n=21)	p
Breathing reserve, %	19 (7-36)	32 (10-38)	0.212
Ventilation peak absolute, L	38.8 (33.6-48.1)	40.0 (35.3-49.6)	0.776
VE/VCO <sub>2</sub> slope	32.4 (29.4-35.3)	28.0 (26.1-33.2)	0.015*
P <sub>ET</sub> CO <sub>2</sub> , mmHg	32.6 (31.2-35.2)	35.6 (33.8-38.9)	0.008*
VE/V CO <sub>2</sub> , intercept	6.3 (3.7-7.6)	5.6 (4.2-6.4)	0.536
VE/VCO <sub>2</sub> ratio at nadir, L/L	37 (35-42)	33 (31-37)	0.004*
Tidal volume at rest, L	0.780 (0.635-0.865)	0.720 (0.550-0.915)	0.467
Tidal volume at peak, L	1.194 (0.968-1.395)	1.241 (0.964-1.425)	0.930
Δ Tidal volume peak-rest	0.422 (0.253-0.557)	0.525 (0.231-0.653)	0.361
Breathing frequency at rest, breaths/min	20 (18-26)	21 (18-25)	0.953
Breathing frequency at peak, breaths/min	35 (29-39)	35 (31-37)	0.922
Δ Breathing frequency peak-rest	10 (8-17)	13 (8-16)	0.484
VTpeak/FEV <sub>1</sub>	0.90 (0.75-1.02)	0.80 (0.73-0.92)	0.331
VTpeak/FVC	0.41 (0.34-0.48)	0.46 (0.38-0.53)	0.128

VE, ventilation; VO<sub>2</sub>, oxygen consumption; VCO<sub>2</sub>, carbon dioxide output; VE, ventilation; P<sub>ET</sub>CO<sub>2</sub>, end tidal pressure for carbon dioxide; VT, tidal volume; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity. \*p<0.05.

**Table 3. Difference in terms of effort dependent variables from maximal tests according to phenotype.**

	Emphysematous (n=18)	Non-emphysematous (n=13)	p
VO <sub>2</sub> peak absolute, L	1.159 (0.873-1.309)	1.293 (1.007-1.581)	0.242
VO <sub>2</sub> peak absolute, ml/min/kg	15.9 (13.2-19.0)	19.8 (12.9-21.6)	0.312
VO <sub>2</sub> peak, %predicted	63 (52-78)	85 (63-95)	0.051
Work peak absolute, W	72 (43-82)	89 (60-107)	0.106
Work peak, %predicted	51 (43-70)	72 (69-86)	0.016*
Respiratory Exchange Ratio at peak	1.08 (0.99-1.16)	1.11 (0.99-1.20)	0.594
Heart rate peak, %predicted	86 (71-94)	89 (76-94)	0.755
Oxygen pulse peak absolute, ml/beat	9 (8.1-10.1)	10.0 (8.0-11.7)	0.346
Oxygen pulse peak, %pred	76 (71-93)	98 (78-114)	0.124
Breathing reserve, %	9 (1-20)	26 (7-37)	0.106
Ventilation peak absolute, L	44.3 (35.4-54.3)	40.0 (35.9-56.4)	0.798
VE/VCO <sub>2</sub> nadir, L/L	36 (33-43)	32 (29-34)	0.004*
PET CO <sub>2</sub> , mmHg	33 (30-35)	36 (34-41)	0.012*
Tidal volume peak, L	1.222 (0.969-1.447)	1.241 (1.017-1.425)	1.000
Breathing frequency peak, breaths/min	37 (30-40)	35 (31-39)	0.567
Δ Tidal volume peak-rest, L	0.432 (0.297-0.571)	0.604 (0.416-0.722)	0.125
Δ Breathing frequency peak-rest, breaths/min	11 (8-20)	11 (7-18)	0.798
VTpeak/FEV <sub>1</sub>	0.92 (0.80-1.02)	0.80 (0.73-0.94)	0.293
VTpeak/FVC	0.44 (0.39-0.51)	0.48 (0.41-0.55)	0.125

VE, ventilation; VO<sub>2</sub>, oxygen consumption; VCO<sub>2</sub>, carbon dioxide output; VE, ventilation; P<sub>ET</sub>CO<sub>2</sub>, end tidal pressure for carbon dioxide; VT, tidal volume; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity. \*p<0.05.



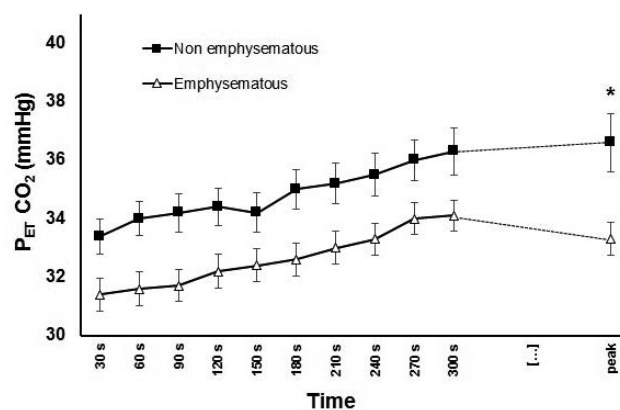
Particularly, the subject of emphysematous patients was explored by different authors in literature: Crisafulli and colleagues [9] demonstrated that, in a cohort of mild-to-moderate patients, the values of VE/VCO<sub>2</sub> slope increase in patients with a higher share of low attenuation areas (<950 HU) at the CAT scan, while Paoletti and colleagues [8] showed that in patients with a more severe disease (evaluated as percentage of emphysema at the CAT, attenuation ranging between -1024 and -910 HU) this values tend to flatten, and decrease.

In our study, emphysematous patients showed a higher VE/VCO<sub>2</sub> slope compared to non-emphysematous, as well as a higher VE/VCO<sub>2</sub> ratio at nadir in maximal tests. We interpreted this result as an indicator of a more pronounced ventilatory inefficiency in the former group. As a matter of fact, in our sample most patients were in GOLD obstruction class 1 or 2 (meaning an FEV<sub>1</sub> >50% of predicted), thus possibly not exhibiting an extremely marked mechanical limitation. This is consistent with the aforementioned study of Crisafulli *et al.* (9), and also with the findings of Jones *et al.* [21] who showed that in a group of mild-to-moderate COPD patients the higher the extent of emphysema (quantified as percentage of area with an attenuation lower than 950 HU at HR CAT scan) the higher the VE/VCO<sub>2</sub> ratio at nadir. Supporting this, the evidence that in our sample those who reached a lower VE/VCO<sub>2</sub> value at nadir (meaning a better ventilation/perfusion matching), exercised more, reaching a higher peak VO<sub>2</sub> (Figure 3). The term ventilatory efficiency relates to the ability of the lung to clear the physiologic carbon dioxide and is determined by two factors, the share of dead space (Vd /Vt phys) and PaCO<sub>2</sub>, and is expressed through the modified Bohr equation:  $VE/VCO_2 = k/PaCO_2 * (1 - Vd/Vt)$ , meaning that high values should be reflective of an increased dead space and/or decreased PaCO<sub>2</sub> set-point. It is possible that the difference we found in ventilatory efficiency is due to a higher dead space [27], typical of the parenchymal structural abnormalities caused by emphysema. This interpretation seems to be more likely than an alteration of the CO<sub>2</sub> set point driving to hypocapnia, given the tendency of COPD patients to develop a higher tolerance to carbon dioxide as the disease progresses instead [28]. Surely, the possible role of dynamic hyperinflation (DH) should be discussed, as a component of the ventilatory inefficiency during exercise. A subgroup of emphysematous patients called “emphysema-hyperinflated” patients is described in literature [29], who are characterized by high total lung capacity (TLC) and residual volume (RV) at rest, and is associated to a higher percentage of emphysema. While many studies showed a correlation among hyperinflation at rest and indices of dyspnea and reduced daily physical activity [30,31], the direct role of dynamic hyperinflation remains debated as Guenette and colleagues did not report any significant difference at CPET between a group of proven emphysematous “dynamic hyperinflated” and patients who did not, in terms of exercise capacity or symptoms, although data about VE/VCO<sub>2</sub> slope or VE/VCO<sub>2</sub> at nadir were not provided in the paper [32]. No conclusion can be taken from our study as we did not evaluate the presence of DH. A heightened ventilatory drive in emphysematous could also be related to different stimuli coming from peripheral muscles involved during exercise, which are more compromised in this group of patients, as demonstrated by Marquez-Martin and colleagues [11]. Nevertheless, no conclusion from our sample can be taken, as no data about blood gases were recorded for our patients. Emphysematous patients show also a significantly lower end tidal pressure for CO<sub>2</sub> at peak compared to non-emphysematous. In this context this can be interpreted as expression of a higher dilution of the gas in the expired volume due to heightened ventilatory drive [33]. Still, this testify their capacity of increasing ventilation.

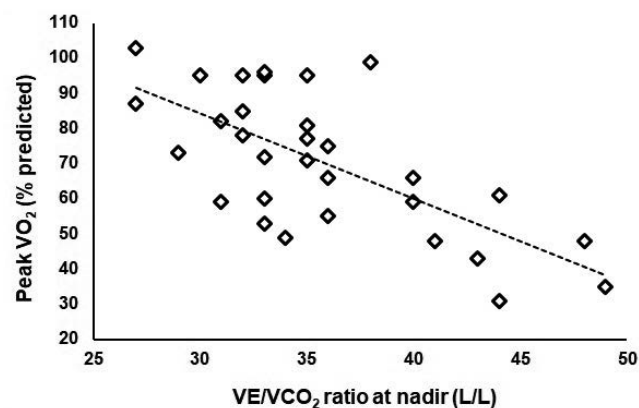
The usefulness of VE/VCO<sub>2</sub> relationship as an outcome for

intervention remains anecdotal in literature and a minimal clinically important difference has not been identified yet, in COPD [34]. Our study may suggest this outcome to be worth to be further explored in this specific group of patients, also considering the correlation between VE/VCO<sub>2</sub> and the extent of emphysema on the CT scan [8].

In terms of maximal exercise capacity our sample shows a lower level of work at peak reached by the emphysematous patients (expressed as percentage of predicted), with the peak oxygen consumption at the limits of statistical significance ( $p=0.051$ ). These findings are consistent with the Marquez-Martin paper, in which are reported oxygen consumption at peak and power from maximal exercise tests [11] in two groups of patients according to phenotypes (emphysematous and non-emphysematous), with similar values of lung function at rest. This study reported a lower



**Figure 2.** Graphical representation of P<sub>ET</sub>CO<sub>2</sub> in the two groups during cardiopulmonary exercise test. \* $p < 0.05$ . P<sub>ET</sub>CO<sub>2</sub>, end tidal pressure for carbon dioxide. Median values and interquartile range of P<sub>ET</sub>CO<sub>2</sub> at peak: emphysematous 33 (30-35), non-emphysematous 36 (34-41);  $p = 0.012$ . No significant differences between P<sub>ET</sub>CO<sub>2</sub> at other time points at the Mann-Whitney U-test with Bonferroni adjustment for multiple measures.



**Figure 3.** Relationship between peak exercise capacity and the carbon dioxide equivalent at nadir during cardiopulmonary exercise test. VO<sub>2</sub>, oxygen consumption; VCO<sub>2</sub>, carbon dioxide output; VE, Ventilation. Spearman's  $r = -0.658$ ,  $p < 0.01$ , 43% of the variation explained.

power (W) at peak in emphysematous patients, not reaching a significance in  $\text{VO}_2$ . This data highlight the importance of the evaluation of the functional impairment related to the disease through the assessment of overall exercise capacity at the CPET, which Chen and colleagues [7] showed to worsen in cohort of COPD patients, as the extent of emphysema at the CT increases. Marquez-Martin and colleagues found also that emphysematous subjects had a lower BMI, which we confirmed, and a difference in peripheral muscle strength, which was reduced in this group. With our study we add an inefficiency in ventilation to the factors contributing to a reduced exercise capacity in patients affected by COPD and characterized by an emphysematous phenotype, compared to non-emphysematous patients.

A number of potential limitations of this study deserve discussion: the fact that most of our patients are mild-to-moderate in terms of disease burden does not allow to extend our finding to every COPD subject. Moreover, we lack data about symptoms (*i.e.*, BORG scale for dyspnea and fatigue) during exercise; this does not let us relate our findings in terms of physiology to patients' perception. In addition, there is for sure the bias of the retrospective nature of this study, with non-consecutive patients that underwent CPET also for clinical reasons, reducing the external validity of our final results.

## Conclusion

Our study extends our knowledge about the characterization of the COPD phenotypical expression of disease, showing that patients affected by emphysema are more prone to ventilatory inefficiency during exercise, and that this is likely to be an important cause of their overall reduced exercise capacity. Cardiopulmonary exercise testing is a useful tool that provides a deeper insight into pathophysiology and phenotypical definition of COPD patients. The usefulness of some variables as outcome for therapeutic intervention, in particular  $\text{VE}/\text{VCO}_2$  slope [3], is worth to be further explored, especially in this specific and selected cluster of patients.

## Abbreviations

*COPD*: Chronic obstructive pulmonary disease; *CPET*: Cardiopulmonary exercise test; *FEV<sub>1</sub>*: Forced expiratory volume in 1 s; *DL<sub>CO</sub>*: Diffusing capacity of the lung for carbon monoxide; *BMI*: Body mass index; *GOLD*: Global Initiative for Chronic Obstructive Lung Disease; *VO<sub>2</sub>*: Oxygen consumption; *VCO<sub>2</sub>*: Carbon dioxide output; *VE*: Ventilation; *P<sub>ET</sub>CO<sub>2</sub>*: End tidal pressure for carbon dioxide; *DH*: dynamic hyperinflation.

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