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

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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/VCO2 slope (median values 32.4 vs 28.0, p=0.015) and VE/VCO2 ratio at nadir (median values 37 vs 33, p=0.004), which resulted higher in emphysematous patients, who also presented lower PETCO2 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.
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 FEV1 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 pletismography, and diffusing capacity study. In our tertiary center all patients affected by COPD are evaluated routinely with body pletismography, and diffusing capacity study. All 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.

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 DLCO (% 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 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/VCO2 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 DLCO 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/VCO2 slope, an effort-independent parameter of ventilatory efficiency, that resulted higher in emphysematous patients (Figure 1). PaCO2 was confirmed to be lower in this group (Figure 2), while VE/VCO2 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 level 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/VCO2 at nadir, as well as a significantly lower end tidal pressure for carbon dioxide. VE/VCO2 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).

![Figure 1. Graphical representation of the median values of VE/VCO2 slope and intercept in the two groups during cardiopulmonary exercise test. VCO2: Carbon dioxide output; VE/VCO2 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/VCO2 intercept median values and interquartile range: emphysematous 6.3 (3.7–7.6), non-emphysematous 5.6 (4.2–6.4); p=0.536.](image)

**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/m²        | 24.5 (21.9-27.4)     | 27.1 (24.9-28.1)         | 0.039*|
| Age, years        | 70 (61-74)           | 71 (64-75)               | 0.345 |
| FEV₁, %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 |
| DLCO, %predicted  | 50 (40-63)           | 75 (65-92)               | 0.000*|
| mMRC⁵            | 1 (1-2)              | 1 (1-1)                  | 0.976 |
| mMRC (0/1/2/4)⁵   | 1/3/6/1/0            | 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 (1/2/4) | 2/18/3               | 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 |

*Available for 26 patients; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; DLCO, 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.

**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.
The relationship between the increase in VE and in CO₂ 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/VCO₂ slope and value of VE/VCO₂ ratio at nadir [13]. As a matter of fact, the relevance of the VE/VCO₂ 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/VCO₂ 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/VCO₂ 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/VCO₂ slope             | 32.4 (29.4-35.3)     | 28.0 (26.1-33.2)         | 0.015* |
| Pₚ₅ CO₂, mmHg             | 32.0 (31.2-35.2)     | 35.6 (33.8-38.9)         | 0.008* |
| VE/VCO₂ intercept         | 6.3 (3.7-7.6)        | 5.6 (4.2-6.4)            | 0.536 |
| VE/VCO₂ 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 (0.233-0.557)  | 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/FEV₁               | 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 |

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

|                           | Emphysematous (n=18) | Non-emphysematous (n=13) | p   |
|---------------------------|----------------------|--------------------------|-----|
| VO₂ peak absolute, L      | 1.159 (0.873-1.309)  | 1.293 (1.007-1.581)      | 0.242 |
| VO₂ peak absolute, ml/min/kg | 153 (13.2-19.0)   | 19.8 (12.9-21.8)         | 0.312 |
| VO₂ 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 (8-10.1) | 10.0 (8.0-11.7) | 0.346 |
| Oxygen pulse peak, %pred   | 76 (71-93)           | 98 (78-114)              | 0.124 |
| Breathing reserve, %       | 9 (7-20)             | 26 (7-37)                | 0.106 |
| Ventilation peak absolute, L | 44.3 (35.4-54.3)   | 40.0 (35.9-56.4)         | 0.798 |
| VE/VCO₂ nadir, L/L         | 36 (33-45)           | 32 (29-34)               | 0.004* |
| PET CO₂, 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) | 0.694 (0.416-0.722) | 0.125 |
| Δ Breathing frequency peak-rest, breaths/min | 11 (8-20) | 11 (7-18) | 0.798 |
| VTpeak/FEV₁                | 0.92 (0.80-1.02)     | 0.80 (0.73-0.94)         | 0.293 |
| VTpeak/FVC                 | 0.44 (0.39-0.51)     | 0.46 (0.41-0.55)         | 0.125 |

VE, ventilation; VO₂, oxygen consumption; VCO₂, carbon dioxide output; VE, ventilation; Pₚ₅ CO₂, end tidal pressure for carbon dioxide; VI, tidal volume; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity. *p<0.05.
were recorded for our patients. Emphysematous patients show also
sion from our sample can be taken, as no data about blood gases
by Marquez-Martin and colleagues [11]. Nevertheless, no conclu-
coming from peripheral muscles involved during exercise, which
of increasing ventilation.

did not evaluate the presence of DH. A heightened ventilatory
efficiency in the former group. As a matter of fact, in our sample most
patients were in GOLD obstruction class 1 or 2 (meaning an FEV1
>50% of predicted), thus possibly not exhibiting an extremely
marked mechanical limitation. This is consistent with the afore-
mentioned 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-mod-
erate 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/VCO2 ratio at nadir. Supporting this,
evidence that in our sample those who reached a lower
VE/VCO2 value at nadir (meaning a better ventilation/perfusion
matching), exercised more, reaching a higher peak VO2 (Figure 3).
The term ventilatory efficiency relates to the ability of the lung to
clear the physiologic carbon dioxide and is determined by two fac-
tors, the share of dead space (Vd /Vt phys) and PaCO2, and is
expressed through the modified Bohr equation: VE/VCO2 =
\[ \frac{k}{PaCO2} \times (1-Vd/Vt) \]
meaning that high values should be reflective
of an increased dead space and/or decreased PaCO2 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 struc-
tural abnormalities caused by emphysema. This interpretation
seems to be more likely than an alteration of the CO2 set point driv-
ing to hypocapnia, given the tendency of COPD patients to devel-
A subgroup of emphysematous patients
called “emphysema-hyperinflated” patients is described in litera-
ture [29], who are characterized by high total lung capacity (TLC)
and residual volume (RV) at rest, and is associated to a higher per-
centage 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 hyperin-
flation remains debated as Guenette and colleagues did not report
any significant difference at CPET between a group of proven
emphysematous “dynamic hyperinflators” and patients who did
not, in terms of exercise capacity or symptoms, although data
about VE/VCO2 slope or VE/VCO2 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 conclu-
sion 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 CO2 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/VCO2 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 cor-
relation between VE/VCO2 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 oxy-
gen 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 sim-
ilar values of lung function at rest. This study reported a lower

Figure 2. Graphical representation of P\textsubscript{ET}CO\textsubscript{2} in the two groups
during cardiopulmonary exercise test. *\(p<0.05\). P\textsubscript{ET}CO\textsubscript{2}, end tidal
pressure for carbon dioxide. Median values and interquartile
range of P\textsubscript{ET}CO\textsubscript{2} at peak: emphysematous 33 (30-35), non-
emphysematous 36 (34-41); P=0.012. No significant differences
between P\textsubscript{ET}CO\textsubscript{2} 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 exer-
cise test. VO\textsubscript{2}, oxygen consumption; VCO\textsubscript{2}, carbon dioxide output;
VE, Ventilation. Spearman’s rs = -0.658, p<0.01, 43% of the
variation explained.
power (W) at peak in emphysematous patients, not reaching a significance in VO2. 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-Martín 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 VE/VCO2, 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; FEV1: Forced expiratory volume in 1 s; DLCO: Diffusing capacity of the lung for carbon monoxide; BMI: Body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; VO2: Oxygen consumption; VCO2: Carbon dioxide output; VE: Ventilation; PpaCO2: End tidal pressure for carbon dioxide; DH: dynamic hyperinflation.

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