RESEARCH ARTICLE

Ventilatory compensation during the incremental exercise test is inversely correlated with air trapping in COPD [version 1; peer review: 2 not approved]

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Abstract

Background: Air trapping and gas exchange abnormalities are major causes of exercise limitation in chronic obstructive pulmonary disease (COPD). During incremental cardiopulmonary exercise testing, ventilatory equivalents for carbon dioxide (V_E/VCO_2) and oxygen (V_E/VO_2) may be difficult to identify in COPD patients because of limited ventilatory compensation capacity. Therefore, we aimed to detect a possible correlation between the magnitude of ventilation augmentation, as manifested by increments in ventilatory equivalents from nadir to peak effort values and air trapping, detected with static testing.

Methods: In this observational study, we studied data obtained previously from 20 COPD patients who, during routine follow-up, underwent a symptom-limited incremental exercise test and in whom a plethysmography was obtained concurrently. Air trapping at rest was assessed by measurement of the residual volume (RV) to total lung capacity (TLC) ratio (RV/TLC). Gas exchange data collected during the symptom-limited incremental cardiopulmonary exercise test allowed determination of the nadir and peak effort values of V_E/VCO_2 and V_E/VO_2 , thus enabling calculation of the difference between peak effort value and nadir values of V_E/VCO_2 and V_E/VO_2 , designated $\Delta V_E/VCO_2$ and $\Delta V_E/VO_2$, respectively.

Results: We found a statistically significant inverse correlation between both $\Delta V_E/VCO_2$ ($r = -0.5058$, 95% CI -0.7750 to -0.08149 , $p = 0.0234$) and $\Delta V_E/VO_2$ ($r = -0.5588$, 95% CI -0.8029 to -0.1545 , $p = 0.0104$) and the degree of air trapping (RV/TLC). There was no correlation between $\Delta V_E/VCO_2$ and peak oxygen consumption, forced expiratory volume in the first second, or body mass index.

Conclusions: The ventilatory equivalents increment to compensate for acidosis during incremental exercise testing was inversely

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correlated with air trapping (RV/TLC) and may be a candidate prognostic biomarker.

Keywords

air trapping, COPD, exercise, isocapnic buffering phase, ventilatory equivalent

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Abbreviations

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in the first second; GOLD, global initiative for chronic obstructive lung disease; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; VCO₂, CO₂ output; V_E, minute ventilation; V_E/VCO₂, ventilatory equivalent for CO₂; V_E/VO₂, ventilatory equivalent for oxygen; Δ V_E/VCO₂, nadir to peak value of V_E/VCO₂; Δ V_E/VO₂, nadir to peak value of V_E/VO₂; VO₂, oxygen consumption; VT, ventilatory threshold.

Introduction

Chronic obstructive pulmonary disease (COPD) patients often demonstrate significant effort limitation, chiefly resulting from gas exchange abnormalities and ventilation-perfusion mismatching¹. This situation is often compounded by hyperinflation and air trapping with dynamic hyperinflation during exercise and gradual reduction of inspiratory capacity². To evaluate exercise capacity and determine the degree of effort limitation and its mechanisms, the incremental exercise test is often applied, during which several ventilatory events occur and draw close attention.

During incremental cardiopulmonary exercise testing, the ratio of minute ventilation (V_E) to carbon dioxide output (VCO₂) and to oxygen consumption (VO₂), also known as ventilatory equivalent for carbon dioxide (V_E/VCO₂) and oxygen (V_E/VO₂), respectively, serve to evaluate ventilatory efficiency. The ventilatory threshold (VT), a term coined in the context of gas exchange measurements and represents to a great extent the VO₂ at anaerobic threshold, heralds the onset of the isocapnic buffering phase, in which there is an increased contribution of anaerobic metabolism to provide the energy required for the increasing demands of exercise, accompanied by increased CO₂ production with corresponding ventilation increase. With the accumulation of lactic acid and H⁺ protons, as the bicarbonate reserves are exhausted beyond the isocapnic buffering phase, an augmented ventilatory response starts at the ventilatory compensation point, which is disproportionate to the degree of CO₂ production, leading to V_E/VCO₂ surge towards peak effort, a phenomenon termed the ventilatory compensation phase.

The V_E/VCO₂ is often increased as a result of ventilation-perfusion mismatching^{1,3}. The nadir V_E/VCO₂ value during incremental exercise is inversely related to the degree of effort limitation⁴, as well as the severity of airway obstruction, as determined by the values of forced expiratory volume in first second (FEV₁)⁵. The nadir value is considered to reflect ventilatory efficiency as higher values obtained at the early stages of the incremental exercise test result from frequently encountered hyperventilation. Interestingly, marked hyperinflation and reduced ventilatory capacity tend to reduce ventilatory equivalents as ventilation may become constrained. Both baseline and peak effort V_E/VCO₂ values were found to be lower in patients with more severe airway obstruction as V_E is decreased relative to VCO₂ in these patients⁶.

Although COPD patients may terminate exercising at an early stage during the incremental exercise test due to airflow obstruction and air trapping, suboptimal effort and deconditioning, the latter of which may be associated with somewhat earlier development of metabolic acidosis, may also lead to early termination of the exercise test. Regardless of the reason causing decreased exercise performance, the ventilatory compensation phase may not be demonstrated. Ventilatory equivalents during incremental exercise may be affected by the above-mentioned processes in different directions. In this study we sought to confirm the presumption that the ability to achieve ventilatory compensation in response to acidosis is related to the degree of air trapping, with the hypothesis that the ability to augment ventilation beyond the ventilatory compensation point in COPD patients is inversely correlated with the degree of air trapping.

Methods

Study design and subjects

A retrospective analysis of data obtained from the medical records of COPD patients who underwent incremental cardiopulmonary exercise testing in the pulmonary function laboratory of the Institute of Pulmonary Medicine in the Hadassah Medical Center, Jerusalem, Israel between June 2010 and August 2016, and in whom whole body plethysmography was performed concurrently, as part of their routine clinical evaluation. The number of patients was determined by the availability of incremental exercise test and plethysmography data that was performed concurrently. Subjects were previously diagnosed with COPD based on post-bronchodilator spirometry showing an FEV₁ to forced vital capacity (FVC) ratio (FEV₁/FVC) of ≤ 0.7 , regardless of the value of FEV₁ (according to 2017 GOLD guidelines). Comorbidities such as obesity, cardiac disease and use of beta blockers were noted, but were not a cause to exclude patients from the study. The research ethics board (REB) of the Hadassah Medical Organization (protocol No. 0040-16-HMO) approved data collection and waived the need for informed consent, as this research was retrospective, did not affect patient management, or involve collecting biospecimens.

Procedures

Pulmonary function tests and exercise tests were performed by technicians in the presence of a physician during exercise tests. Whole-body plethysmography was performed using a commercially available body plethysmograph (Elite series, MedGraphics). Spirometry performance and slow vital capacity determination were followed by assessment of lung volumes, which was performed by direct measurement of thoracic gas volume (TGV), from which the residual volume (RV), total lung capacity (TLC) and RV/TLC ratios could be calculated as the primary method to estimate gas trapping. Additionally, we determined the ratio of inspiratory capacity (IC) to total lung capacity, IC/TLC, which has been proposed to reflect lung expansion as a result of reduced lung recoil in emphysema⁷. Using the same lung function system, transfer factor of the lung for carbon monoxide (TL_{CO}) was measured by the single breath method.

Patients performed incremental symptom-limited cycle ergometry connected to a metabolic system with cycle ergometer (Ultima Cardio₂, MedGraphics). For each patient, baseline measurements were obtained during the resting period of 1 minute, after which the patient would start cycling at a constant rate of 50–60 rpm. Following a 1–2 minute warm-up period at 0 watts and with VO_2 and VCO_2 reaching a plateau, a ramp protocol was started with a workload increase of 15–25 watt per minute, depending on the predicted maximal VO_2 and the general state of the patient. The test was terminated at exhaustion. Routine pre-cordial 12-lead electrocardiogram monitoring, continuous measurements of V_E , VO_2 , VCO_2 (averaged every 10 seconds), heart rate and finger arterial pulse oximetry were recorded. The peak VO_2 and the VT were both noted, as well as nadir ventilatory equivalents (V_E/VCO_2 and V_E/VO_2). Values of V_E/VCO_2 and V_E/VO_2 obtained at the termination of loaded exercise (peak effort) enabled calculation of the difference between peak effort value and nadir values of V_E/VCO_2 and V_E/VO_2 (designated $\Delta\text{V}_E/\text{VCO}_2$ and $\Delta\text{V}_E/\text{VO}_2$, respectively).

Statistical analysis

Statistical analysis was performed using the GraphPad Prism 3.0 program software and Spearman's test was used for correlation analysis, with calculation of the Pearson correlation coefficient (r) between measured parameters. Correlations were considered of statistical importance if two-tailed p value was <0.05 . Unpaired t -test was used to compare between groups, and a two-tailed p value < 0.05 was considered statistically significant

Standards of reporting

This manuscript is compliant with the STROBE guideline.

Results

In total, 20 patients were included in our analysis with a mean $\pm$ SD age of 63 ± 10 years (range 37–77). None of the patients had cardiac failure. Two patients were receiving beta blockers. Table 1 summarizes clinical data of these patients.

We found a statistically significant inverse correlation between both $\Delta\text{V}_E/\text{VCO}_2$ ($r = -0.5058$, 95% CI -0.7750 to -0.08149, $p = 0.0234$) and $\Delta\text{V}_E/\text{VO}_2$ ($r = -0.5588$, 95% CI -0.8029 to -0.1545, $p = 0.0104$), with the degree of air trapping as estimated by the RV/TLC ratio (Figure 1). On the contrary, there was no correlation between the nadir values of the ventilatory equivalents and RV/TLC (Table 2). Interestingly, inspiratory capacity to total lung capacity ratio (IC/TLC), which reflects pulmonary expansion in emphysema, did not show a correlation with either $\Delta\text{V}_E/\text{VCO}_2$ or $\Delta\text{V}_E/\text{VO}_2$ (Table 2).

We examined possible correlation between $\Delta\text{V}_E/\text{VCO}_2$ and other static parameters of pulmonary function or findings on exercise testing (summarized in Table 2). Notably, we found no significant correlation between neither $\Delta\text{V}_E/\text{VCO}_2$ nor nadir V_E/VCO_2 and peak VO_2 or FEV_1 . As expected¹, nadir values of V_E/VCO_2 correlated with TL_{CO} ($r = -0.5281$, 95% CI -0.7923 to -0.09708, $p = 0.0201$); however, we did not find a correlation between $\Delta\text{V}_E/\text{VCO}_2$ and TL_{CO} (Table 2).

Table 1. Patient clinical, pulmonary function and incremental exercise test data.

Age (years)	63 $\pm$ 10
Gender (% of males)	80
BMI (kg/m ²)	27.2 $\pm$ 6.8
Static pulmonary function tests	
FEV ₁ (L)	1.80 $\pm$ 0.70
FEV ₁ (% predicted)	63 $\pm$ 21
FVC (L)	3.07 $\pm$ 1.03
FVC (% predicted)	85 $\pm$ 22
FEV ₁ /FVC (%)	59 $\pm$ 12
RV (L)	3.82 $\pm$ 1.82
RV (% predicted)	166 $\pm$ 60
IC (L)	2.1 $\pm$ 0.6
IC (% predicted)	73 $\pm$ 21
TLC (L)	6.94 $\pm$ 1.81
TLC (% predicted)	111 $\pm$ 24
RV/TLC (%)	55 $\pm$ 11
IC/TLC (%)	31 $\pm$ 8
TL _{CO} (% predicted)	67 $\pm$ 17
No. of patients according to GOLD classification (% of all patients)	
GOLD I	7 (35%)
GOLD II	8 (40%)
GOLD III	4 (20%)
GOLD IV	1 (5%)
Exercise test	
Peak VO_2 (% predicted maximal VO_2)	68 $\pm$ 15
Nadir V_E/VCO_2	36 $\pm$ 7
Peak effort V_E/VCO_2	39 $\pm$ 8
$\Delta\text{V}_E/\text{VCO}_2$	2.6 $\pm$ 3.4
Nadir V_E/VO_2	37 $\pm$ 7
Peak effort V_E/VO_2	45 $\pm$ 10
$\Delta\text{V}_E/\text{VO}_2$	8.0 $\pm$ 7.6
Peak heart rate (% predicted maximal heart rate)	80 $\pm$ 11
Breathing reserve* (%)	30 $\pm$ 15
Arterial blood O ₂ desaturation at peak effort (%)	2.4 $\pm$ 3.6

Values are mean $\pm$ SD.

BMI, body mass index; FEV₁, forced expiratory volume; FVC, forced vital capacity; HR, heart rate; GOLD, Global initiative for chronic Obstructive Lung Disease; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; TL_{CO}, transfer factor of the lung for carbon monoxide; VO_2 , oxygen consumption; V_E/VO_2 , ventilatory equivalent for oxygen; V_E/VCO_2 , ventilatory equivalent for carbon dioxide; Δ is the difference between measured value of ventilatory equivalent at peak effort and nadir value.

*Breathing reserve = (maximal voluntary ventilation - peak ventilation) / maximal voluntary ventilation.

Figure 1. Correlation between $\Delta V_E/VCO_2$ (A), $\Delta V_E/VO_2$ (B) and RV/TLC. RV/TLC, residual volume to total lung capacity ratio; $\Delta V_E/VCO_2$, nadir to peak increment of ventilatory equivalent for CO_2 ; $\Delta V_E/VO_2$, nadir to peak increment of ventilatory equivalent for oxygen. $p < 0.05$ points to a statistically significant correlation.

Table 2. Statistical correlation analysis of nadir to peak increment (Δ) ventilatory equivalents or nadir ventilatory equivalents and other parameters of static pulmonary function, incremental exercise and BMI.

	r	95% CI for r	p value
$\Delta V_E/VCO_2$ to IC/TLC	0.2835	-0.1819 to 0.6452	0.2258
$\Delta V_E/VO_2$ to IC/TLC	0.2369	-0.2298 to 0.6150	0.3145
$\Delta V_E/VCO_2$ to FEV_1	0.2902	-0.1749 to 0.6494	0.2145
Nadir V_E/VCO_2 to FEV_1	0.0894	-0.3677 to 0.5118	0.7077
$\Delta V_E/VCO_2$ to peak VO_2	0.0902	-0.3670 to 0.5124	0.7051
$\Delta V_E/VCO_2$ to TL_{CO}	0.0015	-0.4531 to 0.4555	0.9951
Nadir V_E/VCO_2 to TL_{CO}	-0.5281	-0.7923 to -0.09708	0.0201
Nadir V_E/VCO_2 to RV/TLC	-0.1298	-0.5413 to 0.3319	0.5855
Nadir V_E/VO_2 to RV/TLC	-0.0626	-0.4916 to 0.3909	0.7933
$\Delta V_E/VCO_2$ to BMI	-0.3809	-0.7047 to 0.07421	0.0975
$\Delta V_E/VO_2$ to BMI	-0.3399	-0.6802 to 0.1210	0.1426

p value < 0.05 is considered of statistical importance.

r, Pearson correlation coefficient; BMI, body mass index; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; FEV_1 , forced expiratory volume; TL_{CO} , transfer factor of the lung for carbon monoxide; VO_2 , oxygen consumption; V_E/VCO_2 , ventilatory equivalent for carbon dioxide; V_E/VO_2 , ventilatory equivalent for oxygen; Δ is the difference between measured value at peak effort and nadir value

In an attempt to identify reasons for the lack of increment of $\Delta V_E/VCO_2$ besides factors related to air trapping, we compared values of parameters related to static pulmonary functions and those related to performance of exercise in patients with and without increment in V_E/VCO_2 (i.e., $\Delta V_E/VCO_2 = 0$) (Table 3). While FEV_1 , IC/TLC, TL_{CO} , peak VO_2 , and nadir V_E/VCO_2 were not different between these two groups, RV/TLC and peak respiratory exchange ratio had a statistically important difference between the two groups. However, these latter two factors are inherently derived from the parameters that the correlation study had examined and therefore, this difference is not surprising.

Discussion

Inefficient ventilation in patients with COPD and particularly emphysema is often evidenced by elevated nadir V_E/VCO_2 . The elevation of nadir V_E/VCO_2 may be related to the extent and severity of emphysematous changes in the lungs. It has been shown that in patients with mild to moderate airflow decrease, the values of nadir V_E/VCO_2 correlated with the percentage of low attenuation areas on computerized tomography^{8,9} as well as the decrease in pulmonary perfusion, as estimated by the inert gas rebreathing method⁹. Interestingly, in smokers without COPD, the degree of CO diffusion decrease correlated with elevation of nadir V_E/VCO_2 during the incremental exercise test¹⁰, again pointing to a strong relation between impaired ventilation efficiency and gas exchange ability. Notably, significantly increased ventilatory constraints, as occurs in marked air trapping, decrease V_E , thus leading to lower nadir V_E/VCO_2 in more severe airway obstruction^{2,6}.

In this study we examined the ability of COPD patients during incremental exercise testing to increase ventilation towards peak effort, focusing on the increase in the V_E/VCO_2 and

Table 3. Comparison between patients in whom there was no nadir to peak increment in V_E/VCO_2 ($\Delta V_E/VCO_2=0$) and patients with nadir to peak increment in $\Delta V_E/VCO_2$ from effort ($\Delta V_E/VCO_2>0$).

	$\Delta V_E/VCO_2=0$ (n=10)	$\Delta V_E/VCO_2>0$ (n=10)	p
RV/TLC (%)	60.3 ± 7.7	49.4 ± 11.1	0.0200
peak RER	1.04 ± 0.14	1.20 ± 0.10	0.0105
Nadir V_E/VCO_2	35.9 ± 8.3	42.5 ± 5.8	0.0532
VO_{2peak} (% predicted maximal VO_2)	65.5 ± 20.6	71.3 ± 8.0	0.4171
FEV ₁ (% predicted)	55.9 ± 21.2	70.5 ± 18.9	0.1214
IC/TLC (%)	29.2 ± 8.5	32.9 ± 7.1	0.3005
TL _{CO} (%predicted)	70.4 ± 19.8	63.7 ± 14.3	0.4023

Values are mean ± SD. p<0.05 signifies an important difference.

RER, respiratory exchange ratio; RV, residual volume; TLC, total lung capacity; TL_{CO}, transfer factor of the lung for carbon monoxide; VO_2 , oxygen consumption; FEV₁, forced expiratory volume; IC, inspiratory capacity; V_E/VCO_2 , ventilatory equivalent for CO₂; $\Delta V_E/VCO_2$ is the difference between measured value at peak effort and nadir value of V_E/VCO_2 .

V_E/VO_2 slopes that occur following the ventilatory compensation point. We quantified this phenomenon measuring the difference between the slope values of V_E/VCO_2 and V_E/VO_2 at nadir and peak effort obtained post the ventilatory compensation point, which we termed $\Delta V_E/VCO_2$ and $\Delta V_E/VO_2$, respectively. We found that the ability to increase ventilation during incremental exercise testing in response to metabolic acidosis, as normally occurs in higher exercise intensities beyond the ventilatory compensation point, was diminished in COPD patients and in correlation with the severity of air trapping as represented by RV/TLC obtained at rest. Therefore, inability to compensate for the increased ventilatory demands of acidosis may contribute to termination of effort at lower exercise intensity. Furthermore, this may implicate a difficulty in coping with the ventilatory demands of metabolic acidosis resulting from states such as acute renal failure or septic shock, thus $\Delta V_E/VCO_2$ (and seemingly $\Delta V_E/VO_2$) may allow assessment of the ability of COPD patients to withstand such metabolic challenges.

One way in which pulmonary hyperinflation can be expressed is by the increased ratio of RV/TLC, which reflects air trapping and is associated with airway narrowing. Alternatively, IC/TLC may also be decreased because of lung expansion associated with emphysematous changes and reduced lung recoil. A recent study showed that either increased RV/TLC or decreased IC/TLC or both simultaneously can be present, with airway narrowing on imaging being associated with increased RV/TLC and emphysema associated with decreased IC/TLC⁷. Therefore, it seems that the lack of increments in ventilatory equivalents in our study can be related to air trapping but not to the mere presence of emphysema.

One may argue that the limited rise of ventilatory equivalents beyond the ventilatory threshold during the incremental exercise test may reflect sub-optimal exercise performance; however, we think that the lower respiratory exchange ratio at peak exercise

represents another manifestation of the decreased ventilatory response.

Although both $\Delta V_E/VO_2$ and $\Delta V_E/VCO_2$ seem to show similar correlation to RV/TLC and utility in estimating the ventilation response to acidosis under these conditions, a further study with larger numbers of patients may help distinguish the different roles of these parameters.

This study has several limitations. The retrospective design and the small number of patients included are important limitations, in particular when comparing two subgroups. However, these limitations may be of lesser significance when searching for correlations. Some patients were obese, which may have caused mild restriction, somewhat contributing to air trapping. However, we didn't find a correlation between body mass index (BMI) and either $\Delta V_E/VCO_2$ or $\Delta V_E/VO_2$. The group with the greater ventilatory equivalents increment had a nearly significant higher nadir V_E/VCO_2 value (p = 0.53), suggesting a possible baseline difference between those who develop an increment versus those who don't. This could be explained along the same line in which it is suggested that those patients who can develop an augmented ventilatory response, i.e. increase V_E , are also able to produce a ventilatory equivalent increment towards peak effort. Unfortunately, dynamic hyperinflation, a well-known phenomenon that is associated with ventilatory constraints during exercise in COPD, was not assessed and therefore, we cannot comment on the relation between dynamic hyperinflation (i.e. changes in IC/TLC) and ventilatory equivalents increment in this cohort.

In conclusion, ventilation augmentation during incremental exercise testing at exercise intensities beyond the ventilatory compensation point in COPD patients was diminished in correlation with the severity of air trapping. Future studies will confirm the clinical usefulness of measuring $\Delta V_E/VCO_2$ and $\Delta V_E/VO_2$,

including their potential role as serially measured physiologic parameters to assess effects of interventions (e.g. pulmonary rehabilitation) in COPD.

Data availability

Underlying data

Harvard Dataverse: Ventilatory Equivalents increment during Exercise in COPD. <https://doi.org/10.7910/DVN/QTCV0M>¹¹.

This project contains the following underlying data:

- nadir to peak VE-VCO₂ during exercise in COPD.tab (demographic information and parameter measurements for each patient).

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Summary

Drs Kuint, Berkman, and Nusair retrospectively analyzed 20 COPD patients (GOLD 1: #7, II: #8, III: #4, IV: #1) who had full PFTs with lung volumes and a CPET test over a 7 year period (2010 to 2016). They were interested in air trapping and the effect on exercise performance, specifically trying to better understand the changes in Ventilatory Equivalents for Oxygen and Carbon Dioxide during incremental exercise tests on a cycle ergometer (nadir value to peak value). Further, they relate these changes to resting pulmonary function testing. The study was retrospective. They conclude that "ventilatory equivalents increment to compensate for acidosis during incremental exercise testing was inversely correlated with air trapping (RV/TLC) and may be a candidate prognostic biomarker." The study is well written.

Major Issues

1. The study would have been greatly assisted by obtaining inspiratory capacity (IC maneuvers) during exercise to document dynamic hyperinflation.
2. The study is retrospective, is a very small group, and was collected across 7 years (2010-2016, about 2-3 subjects per year), meaning that there is great potential for changes in devices, calibration, technician training, etc. that may have affected the PFT and CPET measurements.
3. The GOLD III and IV subjects are very poorly represented (Gold III (20%) and Gold IV (5%)), i.e. most subjects (75% were Gold I or II). Per the Neder and Thirapatarapong references in your paper, Gold I-II have lower ETCO₂ and higher VE/VCO₂ reflecting less efficient ventilation, and GOLD III-IV have higher ETCO₂ and lower VE/VCO₂ reflecting mechanical limitation.
4. This paper is also hampered by so many of the changes in VE/VCO₂ (10) and VE/VO₂ (7) from peak-nadir were nil, i.e. = "0"

5. There is no analysis of VE/VCO₂ slope or intercept reported in the paper or data spreadsheet.
6. No blood gases (to document acidosis or lactate levels) or end tidal CO₂ values to document changes in ventilatory efficiency. Importantly, there is no discussion of the determinants of VE/VCO₂, i.e. $VE/VCO_2 = k / (PaCO_2) * (1 - V_D/V_T)$ and how these two variables interact in the current study.
7. COPD patients are less likely to protect their arterial pH and arterial CO₂ during exercise (Casaburi, et al, Am Rev Respir Disease, 143: 9-18, 1991¹) See figure # 8. There is no discussion of this important feature of COPD patients in the manuscript.

Minor Issues

1. Introduction, page 3, First Paragraph, line 2. "Effort" should likely be exercise or activity.
2. Introduction, page 3, First Paragraph, line 3+4. Here you mention gas exchange abnormalities and ventilation perfusion mismatching, but in paragraph 4, lines 3 you also discuss deconditioning. All three mechanisms appear to be important and should be mentioned in both places.
3. Introduction, page 3, Second Paragraph, line 14. "exhausted" should be "decreasing".
4. Introduction, page 3, Third Paragraph, line 6 and 14. Reference 5 and 6 would both seem to contribute to the concepts here, and should both be quoted.
5. Methods, Paragraph 1, Study Design and Subjects, lines 1-5. How are the authors confident that all subjects with COPD and full PFTs studied in the laboratory were identified for the current manuscript?
6. Methods, Paragraph 1+2, Procedures. Were there any changes in PFT or CPET equipment, calibration, or technician protocols during the 7 years of data collection that might affect spirometry, lung volumes, gas transfer or CPET variables?
7. Methods, Paragraph 2, Procedures. 15-25 watts appears to be a very large ramp increment in patients with moderate to severe COPD. Please explain why these very large numbers were chosen, and how that may have affected the findings in the study (i.e. short ramp times may decrease time for ventilatory compensation of metabolic acidosis).
8. Table 1 – Consider including peak VO₂/kg/kg/min, peak WR, peak RER, MMVV-VE (L/min), and end tidal CO₂ values for the various subjects (and in the accompanying spreadsheet). **The spreadsheet accompanying the article is very helpful and the authors should be commended for making the data available.** A large number of subjects (~ 70%) had a VE/MVV below 85% or > 15 liters/minute (MVV-VE) at end exercise, indicating a lack of ventilatory limitation in most of these subjects.
9. Figure 1 – As mentioned above, a large number of the subjects had no change in DVE/VCO₂ or DVE/VO₂. Although Table 3 addresses it, it would appear that the authors have neglected to mention this as a limitation of the entire study in the discussion.

References

1. Casaburi R, Patessio A, Ioli F, Zanaboni S, et al.: Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis.* 1991; **143** (1): 9-18 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exercise Physiology, COPD, Pulmonary Function Testing

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 04 Mar 2020

Samir Nusair, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

We would like to thank Prof. Stringer for his valuable comments. This a retrospective study with small number of patients, and we certainly acknowledge the inherent significant limitations, which are referred to in the Discussion section We consider this work as a preliminary/exploratory study, and as that it has well acknowledged limitations and implications. We added the term "exploratory study" in the abstract and the introduction section to allude to that fact.

We would like to address the concerns raised by the Reviewer.

Re Major comments:

1. At the time of performance of these CPET studies, we did not routinely perform repeated inspiratory capacity maneuvers during exercise to allow detecting dynamic hyperinflation, because of lack of both software add-on and experience in performing these maneuvers. Notably, dynamic hyperinflation is associated with changes in tidal volume/vital capacity ratio (V_t/V_C) towards peak exercise with lower ratios of V_t/V_C as dynamic hyperinflation is more evident during exercising at higher workloads.

(Ref: O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164:770-7)

All in all there was a very little decrease in V_t/V_C obtained at peak exercise, with average values of $46\% \pm 8\%$ (Table 1).

We now added to Table 3 a comparison of V_t/V_C values of patients who had an increment in VE/V_{CO2} as opposed to patients who did not ($\Delta VE/V_{CO2}=0$). We found that the peak exercise V_t/V_C did not differ between the two groups. Despite the limitations of this method, we conclude that dynamic hyperinflation probably did not play a key role in preventing VE/V_{CO2} increment from nadir values to peak exercise in our patients. The last paragraph in the Results section was altered to describe the added data and findings, and also description of findings investigating possible ventilatory mechanical constraints. Additionally, the Discussion alluded to the possible use of V_t/V_C as a way to evaluate mechanical constraints on ventilation (paragraph before last).

2. Throughout the years 2010-2016 we used the same CPET and plethysmography devices described in the methods and applied the same calibration methods as recommended by the manufacturer.

3. As patients have more severe obstructive abnormality (GOLD III-IV more than GOLD I-II), they have lower ventilation, with reduced VE/V_{CO2} and VE/V_{O2} values. This has been referred to in the Introduction section, paragraph 3. Certainly, if we had bigger number of patients and all GOLD classes of patients were represented equally, we may have been able to deduce important differences between these classes. Data on end-tidal PCO_2 has now been provided.

4. The fact that many patients had no increment in ventilatory equivalents from nadir to peak exercise (i.e., $\Delta VE/V_{CO2}=0$) is a limitation of the measurement. As mentioned in the study limitations paragraph, this may as well be explained by suboptimal effort of the patients or the ventilatory limitations of these patients. We referred to this issue now in the Limitations paragraph.

5. Data of VE/V_{CO2} slope was added. There was a significant correlation between Nadir VE/V_{CO2} and VE/V_{CO2} slope ($R=0.82$ 95%CI 0.59-0.92, $p<0.0001$). Data of VE/V_{CO2} intercept was also added. (Represented in all 3 Tables).

6. We do not take arterial blood gases during routine clinical CPET performance to keep the test acceptable for our patients. This may be considered in a future prospective study if approved by ethical board. Alternatively, there are minimally invasive methods to allow blood lactate measurements which we do not have available in our clinical service. Regarding end-tidal CO_2 , we added the end-tidal PCO_2 values at rest and at peak exercise.

(See further, response to comment 7).

7. The reviewer brings our attention to the findings from a previous study which shows that COPD patients have higher arterial PCO₂ and lower pH in response to blood lactate elevation during exercise, compared to people without COPD.

This is somewhat expected, as with the presence of ventilatory constraints, these patients are not able to develop sufficient ventilatory compensation during exercise.

In this study we did not perform these measurements; However, end-tidal PCO₂ did not decrease towards peak exercise, in the patients who did not have VE/VCO₂ increments, thus probably in agreement with the previously published findings highlighted by the reviewer. We added a reference to the suggested paper in our discussion. Note that at the end of the discussion (paragraph 2), we refer to the possible implication of limited ability of COPD patients of coping with metabolic acidosis from other reasons (e.g., diabetic acidosis) when they are not able to generate ventilatory compensation.

Re Minor Comments:

1. We agree with the reviewer and “effort” was changed to “exercise” as suggested.

2. We agree with the reviewer regarding the importance of deconditioning as a reason for reduction in exercise capacity in COPD patients. However, the opening sentences were concentrated around describing the pulmonary mechanisms in exercise limitation in these patients. We do refer to deconditioning in the last paragraph of the Introduction.

3. Introduction, paragraph 2: “exhausted” was changed to “decreased” as suggested.

4. Citations of References 5 & 6 were joined twice in the Introduction (Paragraph 3) as suggested.

5. To identify patients and include them in the study, we looked into the CPET system software and identified all the patients that underwent CPET between the years 2010-2016 (on the same CPET device) and had a background diagnosis of COPD. Then from those patients we included only the patients that underwent body plethysmography concurrently in our laboratory, on the same day of CPET or within few days close to the date of CPET performance.

6. As stated above, there were no changes in the equipment during the 7 years.

7. Ramp increment is routinely chosen to allow for predicted WR to be achieved within 8 minutes of exercise. Only one patient exercised at a ramp of 25W/min. All other patients had a ramp of 15-20W/min. We agree with the reviewer that lower ramps may be warranted for more debilitated patients, which we often offer our patients who report low activity level. However, most patients do not handle a longer period of loaded exercise, because of other factors such as claustrophobia and mental fatigue.

Regarding the effect of short ramp times on ventilatory compensation, we agree with the

reviewer that higher ramps may shorten the time interval of ventilatory compensation and make it harder to evaluate the ventilation increment during the respiratory compensation phase but we doubt that this might affect the findings of our study. Perhaps, a future prospective evaluation, with exercise tests performed at lower ramps may allow a better evaluation of ventilation increment towards peak exercise. A note on that is added in study limitations.

8. We considered the suggestions of the Reviewer regarding the expanding of Table 1 to include data already shared with the readers in the accompanying research data file which is already available at data sharing site. Regarding peak VO₂ in ml/min/kg, peak WR, peak RER, and MVV-VE, were added to Table 1 in the body of the article, and also in Table 3 which shows comparison between those who did not have VE/VCO₂ increment and those who did. Interestingly, VO₂ in ml/kg/min was found to be different between the two groups, unlike VO₂ expressed as % of predicted VO₂max.

9. The absence of ventilatory equivalent increment (i.e., $\Delta \text{VE}/\text{VCO}_2 = 0$) has now been addressed in the study limitations paragraph.

Competing Interests: No competing interests were disclosed.

Reviewer Report 02 December 2019

<https://doi.org/10.5256/f1000research.22475.r56449>

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Gabriele Valli

Emergency Department, San Giovanni Addolorata Hospital, Rome, Italy

In the present study, the authors investigate a possible correlation between the magnitude of ventilation augmentation (manifested by increments in ventilatory equivalents from nadir to peak effort) and the lung air trapping indexes measured at rest. The authors analyzed retrospectively data from 20 symptom-limited incremental exercise test performed by 20 COPD patients. Patients underwent to CPET as part of a routine evaluation. The differences between nadir to peak exercise of VE/CO₂ were correlated to air trapping parameters measured at rest in a plethysmography. A positive correlation was found between nadir to peak exercise VE/CO₂ and VE/VO₂ and the degree of air trapping expressed as RV/TLC. The authors concluded that ventilatory equivalents increment (above anaerobic threshold) could be inversely correlated with air trapping and it may be a candidate prognostic biomarker.

Although the paper is well written I have some comments to do:

1. The authors choose to calculate ventilatory equivalent subtracting the values at peak exercise to the values measured at the nadir, assuming that the reduced increment of ventilatory equivalent after the minimum values could be mainly referred to a reduced ventilatory capacity of the subject due to air trapping measured at rest. That could be right but it is not completely correct. The simple correlation measured by the authors does not completely clarify the reasons for the interruption of the test by patients, above or below the respiratory compensation point (RCP). Some studies had demonstrated a reduced ventilatory compensation capacity in patients with a more severe emphysema i.e Paoletti *et al*, 2011¹ nevertheless it should take in account that several metabolic alterations occur after the anaerobic threshold that are independent to the ventilatory mechanics and that are more closely related to physical conditioning of the patient. After the anaerobic threshold, peak ventilatory response could be related to several different causes: the exercise intensity and the power increments, the anaerobic reserve of the subject, the muscular O₂ extraction capacity, the amount of metabolic acidosis, the increase in catecholamine levels, the developed or not of dynamic hyperinflation, the ventilatory chemiosensitivity of the carotid bodies, some cardiovascular alteration as an opening of PFO or the develop of pulmonary hypertension, even the individual motivation to complete the exercise and the subject propensity to perform that specific exercise. It is difficult to understand which is the real cause of exercise interruption and this could significantly affect the amount of nadir to peak ventilatory equivalent difference. The difference between nadir to peak ventilatory equivalents does not seems to be a good estimate of patient's ventilatory compensation during the exercise.
2. It should be noted that, in the regression analysis there are half of the patients that did not increase ventilatory equivalents, which means that they stop the exercise at RCP or immediately after. Table 3 show a significant difference in peak RER between the patients who have not shown increments in VE/CO₂ and the ones who have continued to increase ventilation, suggesting that the two groups reach different intensity exercise domain and probably are different populations (i.e. RC/TLC significantly different). A more complete table, that includes Watt Max, VO₂ peak in ml/kg, VO₂ pulse, VE/MV_{peak} and FEV₁/FVC of the two groups could be helpful. Unfortunately it is impossible to know why the subject who showed no increase in VE/VCO₂, interrupt the exercise immediately after the reach of RCP. To put all the results in the same regression appear as an hazard, there are too many unpredictable sources of error. The authors must provide consistent evidence that the observed correlation is not only apparent. The estimated coefficients of the linear regression and the relative interval of confidence should be calculated. An estimation of the standard error of regression coefficient R² should be provide together with the 95% confidence band for R. A residual analysis could help to understand how good is the correlation and if the assumption of normality of the distribution is preserved.
3. The variable chosen by the authors to represent the exercise ventilatory compensation of the patients is not the one universally accepted and utilized for this propose. The authors should clarify why they have not utilized, for instance, the VE/CO₂ slope. In a recent paper Gargiulo P. and coworkers demonstrated that the analysis of VE/CO₂ slope and its intercept on the abscissa (VE_{int}), that represent the ventilatory requirements when pulmonary gas exchange is null, represents better the ventilatory efficiency (Gargiulo P et al. 2014²). In COPD patients VE_{int} correlate with the VD and Neder and colleagues recently showed that increases in VE_{int} better reflected the progression of functional impairment form mild to

end-stage of COPD (Neder JA et al. 2015³). I suggest to test also these parameters in you analysis that are more clearly related to pulmonary efficiency and that are less dependent from the individual motivation of the patients to tolerate the effort.

4. The authors conclude the abstract suggesting that the reduced ventilatory increment in VE/VCO_2 from rest to peak exercise could be a prognostic biomarker. This assumption is not clarified in the text, no data was provided to support this statement and the assumption remains speculative.

Minor comments:

Abstract

Line 4, p 1_ *"During incremental cardiopulmonary exercise testing, ventilatory equivalents for carbon dioxide..... may be difficult to identify in COPD patients because of limited ventilatory compensation capacity"*. This is not correct. Ventilatory equivalents are always identifiable, in COPD patients could be difficult to identify the respiratory compensation point, the point at which it could be observed an hyperventilatory response to late-exercise acidosis.

Line 19, p 1_ *" DV_E/VCO_2 and DV_E/VO_2 "*. DV_E/VCO_2 abbreviation is usually utilized to indicate VE/CO_2 slope and could be confounding, I suggest to change it with a new acronym that specifies that it is the difference between the peak and nadir values.

Line 28, p 1_ *"...and may be candidate prognostic biomarker"* the statement is speculative and not investigated in the study.

Introduction

Line 26, p 3_ *"The ventilatory threshold (VT).... "*. I suggest to utilize a different abbreviation (i.e. AT or LT), "VT" could be confused with Tidal Volume.

Methods

Lines 1-10, p 4_ *"Patients performed incremental symptom-limited cycle ergometer..."* The authors mentioned a 1-2 minute of warm-up period at 0 watt. 0 watts assumes that an ergometer with pedal assistance has been used. What kind of cycle ergometer was used? did you mean a period of free pedaling at the minimum of watts? Have you estimated the amount of the minimum load of your cycle-ergometer? 1-2 min of warm up could be correct with a real 0 watts ergometer but it could be a too short period if the minimum load provide by the ergometer was 20W or greater.

Line 10, p4_ *"the test was terminated at exhaustion"* Can you please better define "exhaustion"?

Results

Table 1. The table should be integrated with the absolute value of $VO_{2\text{ peak}}$ in ml/kg, $VO_{2@AT}$ in ml/kg, Watt Max and RER at peak exercise. I suggest to put $SpO_{2\text{ peak}}$ rather than the desaturation at peak effort. An explication of how the authors calculated BR should be added to Methods. The percentage of tests in which the respiratory compensation point was identifiable should be added somewhere. DVE/CO_2 should be change with some other abbreviation.

Lines 5-16, p4 – “ DV_E/VCO_2 ($r = -0.5058$, 95% CI -0.7750 to -0.08149 , $p = 0.0234$)...” a $p = 0.0234$ looks quite significantly, nevertheless the adaptation of the regression appear very low, it seems that R^2 is not more than 0.25. I suggest to add to your plot the regression coefficients with the respective standard errors. It could be useful analyzed the residual plot in order to increase the adaptation.

Lines 19-20, p4. “Notably, we found no significant correlation between neither DVE/VCO_2 nor nadir VE/VCO_2 and peak VO_2 or FEV_1 .”. Do you mean the absolute values or % predicted?

Table 3. The table shows a significant difference in RER peak between the two population analyzed. The patients with a significant increase in DVE/VCO_2 probably achieve a greater effort intensity. As the entire correlation depends on the patients who sustain the effort beyond their VE/VCO_2 nadir, it is likely that the correlation is no longer detectable in the more severe patients. I would like to know the differences between the two groups in $VO_{2\text{ peak}}$ expressed as ml/kg, Watt Max, BR%, Heart Rate Reserve (220-age), $VO_{2\text{ pulse}}$ at peak exercise, FEV_1 in mL and FEV_1/VC .

Discussion

Lines 17-19, p 5. “In this study we examined the ability of Focusing on the increase in the V_E/VCO_2 and V_E/VO_2 ”. This is not correct. You have not measured any slope. You measure just a difference.

Lines 14-19, P 6. “Therefore the inability to compensate...”. This statement is entirely speculative, beyond the scope of the study and not supported by any data that can be highlighted in the paper.

Lines 28-34, p 6. “Therefore, it seems that the lack of increment....” You are comparing a static measurement with a dynamic alteration that occurs in the moment of maximum stress. The problem is that you have not measured any indexes of dynamic hyperinflation. Your conclusion cannot be proven.

Lines 34-35, p. 6 “however, we think that the lower respiratory exchange ratio at peak exercise represents another manifestation of the decreased ventilatory response”. Unfortunately it does not stand out easily if the patient has stopped due to actual exhaustion or to other reasons. Especially in a retrospective study.

Lines 49-50, p. 6 “Some patients were obese, which may have caused mild restriction...” You should take in account that BMI could largely affect the VCO_2 body storage and, as a consequence, the RCP detection or $VE/VCO_{2\text{ peak}}$ values. Is there any differences between the two groups (No Nadir to Peak increment vs patients with nadir to peak increment) in BMI? Can you provide this data?

References

1. Paoletti P, De Filippis F, Fraioli F, Cinquanta A, et al.: Cardiopulmonary exercise testing (CPET) in pulmonary emphysema. *Respir Physiol Neurobiol.* 2011; **179** (2-3): 167-73 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Gargiulo P, Apostolo A, Perrone-Filardi P, Sciomer S, et al.: A non invasive estimate of dead space ventilation from exercise measurements. *PLoS One.* 2014; **9** (1): e87395 [PubMed Abstract](#) | [Publisher Full Text](#)
3. Neder JA, Arbex FF, Alencar MC, O'Donnell CD, et al.: Exercise ventilatory inefficiency in mild to end-stage COPD. *Eur Respir J.* 2015; **45** (2): 377-87 [PubMed Abstract](#) | [Publisher Full Text](#)

4. Neder JA, Berton DC, Arbex FF, Alencar MC, et al.: Physiological and clinical relevance of exercise ventilatory efficiency in COPD. *Eur Respir J*. **49** (3). [PubMed Abstract](#) | [Publisher Full Text](#)
5. Apostolo A, Laveneziana P, Palange P, Agalbato C, et al.: Impact of chronic obstructive pulmonary disease on exercise ventilatory efficiency in heart failure. *Int J Cardiol*. 2015; **189**: 134-40 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

No

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Exercise Physiology - Hypoxia - Ventilatory Response to Exercise and High Altitude - Critical Care and Emergency Medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 04 Mar 2020

Samir Nusair, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

The authors would like to thank Dr. Gabriele Valli for his valuable comments. This is a retrospective study with a small number of patients, and we certainly acknowledge the inherent significant limitations, which we refer to in the Discussion section. We sought to study changes in VE/VCO₂ during the incremental exercise test in COPD patients, a very intriguing subject. Furthermore, we consider this work as a preliminary/exploratory study, and as that it has well acknowledged limitations and implications. Furthermore, we added data of VE/VCO₂ slope and VE/VCO₂ line intercept as suggested, providing further insight into our cohort.

We would like to address the concerns raised by the Reviewer.

Re Major Comments:

1. We certainly agree with the reviewer that there are several possible mechanisms and factors that may contribute to exercise limitation in patients with COPD. In this study we aimed at studying the changes in VE/VCO₂ during exercise in these patients. We investigated a possible relationship between airway trapping (defined by increased RV/TLC) and the decreased ability to increase ventilation in response to acidosis as seen by the lack of VE/VCO₂ rise and absence of the ventilatory compensation phase seen in people without COPD. We certainly do not claim cause and effect on the basis of our findings.

2. We have now added information as requested by this reviewer to Table 1 and Table 3 of peak Work Rate, peak VO₂ (ml/kg/min), FEV₁/FVC and exercise ventilatory mechanical data (VE/MVV, peak exercise Vt/VC).

Patients who had an increment in VE/VCO₂ had higher VO₂ (per body weight), higher peak WR and higher RER. Again, this is not about cause and effect but epiphenomena. Whether these patients were “more motivated” to perform exercise than those who did not cannot be absolutely excluded, yet with all patients motivated to perform exercise until exhaustion, (i.e., could not keep required cycling pace) or had marked symptoms such as shortness of breath, simple lack of motivation to exercise is unlikely sole explanation. Adding data regarding end-tidal PCO₂ at baseline and at peak exercise in both groups should be also helpful.

We sought to find a correlation between increments of ventilatory equivalents and air trapping (see Results section, paragraph 2). We did not seek to find a linear regression. We agree with the reviewer about the “hazards” in creating a linear regression of all the data, especially when many other factors could be involved. Therefore we take a step back and present the data of correlation we intended to show originally, adding it to Table 2, in the first two rows. We deleted Figure 1 as it is irrelevant.

3. In this work, we originally wanted to look at the changes in VE/VCO₂ during exercise, the isocapnic buffering phase and the ventilatory compensation phase. Previous observations have noted the absence of significant ventilatory compensation in patients with COPD (Ref 6). Since there are previous descriptions of correlation between VE/VCO₂ slope and air trapping (Refs 1,3 &5 in the manuscript) we attempted to somehow quantitate the increment in VE/VCO₂ during incremental exercise, expecting that some patients may not have an increment ($\Delta\text{VE/VCO}_2=0$). To the best of our knowledge this is a somewhat novel approach.

In our opinion, nadir VE/VCO₂ may be easier to identify in routine clinical practice and also to relate to peak VE/VCO₂. In this cohort, we found a high correlation between Nadir VE/VCO₂ and VE/VCO₂ slope. Data of VE/VCO₂ slope was added. There was a significant correlation between Nadir VE/VCO₂ and VE/VCO₂ slope ($R=0.82$ 95%CI 0.59-0.92, $p<0.0001$).

Data of VE/VCO₂ intercept was also added. (All 3 Tables). In Table 3 we show that VE/VCO₂ intercept was significantly higher in patients in whom $\Delta\text{VE/VCO}_2=0$. We now show that our findings are in agreement with this parameter which represents dead space breathing.

4. Reference to a “possible prognostic biomarker” in the end of the abstract was deleted.

Re Minor Comments:

Abstract:

1. Sentence was corrected “During incremental cardiopulmonary exercise testing, actual nadir values of ventilatory equivalents for carbon dioxide (V_E/VCO_2) and oxygen (V_E/VO_2) may be difficult to identify....”

2. The authors have checked before writing this manuscript the use of the symbol delta, and we did not find a similar use of it in this context, even in reference to VE/VCO_2 slope, therefore we resort to continue using this symbol in our manuscript. Another acronym/abbreviation will be more difficult to use at this stage.

3. The reference to “biomoarker” was omitted.

Introduction:

1. The abbreviation “VT” in relation to ventilatory threshold was deemed unnecessary at this stage and it is no longer used.

Methods:

1. Sentence was re-written “Following a 1–2 minute warm-up period of unloaded exercise and with VO_2 and VCO_2 reaching a plateau,....”. We accept the reviewer’s note that this cannot be defined as $WR=0$, since it was pedaling against the inherent resistance of the cycle machinery without motored assistance.

2. Exhaustion in the context of exercise test performance is now defined. The sentence was re-written:

“The test was terminated at exhaustion, when the patient could not keep the required cycling pace or asked for exercise termination.”

Results:

1. More information added to Table 1 and other tables. Breathing reserve is defined at the bottom of Table 1.

The percentage of patients with identified respiratory compensation point would be 50% and is represented by a $\Delta VE/VCO_2 > 0$.

2. As noted above we performed correlation estimations and not linear regression (explained above and changes described)

3. There was no correlation between neither $\Delta VE/VCO_2$ nor nadir VE/VCO_2 and peak VO_2 and FEV1, as percentage of predicted. We added also a correlation with VO_2 in ml/kg/min,

which just achieved a significant correlation with a $p=0.0462$.

4. Table 3 is now expanded and more parameters are compared.

Discussion:

1. The sentence now has been changed “.....focusing on the increase in V_E/VCO_2 and V_E/VO_2 that occur following the ventilatory compensation point.” The word “slopes” was deleted.

2. The entire sentence “Therefore, inability to compensate for the increased ventilatory demands of acidosis may contribute to termination of exercise at lower exercise intensity.” was deleted.

3. The sentence has been changed and “can be related to” is changed to “is correlated with”.

4. Instead of “represents” the phrase is changed to “may represent”, thus expressing some reservation about this conclusion.

5. Comparison of BMI between the two groups has been added. There was no difference in BMI between the two groups.

Competing Interests: No competing interests were disclosed.

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