Assessment of Partial Pressure of Carbon Dioxide during Incremental Exercise Test, in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Purpose: Respiratory pump failure in COPD patients can lead to CO2 retention during exercise, but little is known about the factors determining CO2-levels during exercise in COPD patients. The aim of this study is to investigate the pattern of TcPCO2 in COPD patients during exercise and factors driving this CO2 response.

Patients and methods: 24 COPD patients (age 66(8) y, FEV1 43(18)%pred, TcPCO2 at rest 37(4) mmHg, oxygen users 6/24) performed lung function and cardiopulmonary exercise test (CPET). During CPET TcPCO2 was measured continuously and in O2 users the CPET was performed with supplemental oxygen.

Results: At baseline, 16 patients were normocapnic (TcPCO2 ≤ 35 mmHg) and 8 hypocapnic (TcPCO2 < 35 mmHg). At the end of the CPET, 9 patients were normocapnic, 2 showed hypocapnia and 10 were hypercapnic. CO2-retention (ΔTcPCO2 > 4 mmHg) was observed in 18 patients. ΔTcPCO2 correlated significantly with VeMax (r = .64; p = .004), FEV1 %predicted (r = .53; p = .008), RV %predicted (r = .54; p = .007), RV/TLC (r = .56; p = .005), sRAW (r = .61; p = .005), sGAW (r = .60; p = .002), and maximal TcPCO2 (r = .63; p < .001), but did not correlate with baseline TcPCO2 (r = .08; p = .728). Furthermore, baseline TcPCO2 correlated with the maximal TcPCO2 (r = .67; p < .001).

Conclusion: The CO2-response of COPD-patients during CPET is heterogeneous with 10/24 developing hypercapnia. This study revealed that the lung mechanics are the most important factor correlating with CO2 retention during exercise while ΔTcPCO2 was not associated with baseline TcPCO2.

Keywords: COPD, CPET, Pathophysiology; Pulmonary rehabilitation; Transcutaneous PCO2
Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality worldwide and its prevalence is expected to increase in the upcoming years. COPD is regarded as a preventable and treatable chronic disease, characterized by a persistent shortness of breath, which progressively worsens in time due to structural changes in the airways and alveoli. It is generally triggered by the inhalation of cigarette smoke. The chronic disease pathway is sometimes interrupted by exacerbations. This is clinically described as an episode of increase in respiratory symptoms, mainly shortness of breath, coughing and the presence of more (purulent) sputum. The exacerbations are often cause of hospital admission. These hospitalizations are a burden on the quality of life of the patients and increase the risk of readmission. There is a significant social cost associated with this as well.

The treatment of COPD is based on pharmacologic optimisation and pulmonary rehabilitation. The cornerstones of rehabilitation are exercise and education, which stimulate the patient’s ability for self-management. This treatment plan aims to increase or to preserve the patient’s quality of life. Hence avoid hospitalizations.

Previous research revealed that acute and chronic hypercapnic respiratory failure (HRF) is often the driver for hospitalization and necessitates (invasive) respiratory ventilation. HRF is defined by elevation of carbon dioxide levels in the blood (PaCO₂ > 45 mmHg). Due to failure of the respiratory pump in COPD patients, keeping normocapnia (PaCO₂ 35-45 mmHg), certainly during exercise (part of rehabilitation), is difficult for a substantial number of these patients.

In normal physiological situations the PCO₂ will remain constant during exercise (isocapnic), until the isocapnic buffering is insufficient. Due to lowering of pH in the blood, hyperventilation will occur to avoid an increase in acidity due to an increase in CO₂. Hence the PCO₂ in the blood will drop. At sea-level the cardiovascular system is the limiting factor for a maximal aerobic exercise in healthy people. The breathing mechanics are no limiting factor as opposed to COPD patients. In the latter group, the maximal exercise is generally limited by alterations in lung dynamics, deconditioning and fatigue of the respiratory muscles, diminished ability to exchange gas in the lungs, abnormal sensation of dyspnea and breathing control, cor pulmonale, and diminished nutritional status.

Even though exercise induced changes in PCO₂ are a clear sign of different pathophysiological mechanisms in COPD, which can lead to respiratory failure, research in this specific field is limited. Previous research has shown that COPD patients who are normocapnic in rest can become hypercapnic during exercise. The hypothesis can be made that patients who have a high PCO₂ at rest can show a stronger increase during exercise. Many patients receive additional oxygen during exercise, however the research of Abd el et al shows that in COPD patients, this can lead to hypercapnia, due to the suppression of the ventilatory response to the hypoxemia. This led to the following hypothesis: the higher the baseline PCO₂, the stronger the increase of PCO₂ during exercise. A second hypothesis can be made: COPD-patients who are oxygen dependent will display a stronger increase in TcPCO₂ when compared to non-oxygen dependent patients.

This pilot study aims to investigate if patients with a high baseline PCO₂ or oxygen dependency can safely participate in a pulmonary rehabilitation program without exponential increasing their PCO₂. Through this knowledge, a larger study can be conducted to investigate the predictors of CO₂ retention to personalize the patients exercise therapy.

Material and methods

STUDY DESIGN AND PARTICIPANTS

This prospective pilot study is performed in 2 different centers: multidisciplinary medical private practice MedImprove BV (Kontich, Belgium) and general hospital AZ Voorkeken Emmaüs (Malle, Belgium).

INCLUSION- AND EXCLUSION CRITERIA

Participants were eligible to be included in the study if they were 18 years or older and have a diagnosis of COPD according to GOLD standards. Patients were excluded if they were clinically unstable, had a COPD exacerbation less than 4 weeks prior to the inclusion, or were diagnosed with a different lung disease.

ETHICAL APPROVAL

The study was reviewed and ethically approved by the central ethical committee of the university hospital of Antwerp on December 14th, 2020 (20/46/615). Prior to this approval on December 3rd, 2020, a positive advice was given by the local ethical committee of vzw Emmaüs (EC2053-EC2053a).

Data collected in this study was anonymized. All
participants signed the informed consent form before the start of the first study procedure.

STUDY PROCEDURE
After signing the informed consent, demographic data and clinical parameters of the patients were collected (gender, age, length, and weight). Post-bronchodilator lung function testing was performed. Dynamic lung volumes, obtained by means of spirometry (FVC, FEV1), static lung volumes and resistance measured by means of Body Plethysmography (TLC, RV, resistance) and diffusion capacity (DLCO) were gathered. Maximal Voluntary Volume (MVV) was calculated using the following formula 35*FEV1. Patients were asked to perform an incremental exercise test (IET). Standard protocol used in this study was a starting load of 5 Watt with an increase of 5 Watt each minute. In patients where the pulmonologist considered it feasible a deviation of this protocol could be made. This deviation mainly focused on a higher load in the initial phase. Oxygen dependent patients performed an ergometric test instead of an ergospirometry test.

Oxygen saturation, heart rate, and transcutaneous CO2-level (TcPCO2) as surrogate for arterial PaCO2 were measured through a capnograph (SenTec AG, Therwill, Switzerland).

Following ergospirometric parameters were recorded: maximal breathing volume that the patient reached during the test (VeMax) and Respiratory Exchange Ratio (RER). To obtain the breathing reserve (BR), VeMax was compared to the MVV: BR% = (MVV-VeMax)/MVV*100. A BR%<20% before reaching RER = 1, points out that the patient is ventilatory limited. Exercise induced desaturation was defined as oxygen saturation of <88%. Increase or decrease of >4 mmHg in TcPCO2 during the cycling test was seen as non-isocapnic. An increase in TcPCO2 >4 mmHg was considered as CO2-retention. A TcPCO2 passing the >45 mmHg during testing was considered as exercise induced hypercapnia.

A TcPCO2 <35 mmHg was defined as hypocapnia.

STATISTICAL ANALYSIS
Analysis of the data was performed in the Statistical Package for the Social Sciences® (SPSS®) version 29.0. The demographic data were analyzed using descriptive statistics. Continuous variables were analyzed by means, standard deviation, minimum and maximum. In the analysis it was noted if hypocapnia or normocapnia was recorded during the different stages of the exercise testing. Non-parametric statistics were used to analyze the difference (Mann-Whitney U) and correlations (Spearman’s Rho) between groups. Predictions were made using multiple regression analysis. Level of significance was set at <.05.

Results
In this study, twenty-four (12F/12M) patients were included with a mean age of 65 years. Demographic data are presented in table 1.

| Table 1: Descriptive statistics of basic characteristics |
|-----------------|---------|---------|---------|---------|
|                 | N      | Mean    | SD      | Min     | Max     |
| Age             | 24     | 66      | 8       | 52      | 78      |
| Body Mass Index (BMI) | 24     | 24      | 4       | 16      | 33      |
| Forced Vital Capacity (FVC) | % pred | 24     | 81      | 19      | 111     |
| Forced Expiratory Volume in 1 second (FEV1) | % pred | 24     | 43      | 18      | 75      |
| Tiffeneau Index (FEV1/FVC) | % | 24     | 40      | 12      | 60      |
| Total Lung Capacity (TLC) | % pred | 24     | 117     | 25      | 167     |
| Residual Volume (RV) | % pred | 24     | 180     | 64      | 307     |
| Proportion RV/TLC | % | 24     | 58      | 13      | 83      |
| Diffusion Capacity (DLCO) | % pred | 24     | 50      | 17      | 77      |
| sRaw | % pred | 24     | 452     | 247     | 142     |
| sGAW | % pred | 24     | 36      | 26      | 106     |
| Baseline saturation | % | 24     | 99      | 1       | 100     |
| Baseline TcPCO2 | mmHg | 24     | 37      | 4       | 26      | 44      |

Patients included in this study had a mean BMI of 24.3 kg/m². The means at baseline showed an increased airway resistance (sRaw), hyperinflation (RV/TLC >60%), and an impaired diffusion capacity (DLCO <60%). Of the 24 patients, seven were categorized as moderate COPD (GOLD II, FEV1 between 50% - 80%), 11 as severe COPD (GOLD III, FEV1 between 30% - 50%) and 6 patients had very severe COPD (GOLD IV, FEV1 <30%). An overview is presented in figure 1a.
Assessment of Partial Pressure of Carbon Dioxide during Incremental Exercise Test, in Patients with Chronic Obstructive Pulmonary Disease

Figure 1: Pie diagrams

OBSERVATIONS OF MEASURED PARTIAL PRESSURE OF CARBON DIOXIDE

As presented in Figure 1b, 8 patients showed hypocapnia at baseline (TcPCO2 <35mmHg). The majority of patients (n=16) were normocapnic (TcPCO2 between 35mmHg and 45mmHg), and no one was hypercapnic (TcPCO2 > 45mmHg) at baseline. A representation of the patient’s CO2 reaction to exercise testing is shown in figure 1c.

From the 16 normocapnic patients at baseline, 12 patients developed TcPCO2 retention (ΔTcPCO2 >4mmHg), of whom 9 exceeded the limit for hypercapnia (TcPCO2 > 45mmHg). The other 3 patients were described as normocapnic CO2 retention. From the 8 hypocapnic patients at baseline, two subjects remained in hypocapnia during the test, 5 became normocapnic and 1 patient developed hypercapnia.

There were six patients participating in this study who were oxygen dependent and only performed an ergometric test. The other 18 patients performed the test with gas exchange analysis. In total, three of these patients reached their anaerobic threshold (RER=1) with a breathing reserve >20%. None of these three patients did develop hypercapnia or CO2 retention during exercise testing.

The correlations presented in table 2 shows that the change in TcPCO2 (ΔTcPCO2) during exercise testing, correlated with VeMax (r = -.64; p = .004) and lung function parameters as FEV1 (r = -.53; p = .008), RV (r = .54; p = .007), RV/TLC (r = .56; p = .005), sRAW (r = -.61; p = .005), and sGAW (r = -.60; p = .002).

The baseline TcPCO2 did not correlate to any of the lung function parameters, nor with change in TcPCO2 during exercise testing. However, a significant correlation was noted between baseline TcPCO2 and maximal TcPCO2 (r = 0.67; p < .001).

The maximal TcPCO2 correlated significantly with FEV1 (r = -.57; p = .004) and resistances sRAW (r = .49; p = .035), and sGAW (r = -.45; p = .029).

Although the VeMax correlated with ΔTcPCO2, it does not correlate with baseline TcPCO2 (r = .12; p = .650) nor maximal TcPCO2 (r = -.29; p = .246).
Assessment of Partial Pressure of Carbon Dioxide during Incremental Exercise Test, in Patients with Chronic Obstructive Pulmonary Disease

The differences between oxygen dependent patients and non-oxygen dependent patients are provided in table 3. No significant differences in baseline TcPCO₂ (p = .110), maximal TcPCO₂ (p = .060) nor ∆TcPCO₂ (p = .352) were detected. However, the two groups differentiated significantly in COPD severity, FEV₁ (p < .001), RV (p = .038), RV/TLC (p = .003), sRAW (p = .002) and sGAW (p < .001).

Furthermore, no significant differences were found in maximal TcPCO₂ nor ∆TcPCO₂ between patients who are or are not obese (BMI > 24 kg/m²). No trend was found between BMI and maximal TcPCO₂ nor ∆TcPCO₂.

Another significant correlation was found between change in TcPCO₂ and change in saturation during the test (r = .50; p = .013).

Table 3: Difference between patients with or without supplemental oxygen

<table>
<thead>
<tr>
<th></th>
<th>With O2 n = 6</th>
<th>Without O2 n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Base CO₂ (mmHg)</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td>Max TcPCO₂ (mmHg)</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>∆TcPCO₂ (mmHg)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>71</td>
<td>20</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
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<td>8</td>
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<tr>
<td>RV (%)</td>
<td>245</td>
<td>76</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>sRAW (%)</td>
<td>685</td>
<td>184</td>
</tr>
<tr>
<td>sGAW (%)</td>
<td>15</td>
<td>4</td>
</tr>
</tbody>
</table>

Difference is significant with *p<0.05; **p<0.01 and ***p<0.001

Base CO₂: baseline TcPCO₂; Max TcPCO₂: maximal reached CO₂ during the test; ∆TcPCO₂: the change of TcPCO₂ during the test; FVC: Forced Vital Capacity; FEV₁: Forced Expiratory Volume in 1 second; RV: Residual Volume; RV/TLC: Proportion of Residual Volume and Total Lung Capacity; DLCO: Diffusion Capacity; sRAW: specific resistance; sGAW: specific conductance.

Figure 2: Correlation between changes in TcPCO₂ and changes in saturation during CPET

Increase in desaturation led to higher increases in PCO₂.
Discussion

In this study, we investigated the evolution of the TcPCO$_2$ during exercise in patients with COPD. We enrolled 24 patients in this study. At baseline, sixteen patients were normocapnic. In twelve patients, CO$_2$ retention was noticed. Within these twelve patients nine of them developed hypercapnia. A decline in maximal breathing volume that the patients reached during the test (VeMax) and FEV1 on one hand, and an increase of RV, RV/TLC, and resistance on the other hand, were the most important factors correlating with CO$_2$ retention during exercise. Interestingly, both VeMax and ∆TcPCO$_2$ were not related to baseline TcPCO$_2$.

The individual response of TcPCO$_2$ during exercise testing in COPD-patients seems heterogeneous, which was confirmed by earlier research. Although BMI was seen as a protective factor against hypercapnia in that study, these results could not be confirmed in this study. The lower sample size might be an explanation.

Three out of the 18 patients who performed an ergospirometric test, reached their anaerobic threshold (RER ≥1) with a breathing reserve over the 20%, indicating that the patient’s lung dynamics was not a limiting factor. This was reflected in their TcPCO$_2$-resons, as these 3 patients completed the test without developing CO$_2$-retention and without hypercapnia.

In this study, it is shown that baseline TcPCO$_2$ does not correlate significantly with VeMax, which indicates that there is another factor, besides breathing mechanics, that influences the presence of a raised baseline TcPCO$_2$. Breathing control is an important factor in these situations. The breathing is partially controlled by CO$_2$ receptors that are situated centrally and O$_2$-receptors that lay more peripherally in the carotid bodies. The CO$_2$-receptors in the medulla oblongata can change their sensitivity. When receptors have a decreased sensitivity for CO$_2$, for example due to long term exposure of (exercise induced) hypercapnia, the breathing center showed less stimulation, causing increased TcPCO$_2$ at baseline. It is important to note that an increased TcPCO$_2$ at baseline does not correlate with ∆TcPCO$_2$. This refutes the hypothesis that patients with an elevated TcPCO$_2$ at baseline will experience a strong increase of the TcPCO$_2$ during exercise. This can be an explanation why patients with increased baseline TcPCO$_2$ are able to perform an ergospirometric cycling test, without showing an exponential increase in TcPCO$_2$ and can participate in a pulmonary rehabilitation program.

The breathing mechanics have an important influence on the increase of CO$_2$-tension in the blood during exercise. The residual volume (RV) and proportion RV/TLC, correlate significantly with the ∆TcPCO$_2$. This was expected, given the greater RV, which compromised the patient’s remaining lung capacity for a sufficient gas exchange. The RV was measured in resting conditions and is often increased in COPD-patients. This because of the early closing of the small airways due to the presence of emphysema, inflammation, and edema. Often this increases during exercise because the expiration time during exercise is shorter. This results in hyperinflation and decreasing minute volume during exercise, which can in turn lead to an increase in PaCO$_2$. However, this phenomenon of dynamic hyperinflation was not measured in this study.

Furthermore, no differences were found for baseline and maximal TcPCO$_2$ between oxygen dependent and oxygen independent patients. The significant difference in other lung function parameters between both groups revealed that oxygen dependent patients had more severe COPD. However, no significant difference was found in ∆TcPCO$_2$ between both groups. This rejects the hypothesis that oxygen dependent patients have a stronger increase of their TcPCO$_2$ during exercise. Due to the severity of the COPD disease, (exercise induced) hypercapnia is common in oxygen dependent patients and will require attention. Administration of supplemental oxygen is nevertheless necessary, as a decline in saturation is associated with an increase in TcPCO$_2$.

**RELEVANCE FOR THE CLINICAL PRACTICE**

Impaired breathing mechanics correlate significantly with an increase in CO$_2$ during exercise. The breathing mechanics can be improved in 2 areas. First and foremost, an increase in respiratory force, by training the breathing muscles. Secondly by lowering the airway resistance with anti-inflammatory therapy and bronchodilation. A raised baseline TcPCO$_2$ is presumably caused by a decreased CO$_2$-sensitivity and to a lesser extent by disrupted breathing mechanics, as no correlation between VeMax and baseline TcPCO$_2$ could be found. Patients with elevated baseline TcPCO$_2$ can still perform a meaningful exercise with the absence of a strong increase in TcPCO$_2$ during exercise.

To lower the baseline TcPCO$_2$, non-invasive ventilation (NIV) can be applied, which has been shown to have a positive influence on blood gas
Assessment of Partial Pressure of Carbon Dioxide during Incremental Exercise Test, in Patients with Chronic Obstructive Pulmonary Disease

values and lung function tests in hypercapnic COPD-patients.\textsuperscript{18}

Even patients who are oxygen dependent are safe to train in pulmonary rehabilitation settings (without significant increase of their TcPCO\textsubscript{2}). Under condition that extra oxygen is provided with monitoring of oxygen saturation.

In our study, 10 out of 24 patients became hypercapnic during cardiopulmonary exercise testing. CPET is a diagnostic tool to evaluate the patient’s physical fitness and CO\textsubscript{2} response during exercise. The pulmonary rehabilitation program should be tailored to each patient specifically. This is set at 60\% of the maximum load during CPET. If hypercapnia occurs at this load, non-invasive ventilation (NIV) during exercise training might support the patient. NIV will sustain the breathing mechanics by supporting the respiratory muscles and increasing the ventilation. Thereby, NIV may help sustain higher levels of training intensity for COPD individuals.\textsuperscript{19}

STRENGTHS AND SHORTCOMINGS
To the best of our knowledge, transcutaneous capnography has not yet been used to monitor the CO\textsubscript{2} response of COPD patients during cycling ergo(spiro)meters. By combining these results with ventilatory parameters more insight can be gained into the CO\textsubscript{2}-response of COPD patients during exercise(testing).

As this study has a small sample size, a larger study should be conducted to confirm the predictors for CO\textsubscript{2}-retention or hypercapnia during exercise in patients with COPD. Future research including the measurement of dynamic hyperinflation during exercise tests would give additional insights into the pathophysiologic mechanisms\textsuperscript{20} especially when these results are correlated with a quantitative CT thorax analysis as there is Functional respiratory Imaging might provide greater insights in the pathophysiology of CO\textsubscript{2}-retention.

Conclusion
It’s clear that some COPD patients have a dysfunctional CO\textsubscript{2}-response during exercise. Both hyper- and hypocapnia at baseline was recorded in this sample. The preconceived hypothesis that people with increased baseline TcPCO\textsubscript{2} or the ones with oxygen dependency, show a stronger increase in TcPCO\textsubscript{2} during exercise is rebutted. Parameters reflecting impaired breathing mechanics and hyperinflation, determine the increase of TcPCO\textsubscript{2} during exercise. Baseline TcPCO\textsubscript{2} on the other hand seems to have no direct contribution to the increase. Based on these new insights, the patient’s treatment can be adjusted, whereas patients with high baseline TcPCO\textsubscript{2} defacto do not have to be excluded from rehabilitation programs. Also, oxygen dependent patients can train in a safe manner while being monitored and receiving supplemental oxygen.

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Disclosure
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