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# Transcutaneous carbon-dioxide partial pressure trends during six-minute walk test in patients with very severe COPD

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ABSTRACT

*Background:* Transcutaneous carbon-dioxide partial-pressure ($T_CPCO_2$) can be reliably measured and may be of clinical relevance in COPD. Changes in $T_CPCO_2$ and exercise-induced hypercapnia (EIH) during six-minute walk test (6MWT) need further investigation. We aimed *(1)* to define patterns of $T_CPCO_2$ trends during 6MWT and *(2)* to study determinants of CO2-retention and EIH.
*Methods:* Sixty-two COPD patients (age: 63 ± 8years, FEV1: 33 ± 10%pred.) were recruited and $T_CPCO2$ was recorded by SenTec digital-monitoring-system during 6MWT.
*Results:* Half of patients (50%) exhibited $CO_2$-retention ($T_CPCO_2$ *[Δ]* >4 mmHg); 26% preserved and 24% reduced $T_CPCO_2$. Nineteen (31%) patients presented EIH ($T_CPCO_2$ >45 mmHg). EIH was associated to higher baseline-$P_CCO_2$, worse FEV1, lower inspiratory-pressures, underweight/normal BMI, and pre-walk dyspnea. Stronger determinants of $CO_2$-retention were FEV1 and pre-walk dyspnea, whereas baseline-$P_CCO_2$ and pre-walk dyspnea better predict EIH.
*Conclusions:* $PCO_2$ response to 6MWT is highly heterogeneous; however, very low FEV1 and elevated baseline-$P_CCO_2$ together with pre-walk dyspnea increase the risk for $CO_2$-retention and EIH. Overweight-BMI seems to carry a protective effect against EIH in very severe COPD.


## 1. Introduction

Six-minute walk test (6MWT) is widely used to assess functional exercise performance and prognosis in patients with chronic obstructive pulmonary disease (COPD) (Holland et al., 2014; Singh et al., 2014; Spruit et al., 2012). Moreover, the 6MWT is used as field test to assess exercise-induced oxygen desaturation (Andrianopoulos et al., 2014; Poulain et al., 2003) which has an additional prognostic value besides the 6-min walk distance (6MWD) (Andrianopoulos et al., 2015; Casanova et al., 2008). Also, transcutaneous carbon-dioxide pressure ($T_CPCO_2$) can be measured reliably as an indicator of ventilatory adequacy and may be of clinical relevance in patients with COPD (Chhajed et al., 2010; Domingo et al., 2006; Nicolini and Ferrari, 2011; Stege et al., 2009).

*Abbreviation:* Bf, breathing frequency; BMI, body mass index; BGA, blood gas analysis; CBG, capillary blood gas; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory disease questionnaire; $DL_{CO}$, carbon monoxide diffusing capacity; EID, exercise-induced oxygen desaturation; EIH, exercise-induced hypercapnia; $FEV_1$, forced expiratory volume in 1 second; HADS, hospital anxiety and depression scale; LTOT, long-term oxygen therapy; $V_E$, expired ventilation; $P_CCO_2$, capillary carbon-dioxide partial pressure; Pi max, maximal inspiratory mouth pressure; $P_CO_2$, capillary oxygen partial pressure; $T_CPCO_2$, transcutaneous carbon-dioxide partial pressure; Vt, tidal volume; 6MWD, six-minute walk distance; 6MWT, six-minute walk test.

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Resting $PCO_2$ is highly variable amongst patients with COPD (Oliven et al., 1983). Respiratory mechanics impairments, reduced ventilation (hypoventilation), hyperinflation, and reduced gas exchange capabilities (ventilation/perfusion mismatch) may account for $CO_2$ retention and often lead to hypercapnia (Gorini et al., 1996; Light et al., 1988; O'Donnell et al., 2002; Sieker and Hickam, 1956). During exercise, a substantial $CO_2$ retention ($T_CPCO_2$ $[\Delta]$ >4 mmHg from baseline) may also occur frequently in patients with COPD and can result in exercise-induced hypercapnia (EIH; defined by an elevation of $PCO_2$ levels greater than 45 mmHg/6.0 kpa) (Light et al., 1988; O'Donnell et al., 2002).

Indeed, exercise-induced changes in $PCO_2$ are highly dependent upon several pathophysiological mechanisms in COPD (O'Donnell et al., 2002; Rodriguez-Roisin et al., 2009). Even though many COPD patients are normocapnic at rest, some patients may exhibit substantial $CO_2$ retention during exercise, which often results in EIH and it is associated with a greater tendency toward respiratory failure (Laserna et al., 2012; Simard et al., 1995). In contrast, other patients with COPD may significantly reduce $PCO_2$ on exertion even to hypocapnic levels and be at risk of acute respiratory alkalosis due to hyperventilation (Lindinger and Heigenhauser, 2012). Indeed, levels of $PCO_2$ have been reported as independent prognostic factor with a U-shaped association with mortality in COPD (Ahmadi et al., 2014).

A decline of $PCO_2$ levels is less common than $CO_2$ retention and the occurrence of EIH in very severe COPD. Although, EIH has been proposed as an indication for the progress of disease severity regarding resting hypercapnia (Simard et al., 1995) and also determines a condition of acute respiratory failure, which is related to high risk for death in patients with advanced COPD (Budweiser et al., 2008), the current literature provides only scarce information on $CO_2$ responses at cycle ergometer test (Liu et al., 1995; O'Donnell et al., 2002; Prior et al., 1985) or 6MWT (Diaz et al., 2010). To date, the determinants of $CO_2$ retention and EIH have never been investigated using continuous recording of $T_CPCO_2$ during the 6MWT in patients with very severe COPD.

Herein, we report an analysis of $CO_2$ response to exercise during the 6MWT in patients with very severe COPD. We aimed to *(1)* to define patterns of $T_CPCO_2$ trends during the 6MWT and *(2)* to study the determinants of $CO_2$ retention and the occurrence of EIH during walking in very severe COPD.

## 2. Material and methods

### 2.1. Setting and participants

Patients aged 30–75 years with very severe COPD (GOLD IV), with and without the presence of chronic respiratory failure, were recruited prospectively. Exclusion criteria were resting capillary $P_CCO_2$ >55 mmHg, use of non-invasive ventilation, and/or acute exacerbation in the last 4 weeks. The Bavarian ethical committee approved this study and all subjects provided written informed consent (Germany: Ethic committee approval number: 12007). Sixty-two (n = 62) out of 75 patients with very severe COPD, participating in an inpatient Pulmonary Rehabilitation at Schoen Klinik Berchtesgadener Land (Schoenau am Koenigssee, Germany) were used for data analyses. Data from 13 patients were incomplete, and, in turn, not used for further analyses.

### 2.2. Assessments

All patients underwent physical examination, anthropometric and lung function measurements. Capillary blood gases (CBG) at rest were obtained under normal ambient condition and a complete medical history was recorded. Lung function was assessed by post-bronchodilator spirometry, plethysmographic lung volumes at rest (i.e. tidal volume [Vt], maximal inspiratory mouth pressure [Pi max], expired ventilation [VE]), measures of carbon monoxide diffusing capacity (DLCO), and CBG analysis ($P_CO2$, $P_CCO_2$). Body mass index (BMI, $kg/m^2$) was defined as weight divided by squared height, and fat mass index (FMI, $kg/m^2$) was calculated as the fat mass (kg) divided by the squared height ($m^2$). Fat mass and fat-free mass were measured using bioelectrical impedance (NutriGuard MS, Poecking, Germany). Patients completed the self-administered and validated version of the Hospital Anxiety and Depression Scale (HADS) (Herrmann, 1997) and the Chronic Respiratory Questionnaire (CRQ) (Guyatt et al., 1987).

Two 6MWTs were performed one week apart according to the international guidelines (Holland et al., 2014; Singh et al., 2014). The test with the longest walking distance was used for further analysis. Participants were asked to walk indoors in a flat, straight, 30-m walking course supervised by a well-trained health-care professional. Patients were encouraged using standard methodology every minute of the 6MWT (Holland et al., 2014). They were allowed to stop and rest during the test, but were instructed to resume walking as soon as possible. Oxygen saturation (SpO2), heart rate (HR) and transcutaneous $CO_2$ levels ($T_CPCO_2$) as surrogate for arterial carbon-dioxide partial pressure ($PaCO_2$) (Rodriguez et al., 2006) were measured continuously using the SenTec digital-monitoring system (Sentec AG, Therwill, Switzerland) carried by a well-trained health-care professional (Domingo et al., 2006). Perceived dyspnea and leg fatigue of patients at the 6MWT were quantified by a 10-scale Schoen Klinik index (modified Borg scale) before and at the end of the exertion (please see the online supplement for all details – Online Table). Exercise-induced desaturation (EID) was defined as SpO2 nadir ≤88%. Major changes in $T_CPCO_2$ ($T_CPCO_2$, $[\Delta]$ > 4 mmHg) during the 6MWT defined patients as "non-isocapnic" including those who presented either a decreasing $CO_2$ pattern (decline of $T_CPCO_2$ >4 mmHg) or an increasing $CO_2$ pattern (increase of $T_CPCO_2$ > 4 mmHg) at exertion. Moreover, the non-isocapnic patients who substantially increased $T_CPCO_2$ ($T_CPCO_2$, $[\Delta]$ > 4 mmHg from baseline) were characterized as "$CO_2$ retainers". Exercise-induced hypercapnia (EIH) was considered as the peak of $T_CPCO_2$ > 45 mmHg during the 6MWT.

### 2.3. Statistical analysis

Results are expressed as mean (standard deviation) or proportion (%). The statistical significance of differences between groups was assessed by analysis of variance, paired T-tests and Chi-square, as appropriate. Pearson's correlation coefficients were used to assess bivariate relationship between changes of carbon dioxide pressure ($T_CPCO_2$, $[\Delta]$) during the 6MWT, and physiological characteristics. Spearman's rank correlation was used to determine the repeatability of the $T_CPCO_2$ trends (Patterns: Reducing, Isocapnic, Increasing) at 6MWT. Binary logistical regression assessed individual predictors of $CO_2$ retention and EIH. An adjusted logistic regression model was used to estimate odds ratio for $CO_2$ retention and EIH. Receiver operating characteristics (ROC) curves were used to determine threshold values to predict EIH. The Area Under the curve (AUC) was calculated by the trapezoidal rule and the confidence intervals of the AUC was computed by the method of DeLong (DeLong et al., 1988). *T*wo-sided level of significance was set at $P < 0.05$. Statistical analyses were carried out using the software of MedCalc v.12 and SPSS v.19.0.