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Cerebral oxygen availability during exercise in COPD patients with cognitive impairment

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ABSTRACT

Insufficient cerebral blood flow regulation to meet increasing metabolic demand during physical exertion could be associated with cognitive impairment. We compared cerebral oxygen availability during exercise in cognitively impaired (CI) to cognitively normal (CN) COPD patients.

Fifty-two patients (FEV_1: 51 ± 16%) were classified as CN or CI according to the Montreal Cognitive Assessment. Patients performed cycle-ergometry at 75% peak capacity with continuous measurement of Near-Infrared Spectroscopy frontal-cortex Tissue oxygen Saturation Index (TSI), cerebral haemoglobin indices (oxy/deoxy/total- Hb), transcutaneous carbon-dioxide partial pressure ($TcPCO_2$), and arterial oxygen saturation (SpO_2).

Twenty-one patients (40%) presented evidences of CI. During exercise, CN and CI patients exhibited mild to moderate SpO_2decline (nadir[Δ] ≥ −3 ± 2% and −5 ± 3%, respectively) but preserved baseline frontal-cortex TSI levels, whilst presenting small $TcPCO_2$ perturbations and increased cerebral total-Hb (post [Δ] ≥ 2.0 ± 3 μM sec^{-1}).

CI patients preserve the capacity to adequately maintain cerebral oxygen availability during submaximal exercise. Therefore, rehabilitative exercise training in CI patients with COPD exhibiting mild to moderate exercise-induced SpO_2 decline does not appear to lead to reduced cerebral oxygen availability.

1. Introduction

Cerebral blood flow (CBF) regulation is an intrinsic mechanism for maintaining constant cerebral perfusion and brain tissue oxygenation by dilatation or contraction of the cerebral vasculature (Willie et al., 2014). During increased states of cerebral activation and brain metabolism, cerebral blood vessels have an inherent ability to dilate, thereby increasing cerebrovascular and regional oxygen availability (Paulson et al., 2010). Several modulating variables such as carbon-dioxide partial pressure ($PaCO_2$) and arterial oxygen saturation (SpO_2) can influence the dilatation of blood vessels. (Querido and Sheel, 2007) Indeed, a graded reduction of SpO_2 can determine the capacity of the cerebral blood vessels to alter CBF, thereby compensating for reduced oxygen delivery in cerebral cortex (Steinback and Poulin, 2016).

In Chronic Obstructive Pulmonary Disease (COPD), chronic exposure to low arterial oxygen partial pressure (PaO_2), elevated $PaCO_2$,

Abbreviations: ACE-R, Addenbrooke's cognitive examination-revised; BMI, body mass index; CAT, COPD assessment test; CBF, cerebral blood flow; CHV, cerebral haemoglobin volume; CET, cycle endurance test; CI, cognitive impaired; CN, cognitive normal; COPD, chronic obstructive pulmonary disease; EID, exercise induced oxygen desaturation; FEV_1, force expiratory volume in the 1 st sec; FVC, force vital capacity; HADS, hospital anxiety and depression scale; MAP, mean arterial pressure; MMRC, modified medical research council dyspnea scale; MoCA, montreal cognitive assessment; $PaCO_2$, partial arterial pressure for oxygen; PaO_2, partial arterial pressure for carbon dioxide; PASE, physical activity scale for elderly; SGRQ, Saint George's respiratory questionnaire; S-MMSE, standardized mini-mental status examination; SpO_2, saturation of arterial oxygen; $TcPCO_2$, transcutaneous carbon-dioxide partial pressure; T-ICS, telephone – interview for cognitive Status; TSI, tissue oxygen saturation index; 6MWT, six-minute walk test

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pH imbalance, increased oxidative stress, vascular dysfunction and autonomic disturbances can all impair cerebrovascular regulation (Verges et al., 2012). During exercise in COPD, underlying cardiovascular and respiratory impairment may lead to irregularities in CBF (Bernardi et al., 2008), increased physiological stress (Vogiatzis et al., 2012) and, therefore, can potentially challenge the effectiveness of dynamic CBF regulation to maintain cerebral oxygen availability to normal levels (Ainslie and Duffin, 2009; Vogiatzis et al., 2013). Furthermore, cerebral oxygen availability during exercise depends upon the dynamic balance between oxygen delivery and oxygen utilisation (Vogiatzis et al., 2013). Hence, impaired cerebrovascular haemodynamic response resulting in reduced cerebral oxygen availability is potentially posing a risk to cognitive function in patients with COPD.

As a matter of fact, inadequate blood supply and oxygen delivery to cerebral neurons during exercise has been proposed to be linked to the occurrence of cognitive impairment in COPD as brain tissue is highly sensitive and exposed to ischaemic damage (Ortapamuk and Naldoken, 2006). Moreover, reduced cerebral oxygen availability may accelerate the loss of cortical neurons over time (Thakur et al., 2010). In addition, chronic cerebral hypoperfusion may affect the brain's cellular health and trigger the development of neurodegenerative pathologies (Ruitenberg et al., 2005). Consequently, it is reasonable to hypothesize that cognitively impaired (CI) patients, inferred by compromised cognitive performance to reference norms (Hung et al., 2009), may exhibit insufficient cerebrovascular regulation to meet increasing metabolic demand during physical exertion compared to cognitively normal (CN) counterparts. Insufficient dynamic cerebrovascular regulation to compensate for restrained blood flow coupled with low oxygen content at increased metabolic demands during exercise may compromise cerebral oxygen availability with potential negative impact on cognitive function. Under these circumstances, reduced oxygen availability during exercise may constitute a pathologic characteristic of CI patients with COPD that is associated with manifestations of cognitive impairment. This would further suggest that regular exercise training within the frame of pulmonary rehabilitation (PR) could potentially adversely affect the progress of cognitive impairment in CI patients with COPD.

To date, it is still unknown whether cerebral oxygen availability during exercise is compromised in COPD patients with cognitive impairment. In order to address this issue, we investigated whether differences in cerebral oxygen availability during exercise are presented between CI and CN patients with COPD.

2. Materials and methods

2.1. Setting and participants

Fifty-two patients (n = 52) with clinically stable COPD took part in the study prior to commencing a comprehensive 3-week inpatient PR program (Schoen Klinik Berchtesgadener Land, Germany). Recruitment to the study was conducted according to the following inclusion criteria: 1) diagnosed GOLD stage II–IV, 2) aged 40–85 years old, 3) Normotensive (Arterial blood pressure range: 101–143/62–91). Exclusion criteria included resting hypoxia (PaO_2 < 55 mmHg), resting hypercapnia ($PaCO_2$ > 45 mmHg), long-term oxygen therapy (LTOT), last exacerbation of COPD within previous 4 weeks, chronic heart failure, history of stroke, severe cognitive impairment/dementia (Montreal Cognitive Assessment score < 17points) or other diagnosed neuropsychiatric symptoms. Initially, a power calculation was performed, suggesting the inclusion of a minimum sample size of 21 patients per group in order to demonstrate an exercise-induced difference in frontal cortex Tissue oxygen Saturation Index of 6% (± SD: 8%) between CI and CN patients with COPD based on published data (Tarumi et al., 2014) (See online supplement for details). The study was approved by the Bavarian ethical committee in Munich (ID: 15134) and was conducted in accordance with the guidelines of the Helsinki Declaration. Prior to participation in the study, all subjects provided written, signed, informed consent.

2.2. Assessment

As part of the pre-rehabilitation clinical routine assessment before commencing the rehabilitation programme, patients underwent physical examination, anthropometric, and lung function measurements. Moreover, the six-minute walk test (6MWT) was performed according to international guidelines (Holland et al., 2014; Singh et al., 2014). Blood gas analysis at rest was performed under ambient conditions and a complete medical history was recorded. Additionally, self-administered questionnaires were given to participants of this study including the COPD Assessment Test (CAT) (Jones et al., 2009), the St. George Respiratory Questionnaire (SGRQ) (Jones et al., 1992), and the Hospital Anxiety and Depression Scale (HADS) (Herrmann, 1997) and the Physical Activity Scale for Elderly (PASE)(Washburn et al., 1993). The PASE is a validated 12-item self-administered questionnaire designed to estimate the amount of daily-life physical activity. We asked patients to report the frequency, duration, and intensity level of specific activities during a regular week as they mentioned in each of the 12 items. Total score was ranging from 0 to 793, with higher scores indicating greater physical activity (Washburn et al., 1993).

The study protocol included two visits. In the first visit (V1), a comprehensive cognitive assessment was performed providing overall and domain-specific cognitive evaluation of patients' mental status. Additionally, evaluation of cognitive reaction time and accuracy was achieved by the Stroop test (ST) (Jensen and Rohwer, 1966) reflecting patients' selective attention skills at rest (See online supplement for details). On the second visit (V2), patients performed a symptom-limited cycle endurance test (CET) at 75% of the estimated peak Work Rate (WRpeak) on an electromagnetically-braked cycle ergometer (Ergoline – type-K; Ergoline GmbH, Bitz, Germany). WRpeak was estimated based on the 6MWT of the initial assessment by the equation of Luxton and colleagues (Luxton et al., 2008) (see online supplement for details).

During exercise, Near-Infrared Spectroscopy (NIRS) was employed for assessing cerebral oxygen availability in response to exercise (Kuebler, 2008). In addition, transcutaneous carbon-dioxide partial pressure ($TcPCO_2$) as surrogate for arterial carbon-dioxide pressure (Rodriguez et al., 2006), arterial oxygen saturation (SpO_2) and heart rate (HR) were continuously acquired by transcutaneous monitoring at the earlobe (Domingo et al., 2006). Cognitive reaction time and accuracy were measured again at the end of exercise by the Stroop test (Jensen and Rohwer, 1966).

2.3. Frontal cerebral cortex oxygenation by near-infrared spectroscopy

Near-Infrared spectroscopy (NIRS) is a non-invasive technique for evaluating tissue oxygenation and cerebrovascular responses to exercise (Habazettl et al., 2010). Frontal cortex Tissue oxygen Saturation Index (TSI) and relative concentration changes [Δ] from baseline in oxygenated haemoglobin (oxy-Hb), deoxygenated haemoglobin (deoxy-Hb) and total haemoglobin (total-Hb) were continuously recorded by the PortaLite NIRS system (Artinis Medical Systems, Elst, the Netherlands). The NIRS-derived haemoglobin signal provides tissue microvascular (de)oxygenation (or fractional O_2 extraction) that is reflective of the dynamic O_2 delivery/utilization balance. One set of NIRS optodes was placed on the skin over the left frontal cortex region of the forehead at an adequate distance to avoid interference with the midline sinus, which may cause readings non-reflective of brain tissue, and secured using double-sided adhesive tape. A special black strap was used to hold the probe firmly attached over the cortex region and shield from ambient light. Near-Infrared light was transmitted with two wavelengths, 760 nm and 850 nm penetrating (depth of ~2 cm) cerebral cortex, thus absorbing by haemoglobin chromophores in the cortical layer microcirculation (Habazettl et al., 2010). Data were sampled at 10 Hz and collected by oxysoft v3.0.52 (Artinis Medical Systems, Elst, the