Neurovascular coupling and EEG band distribution in patients with chronic obstructive pulmonary disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) patients often complain of neurological symptoms which were usually referred to oxygen deficit or neurovascular dysfunction. To address this issue we studied neurofunctional and neurovascular parameters in COPD patients without chronic oxygen treatment.

Methods: Severity of the COPD disease was classified according to the BODE score. Besides body plethysmography and capillary blood gas analysis, vascular risk factors, medication, CRP, and nitric oxide levels were obtained. Using a visual stimulation paradigm evoked potential amplitudes over the occipital cortex as well as hemodynamic responses in the posterior cerebral artery were obtained with a simultaneous EEG-Doppler technique. EEG frequency bands as well as flow velocity were also obtained during resting conditions.

Results: As expected a significant decline in the pO2 level (Bode 0: 77±11 vs. Bode 7-10: 61±5 mmHg; p<0.005), and increase in the pCO2 level (Bode 0: 35±3 vs. Bode 7-10: 43±7 mmHg; p<0.05) was found with disease progression. However, resting flow velocity levels, neurovascular coupling responses, potential amplitudes, or EEG band distribution were similar between groups. The pH levels were similar between groups showing complete metabolic compensation of hypercapnia. Hemoglobin, CRP, and NO levels were also similar between groups.

Conclusion: According to the present study there seems to be no simple association between COPD disease severity, reported neurological complaints, and neuronal or neurovascular parameters. Further investigations are warranted to investigate this issue in patients with stronger hypoxia or induced inflammation.

Keywords: Chronic obstructive pulmonary disease, Neurovascular coupling, Transcranial Doppler, Electroencephalogram.
Introduction

Chronic obstructive pulmonary disease (COPD) is a condition of major public health concern [1]. It is defined as a chronic airflow limitation characterized by a progressive and not fully reversible loss of lung function.

COPD is increasingly recognized as a systemic disease involving various organ systems. A disturbed oxygen and carbon dioxide gas exchange can impair oxygen supply of various organ systems and related inflammatory mediators can also have systemic effects on the microcirculatory function leading to organ dysfunction [2].

The brain, due to its high energy demand and strict aerobic metabolic state, may be vulnerable to the systemic effects of COPD. Many recent studies showed that COPD patients suffer from an increased incidence of fatigue, cognitive decline, dementia and stroke [3-5]. An increased arterial stiffness was associated with COPD, which may be responsible for the increased stroke risk and cognitive decline [6-8]. Other authors report co-morbid heart failure to play a considerable role [9, 10]. Cerebral perfusion deficits in the brain of COPD patients were found in frontal and temporal brain areas related to the clinical finding of a frontotemporal pattern of cognitive decline in these patients [5, 11].

The question arises whether the reduced perfusion is the cause or a result of the decreased cognitive function. This issue is complex because the neurovascular coupling adapts local cerebral blood flow in accordance with the metabolic demands of the underlying active neurons [12]. In case of a reduced number of neurons, i.e. due to neurodegeneration, the metabolic demands are less and the blood flow into these brain areas would be accordingly reduced. In case of a dysfunctional neurovascular coupling inadequate perfusion of active neurons may occur, then triggering secondary neurodegeneration.

Among patients with established COPD we investigated the impact of disease severity and impairment of respiratory physiology on the neurovascular coupling and neurofunctional parameters such as visually evoked potentials and EEG band distribution.

Methods

The local Ethics Committee of the Justus-Liebig University of Giessen approved this non-interventional, prospective clinical study, which was performed in accordance with the ethical standards of the Declaration of Helsinki (1975). All subjects were informed about the study and gave written informed consent to participate.

Patients with cognitive complaints assessed from biography and clinical examination were tested with the Mini Mental State Examination [13]. Scores of 24 or lower led to exclusion from the study. Consecutively, patients admitted to the internal medicine department for diagnostic workup and severity classification of COPD disease were included.

Patients with normal pulmonary function and exclusion of a COPD during the workup served as a reference group (see further on). Because of typical vascular risk factors and due to the specific medications of COPD patients, a healthy volunteer group was not considered an adequate control group. Patients received standard management for their COPD with long-acting inhaled β2-agonists, inhaled anticholinergic agents, inhaled glucocorticosteroids and sustained release theophylline. Patients on continuous oxygen therapy or patients with disturbances of the visual system, previous stroke, or with significant stenoses of the cerebral vessels examined by transcranial Doppler were excluded. Patients with an induced C-reactive protein (CRP) level or with a cardiac ejection fraction lower than 35% from documented records were also excluded.

The diagnostic workup included a clinical examination, technical, and laboratory tests. Clinical examination included determination of the body mass index (BMI), smoking pack years, age, medication (long-acting inhaled β2-agonists, inhaled anticholinergic agents, inhaled glucocorticoids, and sustained release theophylline) as well as arterial blood pressure (measured with a cuff technique on the upper arm after a 10-minute resting period), and a six-minute walk. Laboratory tests included measurement of the CRP level, HbA1c level, blood gas analysis at room temperature while in a seated position at rest (pO$_2$, pCO$_2$, pH, hemoglobin), and spirometry according to the American Thoracic Society (ATS) Guidelines [14, 15]. We used a MasterScreenBody plethysmograph with MS-PTF analyzer unit (Jaeger Toennies) for determining the pulmonary function and CO diffusion capacity during a single breath (DlCO-SB). For capillary blood gas analysis we used an ABL 800 Flex (Radiometer, Wilich, Germany).

We chose the validated BMI, Obstruction (degree of airflow obstruction measured by FEV1), Dyspnea (examined by the modified Medical Research Council (MRC) Dyspnea Scale), Exercise Capacity (measured by the six-minute walk) (BODE) Index, to score the disease severity [16, 17]. Patients were grouped accordingly to the following scores between 1 and 2, 3 and 4, 5 and 6, and 7 and 10, to reduce the class numbers. Patients with a BODE score of 0 were regarded as reference group.

Stimulation paradigm

We used a modified checkerboard test in which the volunteers focused on a spot in the centre of a 21" LCD stimulation monitor as a stimulation paradigm. The monitor had a picture repetition time of 5ms (Iiyama Corp, Kitaowaribe-Nagano-Shi, Japan). The volunteers sat quietly at 1m from the monitor. The stimulation protocol consisted of 10 cycles, each with a resting phase of 20 seconds and a stimulating phase of 40 seconds. During resting periods volunteers were instructed to close their eyes, during stimulation phases they had to look at the screen. Changes between phases were signalized acoustically by a tone. The stimuli consisted of black and white pictures which alternated with...
their negatives to induce contrast-based visually evoked responses. The contrast between white and black areas was calculated to c=92%. The present stimulation paradigm was much more comfortable for the volunteers as compared to a classical checkerboard pattern [18]. The flickering frequency was set to 1 Hz, which means that a picture was shown for 500ms followed by its negative for 500ms. During the 40s stimulation phase 80 reversals were performed.

Doppler recording
For the Doppler recording, two 2MHz–probes were mounted on an individually fitted head-band. In all cases, the P2-segment of both posterior cerebral arteries was insonated. Peak systolic blood flow velocities were recorded using a Multidop-T2-Doppler device (DWL, Singen, Germany). The reason for evaluating systolic velocities is that the index is less prone to Doppler artifacts. The beat-to-beat intervals of cerebral blood flow velocity were interpolated in a linear fashion with a “virtual” time resolution of 50ms. To assure independence from the insonation angle and to allow for comparisons between volunteers, absolute values were transformed into relative changes of cerebral blood flow velocity in relation to the baseline. The baseline was calculated from the blood flow velocity averaged over a timespan of 5s before the beginning of the stimulation phase and set to zero.

The method and algorithm for analyzing the data sets in terms of a control system are described in detail elsewhere [19]. The following parameters were specified: K represents the gain, Tv the rate time, ω the undamped natural angular frequency (natural frequency) and ζ the attenuation parameter of the system.

The parameters describe the dynamic features of the NC with an initial rapid upstroke of flow velocity, overshoot and succeeding decay to a stable flow velocity level above baseline. The gain represents the flow velocity difference between conditions of rest and activation under stable hemodynamic conditions. The rate time indicates the steepness of the initial flow velocity increase. Natural frequency and the attenuation describes oscillation features of the system. The natural frequency is assumed to represent the tonus and the speed of the system, whereas the attenuation describes dampening features such as elastic properties of the vessel wall.

EEG recording
From a 16-channel digital EEG (Schwarzer, Munich, Germany), 6 channels were used for electrical VEP recording of the field potential. Signals were recorded from Fp1 and Fp2, O1 and O2, as well as from the ears, A1 and A2. The reference electrode was set to Fz. The electrodes were placed according to the positions specified in the international 10–20-system. Also, an electrocardiogram was obtained with electrodes placed on both forearms and digitized with the EEG-data. Data were sampled at a rate of 1 kHz. An online band-pass filter was applied with a high-pass filter setting of 0.3 Hz and a low pass-filter setting of 70 Hz. Functionally evoked electrical activity changes were recorded from the scalp by means of silver chloride electrodes fixed by an EEG headset. Resistance was kept below 5 kΩ. The resting EEG activity was Fourier transformed to calculate the percent distribution of the typical EEG bands. The frequencies below 4Hz were assumed to be in the range of the delta band, frequencies between 4 and 7 Hz as theta, between 8 and 12 Hz as alpha and between 13 and 30 Hz as beta waves. Calculations were performed by the EEG device. VEPs were calculated offline from the EEG signals. To quantify the typical peaks from the VEP waveform, the data from 80 stimulations during a 40 s stimulation phase were averaged. Analysis of typical peaks (N75, P100) was performed and amplitude differences were calculated [18].

Nitric oxide measurements
NO metabolite (nitrite and nitrate) concentrations were determined for each subject using the NOASievers 280 (FMI GmbH, Seeheim, Germany) according to the manufacturer’s instructions. Plasma samples were drawn under resting seated conditions into heparin-containing tubes, and immediately centrifuged then stored at -20ºC until measurements were taken. NO reaction products in samples were reduced by vanadium chloride. Resulting gaseous NO was detected by NOA Sievers 280, which was connected to a computer for data transfer and analysis by “NOAWIN32” software (DeMeTec, Langgöns, Germany).

Statistical analysis
Neurovascular and neurofunctional parameters of the different BODE groups were compared with the ANOVA test. A paired comparison with the Scheffé post-hoc-test was performed, when a significant result was noted. Normally distributed data was tested with an F-test. Alternatively, a non-parametric Kruskal-Wallis test was used. The level of significance was set to p<0.05.

Results
One hundred twenty (120) patients were screened for inclusion into the study, from which 50 did not fulfill the inclusion criteria. Among the excluded subjects, 10 had non-correctable vision disturbances or insufficient temporal bone window. From the 70 patients investigated four patients did not have a complete data set for the EEG and Doppler recording due to measurement artifacts and were therefore excluded.

General findings
Patients were not evenly distributed in the different groups (see Table 1). The reference group (BODE 0) and the most severely affected BODE 7–10 group consisted of 7 patients, whereas the BODE 3–4 group had 23 patients. Nevertheless, age range, vascular risk factor profiles for blood pressure, diabetes mellitus, and smoking pack years as well as fraction...
Table 1. Clinical, technical, and laboratory data for the different BODE groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BODE 0</th>
<th>BODE 1-2</th>
<th>BODE 3-4</th>
<th>BODE 5-6</th>
<th>BODE 7-10</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects/females</td>
<td>7/3</td>
<td>16/6</td>
<td>23/9</td>
<td>13/5</td>
<td>7/3</td>
<td>N.S.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 15</td>
<td>60 ± 10</td>
<td>62 ± 8</td>
<td>64 ± 10</td>
<td>60 ± 11</td>
<td>P&lt;0.05; R-B7-10:p&lt;0.01; B1-2-B5-6:p&lt;0.005; B3-4-B7-10:p&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 8</td>
<td>28 ± 5</td>
<td>26 ± 5</td>
<td>25 ± 6</td>
<td>20 ± 5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Smoking pack years (y)</td>
<td>41 ± 18</td>
<td>46 ± 17</td>
<td>46 ± 19</td>
<td>38 ± 20</td>
<td>60 ± 25</td>
<td>N.S.</td>
</tr>
<tr>
<td>Active smokers (%)</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>15</td>
<td>13</td>
<td>N.S.</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128 ± 15</td>
<td>126 ± 13</td>
<td>129 ± 23</td>
<td>123 ± 16</td>
<td>118 ± 26</td>
<td>N.S.</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 13</td>
<td>76 ± 10</td>
<td>76 ± 9</td>
<td>75 ± 10</td>
<td>70 ± 11</td>
<td>N.S.</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.1 ± 0.8</td>
<td>6.1 ± 1.0</td>
<td>5.3 ± 1.7</td>
<td>5.8 ± 0.7</td>
<td>5.4 ± 0.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>Inhaled glucocorticosteroids (%)</td>
<td>57</td>
<td>63</td>
<td>87</td>
<td>100</td>
<td>100</td>
<td>P&lt;0.01; R-B5-6 and B1-2-B5-6:p&lt;0.01; R-B7-10, B1-2-B3-4 and B1-2-B7-10:p&lt;0.05</td>
</tr>
<tr>
<td>Inhaled long-acting β2-agonists (%)</td>
<td>43</td>
<td>94</td>
<td>91</td>
<td>100</td>
<td>100</td>
<td>P&lt;0.001; R-B1-2 and R-B3-4:p&lt;0.0001; R-B5-6 and R-B10:p&lt;0.001; B1-2-B7-10:p&lt;0.05</td>
</tr>
<tr>
<td>Sustained release theophyllines (%)</td>
<td>14</td>
<td>6</td>
<td>14</td>
<td>30</td>
<td>28</td>
<td>N.S.</td>
</tr>
<tr>
<td>Inhaled anticholinergic agents (%)</td>
<td>43</td>
<td>88</td>
<td>87</td>
<td>100</td>
<td>100</td>
<td>P&lt;0.005; R-B5-6:p&lt;0.001; R-B1-2, R-B3-4, and R-B10:p&lt;0.005</td>
</tr>
<tr>
<td>FEV1 (L/s)</td>
<td>2.2 ± 0.8</td>
<td>2 ± 0.7</td>
<td>1.4 ± 0.4</td>
<td>0.9 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>P&lt;0.001; R-B5-6, R-B7-10, B1-2-B3-4, B1-2-B5-6, and B1-2-B7-10:p&lt;0.0001; R-B3-4:p&lt;0.005; R-B3-4 and R-B1-2-B7-10:p&lt;0.05</td>
</tr>
<tr>
<td>DLCOC SB (mL/min/mmHg)</td>
<td>60 ± 19</td>
<td>57 ± 14</td>
<td>37 ± 15</td>
<td>27 ± 7</td>
<td>23 ± 18</td>
<td>P&lt;0.0001; R-B5-6 and B1-2-B5-6, and B1-2-B7-10:p&lt;0.0001; R-B3-4:p&lt;0.005; R-B3-4 and R-B1-2-B7-10:p&lt;0.05</td>
</tr>
<tr>
<td>pO₂ (mmHg)</td>
<td>77 ± 11</td>
<td>68 ± 7</td>
<td>65 ± 11</td>
<td>63 ± 12</td>
<td>61 ± 5</td>
<td>P&lt;0.05; R-B3-4:p&lt;0.01; R-B5-6 and R-B7-10:p&lt;0.005</td>
</tr>
<tr>
<td>pH</td>
<td>7.44 ± 0.02</td>
<td>7.43 ± 0.03</td>
<td>7.44 ± 0.02</td>
<td>7.42 ± 0.03</td>
<td>7.44 ± 0.04</td>
<td>P&lt;0.05; R-B3-4:p&lt;0.01; R-B5-6 and R-B7-10:p&lt;0.005</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>35 ± 3</td>
<td>38 ± 5</td>
<td>40 ± 5</td>
<td>43 ± 8</td>
<td>43 ± 7</td>
<td>N.S.</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>144 ± 17</td>
<td>149 ± 11</td>
<td>143 ± 13</td>
<td>144 ± 10</td>
<td>141 ± 14</td>
<td>N.S.</td>
</tr>
<tr>
<td>NO (µMol/L)</td>
<td>55 ± 26</td>
<td>54 ± 28</td>
<td>66 ± 32</td>
<td>53 ± 21</td>
<td>59 ± 45</td>
<td>N.S.</td>
</tr>
<tr>
<td>CRP level (mg/L)</td>
<td>5 ± 5</td>
<td>4 ± 5</td>
<td>10 ± 13</td>
<td>12 ± 16</td>
<td>9 ± 10</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation, unless otherwise indicated.

BMI = Body mass index; FEV1 = Forced expiratory volume in one second; DLCOC SB = single breath CO diffusing capacity; Hb = Hemoglobin; CRP = C-reactive protein; N.S. = Non-significant

of active smokers were evenly distributed between groups. Only the BMI was significantly lower in the BODE 7-10 group reaching normal values whereas the other groups had a moderately increased BMI between 25 and 30 kg/m².

Regarding medication there was a significant increase in inhaled glucocorticosteroids, long-acting inhaled β2-agonists, and inhaled anticholinergic therapy with disease severity, whereas theophylline treatment was comparable (Table 1). Pulmonary functional parameters significantly differed between groups as a result of classification to the BODE score. Compared to the reference group (BODE 0) blood gas analysis revealed a progressive decline in the pO₂ tension with disease severity starting in the BODE 3-4 group and reaching values of 61±5 mmHg in the BODE 7-10 group. A significant increase in the pCO₂ tension was seen with disease severity starting from 35±3 mmHg in the reference group and increasing to 43±7 mmHg in the BODE 7-10 group. The decline in the pO₂ tension did not result in a change in hemoglobin level between groups. The hypercapnia was metabolically totally compensated as seen in the stable pH values between groups. CRP and NO levels were also not different between the groups.

**Neurofunctional results**

The visual evoked potentials (VEPs) amplitudes and the EEG frequency band distribution were similar in all COPD groups (Table 2). Also, the resting as well as evoked flow velocity data did not differ between groups. Neurofunctional parameters were independent from COPD severity.
Table 2. Neurofunctional and neurovascular results of the different BODE groups given as mean ± SD together with the statistical results. No significant difference between groups was found.

<table>
<thead>
<tr>
<th></th>
<th>BODE 0</th>
<th>BODE 1-2</th>
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<th>BODE 5-6</th>
<th>BODE 7-10</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting flow velocity (cm/s)</td>
<td>53 ± 4</td>
<td>44 ± 8</td>
<td>45 ± 8</td>
<td>40 ± 5</td>
<td>54 ± 18</td>
<td>N.S.</td>
</tr>
<tr>
<td>Gain (%)</td>
<td>14 ± 3</td>
<td>15 ± 5</td>
<td>18 ± 6</td>
<td>15 ± 5</td>
<td>14 ± 5</td>
<td>N.S.</td>
</tr>
<tr>
<td>Natural frequency (1/s)</td>
<td>0.2 ± 0.06</td>
<td>0.18 ± 0.04</td>
<td>0.21 ± 0.05</td>
<td>0.2 ± 0.02</td>
<td>0.2 ± 0.07</td>
<td>N.S.</td>
</tr>
<tr>
<td>Attenuation (-)</td>
<td>0.5 ± 0.2</td>
<td>0.49 ± 0.2</td>
<td>0.42 ± 0.14</td>
<td>0.4 ± 0.09</td>
<td>0.5 ± 0.14</td>
<td>N.S.</td>
</tr>
<tr>
<td>Rate time (s)</td>
<td>3.1 ± 2.2</td>
<td>3.9 ± 2.5</td>
<td>3.0 ± 1.7</td>
<td>3.6 ± 1</td>
<td>2.8 ± 1.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>VEP (µV)</td>
<td>11 ± 8</td>
<td>12 ± 13</td>
<td>11 ± 5</td>
<td>9 ± 7</td>
<td>11 ± 7</td>
<td>N.S.</td>
</tr>
<tr>
<td>EEG Delta band (%)</td>
<td>25 ± 12</td>
<td>29 ± 18</td>
<td>21 ± 13</td>
<td>30 ± 14</td>
<td>20 ± 10</td>
<td>N.S.</td>
</tr>
<tr>
<td>EEG Theta band (%)</td>
<td>13 ± 5</td>
<td>12 ± 5</td>
<td>20 ± 13</td>
<td>15 ± 9</td>
<td>15 ± 7</td>
<td>N.S.</td>
</tr>
<tr>
<td>EEG Alpha band (%)</td>
<td>34 ± 15</td>
<td>36 ± 14</td>
<td>38 ± 13</td>
<td>30 ± 14</td>
<td>43 ± 12</td>
<td>N.S.</td>
</tr>
<tr>
<td>EEG Beta band (%)</td>
<td>28 ± 5</td>
<td>23 ± 7</td>
<td>21 ± 9</td>
<td>25 ± 11</td>
<td>22 ± 10</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

VEP = Visual evoked potential; EEG = Electroencephalogram

Discussion

The new finding of the present study is that severity of COPD was not associated with a change in neurophysiologic or neurovascular data.

In some way, trivial groups significantly differed regarding their pulmonary functional data as well as treatment regimen. However, groups did not differ regarding their age range, vascular risk factor profile, the CRP and NO levels and blood gas analysis with the sole exception of a progressive decline in the pO2 tension and increase in the in the pCO2 tension with disease severity. CRP levels were only slightly elevated above the cut off level of 5mg/L in all groups. NO levels were in the range of published data from healthy control persons of similar age (50±20µMol/L) [20].

The lack of differences between groups regarding the neurofunctional data needs further consideration. In terms of VEP responses, most studies in COPD patients focused on the VEP latencies which were not the focus of the present investigation [21]. In one study in which patients did not complain of any visual disturbances, authors found depressed VEP amplitudes in only 7.5% of patients [21], whereas another study—in which the patients complained of visual disturbances—VEP amplitudes were depressed in 25% of patients [22]. Since we excluded patients with visual disturbances, our data are in line with the data presented in the first study [21]. Slowing of the EEG into the theta and delta band or a reduction in the alpha frequencies was reported in narcoleptic patients and during fatigue [23-25]. However, this is not a common finding since it was shown that repeated test conditions which resulted in a sleepy state of volunteers and could also result in an induction of the alpha band [26]. Although COPD patients often complain of fatigue and cognitive disturbances, we did not find a change in the EEG band distribution in our patient group. Since we investigated patients without constant oxygen therapy, the matter might be different in patients with stronger hypoxemia.

Smoking is a strong risk factor for COPD and most patients were smokers. Since smoking is also a vascular risk factor, lacking differences regarding the neurovascular coupling is at first sight an unexpected finding. Recently we demonstrated a disturbed neurovascular coupling in clinically asymptomatic young smokers [27, 28]. An explanation for the intact coupling might be that most patients stopped smoking for years.

The present data indicate an intact neurovascular coupling. A reduced perfusion of cortical areas related to cognitive decline might therefore be rather a consequence than a cause of a neurodegenerative process. This might also explain why the other brain areas had a reported to be normal blood flow [5].

Although quite a lot of patients classified as BODE 0 were already at specific medication, there was still a significant difference in the medical regimen as compared to the more severely affected patients. All patients classified as BODE 5-6 and BODE 7-10 had continuous inhaled glucocorticosteroid, inhaled long acting β2-agonist, and inhaled anticholinergic agent therapy. However, due to the inhalative therapy a relevant medication effect on the coupling was not seen.

The capillary pO2 levels in the BODE 2-3 to 7-10 groups were in a range between 60 and 70mmHg thus indicating moderate hypoxia. Since cerebral blood flow had been shown to increase at levels below 50mmHg pO2 [29-31], resting flow velocity levels were not affected by the present oxygen reduction. This is in line with a previous study which also did not find changes in cerebral blood flow levels in COPD patients [30, 32]. However, insignificant findings in stronger hypoxic patients were explained by a neutralizing net effect of a combination of a cerebral vasodilation due to hypoxia and a hypocapnia induced vasoconstriction from compensating hyperventilation [30]. The trend to higher pCO2 levels with disease severity did not affect the resting flow velocity levels since its pH-effect was metabolically compensated in all patients.

Systemic inflammatory processes related to COPD have
been assumed to play a considerable role in dysfunctional pulmonary vasoregulation and disease progression [33]. Non-induced CRP and nitric oxide levels exclude such an effect in the present study.

Although the BODE 0 and BODE 7–10 groups consisted of only seven volunteers, we do not assume our insignificant findings to be a result of underpowering. The standard deviations of the neurofunctional and neurovascular parameters were comparable to that of the BODE 3–4 group consisting of 23 patients.

Conclusions

COPD patients without oxygen therapy and under medical control did not present a relevant disturbance of the neurovascular coupling. Neurofunctional parameters such as VEP amplitudes and distribution of EEG bands were also not affected by disease severity. Reduction of cerebral blood flow in cortical areas related to cognitive decline might therefore be caused by the atrophy of the brain in these patients. Further investigations are warranted to address the issue in patients with stronger hypoxia or induced inflammatory response.

Abbreviations

BODE: Body mass index, airflow obstruction, dyspnea, and exercise capacity; BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; EEG: Electroencephalogram; MRC: Medical Research Council; VEP: Visual evoked potentials

Acknowledgments

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Competing interests

The authors declare no conflict on interest.

References


