Stability of oxyhemoglobin affinity in patients with obstructive sleep apnea-hypopnea syndrome without daytime hypoxemia

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Clause D, Detry B, Rodenstein D, Liistro G. Stability of oxyhemoglobin affinity in patients with obstructive sleep apnea-hypopnea syndrome without daytime hypoxemia. J Appl Physiol 105: 1809–1812, 2008. First published October 23, 2008; doi:10.1152/japplphysiol.90860.2008.—A decrease in hemoglobin affinity for oxygen is considered an adaptive mechanism against tissue hypoxia. Obstructive sleep apnea-hypopnea syndrome (OSAHS) is characterized by recurrent episodes of apnea and hypopnea resulting in arterial oxygen desaturations during sleep. Maillard et al. (10) observed a right shift of the oxyhemoglobin dissociation curve (ODC) and an increase in 2,3-diphosphoglycerate (2,3-DPG) concentration ([2,3-DPG]) in 15 patients with severe OSAHS, but some had slight daytime arterial hypoxemia while breathing room air. The aim of our study was to measure the ODC and 2,3-DPG concentrations in a group of subjects normoxic during daytime referred to our sleep laboratory for suspicion of snoring or OSAHS. The patients were recruited during a period of 6 mo. All arterial and venous blood samples were taken early in the morning within 1 h of awakening following a full-night polysomnography. ODC and 2,3-DPG were analyzed in 88 patients: 56 OSAHS (oxygen desaturation index: 27.5 ± 24.5) and 32 non-OSAHS. We found a significant correlation between the P50 and 2,3-DPG levels in the 88 patients: r = 0.502, P < 0.001. We observed no difference between OSAHS and non-OSAHS for the P50 and for [2,3-DPG]. Finally, there was no change in these parameters measured at baseline, after 3 days and after 1 mo of treatment by nasal continuous positive airway pressure (nCPAP) on these parameters in a subgroup of patients with severe OSAHS.

The 2,3 diphosphoglycerate (2,3-DPG) blood concentration allows during hospital stay, which means that patients did not smoke for 6 mo were asked to participate in the study. The subjects gave an informed consent, and the protocol was approved by the Ethics Committee of our hospital. A total of 132 patients were examined and had a full-night polysomnography (PSG). A complete physical examination was followed by an ear, nose, and throat examination, which included anterior rhinoscopy, endonasal flexible endoscopy, and a complete rhinomanometry. Other routine tests included glucose and Hb blood levels along with thyroid, hepatic and renal function tests, plain chest radiography, and an electrocardiogram (ECG). All subjects had standard spirometric measurements, maximal inspiratory and expiratory flows volume curves, a carbon monoxide transfer test (Morgan TLC; Morgan Medical, Rainham, UK), resting arterial blood gases (Ciba Corning Blood gas system 288; Ciba Corning Diagnostic, Medfield, MA), and carbon monoxide measurements (OSM III Radiometer, Copenhagen, Denmark).

The exclusion criteria were abnormal lung function tests, heart failure, diabetes, thyroid dysfunction, renal insufficiency, liver cirrhosis, anemia, and rest hypoxemia (PaO_2 < 70 mmHg) during wakefulness. Heavy smokers (>10 cigarettes/day) were also excluded. Smoking was not allowed during hospital stay, which means that patients did not smoke for 24 h before the blood samples were taken.

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A full-night diagnostic PSG was performed in each subject according to standard criteria as described previously (1). A microphone was glued onto the anterior face of the patient’s neck, level with the larynx. Airflow was monitored by three thermocouples placed in front of the mouth and each nostril and linked to independent channels. Body position was recorded (Pro-Tech body position sensor; Pro Tech, Woodinville, WA) via one channel. All signals were recorded with a digital acquisition system (OSG Brainlab, Antwerp, Belgium). Sleep and respiratory parameters were recorded at the following sampling rates: electrooculogram (two channels, right and left), 128 Hz; chin electromyogram (EMG) (one channel), 512 Hz; electroencephalogram (EEG) (three channels, C4-A1, C3-A2, and C4-O2), 128 Hz; ECG, 128 Hz; thoracoabdominal movements, 64 Hz; and arterial oxygen saturation and pulse rate, 16 Hz, as previously described (13). Snoring was designated by the characteristic microphone trace during sleep. The oxygen desaturation index (ODI) was the number of oxygen desaturations per hour of sleep. A movement arousal (MA) was defined as the reappearance of an $\alpha$-rhythm in the EEG during a sleep epoch, accompanied by an increase in EMG, both lasting for $\geq 2$ s (5). The MA index (MAI) is the number of MAs per hour of sleep. The diagnosis of OSAHS was retained if the subject had an ODI $>5$. The patients were classified into two groups (non-OSAHS or OSAHS) according to an ODI inferior or equal/superior to 5 events per hour of sleep.

A treatment by nCPAP was offered to those patients with MAI $\geq 30$/h and ODI $>20$/h. After a 3-day training period for accommodation to nCPAP, patients underwent a control PSG to assess treatment efficacy. After a mean follow up of 1.7 mo (range 1–3 mo), patients treated by nCPAP were reexamined, and treatment compliance was checked.

Nocturnal oxygenation. Nocturnal oxygenation was assessed by the oxygen desaturation index and by the mean SpO$_2$ during the nocturnal sleep time. To better describe the duration of sleep hypoxia, we measured the time spent below 90% of SpO$_2$. We arbitrarily fixed a limit at 120 min to separate the patients into two groups: a hypoxic group (time spent below 90% SpO$_2$: $>120$ min) and a nonhypoxic group (time spent below 90% SpO$_2$: $<120$ min).
Table 2. Comparison between matched groups for age, BMI, and \( {P}_{A{O}_{2}} \)

<table>
<thead>
<tr>
<th></th>
<th>Non-OSAHs</th>
<th>OSAHS</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>( n = 18 )</td>
<td>( n = 18 )</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>49.0±10.7</td>
<td>50.8±10.4</td>
<td>NS</td>
</tr>
<tr>
<td>( {P}<em>{A{O}</em>{2}} ), mmHg</td>
<td>29.6±4.0</td>
<td>29.6±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>ODI/h</td>
<td>8.1±9.3</td>
<td>40.5±25.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>( {P}_{50} ), mmHg</td>
<td>26.8±1.2</td>
<td>26.9±1.5</td>
<td>NS</td>
</tr>
<tr>
<td>( {P}_{90} ), mmHg</td>
<td>61.6±1.8</td>
<td>61.3±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>2,3-DPG, ( 10^{-6} ) mol/g Hb</td>
<td>16.2±3.1</td>
<td>16.1±2.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD. 2,3-DPG, 2,3-diphosphoglycerate.

Comparison between non-OSAHs and OSAHS groups. Patient characteristics are detailed in Table 1. The two groups were different for age and BMI, and average \( {P}_{A{O}_{2}} \) during wakefulness was lower in the OSAHS group. The sleep characteristics of the two groups are reported.

Average values of \( {P}_{50} \) and 2,3-DPG were not statistically significantly different between non-OSAHs and OSAHS patient populations. \( {P}_{50} \) (means ± SD mmHg): 26.5 ± 1.3 vs. 26.4 ± 1.3 (\( P > 0.05 \)), 2,3-DPG (means ± SD \( \mu \)mol/g Hb): 15.8 ± 2.8 vs. 16.5 ± 1.9 (\( P > 0.05 \)). Comparable results were found after matching the men for age, BMI, and \( {P}_{A{O}_{2}} \) (Table 2). Only the men were selected for matching because the number of women was too weak.

There were no significant differences in the \( {P}_{50} \), \( {P}_{90} \), and 2,3-DPG between the non-OSAHs group (\( n = 32 \)) and subgroups of patients classified according to the severity of ODI (Table 3). No difference was found in Hb concentrations, and the ODC traces were superimposable. The reference levels of \( {P}_{50} \) and 2,3-DPG determined in six healthy subjects were 26.3 ± 1.4 mmHg and 15.9 ± 1.2 \( \mu \)mol/g Hb.

Effects of nCPAP. nCPAP treatment was effective after a 3-day treatment in all patients as demonstrated by PSG. We followed 13 patients treated by nCPAP, and we obtained a blood sample in 7 of them after 3 days of nCPAP treatment (Table 4). The 13 patients were examined after 1–3 mo of nCPAP treatment (Table 4). Compliance was checked using the built-in time counter of the nCPAP. All these patients used their machine more than 4 h/night. Despite an effective treatment, there was no change in P50 or 2,3-DPG concentration, early or later after treatment (Table 4), and the ODC were also superimposable.

Comparison between hypoxic and nonhypoxic groups. Patient characteristics are detailed in Table 5. Hypoxic patients had a higher BMI and Hb concentration. They also had slightly less daytime \( {P}_{A{O}_{2}} \) compared with nonhypoxic subjects.

All parameters of nocturnal oxygenation were significantly different although the \( {P}_{50} \) and \( {P}_{90} \) values, 2,3-DPG concentrations, and the ODC plots were similar for the two groups (Table 5).

Table 3. Subgroups of patients classified according to the severity of the ODI

<table>
<thead>
<tr>
<th></th>
<th>OSAHS</th>
<th>OSAHS</th>
<th>OSAHS</th>
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<tbody>
<tr>
<td></td>
<td>Non-OSAHs (&lt;15)</td>
<td>Non-OSAHs (&lt;30)</td>
<td>OSAHS (\geq 30)</td>
</tr>
<tr>
<td>( {P}_{50} ), mmHg</td>
<td>26.5±1.3</td>
<td>26.5±1.1</td>
<td>26.2±1.3</td>
</tr>
<tr>
<td>( {P}_{90} ), mmHg</td>
<td>60.7±2.1</td>
<td>60.7±2.3</td>
<td>60.3±2.0</td>
</tr>
<tr>
<td>2,3-DPG, ( \mu )mol/g Hb</td>
<td>15.8±2.8</td>
<td>16.4±1.7</td>
<td>16.3±1.6</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>14.7±1.1</td>
<td>14.8±1.8</td>
<td>15.1±1.1</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD.

Table 4. Effects of nCPAP treatment for 3 days or 1–3 months

<table>
<thead>
<tr>
<th></th>
<th>Before nCPAP</th>
<th>After 3 days nCPAP</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( {P}_{50} ), mmHg</td>
<td>27.2±1.4</td>
<td>27.1±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>2,3-DPG, ( \mu )mol/g Hb</td>
<td>16.8±1.3</td>
<td>16.6±2.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

All data are expressed as mean ± SD. 2,3-DPG, 2,3-diphosphoglycerate.

DISCUSSION

We have shown that intermittent arterial desaturations during sleep do not induce a change in the affinity of Hb for oxygen during daytime. Hence, patients with OSAHS without daytime hypoxia do not benefit from a right shift of the ODC before the beginning of apneas and hypopneas.

The shift of the ODC to the right is considered a protective mechanism against tissue hypoxia, enabling Hb, for a given \( {P}_{A{O}_{2}} \), to unload more oxygen to the tissues. The affinity of Hb to oxygen is decreased by an increase in 2,3-DPG attributable to the mechanism against tissue hypoxia, enabling Hb, for a given \( {P}_{A{O}_{2}} \), to unload more oxygen to the tissues. The affinity of Hb to oxygen is decreased by an increase in 2,3-DPG attributable to the shift of the ODC to the right.

The results reported here are consistent with that view, but we found no change in P50 or 2,3-DPG concentrations, and the ODC plots were similar for the two groups (Table 5).

We did not find any increase in \( {P}_{50} \) or 2,3-DPG in patients with OSAHS, and no change was observed after nCPAP treatment. Even after matching for age, BMI, and \( {P}_{A{O}_{2}} \) after nCPAP.
stratification of the subjects following the level of sleep-related hypoxia, no difference was observable.

We were not able to reproduce the results of Maillard et al. (10). These authors compared 15 patients with severe sleep apnea to a group of 10 healthy subjects. They observed higher P50 and 2,3-DPG levels in the OSAHS, showing a right shift of the ODC. These values returned within the normal range after surgical or nCPAP treatment in five patients. However, as stated by the authors, they did not exclude patients with daytime “slight” arterial hypoxia. In fact, the OSAHS had a mean ± SD PaO2 of 77 ± 11 mmHg, which means that, if these values were normally distributed, the lower limit of PaO2 was <60 mmHg. By contrast, the mean PaO2 of our patients was 85.3 ± 8.8 mmHg, and we excluded patients with daytime hypoxemia. We also carefully controlled potential confounding factors like carboxyhemoglobin and inorganic ion concentrations since they affect the ODC (6).

In 1990, in a study comparing patients with sleep apnea (N = 26) with non-OSAHS subjects (N = 42), McKeon and colleagues (11) found higher blood 2,3-DPG in apneic subjects. However, daytime hypoxemia could not be excluded as a confounding factor, in view of the absence of arterial blood gases.

The highly accurate analysis method used in our study offered the analysis of the whole ODC plotting, which enables the determination not only of P50 but also of blood oxygen saturation at several levels of PO2. This method is also useful for the analysis of the potential impact of oxyhemoglobin affinity changes on tissue oxygen delivery. Indeed, the ODC right shift reduces both the arterial oxygen and mixed venous oxygen saturations (SvO2). For PaO2 equal to or above 60 mmHg, changes of SaO2 occur on the flat part of the ODC and are negligible compared with the reduction of SvO2. The result is an increase in arteriovenous oxygen content. However, right shift in patients with a PaO2 less than 60 mmHg is unlikely to be of benefit because SaO2 changes then occur on the steep portion of the ODC.

The lack of increase in 2,3-DPG in patients with OSAHS may be related to different causes. Several hours of sustained hypoxia appear to be necessary to induce a significant elevation in 2,3-DPG levels, probably because these depend on the hypoxia duration and on the half-life of 2,3-DPG. The shortest period of hypoxia sufficient to induce a significant rise in blood 2,3-DPG is unknown, but it appears from this study that short hypoxemic episodes in OSAHS are not sufficient to result in any significant rise in 2,3-DPG and thereby in a shift of the ODC. Data from experimental hypobaric hypoxia exposures showed a small but significant increase in DPG after 2.5 h of sustained hypoxia (15). However, one must keep in mind that other factors may produce a shift of the ODC and changes in 2,3-DPG levels; during apnea and hypopnea, the resulting alveolar hyperventilation increases arterial PCO2 and lowers the pH. A low pH shifts the ODC to the right (Bohr’s effect), but the concentration of 2,3-DPG is also decreased by acidosis (14). Therefore, the episodes of successive respiratory acidosis during sleep might neutralize the hypoxia-related induction of 2,3-DPG accumulation. Opposite effects of pH and hypoxia on 2,3-DPG were shown by Lenfant et al. (9). These authors demonstrated that the increase of 2,3-DPG at high altitude does not occur when the volunteers receive acetazolamide, which prevents the hypoxia-induced alkalosis.

Choice of monitoring parameters. We did not use the apnea index (AI) to separate patients because AI is based exclusively on the study of respiratory events (cessation of respiration), whereas the ODI takes into account the variations of SpO2 equal to or greater than 4%. We also measured the time spent below 90% of SpO2 because it better reflects actual hypoxemia. Indeed, when investigating OSAHS without preexistent respiratory pathology and with normal basal PaO2, one can observe very disturbed PSG parameters (AI and ODI), but the oscillations of the SpO2 may stay between 92 and 96%, for example.

Conclusion. This study, which included a substantial number of patients, demonstrates that patients with OSAHS without daytime hypoxemia do not have permanent oxyhemoglobin affinity changes.

REFERENCES