EEG arousal prediction via hypoxemia indicator in patients with Obstructive Sleep Apnea Syndrome

Dr. Liang-Wen Hang, Mr. Jen-Feng Wang, Dr. Chen-Wen Yen, and Dr. Chen-Liang Lin

*Sleep Medicine Center, †Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan
‡Department of Mechanical and Electro-Mechanical Engineering, National Sun Yat-Sen University, Kaohsiung, Taiwan
¶Medical Electronics and Device Technology Center, Industrial Technology Research Institute, Hsinchu, Taiwan

(Received 11 September 2008 and accepted 01 November 2008)

ABSTRACT: Obstructive sleep apnea syndrome (OSAS) is a sleep breathing disorder characterized by recurrent airflow obstruction caused by a total or partial collapse of the upper airway. OSAS is a common affliction suffered by millions. The arousal index (ArI) is the best predictor of daytime somnolence for patients with OSAS, however, the polysomnography (PSG) examination in the sleep lab is expensive, time consuming and labor intensive. The objective of this study is to evaluate the ability and reliability of arousal prediction via the hypoxemia indicator in patients with OSAS. Patients with a diagnosis of OSAS by standard polysomnography were recruited from China Medical University Hospital Center. There were 248 patients in the learning set and 255 patients in the validation set. The presence of OSAS was defined as an Apnea Hypopnea Index (AHI) >5/h. We used the hypoxemia indicator to predict ArI in patients with OSAS by linear regression and evaluated the prediction performance in different clinical characteristics subsets. The standard error of estimate of ArI prediction was 12.9 in the learning set. For predicting the severity of ArI, for ArI exceeding 15/h or 30/h, the sensitivity was 53.4% and 75.7%, respectively, with corresponding specificity of 96.6%, and 77.4%, respectively. We analyzed the hypoxemia indicator for predicting the severity of sleep fragmentation. The result demonstrated it is possible to predict ArI via the hypoxemia indicator, especially in severe patients.

KEY WORDS: Pulse oximetry; Obstructive Sleep Apnea Syndrome; Polysomnography; Arousal index

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a sleep breathing disorder characterized by recurrent airflow obstruction caused by total or partial collapse of the upper airway.1 Cardiovascular and neuropsychological morbidity has been demonstrated in untreated sleep apnea.2,4 This morbidity, plus the occurrence of an increased risk of auto accidents and a relatively increased mortality, make treatment imperative.4 The prevalence of OSAS in middle-aged populations is currently estimated to be 2% in women and 4% in men.5,6 At present, the gold standard for a definitive diagnosis of OSAS is in-laboratory
polysomnography (PSG). However, this approach has its limitations; PSG is expensive, time consuming and labor intensive. The lack of airflow during apnea or hypopnea periods can lead to recurrent episodes of hypoxemia that can be detected as fluctuations in oxyhemoglobin saturation (SpO2). Thus, some studies have shown that nocturnal pulse oximetry, which is readily available and relatively inexpensive, could potentially meet the large demand for diagnostic testing in the community, and can be done easily at home, and repeated.

The arousals are transient and generally do not result in behavioral awakening, and recur in some conditions as often as once per minute. The important fact is that the arousals result in fragmented sleep rather than shortened sleep. It is clear now that sleep fragmentation leads to increased daytime sleepiness. Current models of alertness regulation suggest that the occurrence of daytime sleepiness depends on the duration of prior sleep and on the presence of sleep fragmentation. The arousal index (ArI) is the best predictor of daytime somnolence for patients with OSAS, but this process still requires PSG examination in the sleep lab.

Oximetry has been one of the more popular AASM (American Academy of Sleep Medicine) Type 4 monitoring techniques used in attempts at screening for sleep apnea in the home. The objective of this study was to evaluate the ability and reliability of arousal prediction via the hypoxemia indicator.

**METHODOLOGY**

**Material**

Patients with a diagnosis of OSAS by standard polysomnography were recruited from China Medical University Hospital Centre. There were 248 patients in the learning set and 255 patients in the validation set. Clinical data were collected retrospectively. Table 1 shows the clinical features. No patient had a history of heart failure or neurovascular disease. Exclusion criteria were chronic obstructive pulmonary disease (COPD), chronic chest wall disease, a total recording time of less than 3 hours and sleep efficiency less than 0.6. The study was approved by the Medical Research Ethics Committee of China Medical University Hospital. The study number is DMR 96-IRB-17.

| Table 1 - Clinical characteristics of the subjects and polysomnographic results in the learning set and validation set |
|---|---|---|
| **Clinical characteristics** | **Learning set (n = 248)** | **Validation set (n = 255)** |
| | Mean ± SD | Range | Mean ± SD | Range |
| Age (years) | 45.9±12.1 | 16-79 | 43.9±11.8 | 16-80 |
| Male / Female | 185/63 | | 213/42 | |
| BMI (kg/m2) | 27.5±4.2 | 18-44 | 26.8±4.4 | 18-44 |
| ESS | 9.6±5.4 | 0-24 | 9.4±5 | 0-24 |
| AHI (/h) | 37.9±27.2 | 5.2-166.2 | 36.3±27.1 | 5.1-147.4 |
| ArI (/h) | 34.6±20.4 | 5.0-131.9 | 34.5±20.5 | 4.3-131.9 |

**Oximetry**

Oximetry has been one of the more popular AASM (American Academy of Sleep Medicine) Type 4 monitoring techniques used in attempts at screening for sleep apnea in the home. The objective of this study was to evaluate the ability and reliability of arousal prediction via the hypoxemia indicator.

**METHODOLOGY**

**Material**

Patients with a diagnosis of OSAS by standard polysomnography were recruited from China Medical University Hospital Centre. There were 248 patients in the learning set and 255 patients in the validation set. Clinical data were collected retrospectively. Table 1 shows the clinical features. No patient had a history of heart failure or neurovascular disease. Exclusion criteria were chronic obstructive pulmonary disease (COPD), chronic chest wall disease, a total recording time of less than 3 hours and sleep efficiency less than 0.6. The study was approved by the Medical Research Ethics Committee of China Medical University Hospital. The study number is DMR 96-IRB-17.

| Table 1 - Clinical characteristics of the subjects and polysomnographic results in the learning set and validation set |
|---|---|---|
| **Clinical characteristics** | **Learning set (n = 248)** | **Validation set (n = 255)** |
| | Mean ± SD | Range | Mean ± SD | Range |
| Age (years) | 45.9±12.1 | 16-79 | 43.9±11.8 | 16-80 |
| Male / Female | 185/63 | | 213/42 | |
| BMI (kg/m2) | 27.5±4.2 | 18-44 | 26.8±4.4 | 18-44 |
| ESS | 9.6±5.4 | 0-24 | 9.4±5 | 0-24 |
| AHI (/h) | 37.9±27.2 | 5.2-166.2 | 36.3±27.1 | 5.1-147.4 |
| ArI (/h) | 34.6±20.4 | 5.0-131.9 | 34.5±20.5 | 4.3-131.9 |

**Polysomnographic study:** Polysomnography (PSG) data were recorded with a computerized polysomnographic system (Alice 4, Healthdyne Technologies, Atlanta, Georgia, USA). This included a standardized montage: two-channel electroencephalograms (EEG; C4/A1, C3/A2), bilateral electro-oculograms (EOG), submental electromyogram (EMG), bilateral leg EMGs, and electrocardiography (ECG). Oxyhemoglobin saturation was recorded using finger-probe oximetry (935 Oximeter Sensor, Respironics). The sampling rate of the oximetry was 1 Hz. Airflow was measured using an oronasal pressure (1287 nasal flow, PTAF 2, PRO-TECH), and respiratory effort was assessed by inductance plethysmography (3240 Chest Effort Sensor Adult, Respironics). The stored data were digitalized for computer analysis by data analysis software (Matlab; MathWorks Inc, USA). Artifacts were removed by eliminating all changes of oxygen saturation between consecutive sampling intervals of >4%/s, and any oxygen saturation <50%. A well-trained
observer reviewed and a medical doctor rechecked the PSG records. Sleep stages were scored according to the criteria of Rechtschaffen and Kales. Arousals were defined as episodes lasting 3 seconds or longer in which there was a return of alpha activity associated with a discernible increase in EMG activity. Apnea was defined as a cessation of oronasal airflow for a minimum of 10s. Hypopnea was defined as a reduction, for at least 10s, of oronasal airflow to 50% or less of the value prevailing during a preceding period of normal breathing, and associated with 4\% oxyhemoglobin desaturation and (or) EEG arousal.\textsuperscript{20,21}

### Methods

In this study, we used the hypoxemia indicator to predict the ArI, as shown equation (1).

\[
\text{ArI}_{\text{ODI4}} = a_1 \times \text{ODI4} + a_2
\]  

The correlation between ODI4 and ArI was \((r = 0.78; \ P < 0.001)\) in the learning set and \((r = 0.77; \ P < 0.001)\) in the validation set. The linear regression model built by the learning set is shown as (2). The SEE of learning set was 12.9. The plot of the actual ArI and ArI\textsubscript{ODI4} is shown in Figure 1.

\[
\text{ArI}_{\text{ODI4}} = 0.625 \times \text{ODI4} + 19.164
\]  

Subsequently, Figure 2 displays the ROC analysis at different ArI thresholds.

---

**RESULTS**

From PSG, an ArI \(\geq 15\text{ h}^{-1}\) was confirmed in 219 (88.3%) of 248 and 223 (87.5%) of 255 subjects, and 115 (46.4%) of the 248 and 127 (49.8%) of the 255 subjects had an ArI \(\geq 30\text{ h}^{-1}\). The correlation between ODI4 and ArI was \((r = 0.78; \ P < 0.001)\) in the learning set and \((r = 0.77; \ P < 0.001)\) in the validation set. The linear regression model built by the learning set is shown as (2). The SEE of learning set was 12.9. The plot of the actual ArI and ArI\textsubscript{ODI4} is shown in Figure 1.

\[
\text{ArI}_{\text{ODI4}} = 0.625 \times \text{ODI4} + 19.164
\]  

Subsequently, Figure 2 displays the ROC analysis at different ArI thresholds.

---

**RESULTS**

From PSG, an ArI \(\geq 15\text{ h}^{-1}\) was confirmed in 219 (88.3%) of 248 and 223 (87.5%) of 255 subjects, and 115 (46.4%) of the 248 and 127 (49.8%) of the 255 subjects had an ArI \(\geq 30\text{ h}^{-1}\).
validation set. When the ArI cutoff was 30/h, the AUC of the ROC curve was larger than the ArI cutoff of 15/h.

Table 2: AUC and optimal cutoff of ROC by ArI ODI4 at different ArI thresholds in the learning set (n=248) and validation set (n = 255)

<table>
<thead>
<tr>
<th>Arousal index cutoff</th>
<th>Learning set</th>
<th>Validation set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15/h 30/h</td>
<td>15/h 30/h</td>
</tr>
<tr>
<td>AUC</td>
<td>0.80 0.82</td>
<td>0.76 0.78</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>53.4 75.7</td>
<td>63.2 66.1</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>96.6 77.4</td>
<td>84.4 85.2</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>99.2 74.4</td>
<td>96.6 81.6</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>21.5 78.6</td>
<td>24.8 71.7</td>
</tr>
</tbody>
</table>

The SEE of the overall learning set was 12.9. We separated the learning set into several subsets by clinical characteristics such as (age <40), (40 ≤ age <60), (age ≥ 60), (BMI <25), (25 ≤ BMI <30), (BMI ≥ 30), (Male), and (Female) to test arousal prediction by (2). The SEE difference between the overall learning set and the subset is shown in Figure 3.

Figure 3: The error analysis of subsets in the learning set. The subset index from 1 to 8 was (age <40), (40 ≤ age <60), (age ≥ 60), (BMI <25), (25 ≤ BMI <30), (BMI ≥ 30), (Male), and (Female), respectively. The SEE of the overall learning set was 12.9 and the number above or below the bar is the SEE of each subset.

DISCUSSION AND CONCLUSION

Pulse oximetry has been proposed as a useful diagnostic and screening tool for OSAS in several studies. It is due to the lack of airflow during apnea or hypopnea periods may lead to recurrent episodes of hypoxemia that can be detected on oxyhemoglobin as fluctuations in oxyhemoglobin saturation. The role of arousals in sleep is getting interest among both basic researchers and clinicians. In the last 20 years increasing evidence shows that arousals are deeply involved in the pathophysiology of sleep disorders. This study evaluated the ability of arousal prediction via the hypoxemia indicator. In our study, hypoxemia had a significant correlation with arousal index. The result demonstrated the hypoxemia indicator may predict arousal index, especially in severe patients.

The association between sleep-related respiratory events and EEG arousals is more frequently reported in OSAS than in UARS (Upper Airway Resistance Syndrome). This is possible because OSAS subjects present increase in effort accompanied by apneas and hypopneas, and sometimes by short and limited oxyhemoglobin saturation drops, requiring a more intense stimulus to arouse. Oxyhemoglobin saturation data were collected as part of a standard laboratory PSG, and this signal could be obtained by the pulse oximetry. Therefore, pulse oximetry may reduce sleep laboratory efforts to screen more severe sleep fragmentation patients.

After separating the learning set into 8 subsets, the older (age ≥ 60), obese (BMI ≥ 30), and male subsets had a higher SEE of ArI prediction via hypoxemia indicator. Krieger et al defined three indices of respiratory effort during OSAS using esophageal pressure measurement during sleep, and found that respiratory effort decreases with increasing age. Visser et al reported that higher BMI is associated with higher C-reactive protein (CRP) concentrations. Shamsuzzaman et al reported the severity of OSAS is proportional to the CRP level, and is associated with hypoxemia. Ryan et al reported male and female patients with OSAS may have different upper airway functioning during sleep. Therefore, it might be the next step to consider about the individual variance when building the regression model.

REFERENCES


