WHAT IS THE CLINICAL SIGNIFICANCE OF MIXED APNEA IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: A RETROSPECTIVE STUDY

SEBAHAT GENC1, ERTAN TUNCEL1, NAZAN SAVAS2, MESUT DEMIRKOSE1, NURSEL DIKIMEN1
1Mustafa Kemal University, Faculty of Medicine, Department of Pulmonary Diseases, Hatay - 2Mustafa Kemal University, Faculty of Medicine, Department of Public Health, Hatay - 3Kahramanmaras State Hospital, Department of Pulmonary Diseases, Kahramanmaras/Turkey

ABSTRACT

Aim: Mixed apnea is defined as absent inspiratory effort in the initial portion of apnea, followed by resumption of inspiratory effort in the second portion. However, the pathophysiological and clinical significance of mixed apnea has not been well defined. This study investigated the likely clinical importance of mixed apnea.

Materials and methods: Patients diagnosed with severe obstructive sleep apnea (OSA) in polysomnographic studies were enrolled. Those with a mixed-apnea index value of 5/h or higher were grouped as mixed-OSA (Group 1), and those with a mixed-apnea index value below 1/h were grouped as pure-OSA (Group 2). The patients' demographics, symptoms, clinical and polysomnographic findings, and laboratory examination results were reviewed retrospectively.

Results: Groups 1 and 2 contained 24 and 42 patients, respectively. The mean age was significantly lower in Group 1 than those in Group 2 (47.4±10.4 vs 52.2±8.3, respectively, p<0.05). The patients in Group 1 displayed significantly higher apnea / hypoapnea index (AHI) values (p <0.001). Sleep duration, arousal index, and duration of apneas were significantly higher in Group 1 (p=0.006, p=0.013, p=0.008, respectively). While minimum oxygen saturation and mean oxygen saturation levels were significantly lower (p<0.001), mean oxygen desaturation percentages were significantly higher in Group 1 than those in Group 2 (p=0.001).

Conclusions: These findings suggest that mixed apnea is not just a subtype of obstructive apnea, and OSA with mixed apnea can be referred as a different phenotype of OSAS. Although there are studies about the alterations in neurochemical control of respiration, pathophysiology is not yet clear. So new studies are needed to investigate the underlying pathophysiology and clinical outcome.

Key words: Sleep apnea; mixed apnea; central apnea; intermittent hypoxia.

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Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a common disease. It is reported in several population based studies that the prevalence of obstructive sleep apnea associated with accompanying daytime sleepiness is approximately 3 to 7% for adult men and 2 to 5% for adult women in the general population1-3. OSAS is a result from collapse of the pharyngeal airway during sleep4. Even some theories are still considered true, it is not fully understood why the human airway is vulnerable and what the physiologic and structural disturbances are that create collapse5-8.

Mixed apnea is defined as absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion9. It is accepted as obstructive apnea in polysomnographic examinations and managed clinically as obstructive sleep apnea (OSA). However, there has been little detailed research on the pathophysiology and clinical significance of the presence of mixed apnea. Why some patients have mixed apnea remains unknown, but its occurrence suggests that the underlying pathology is more complicated than simply upper airway resistance. Potential causes of mixed apnea are instability of the respiratory control system involving respiratory rhythm
generation and/or central and peripheral chemoreception\(^\text{(10-11)}\).

Recently, there are studies investigating the OSAS phenotypes\(^\text{(12)}\). Yamauchi et al suggested that, patients with mixed apnea dominant OSAS, can be a different phenotype, and adherence to therapy is poor in these patients\(^\text{(11)}\).

The aim of this study was to investigate the clinical and polysomnographic differences between OSA patients with mixed apneas, and those with pure obstructive apneas, and the effect of mixed apnea on patients’ clinical status.

**Materials and methods**

**Subjects**

Subjects were selected from 441 patients referred to our sleep laboratory with suspected sleep-disordered breathing. All patients underwent diagnostic polysomnography (PSG) between February 2010 and February 2011.

Twenty four patients with mixed apnea (5.4% of the sample population) were identified and compared with 42 patients (9.5% of the sample population) with obstructive apnea or hypopnea, extracted from the same database. All but one patients with mixed apnea had apnea/hypopnea index (AHI) over 30/h, therefore we have just included consecutive patients with AHI over 30/h for comparison. Patients whose data are incomplete were excluded. The study did not include a control group, as the database contained a limited number of normal PSG results.

Patients with a mixed-apnea index (MAI) value of 5/h or higher were included in the mixed OSA group (Group 1), while those with a MAI value <1/h were included in the pure OSA group (Group 2). Patients with MAI values of between 4.9/h-1/h were excluded.

Data on demographics, symptoms, laboratory examination results, the Epworth Sleepiness Scale (ESS) score, medical history, current medications and findings on PSG were collected retrospectively.

**Sleep Study**

PSG was performed using Compumedics E Series 44 channel polysomnograph, Profusion PSG3 Software (Abbotsford, VIC, Australia). EEG, EOG, submental EMG, ECG, finger pulse oxymetry, thoracic and abdominal movements, body position, and bilateral anterior tibial EMG were recorded. An oronasal thermistor and nasal canulas were used to detect apnea and hypopnea.

All signals were digitized and stored on a personal computer. Scoring was performed according to the recommendations of Rechtschaffen and Kales and the AASM rules\(^\text{(9, 13)}\).

The Ethics Committee of the University Hospital approved the study (Approval number: 2013/76), and all subjects signed a consent form for their participation.

**Statistical analyses**

Statistical analyses were performed using SPSS version 16.0 for Windows software (SPSS Inc.; Chicago, Illinois). Differences in categorical variables were evaluated using a chi-square test for independence, while Mann Whitney-U test was used to compare numeric values.

Correlation analyses were performed using the Spearman test. The causality of relationship between the variables that correlated significantly was shown by using simple linear regression modeling. A p value < 0.05 was considered to indicate statistical significance. All results are expressed as means ±SD.

**Results**

Groups 1 and 2 consisted of 24 and 42 patients, respectively. The characteristics of each group are shown in Table 1. While there was no significant difference in gender, the mean age was significantly lower in Group 1 than those in Group 2 (47.4±10.4 vs 52.2±8.3, respectively, p<0.05).

Body mass index (BMI) values were similar. There were no difference in the smoking and alcohol usage history in both groups. Duration of symptoms was also similar (11.7±3±7.48 vs 11.3±7±8.21, respectively, p>0.05).

While all the patients in Group 1 had excessive daytime sleepiness, 33 (78.6%) of the patients in Group 2 had excessive daytime sleepiness (p<0.05). There were no statistically significant differences in terms of concomitant diseases, cardiovascular diseases, and laboratory findings between two groups (Table 1).

AHI values were also significantly higher in Group 1 (80.48±19.51 vs 57.99±21.31, respectively, p=0.001) than those in Group 2. Sleep duration, arousal index, and duration of apneas were significantly higher in Group 1 (7.74±0.98 vs 6.90±1.30, p=0.006; 73.19±17.68 vs 61.33±24.18, p=0.013, 29.17±6.19 vs 24.13±7.51, p=0.008, respectively).
While minimum oxygen saturation (MOS) and mean oxygen saturation levels were significantly lower (p<0.001), mean oxygen desaturation (MOD) percentages were significantly higher in Group 1 than those in Group 2 (p=0.006). Forteen (58.3%) and 7 patients had central apneas in Group 1 and Group 2, respectively (p<0.001) (Table 2).

There were strong positive and negative correlations between MAI and duration of desaturation (r=0.512, p=0.013), and mean Oxygen saturation (r=-0.541, p=0.006), respectively. Mean apnea duration and MOD were intermediately correlated with MAI (r=0.489, p=0.018; r=0.469, p= 0.021, respectively), while MOS was not correlated (r=-0.202, p=0.345) (Table 3).

To prove the linear causal relationship between the parameters which significantly correlated, we used lineary regression analysis. Linear regression analysis revealed that there was a statistically significant linear causal relationship between MAI and apnea duration, duration of desaturation, and mean oxygen desaturation and linear models were created for each couple (Figures 1, 2).

Table 1: Patient Characteristics.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Patients with mixed apnea</th>
<th>Patients without mixed apnea</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (F/M)</td>
<td>24 (1/23)</td>
<td>42 (6/36)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>47.4±10.4</td>
<td>52.2±8.3</td>
<td>P=0.038*</td>
</tr>
<tr>
<td>Obesity</td>
<td>22/24 (91.7%)</td>
<td>31/42 (%73.8)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>31.7±4.9</td>
<td>32.9±5.8</td>
<td>NS</td>
</tr>
<tr>
<td>Durationa</td>
<td>11.7±3.7</td>
<td>11.37±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>7 (31.8%)</td>
<td>21 (52.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5 (22.7%)</td>
<td>11 (27.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>EDS</td>
<td>24 (100%)</td>
<td>33 (75.8%)</td>
<td>P=0.021**</td>
</tr>
<tr>
<td>ESS</td>
<td>10.5±6.8</td>
<td>8.9±6.5</td>
<td>NS</td>
</tr>
<tr>
<td>CVD</td>
<td>10 (42.5%)</td>
<td>18 (42.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>HT</td>
<td>9 (37.5%)</td>
<td>15 (35.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>HF</td>
<td>1 (4.2%)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>CAD</td>
<td>3(12.2%)</td>
<td>4 (9.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>2(9.5%)</td>
<td>11(26.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>184.7±34.12</td>
<td>199.3±46.4</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>29.8±7.8</td>
<td>32.2±10.2</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>125.10±33.53</td>
<td>125.30±39.75</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>206.4±184.9</td>
<td>182.16±147.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2: Polysomnografic findings of the two patient groups.

AHI: Apnea/hypopnea Index, NREM1: Non-REM Stage1, NREM2: Non-REM Stage2, NREM3: Non-REM Stage3, WASO: Wake After Sleep Onset, * Mann Whitney-U test, ** Chi Square test

To prove the linear causal relationship between the parameters which significantly correlated, we used lineary regression analysis. Linear regression analysis revealed that there was a statistically significant linear causal relationship between MAI and apnea duration, duration of desaturation, and mean oxygen desaturation and linear models were created for each couple (Figures 1, 2).

In Group 1, Continuous Positive Airway Pressure (CPAP) therapy was recommended for 23 patients (92%) and bi-level positive airway pressure (BiPAP) therapy was recommended for 2 patients (8%). Eight patients (32%) were using their CPAP or BiPAP devices, while 6 (24%) were not using their devices for various reasons. The remaining 11 patients (44%) were lost to follow-up. In Group 2, CPAP therapy was recommended for 45 patients (81.8%) and BiPAP therapy was recommended for 7 patients (16%). During follow-up, 18 patients (32.7%) were using CPAP or BiPAP, but 15 (27.2%) were not using their devices.
The remaining 20 patients (36.3%) were lost to follow-up. There were no significant differences between the two groups in terms of treatment compliance (p>0.05).

**Discussion**

In this study, we sought to identify the clinical importance of the presence of mixed apnea in patients with OSA. An initial comparison considering the BMI of the two groups found no correlation between mixed apnea and BMI. However, these patients were surprisingly younger than pure OSA group.

While NREM 2 sleep was longer, NREM 3 was shorter than those in pure OSA patients. This finding can be due to the higher AHI in these patients.

We included all the patients having MAI>5/h in mixed apnea group. This can be controversial. Because most patients were having obstructive apneas more than mixed apneas in this group. Yamauchi et al included patients with MAI>30% of the total number of apneic events\(^{11}\). However, none of the patients had pure mixed apneas, and we decided that MAI>5/h is enough to find out the different characteristics of patients having mixed apneas and, the effect of mixed apneas to the clinical status of the patients.

The pathophysiology of OSA is multifactorial. In most patients, both anatomical and neurochemical factors play a role. Instability of central respiratory motor output also contributes to the pathogenesis. Mixed apnea is frequently observed in patients with congestive heart failure\(^{14}\). However, there were no patients with congestive heart failure in our patient group.

Xie et al suggested that the impairment of neurochemical control is more important in the pathogenesis of mixed or central apnea, when comparing mixed apnea and pure OSA\(^{10}\). Yamauchi et al found that, during wakefulness, the breathing pattern of patients with mixed apnea was irregular\(^{11}\). They suggested that this might be genetic or related to other medical conditions. In our patient groups, no differences with regards to any other medical conditions were observed.

We observed high oxygen desaturation levels in patients with mixed apnea, which may have contributed to its development. Repeated hypoxia is responsible for fatigue of the upper-airway muscles. Tired upper-airway muscles tend to collapse more easily\(^{15}\).

Chowdhuri et al hypothesized that exposure to acute episodic hypoxia during sleep can alter chemoreflex characteristics\(^{16}\). Several studies in both animals and humans have demonstrated that
intermittent hypoxia (IH) increases chemoreflex sensitivity during wakefulness\(^{(5,10)}\). This may lead to the development of central apnea by inducing hypocapnia\(^{(10)}\). Moreover, due to hypocapnia, upper-airway-muscle long-term facilitation may be ineffective\(^{(21)}\). This may lead to the development of an obstructive event\(^{(22,23)}\). Sensitivity to CO\(_2\) may in part be related to genetic influences\(^{(24,25)}\).

Badr et al. showed that pharyngeal cross-sectional area is reduced during central apnea in the absence of an inspiratory effort\(^{(17)}\).

The conclusion of that study was that subatmospheric intraluminal pressure is not necessary for pharyngeal occlusion. This may represent one of the mechanisms underlying mixed apnea.

All of the studies completed to date report that acute exposure to moderate or severe levels of hypoxemia (e.g., 25-45 mmHg) can lead to an enhanced chemoreceptor response to hypocapnia, but not to mild hypoxemia\(^{(27-29)}\). In this study, we found a significantly higher degree of hypoxemia in the mixed-apnea group than in the obstructive apnea–hypopnea group (66.68 ± 10.78 versus 78.81 ± 8.46, \(p<0.001\)). Bradford et al. speculated that IH is responsible for the progression of OSA\(^{(30)}\). Impairment of the neural control systems that regulate upper-airway patency and altered respiratory muscle contractile function due to IH may lead to the establishment of a vicious cycle of further airway obstruction and hypoxia that chronically exacerbates and sustains the condition. Our PSG findings showed that the occurrence of desaturation and mixed apnea increases with increasing disease severity. These findings made us think that hypoxemia can be associated with occurrence of mixed apneas. Long-term exposure to IH can cause accumulation of reactive oxygen species, either at the muscle level or at the hypoglossal motor nucleus\(^{(30,31)}\). Both may lead to reduced muscle function.

Yamauchi et al. found that adherence to PAP therapy was significantly lower in mixed-apnea patients\(^{(31)}\). Our study showed no differences in PAP adherence between the two groups. However, as a significant proportion of our patients were lost to follow-up, it remains unclear whether mixed apnea influences therapy compliance.

Insufficient follow-up is one of the main restrictions of our study. The other restrictions of our study are that it is retrospective and there is no anatomical investigation. Although mixed apnea patients were younger, they had more severe AHI than pure OSA patients, and BMIs were not different. Anatomical factors may explain this higher AHI in these patients.

In conclusion, patients with mixed apnea are younger, more symptomatic, more hypoxic, and have more severe OSAS than patients with pure OSA. Otherwise, duration of apnea is longer in mixed apnea patients than those in pure OSA. The long duration of apnea, and severe hypoxemia may contribute to the occurrence of mixed apnea. These findings suggest that mixed apnea is not just a subtype of obstructive apnea, and OSA with mixed apnea can be referred as a different phenotype of OSAS. Although there are studies about the alterations in neurochemical control of respiration, pathophysiology is not yet clear. So new studies are needed to investigate the underlying pathophysiology and and clinical outcome.

References


Compliance with ethical guidelines This study was in accordance with the ethical standards of the institutional review board and the study was conducted in accordance with the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki of 1975, as revised in 2000 and 2008, and other applicable local regulations. Written informed consent was obtained from all patients before enrollment.

Request reprints from:
SEBAHAT GENC, MD, Associate Professor
Mustafa Kemal University
Faculty of Medicine, Department of Pulmonary Diseases
31100 Antakya
Hatay
(Turkey)