# The effect of nightly nasal CPAP treatment on nocturnal hypoxemia and sleep disorders in mustard gas-injured patients

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ORIGINAL ARTICLE

# The effect of nightly nasal CPAP treatment on nocturnal hypoxemia and sleep disorders in mustard gas-injured patients

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**Abstract**
*Introduction* Sleep-related breathing disorders are associated with unusual respiratory pattern or an abnormal reduction in gas exchange during sleep that is common in sulfur mustard (SM) exposure.
*Methods* We compared 57 Iranian male patients injured with SM and had any complaints of sleep problems with an age-matched group of 21 Iranian male patients who had complaints of sleep problems and were not chemically injured; this group had Epworth Sleepiness Scale (ESS) above 10 and whom referred for polysomnography. Split-night studies were performed for patients with diagnostic polysomnography for obstructive sleep apnea (OSA) and respiratory events. We then studied respiratory events including episodes of OSA, apnea–hypopnea index (AHI) and respiratory disturbance index (RDI).
*Results* The mean age in mustard-exposed patients was 48.14 ±8.04 years and in age-matched group, 48.19±8.39 years. In mustard exposed patients, there were statistical differences for the episodes of OSA ($p$=0.001), AHI ($p$=0.001), and RDI ($p$=0.001) between two segments of split-night studies. In the age-matched group, there were statistically differences for each parameter (episodes of OSA ($p$=0.001), AHI ($p$=0.001), and RDI ($p$=0.001)). There were no significant differences between two groups.
*Conclusion* This study indicated that the incidence of respiratory events and nocturnal hypoxemia during sleep in mustard-exposed patients were high and treatment with CPAP significantly reduced all these events.

**Keywords** Obstructive sleep apnea · Continues positive airway pressure · Sleep-related breathing disorders · Mustard gas

*At a glance summary*: This study indicated that the incidence of respiratory events, nocturnal hypoxemia, and arousal with respiratory events during sleep in mustard-exposed patients were very high, and treatment with positive airway pressure (PAP therapy) significantly reduced all these events.

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## Introduction

Sleep-related breathing disorder (SRBD) includes any unusual respiratory pattern such as obstructive sleep apnea (OSA), hypopnea, and Respiratory Effort Related Arousal (RERA). Hypoventilation or any reductions in gas exchange that occur during sleep are also included in SRBD [1]. chronic obstructive pulmonary disease (COPD) is one of the most common causes of pulmonary diseases that is associated with sleep disorder and OSA as named overlap syndrome. Overlap syndrome refer to existence of both COPD and OSA in the same patient [2]. Obstructive lung diseases lead to poor sleep

quality [3–6]. Recurrent arousals during sleep and reduced sleep time in individuals with obstructive airway disease probably due to impaired quality of sleep [6, 7]. Sulfur mustard (SM) exposed patients have many complaints of sleep quality such as sleep fragmentation, which is probably due to respiratory symptoms, productive cough, and dyspnea. Additionally, psychiatric problems, for example, posttraumatic stress disorder (PTSD), depression, or other unknown neurological disorders associated with SM exposure also contribute to sleep problems in these patients [8].

The 1980–1988 Iraq–Iran war, chemical weapons including SM were used by Iraq against Iranian army [9]. SM is seriously toxic, after exposure to SM patients affected by acute and chronic process; specifically inflammation and hyperactivity are seen in respiratory systems [10, 11]. It has been shown that SM induces structural damage and rupture of respiratory tissue causing short- and long-term effects on respiratory system. In another study, we found that SM-exposed patients had some degree of obstructive lung disease, and we do not know that this respiratory problems have any effects on sleep pattern or SRBD, so we prepare this study for approach to sleep problem in this group of patients [12–14].

For treatment, continuous positive airway pressure (CPAP) is the treatment of choice for moderate to severe OSA. It keeps the airway open during sleep by delivering positive air pressure via a nasal mask or nasal pillows, which fit snugly in the nostrils. CPAP pressures are titrated to eliminate apneas and snoring in a follow-up polysomnogram for the diagnostic purposes [15–17]. Study population was SM-exposed patients with skin, eyes, and respiratory symptoms shortly after gas exposure. These complaints were investigated in other publications [18]; now they are suffering from chronic respiratory complain, and so they have some problem about sleep such as sleep quality, sleep frequency, snoring, and daily somnolence. In this study, we compared one group of SM-exposed patients with any complain of sleep with another group of patients with sleep problems whom referred for polysomnography, and we compared respiratory events in two groups in a split-night test before and after of CPAP, if indicated.

## Materials and methods

### Recruitment

We studied 57 Iranian men from the Chemical Warfare Exposure Clinic at the Baqiyatallah Hospital who were injured with SM, including military personnel who had any complaints of sleep problems and then compared them with an age-matched group of 21 Iranian male patients who had complaints of sleep problems and were not chemically injured; this group had Epworth Sleepiness Scale (ESS) above 10 and whom referred for polysomnography. The mustard-exposed patients were included from military personnel that participated in Iraq–Iran War (1980–1988), and for matching, we had to use only male patients in the age-matched group. According to our previous publication, we evaluated mustard gas exposure by a standard scale [13]. A consent form was completed by all the participants prior to study. After approval by the ethics committee of the university, patient's demographic information was obtained from a large database of the chemically exposed patients during the Iran–Iraq War. We used polysomnographic evaluations for all the participants (the mustard-exposed patients and the age-matched control group) and excluded patients with serious systematic diseases such as congenital heart disease (CHD), chronic renal failure (CRF), etc.

### Diagnostic evaluation

For the diagnosis of sleep disorders, polysomnographic evaluations were used for all patients. Polysomnography was performed in standard conditions (sound-attenuated, electrically shielded, temperature-controlled and private bedrooms). Computerized polysomnographic system (ALICE 5, Healthdyne, Atlanta, GA, USA) was used for recording sleep.

Sleep data were recorded and scored by the Rechtshaffen and Kales criteria [17]. American Academy of Sleep Medicine (AASM) criteria were used for scoring apneas and hypopneas [19]. Nasal–oral thermocouples used for monitoring airflow and respiratory efforts were simultaneously monitored by thoracic and abdominal movements. Apnea was recorded when there was a pause of airflow for at least 10 s. Obstructive apnea was scored if airflow was absent or nearly absent. Arousals characterized by increasing respiratory effort or flattening of the nasal pressure wave form [20]. Pulse oximeter was used for monitoring blood oxygen saturation.

### Split-night studies

Patients were categorized into four groups by respiratory disturbance index (RDI) (normal 0–4.9, mild 5–14.9, moderate 15–29.9, and severe greater than 30) [21]. Split-night studies were performed for patients with RDI>5, according to AASM [22, 23]. CPAP titration was initiated for patients who had a diagnostic polysomnography for OSA (exhibited an apnea–hypopnea index (AHI)>5 during the first 4 h of sleep). CPAP was delivered via a full face mask in which a mask is worn over the nose and mouth during sleep. Sleep study was performed in two segments: in the first segment (first 4 h of sleep (SS1)) without CPAP and in the second segment (second 4 h of sleep (SS2)) with CPAP titration if indicated, and then, comparison of the two segments was performed also; comparison of two groups (mustard-exposed patients and age-matched group) was performed (Fig. 1).

### Statistical analysis

Polysomnographic data included total sleep time, sleep latency, sleep efficiency, episodes of OSA, and episodes of hypopnea, AHI, RDI, $O_2$ saturation, lowest $O_2$ saturation, desaturation, and arousal index.

Data were presented as mean±SD. Spearman's correlation coefficient was used to show correlations between data. Paired samples *t*-test were used for investigation differences between the two segments (SS1 and SS2) for continuous variables, and independent samples *t*-test were used for investigation of differences between the two groups (mustard-exposed patients and age-matched group). Nonparametric evaluations were also used when the assumptions of the *t*-tests were seriously violated. $p<0.05$ was assumed to represent statistical significance. Data were analyzed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc, Chicago, Illinois, USA).

## Results

Seventy-eight male patients in two groups (57 mustard-exposed patients and 21 patients in age-matched group) were studied; all had symptoms consistent with the sleep apnea syndrome. In mustard-exposed patients, their mean age (±SD) was 48.14±8.04 years (range=34 to 74 years), their mean height was 168.59±7.99 cm (range=150 to 189 cm), their mean weight was 81.21±11.28 kg (range=50 to 103 kg) giving them a mean body index (BMI) of 28.91±4.13 kg/m$^2$ (range=19.50 to 37.00 kg/m$^2$), their mean neck circumference was 40.54±2.88 cm (range=34 to 46 cm), and their mean waist circumference was 104.54±12.21 cm (range=69 to 143 cm). These data are summarized in Table 1.

In age-matched group, their mean age (±SD) was 48.19±8.39 years (range=29 to 71 years), their mean height was 170.14±7.16 cm (range=159 to 182 cm), their mean weight was 85.14±19.17 kg (range=58 to 122 kg) giving them a BMI of 29.42±5.90 kg/m$^2$ (range=24.10 to 41.20 kg/m$^2$), their mean neck circumference was 40.65±3.42 cm (range=36 to 48 cm), and their mean waist circumference was 107.95±17.46 cm (range=87 to 107 cm).

There were no significant differences in age, BMI, neck circumference, and waist circumference between mustard-exposed patients and age-matched group.

These data are summarized in Table 1.

### Sleep studies

Sleep study was carried out in two parts: part 1 included all the sleep and respiratory data for the time spent without nasal CPAP on, and part 2 included all the sleep and respiratory data for the time spent with nasal CPAP on if indicated. To reemphasize, patients spent the initial part of the night for both the initial (SS1) and follow-up (SS2) sleep studies without nasal CPAP on and the latter part of the night with nasal CPAP in place.

After SS1, 11 mustard-exposed patients excluded (had AHI below 5 (19.29 %)) and nine patients excluded from age-matched group (had AHI below 5 (42.8 %)).

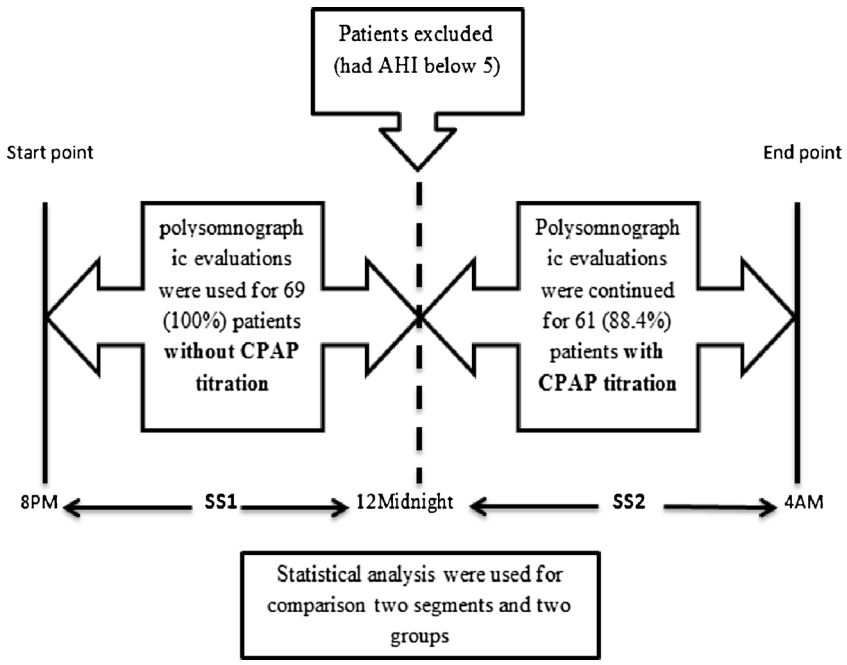


**Fig. 1** Sleep study performed in two segments: first segment without CPAP and second segment with CPAP titration

**Table 1** Baseline patient characteristics

| Parameters | Mustard-exposed patients (Mean±SD) | Age-matched group (Mean±SD) | *p* value* |
|---|---|---|---|
| Age (year) | 48.14±8.04 | 48.19±8.39 | 0.448 |
| Body mass index (kg/m$^2$) | 28.91±4.13 | 29.42±5.90 | 0.689 |
| Neck circumference ratio (cm) | 40.54±2.88 | 40.65±3.42 | 0.780 |
| Waist circumference ratio (cm) | 104.54±12.21 | 107.95±17.46 | 0.428 |

* *p* values<0.05 were assumed to represent statistical significance

There were no significant differences in total sleep time (TST) between SS1 and SS2 in mustard-exposed patients ($p$=0.524). There were no significant differences in TST between SS1 and SS2 in age-matched patients ($p$=0.314). There were significant differences in sleep onset latency (SOL) between SS1 and SS2 in mustard-exposed patients ($p$=0.002). There were no significant differences in SOL between SS1 and SS2 in age-matched patients ($p$=0.092). In mustard-exposed patients, the mean sleep efficiency ($p$=0.035) in SS2 was significantly higher (Table 2), and arousal index ($p$=0.038) in SS2 was significantly higher (Table 3). In age-matched patients, there were no significant differences ($p$=0.180) in sleep efficiency between SS1 and SS2 (Table 2), and there were no significant differences ($p$=0.305) in arousal index between SS1 and SS2 (Table 3). Analysis of the respiratory events data was done for two parts. Overall, in mustard-exposed patients, there were statistical differences for each parameter, including OSA events ($p$=0.001), hypopnea ($p$=0.001), AHI ($p$=0.001), and RDI ($p$=0.001) between SS1 and SS2 (Table 3). Also about age-matched group, there were statistically significant differences for each parameter, including OSA events ($p$=0.003), hypopnea ($p$=0.001), AHI ($p$=0.003), and RDI ($p$=0.003) between SS1 and SS2 (Table 3).

As expected in mustard-exposed patients, the mean $O_2$ saturation ($p$=0.001) and lowest $O_2$ saturation ($p$=0.001) in SS2 were significantly higher. The degree of oxygen desaturation ($p$=0.001) was also lesser in SS2. Additionally, about age-matched group, the mean $O_2$ saturation ($p$=0.002) in SS2 was significantly higher. The mean lowest O2 saturation was higher in SS2 but not significant ($p$=0.270). The degree of oxygen desaturation was lesser in SS2 but not significant ($p$=0.057). This data is summarized in Table 2.

Before titration (SS1) in mustard-exposed patients, 11 patients had RDI below 5 (19.29 %), and 46 (80.07 %) had RDI>5. After CPAP (SS2), 15 patients had RDI below 5 (32.60 %) and 31 patients (67.39 %) had RDI>5 (Table 4). Chi-square test showed that patients with RDI>5 in SS2 were significantly less compared to all the patients enrolled in the study ($p$=0.001).

Out of the total 57 mustard-exposed patients, 20 had BMI< 30 and neck circumference<40. Before titration (SS1), 6 (30 %) had RDI below 5, and 14 (70 %) had RDI>5; 3 (15 %) mild, 7 (35 %) moderate, and 4 (20 %) had severe. After CPAP (SS2), 6 (42.9 %) had RDI below 5, and 8 (57.14 %) had RDI>5; 4 (28.60 %) mild, 3 patients (21.40 %) had moderate, and 1 (7.10 %) had severe. Chi-

**Table 2** Polysomnographic measures of the study population

| Parameters | | Mustard-exposed patients (Mean±SD) | *p* value between two segments | Age-matched group (Mean±SD) | *p* value between two segments | *p* value between two groups |
|---|---|---|---|---|---|---|
| Total sleep time (min) | SS1 | 238.28±67.54 | 0.524 | 257.61±57.60 | 0.314 | 0.248 |
| | SS2 | 236.60±64.28 | | 208.83±50.12 | | 0.171 |
| Sleep onset latency (min) | SS1 | 14.02±17.12 | 0.002* | 18.07±21.60 | 0.092 | 0.705 |
| | SS2 | 6.56±15.4 | | 6.87±6.87 | | 0.027* |
| Sleep efficiency (%) | SS1 | 84.58±10.90 | 0.035* | 82.71±11.46 | 0.180 | 0.510 |
| | SS2 | 88.23±12.87 | | 89.30±10.85 | | 0.842 |
| $O_2$ saturation | SS1 | 91.98±3.39 | 0.001* | 93.42±2.54 | 0.002* | 0.015* |
| | SS2 | 93.07±2.47 | | 93.25±2.76 | | 0.829 |
| Lowest $O_2$ saturation | SS1 | 79.58±9.66 | 0.001* | 79.16±12.45 | 0.270 | 0.015* |
| | SS2 | 81.06±11.95 | | 81.33±8.86 | | 0.817 |
| Oxygen desaturation | SS1 | 28.81±27.26 | 0.001* | 37.14±32.52 | 0.057 | 0.676 |
| | SS2 | 20.58±19.50 | | 23.32±22.59 | | 0.598 |

* *p* values<0.05 were assumed to represent statistical significance

**Table 3** Respiratory events of the study population

| Parameters | | Mustard-exposed patients (Mean±SD) | *p* value between two segments | Age-matched group (Mean±SD) | *p* value between two segments | *p* value between two groups |
|---|---|---|---|---|---|---|
| Arousal index | SS1 | 23.54±23.42 | 0.035* | 26.06±17.72 | 0.305 | 0.219 |
| | SS2 | 22.24±18.90 | | 24.65±13.24 | | 0.694 |
| Obstructive sleep apnea (OSA) | SS1 | 18.98±33.08 | 0.001* | 22.23±40.80 | 0.003* | 0.900 |
| | SS2 | 6.17±16.76 | | 6.58±14.78 | | 0.984 |
| Hypopnea | SS1 | 66.21±46.91 | 0.001* | 55.42±48.68 | 0.001* | 0.376 |
| | SS2 | 35.35±36.99 | | 22.41±20.88 | | 0.252 |
| Apnea-Hypopnea index (AHI) | SS1 | 19.64±18.08 | 0.001* | 14.10±13.79 | 0.003* | 0.208 |
| | SS2 | 8.26±7.51 | | 6.75±6.68 | | 0.530 |
| Respiratory disturbance index (RDI) | SS1 | 28.47±23.56 | 0.001* | 23.44±28.22 | 0.003* | 0.431 |
| | SS2 | 14.11±15.79 | | 10.90±10.49 | | 0.509 |

* *p* values<0.05 were assumed to represent statistical significance

square test showed that the number of patients with RDI>5 in SS2 was not significantly reduced ($p$=0.051) compared to those in SS1.

## Discussion

This study indicated that the incidence of respiratory events, nocturnal hypoxemia, and arousal with respiratory events during sleep in mustard-exposed patients was high, and treatment with CPAP therapy significantly reduced all these events. Additionally about age-matched group, CPAP therapy significantly reduced all these events, but there were no significant differences in treatment with positive airway pressure between two groups of study. The results also indicate that the median weight in SM-exposed patients was raised (BMI= 28.91), which can be due to nocturnal hypoxemia and metabolic syndrome [24, 25]. Arousal due to respiratory events is reduced after CPAP therapy ($p$=0.004).

This study is design for respiratory evaluation in mustard-exposed patients during sleep. According to previous study, often SM can induce injury in upper and lower airway such as tracheobronchomalacia in upper and bronchiolitis in lower airways [26]. Often pulmonary manifestation of SM has been described as asthma, chronic bronchiolitis, bronchiectasia, and tracheobronchmalacia [27]. Pathological finding is reported as bronchiolitis obliterans [28].

**Table 4** Evaluating the effect of CPAP on AHI

| AHI | (Person) | | *p* value |
|---|---|---|---|
| | SS1 | SS2 | (Pearson chi-square) |
| 0–4.9 | 11(19.30 %) | 15 (32.60 %) | 0.001* |
| 5–14.9 | 6(10.50 %) | 16(34.80 %) | |
| 15–29.9 | 19(33.30 %) | 9(19.60 %) | |
| >Severe (30) | 21(36.80 %) | 6(13.00 %) | |

* *p* values<0.05 were assumed to represent statistical significance

In this study, SRBDs in SM patients were seen in 80.07 % of the cases that had patients with RDI>5, which indicate that sleep apnea is common in this group. On the other hand, esophagitis and gastroesophageal reflux is frequently seen in this group [29]. Thus probably, increase of air way resistance and air way collapsibility is a mechanical defense against GERD; however, it induces apnea.

In our study after CPAP therapy, adverse respiratory events were significantly reduced and that there were no significant differences with age-matched group. This highlights the fact that in the pathogenesis of SRBD in mustard-exposed patients, the role of upper airways is more important than the lower airways and bronchiolitis.

According to another study carried out for the evaluation of severity of small airway disease and sleep respiratory events in mustard-exposed patients, correlation between spirometric finding (FEV1 & FEV1/FVC) with sleep hypopnea in this group was seen, and arousal due to respiratory events increased with the severity of small airway disease [8], which indicates that bronchiolitis is also important in the pathogenesis of SRBD. In one patient of case group, we saw a significant hypoxemia (O2 saturation ~60–80 %) without hypopnea or obstructive events, end-tidal PCO2=41–42 %, and hypoxemia=70 %; this events is probably due to SM effect and its needs to another studies for documentation (Fig. 2).

Nocturnal hypoxemia was seen in case groups due to obstructive events or discrete of obstruction we supposed that it would be due to reduction of tidal volume and minute ventilation during sleep in this group [30].

Since sleep apnea occurs due to upper airway collapse, it can lead to intermittent hypoxemia, respiratory acidosis, and

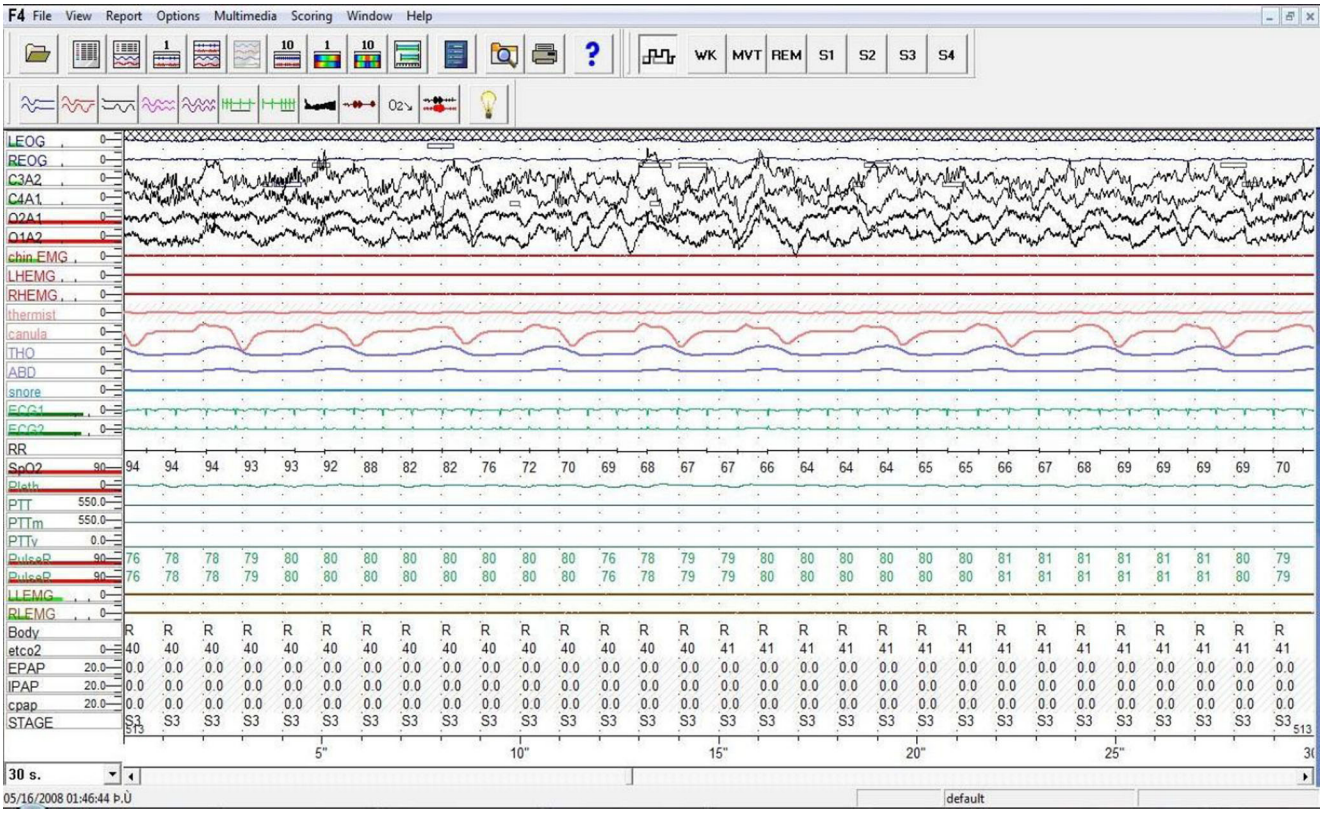


**Fig. 2** Screenshot of a polysomnographic record. In this figure, you can see hypoxemia discrete of flow reduction (apnea or hypopnea) and hypercapnia

hypercapnia [31]. In our study, very high mean hypopnea index (19.64±18.08) and mean RDI (28.47±23.56) indicate that the mustard-exposed patients had intermittent hypoxemia due to sleep apnea hypopnea syndrome or hypoventilation due to respiratory disease or overlap syndrome.

On the other hand, obstructive apnea due to airway collapsibility can induce intermittent hypoxia and sleep fragmentation [32]. Chronic intermittent hypoxia (CIH) involves several mechanisms including inflammatory pathways, and its severity and chronicity leads to various metabolic, cardiovascular, and neurocognitive complications [32–34].

In mustard-exposed patients, tracheobronchomalacia in the upper airway and constrictive bronchiolitis in the lower airways were seen. The higher hypopnea index and RDI mentioned earlier also show increased collapsibility of airway. Thus, the sleep apnea seen in this group is independent to weight and BMI. On the other hand, the change in minute ventilation and probably hypoventilation due to respiratory involvement can induce intermittent hypoxemia and nocturnal hypoxia.

Intermittent hypoxia has been correlated with upper airway muscle dysfunction, reduction of bronchodilation and pharyngeal muscle activity seen in sleep apnea [35].

Chronic intermittent hypoxia could affect pharyngeal muscle stability and reduce EMG response to physiologic activation for muscle dilation in the pharynx [33]. Tracheomalacia, intermittent hypoxia, pharyngeal muscle dysfunction, and respiratory problem could have probably accelerated each other in our patients. This requires further investigation in these patients. In addition, intermittent hypoxia with neural pharyngeal muscle control can induce OSA, so CIH and OSA could also accelerate each other. Hypoxia due to low responsibility of airway muscle and increased resistance is associated with high arousals and lower sleep efficiency [36]. However, in diseases with intermittent hypoxia such as neuromuscular disorders, COPD and OSA, arousal associated with respiratory events is decreased because of raised arousal level [37].

In our study, after CPAP therapy arousal index was reduced probably due to the reduction of nocturnal hypoxia. Additionally, the high mean BMI in our patients could have been due to chronic nocturnal hypoxia. Because metabolic syndrome and insulin resistance are related to hypoxia [24], thus probably hypoxia is one of the risk factors for weight gain in these patients.

However, as the prevalence of OSA (patients with RDI>5) in our patients was independent of BMI and the prevalence of OSA in patients in whom BMI<30 kg/m$^2$ and neck circumference<40 cm was 70 % were near to all the patients enrolled in the study (the prevalence of OSA was 80.07 %), thus probably the mechanism of OSA and hypoxia in mustard-exposed patients is independent to BMI and obesity.

## Suggestions

In SM-exposed patients, intermittent hypoxia and OSA were frequency seen. Often with CPAP therapy, it was reduced significantly. CIH can lead to metabolic and cardiovascular squealae, thus we recommend that the mustard-exposed patients with moderate to severe respiratory problems should be studied with polysomnograph. Further investigation on the relationship between night $O_2$ supplemental therapy and SRBD is suggested in these patients. The association between optimum reflux treatment and the effect of arousal and respiratory events is also recommended.

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**Conflict of interest** The authors declare that they have no conflict of interest. The authors have reported that no potential conflicts of interest exist with any companies or organizations whose products or services may be discussed in this article.

**Authors' contributions** **E.V**: Conceptualised the study, data collection, data analysis, and interpretation of the data; and preparation of the manuscript.

**A.R.F**: Data collection, data analysis, and interpretation of the data; and preparation of the manuscript.

**M.G**: Data collection, data analysis, and interpretation of the data; and preparation of the manuscript.

**S.A**: Data collection data analysis, and interpretation of the data; and preparation of the manuscript.

**Z.P**: Data collection, data analysis, and interpretation of the data; and preparation of the manuscript.

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