ELSEVIER

Respiration Physiology 108 (1997) 215–224

Sleep apnea-like syndrome induced by nitrous oxide inhalation in normal men

L. Beydon, F. Goldenberg, L. Heyer, M.P. d'Ortho, F. Bonnet, A. Harf, F. Lofaso *

Réanimation chirurgicale, Service de Physiologie-Explorations Fonctionnelles and INSERM U296, Hôpital Henri Mondor, 94 010 Créteil, France

Accepted 24 March 1997

Abstract

To study the relationship between sedation and respiration under N_2O, we performed polysomnographic recordings in 15 healthy men with documented normal breathing patterns during sleep. In a first study in five subjects, we found that 50% N_2O in O_2 compared to 50% O_2 increased sleep latency to stage 2 (59 ± 12 vs. 17 ± 3 min), total sleep duration (59 ± 12 vs. 26 ± 11 min), depth of sleep and respiratory events during sleep (18 ± 5 vs. 1 ± 1/h of sleep). In a second study, ten subjects were exposed to N_2O (30 and 50%) in O_2 during two consecutive experimental periods. Eight subjects had EEG features of physiological sleep, but nevertheless exhibited a total of 181 respiratory events. Respiratory disturbance index (RDI) during sleep was similar under 30 and 50% N_2O (25 ± 7 and 25 ± 5/h of sleep, respectively). Obstructive events predominated, except in three subjects during N_2O 30% and one during N_2O 50% exposure. We conclude that N_2O can induce central and obstructive sleep apneas. © 1997 Elsevier Science B.V.

Keywords: Apnea, obstructive, central, N_2O; Gases, N_2O, sleep; Mammals, humans; Sleep, N_2O, obstructive sleep apnea; Upper airways, obstructive sleep apnea

1. Introduction

Nitrous oxide (N_2O) has been used in anesthesia for more than 100 years. It provides inadequate anesthesia for surgery when used alone, but is commonly administered in a concentration of 50% in O_2 to induce light anesthesia and analgesia during labor or dental surgery. Subjects under N_2O are usually arousable upon stimulation. Thus, the reversible loss of consciousness produced by N_2O is clinically similar to physiological sleep.

Most sedative drugs induce both depression of the central respiratory drive (Bailey et al., 1986; Launois et al., 1990) and a decrease in the upper airway muscular tone (Hwan et al., 1983), thereby causing obstructive, central, or mixed apneas

* Corresponding author. Tel.: + 33 1 49812681; fax: + 33 1 49812667.

PII S0034-5687(97)00026-1

(Montravers et al., 1992). Except for one report that N_2O facilitated post-hyperventilation apnea (Northwood et al., 1991), none of the available studies demonstrated that N_2O induced apnea or hypopnea. N_2O stimulated respiration in most studies (Dahan and Ward, 1994; Eckenhoff and Helrich, 1958; Hornbein et al., 1969; Royston et al., 1983). However, when studying the respiratory effects of a drug such as N_2O, the level of sedation must be considered. During previous studies, ventilation was explored either in awake patients (eyes open) (Royston et al., 1983) or during a hypoxic (Dahan and Ward, 1994) or hypercapnic (Dahan and Ward, 1994; Eckenhoff and Helrich, 1958) challenge that may have awakened the subjects, thus interfering with their pattern of breathing.

Despite its weak anesthetic effect, N_2O has been shown to affect upper airway muscle functions, most notably those involved in swallowing (Nishino et al., 1987). Data are lacking on the effect of N_2O on pharyngeal dilator muscle activity. We hypothesized that N_2O inhalation may induce the same adverse respiratory effects as other sedative agents. We studied the relationship between respiratory events and N_2O-induced sedation, hypothesizing that N_2O-induced sedation may be disrupted by respiratory events similar to those seen in sleep apnea syndrome (Guilleminault et al., 1976). To test this hypothesis, we performed conventional polysomnography in 15 healthy volunteers during N_2O inhalation.

2. Methods

2.1. Subjects

In a first series of investigations, five healthy non-obese men (age, 26–40 years; body mass index, 19–27 kg/m^2) were studied in two separate sessions in random order. The subjects breathed 50% oxygen during one session and 50% nitrous oxide in oxygen during the other. Each subject gave informed consent to the protocol, which was previously approved by our Ethics Committee (H. Mondor Hospital). No subjects were currently taking medications and none had clinically detectable sleepiness (i.e. Epworth Sleepiness scale scores (Johns, 1991) were lower than 6). Only three subjects stated that they snored occasionally. In addition, the absence of sleep apnea or arousal disorders was verified in each subject by an overnight polygraphic recording (respiratory disturbance index < 5 and arousal index < 10 per hour of sleep, according to the reference values for our laboratory (Lofaso et al., 1996)).

In a second series of investigations, ten healthy non-obese men (age, 25–42 years; body mass index, 21–26 kg/m^2) were studied while breathing 30 and 50% nitrous oxide in oxygen during the same session. All these subjects met the criteria described above.

2.2. Apparatus

Throughout the study, the subjects wore a sealed face mask. Respiratory flow was measured using a Fleisch no. 2 pneumotachograph (Lausanne, Switzerland) connected to a Validyne MP 45, ± 3 cm H_2O pressure transducer (Northridge, CA). Esophageal pressure (P_{es}) was measured using a balloon catheter inflated with 1 ml of air and connected to a pressure transducer (Validyne MP 45, ± 70 cm H_2O, Northridge, CA). The catheter was positioned so as to obtain the largest possible respiratory swing during quiet tidal breathing. Rib cage and abdominal movements were monitored using inductive plethysmography (Nihon Kohden, Tokyo, Japan). Arterial oxygen saturation was monitored via a finger probe (Nellcor N200, Nellcor, Hayward, USA). Sleep was staged using the signals obtained with standard electrodes for EEG (C3/O1-C4/O2), electro-oculography and chin electromyography. EEG amplifiers were set with a time constant of 0.3 s and a 50 Hz low-pass filter. All these signals were recorded using a 14-channel paper recorder (Electroencephalograph Nihon Kohden, Tokyo, Japan). Furthermore, all signals were digitized at 128 Hz and sampled by an analogic/numeric system (MP100, Biopac System, Goleta, USA) for subsequent analysis.

2.3. Procedure

On arrival at the sleep laboratory, at approximately 09:00, after an overnight fast, each subject was connected to the above-described recording equipment. Subjects were studied supine in a quiet room. They lay quietly in the dark and wore a noise-shielding helmet as soon as oxygen or nitrous oxide inhalation was started. Inspiratory gas composition was adjusted using precision rotameters supplied with N_2O and O_2. Inspiratory flow rate was adjusted to 12 L/min.

The first study involved two separate sessions of about 80 min each, at an interval of at least 1 week. The subjects breathed 50% oxygen during one session and 50% nitrous oxide in oxygen during the other. The order of the two sessions was randomized. The light was turned off when N_2O or O_2 exposure was started.

In the second study, the N_2O concentration in O_2 was increased stepwise as described below. N_2O inhalation was started and the light turned off after a basal 10 min period under 100% O_2, during which the above-mentioned parameters were recorded. Then followed two recording periods of about 40 min each, under 30% N_2O and 50% O_2, respectively. Finally, the subject awoke while breathing 100% O_2.

2.4. Data analysis

All data were analyzed by one of us (FG), who was not aware of the gas used (N_2O or O_2). Since the pattern of the polysomnographic signals during N_2O inhalation was similar to that observed during physiological sleep, we performed sleep staging according to standard criteria (Rechtschaffen and Kales, 1968): stage 1 sleep was defined as the disappearance of alpha frequency (8–12 Hz) and the appearance of theta waves (3–7 Hz); stage 2 sleep as the appearance of so-called spindles (short, >0.5 and usually up to 3 sec, bursts of waves at 13–15 Hz) and K complexes (one big wave lasting approximately 1 sec); slow wave sleep (SWS) as present during more than 20% of the epoch of high amplitude (>75 μV peak-to-peak) slow (0.5–2 Hz) waves; and rapid eye movement (REM) sleep as either a return to an EEG pattern virtually indistinguishable from stage 1 or apparition of a wakefulness EEG pattern with rapid bursts of eye movement and a fall in chin EMG activity. Wakefulness after sleep onset (WASO) included all periods of wakefulness recorded after the onset of sleep, until the final awakening. EEG arousals were detected as abrupt shifts in EEG frequency, including theta activity, alpha activity, and/or frequencies greater than 16 Hz but not spindles and were scored according to the standard criteria of the American Sleep Disorder Association (ASDA, 1992).

Furthermore, in the second study, spectral analysis was performed on EEG signals using fast Fourier transform (FFT) to compare EEG characteristics of stage 2 sleep during normal sleep and 50% N_2O inhalation. A 1 min tracing segment obtained during stable stage 2 sleep was used in each case. The total spectrum was divided into five frequency bands (0.5–4, 4–8, 8–13, 13–20, 20–40 Hz), and the power within these bands was computed.

Respiratory events were evaluated by analyzing both airflow, esophageal pressure swings (P_{es}) and thoraco-abdominal movements, using the following criteria: an abnormal breathing event during objectively-measured sleep was defined according to commonly used clinical criteria as either complete cessation of airflow lasting 10 sec or more (apnea) or a 50% decrease in tidal volume lasting 10 sec or more (hypopnea). The average number of episodes of apnea and hypopnea per hour of sleep was calculated as the respiratory disturbance index (RDI). Respiratory events were classified as obstructive or central according to whether respiratory efforts were increased or decreased, as determined from the esophageal pressure signal.

2.5. Statistics

Results are expressed in the text as means $\pm$ SEM. Comparisons between means were performed using paired t-tests. The level of significance was set at $p < 0.05$.

3. Results

3.1. Comparison between N_2O/O_2 vs. O_2 effects on EEG and respiratory events

All five subjects fell asleep under both conditions of gas exposure but only two achieved stage 2 sleep during O_2 exposure, whereas all five reached stage 2 during N_2O exposure. Mean sleep latency to stage 1 was similar under O_2 and N_2O 50% in O_2 (O_2, 11 ± 4 vs. N_2O, 11 ± 3 min; respectively), but N_2O induced a decrease in sleep latency to stage 2 (O_2, 59 ± 12 vs. N_2O, 17 ± 3 min; $p < 0.05$) and an increase in total sleep duration (O_2, 26 ± 11 vs. N_2O, 59 ± 12 min; $p < 0.05$). In addition, the distribution of sleep stages differed significantly between the two conditions, with deeper sleep under N_2O/O_2 than under O_2 (Fig. 1, $p < 0.05$). No REM sleep was observed in either session. The number of respiratory events per hour of sleep was significantly higher under N_2O/O_2 than under O_2 (18 ± 5 vs. 1 ± 1, respectively; $p < 0.01$). The only subject who exhibited central events under N_2O in O_2 had no such events under O_2; these central events were present only during stages 1 and 2 (21 and 13 per hour of stage 1 and stage 2 sleep, respectively). All five subjects showed obstructive events during N_2O exposure (13 ± 3, 31 ± 4 and 13 ± 11 per hour of stage 1, stage 2 and SWS, respectively).

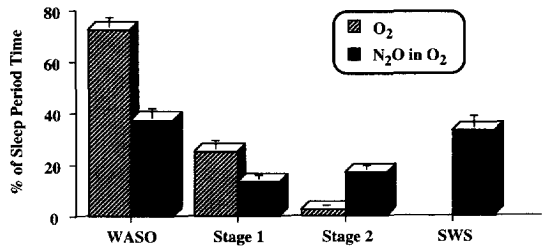

Fig. 1. Distribution of sleep stages in terms of sleep period time under N_2O in O_2 and O_2. A significant difference was seen between the two gases ($p < 0.01$). Values are means ± SEMs. WASO, wakefulness after sleep onset; SWS, slow wave sleep.

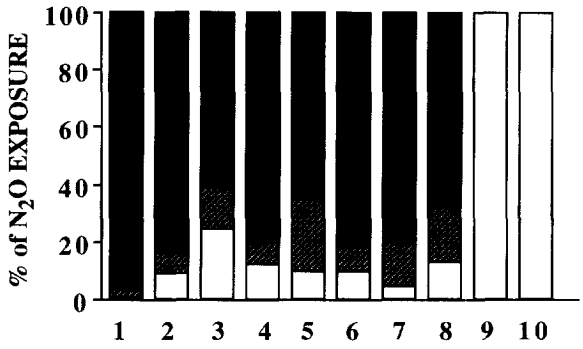

Fig. 2. Distribution of sleep latency, □; sleep, ■; and wakefulness after sleep onset, ▨ (WASO); in each subject under N_2O in O_2. Results are expressed as percentages of total N_2O exposure duration.

3.2. N_2O concentration effect

In the second part of the study, eight subjects fell asleep according to EEG criteria during N_2O exposure. The remaining two subjects seemed to be asleep but did not meet EEG criteria for sleep at either N_2O concentration; in these two subjects, alpha activity was the dominant EEG frequency throughout the N_2O exposure period. In one subject, the effect of N_2O 50% could not be studied because of vomiting at the beginning of N_2O 50% exposure. Mean sleep latency was 10 ± 2 min.

Individual results for sleep latency, time periods of sleep, and WASO are presented in Fig. 2. All the results discussed below were obtained in the eight and seven subjects who slept under N_2O 30% and N_2O 50%, respectively.

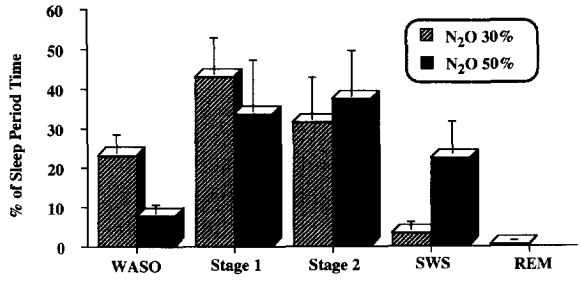

Fig. 3. Distribution of sleep stages in terms of sleep period time under 30 and 50% N_2O. WASO duration was shorter ($p < 0.04$) and slow wave sleep duration (SWS) longer ($p < 0.02$) under 50% N_2O than under 30% N_2O. Values are means ± SEMs. WASO, wakefulness after sleep onset; SWS, slow wave sleep; REM, rapid eye movements.

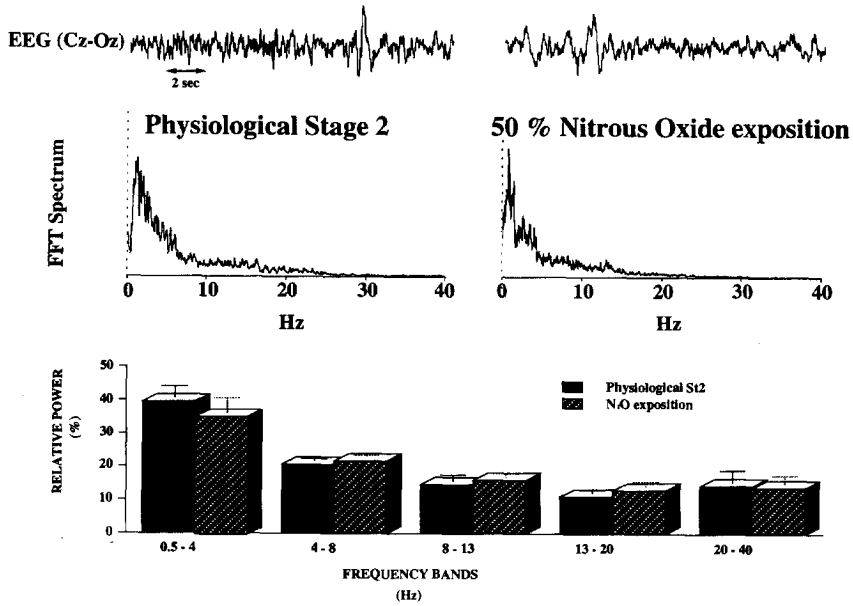

Fig. 4. EEG stage 2 analysis. Top: example of stage 2 EEG recording in a subject during physiological sleep (left) and under 50% N_2O (right). Center: Fast Fourier transform (FFT) spectrum of these two examples. Bottom: average frequency spectra of stage 2 recordings in all subjects ($n = 7$; solid, physiological sleep; hatched, 50% N_2O). There were no statistically significant differences between both conditions for each frequency band. Values are means $\pm$ SEMs.

Results regarding sleep stages at each N_2O concentration are shown in Fig. 3. For the seven subjects who slept under both concentrations of N_2O, N_2O 50% was associated with less WASO ($p < 0.04$) and more SWS ($p < 0.02$) than N_2O 30%.

Stage 1 and 2 EEG patterns were observed in every subject. EEG stage 2 frequency domain characteristics were not different between the physiological and N_2O conditions (Fig. 4), demonstrating that fast activity was not observed with N_2O. REM sleep was observed in only one subject, during less than 1 min. SWS was recorded in six subjects. SWS started during N_2O 30% exposure in one case and during 50% exposure in five cases. Since three of the six subjects had two documented periods of SWS, the total number of SWS periods was nine. The duration of these SWS periods was relatively short (6 ± 3 min) because eight of the nine periods were disrupted promptly by respiratory events that induced lightening of sleep, with or without previous EEG arousal.

We observed a total of 181 respiratory events in eight subjects. The numbers of obstructive and central events were 50 (15 apneas, 35 hypopneas) and 33 (10 apneas, 23 hypopneas), respectively, during N_2O 30% exposure, and 61 (hypopneas) and 37 (15 apneas, 22 hypopneas), respectively, during N_2O 50% exposure. No respiratory events were observed in the two subjects who did not have sleep-like EEG patterns. The eight subjects who fell asleep had respiratory events only while they were sleeping. Fig. 5 shows the indices per hour of sleep of central and obstructive respiratory events in each subject. Subjects 5 and 8 (during N_2O 30% exposure) and subject 2 (during N_2O 30% and 50% exposure) met the criteria for central sleep apnea syndrome (White, 1985) (i.e. more than 55% of respiratory events were central), whereas patterns in the other subjects were similar to those seen in obstructive sleep apnea or hypopnea syndrome.

RDI was not different under 30 and 50% N_2O (25 ± 7 and 25 ± 5 per hour of sleep respectively). In addition, Fig. 6 demonstrates that the duration

of respiratory events did not increase significantly when the N_2O concentration increased. The same Fig. also clearly shows that the duration of obstructive events was significantly longer than that of central events. However, the distribution of central and obstructive events differed between 30 and 50% of N_2O exposure, with a notable difference being persistence of respiratory events during SWS when subjects were exposed to N_2O 50% but not to N_2O 30% (Fig. 7).

Respiratory events were terminated by a decrease in sleep depth and/or by a stage change as observed for SWS. The brief episodes of lightening of sleep corresponded either to K-complex and reactive slow waves (Loomis et al., 1938) or to EEG arousals meeting the standard criteria of the American Sleep Disorder Association, 1992 as illustrated in Fig. 8. Percentages of obstructive and central events terminated by EEG arousal were 88 and 58%, respectively, during 30% N_2O exposure, and 44 and 11%, respectively, during 50% N_2O exposure, yielding arousal index values of 19 ± 7 and 7 ± 3 per hour of sleep for 30 and 50% N_2O exposure, respectively.

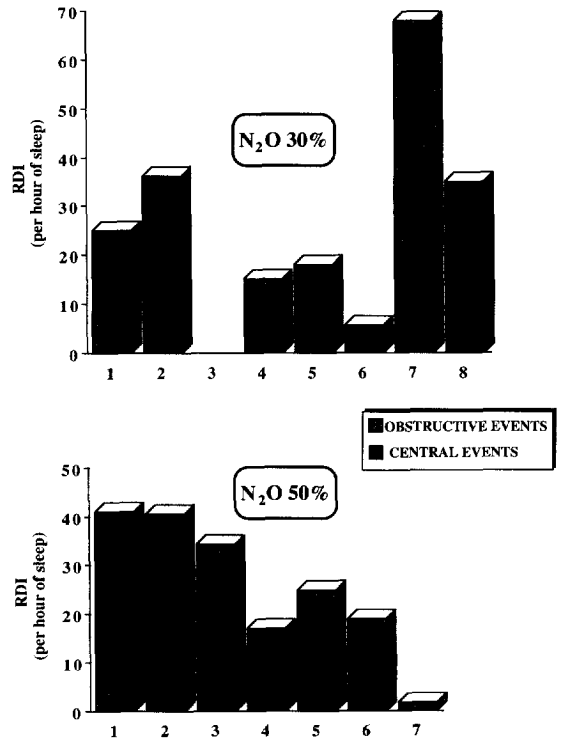

Fig. 5. Distribution of central and obstructive events represented as the respiratory disturbance index (RDI) per hour of sleep for each concentration of N_2O and each patient.

4. Discussion

We found that N_2O in 50% O_2 induced longer and deeper sleep with more frequent respiratory events than 50% O_2. In the first part of the study, N_2O had significant effects on sleep and respiratory pattern as compared to O_2. The second part of the study was designed to investigate whether the effects of N_2O varied with its concentration and showed that (i) widely-used concentrations of N_2O induced EEG patterns similar to physiological EEG sleep in terms of sleep latency, harmonic content, and arousability; and (ii) in subjects documented as normal sleepers N_2O induced respiratory events frequently terminated by EEG arousals. The respiratory events were both central and obstructive and the polysomnographic characteristics were those of central sleep apnea (White, 1985) obstructive sleep apnea, or hypopnea syndrome, with RDI values of about 25 per hour of sleep, similar to those seen in severe sleep apnea syndrome (Partinen and Telakivi, 1992).

Although N_2O can induce post-hyperventilation breath-holding, (Northwood et al., 1991) studies of the respiratory effects of N_2O in low concentrations, such as those used in this study, found stimulating effects, with an increase in tidal volume (Dahan and Ward, 1994; Eckenhoff and Helrich, 1958) and a decrease in inspiratory time (Royston et al., 1983). However, the subjects in these studies were investigated either during wakefulness (eyes open) (Royston et al., 1983) or during induced hyperventilation (Dahan and Ward, 1994; Eckenhoff and Helrich, 1958), which may have modified the breathing pattern. By contrast, in the present study, the subjects were breathing quietly and were allowed to 'sleep'. In this situation, we observed a large number of obstructive and central hypopneas/apneas. Our investigation of correlations between respiratory phenomena and EEG parameters demonstrated that EEG sleep characteristics were consistently present in

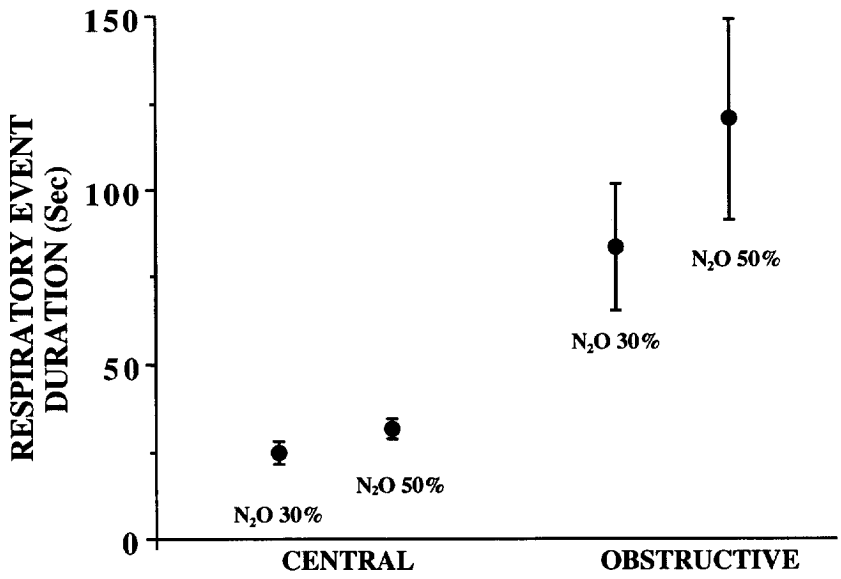

Fig. 6. Duration of respiratory events for both concentrations of N_2O and both types of respiratory events (central and obstructive). There were no statistically significant differences between 30 and 50% N_2O exposure, whereas obstructive events were significantly longer than central events. Values are means ± SEMs.

the subjects who experienced respiratory disturbances under N_2O.

As with most anesthetic drugs, obstructive apnea and hypopnea accounted for most of the respiratory events during N_2O sleep. The effects of anesthetic drugs on upper airway control are complex and depend on many factors (Iscoe, 1988) including the type of drug used, the possibility of additive or synergistic effects between concomitantly administered drugs, individual sensitivity to each drug, upper airway morphology, and position of the head. Most drugs, with the notable exception of ketamine, reduce the inspiratory activity of the upper airway dilating muscles but spare that of the thoracic inspiratory muscles (Hwan et al., 1983).

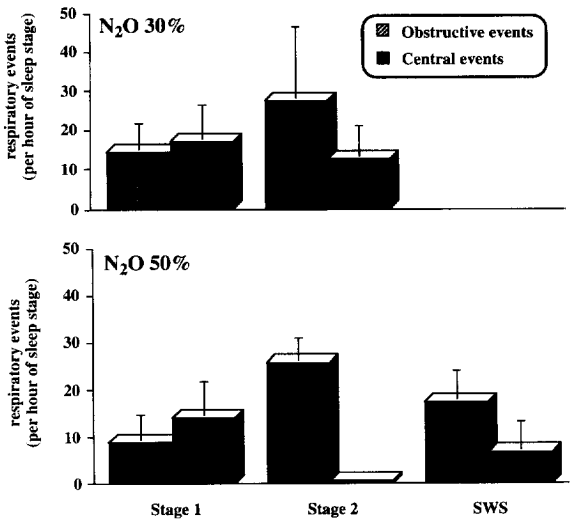

Fig. 7. Distribution of obstructive and central events in each sleep stage in the second study. Respiratory events persisted during SWS when subjects were exposed to N_2O 50% but not to N_2O 30%.

Higher concentrations of anesthetics cause depression of ventilatory control, which results in central apnea (Launois et al., 1990). A surprising finding of our study is that increasing the N_2O concentration did not result in an increase in central respiratory events. This suggests that more than one mechanism may produce central apnea during N_2O exposure, and that these mechanisms may be different from those seen with other drugs. It has been demonstrated that subjects characterized by greater ventilatory responsiveness to hypoxia and hypercapnia are more likely

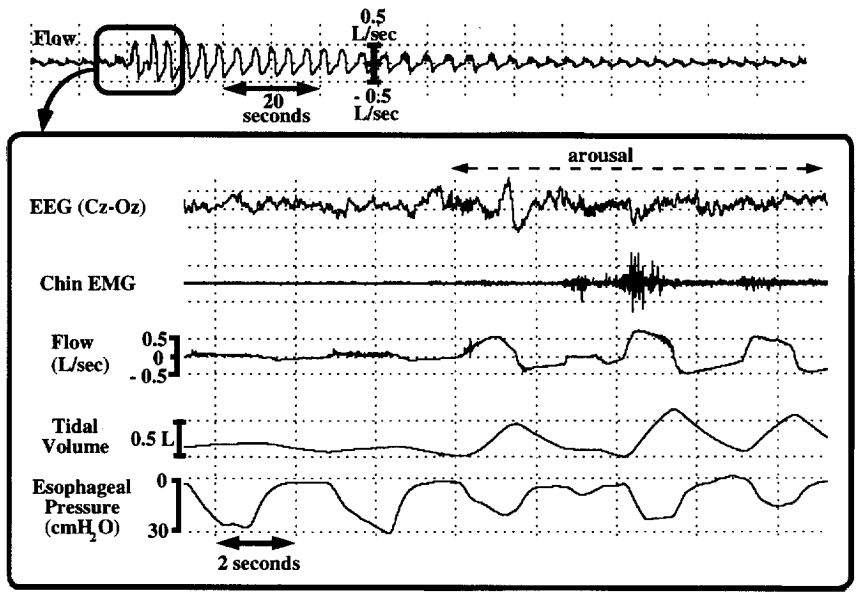

Fig. 8. Polysomnographic recordings in a subject during an episode of obstructive hypopnea under 50% N_2O in O_2. Top panel: flow recording of the transition between obstructed and post-obstructed breathing (solid frame). Corresponding polysomnographic traces are shown in the bottom panel: occlusion ends by an arousal (arrow) with a tonic EMG burst and reappearance of alpha activity on the EEG. Esophageal pressure peak-to-peak amplitude decreases abruptly after arousal, with a simultaneous increase in tidal volume.

to develop central apneas during sleep (Chapman et al., 1988). Furthermore, it has been suggested that central apnea during sleep may be promoted by hyperventilation used to induce sleep (Xie et al., 1994). Since N_2O exposure is known to stimulate ventilation (Eckenhoff and Helrich, 1958; Royston et al., 1983) and ventilatory responses to hypoxia (Dahan and Ward, 1994) and hypercapnia (Eckenhoff and Helrich, 1958), N_2O may precipitate the occurrence of central events. Furthermore, the effects of N_2O are probably complex and consideration should be given not only to its specific effects but also to the possible additive effect of sleep disruption by arousals. Arousals, which occurred more often with 30% N_2O than 50% N_2O and during stage 1 than SWS, may amplify respiratory instability (Khoo et al., 1991; Xie et al., 1994). Arousal from sleep is generally associated with an increase in ventilation, which leads to instability of the chemical feedback system. Thus, the ventilatory oscillations induced by fluctuations in vigilance may interact with those induced by instability of the chemical feedback system that controls ventilation, resulting in facilitation of central respiratory events (Khoo et al., 1991; Xie et al., 1994).

In most cases, respiratory events ceased with arousal. A similar pattern has been reported in sleep apnea syndrome (Guilleminault et al., 1976). In addition, some respiratory events ended without arousal. This was more common during 50% N_2O than 30% N_2O exposure, suggesting that arousability was decreased by N_2O, as it is by hypnotics (Berry et al., 1992). However, the standard scoring methods (ASDA, 1992) that we used to assess EEG arousal do not define as arousals EEG alpha periods shorter than 3 sec, reactive slow waves, or K-complex occurrences, which are accepted as criteria of arousal by some sleep centers. Furthermore, we observed early and frequent SWS disruptions that were not always preceded by EEG arousals but were consistently linked to the end of respiratory events, suggesting that disordered breathing may prevent achievement of deep sedation with stable SWS. Similarly, difficulty in achieving SWS is among the sleep

characteristics of sleep apnea syndrome (Krieger, 1990).

Based on our data, we conclude that N_2O induces pathological breathing patterns in normal volunteers via a mechanism very similar to that observed in sleep disorders (Khoo et al., 1991; Remmers et al., 1978). Several lines of evidence suggest that sedation under N_2O is similar to sleep. First, stage 1 latency was comparable under N_2O and during physiological sleep (Carskadon and Dement, 1988). Second, our comparison of stage 2 EEG tracings between control and 50% N_2O periods found no differences in any frequency band between 0 and 40 Hz (Fig. 4), whereas fast rhythms are frequently observed with other anesthetic drugs (Glaze, 1990). Third, respiratory events affected EEG during N_2O exposure, suggesting persistent arousability. All these similarities with physiological sleep may reflect the relatively low potency of N_2O as compared to other agents (Glaze, 1990). This factor may also explain why two subjects did not sleep during our study. An inability to fall asleep during N_2O exposure may also be related to interindividual variability in the response to N_2O, which is consistent with the minimal alveolar concentration (MAC) concept (Munson et al., 1965). The MAC of N_2O is higher than 100% at ambient pressure (Munson et al., 1965) and the concentration we used was expected to produce only a light hypnotic action.

In conclusion, our study provides additional knowledge on sleep and breathing under N_2O. It demonstrates that N_2O is not without adverse effects on ventilation, contrary to widely-held beliefs. Although N_2O induces poor quality sedation, it may be responsible for sleep-related breathing disorders in normal subjects. In our study, N_2O-induced breathing disorders occurred only during sleep, disrupted sleep by causing frequent arousals and precluded achievement of deep, stable sedation. Our data suggest that non-intubated patients breathing N_2O mixtures during spontaneous ventilation exhibit sleep and breathing patterns similar to those seen in sleep apnea syndrome.

Acknowledgements

This work was supported by INSERM grant no. 92-078. We are grateful to Denise Henry, Antoine Quintel and Richard Morales for their skillful technical assistance.

References

American Sleep Disorder Association, 1992. EEG arousals: scoring rules and examples. A preliminary report from sleep disorders atlas task force and the american sleep disorders association. Sleep 15, 174–184.

Bailey, P., Andriano, K., Goldman, M., Stanley, T., Pace, N., 1986. Variability of the respiratory response to diazepam. Anesthesiology 64, 460–465.

Berry, R.B., McCasland, R., Light, R., 1992. The effect of triazolam on the arousal response to airway occlusion during sleep in normal subjects. Am. Rev. Respir. Dis. 146, 1256–1260.

Carskadon, M.A., Dement, W.C., 1988. The multiple sleep latency test. What does it measure?. Sleep 11, 562–565.

Chapman, K., Bruce, E., Gothe, B., Cherniack, N., 1988. Possible mechanisms of periodic breathing during sleep. J. Appl. Physiol. 64, 1000–1008.

Dahan, A., Ward, D., 1994. Effect of 20% nitrous oxide on the ventilatory response to hypercapnia and sustained isocapnic hypoxia in man. Br. J. Anaesth. 72, 17–20.

Eckenhoff, J.E., Helrich, M., 1958. The effects of narcotics thiopental and nitrous oxide upon respiration and respiratory response to hypercapnia. Anesthesiology 19, 240–250.

Glaze, D.G., 1990. Drug effects. In: Daly, D., Pedley, T. (Eds.), Current practice of clinical electroencephalography. Raven Press, New York, pp. 489–509.

Guilleminault, C., Tilkian, A., Dement, W., 1976. The sleep apnea syndromes. Ann. Rev. Med. 27, 465–484.

Hornbein, T., Martin, W., Bonica, J., Freund, F., Parmentier, P., 1969. Nitrous oxide effects on the circulatory and ventilatory responses to halotane. Anesthesiology 31, 250–260.

Hwan, J., StJohn, W.M., Bartlett, D., 1983. Respiratory related hypoglossal nerve activity: influence of anesthetics. J. Appl. Physiol. 55, 785–792.

Iscoe, S.D., 1988. Central control of the upper airway. In: Mathews, O., Sant'Ambrogio, G. (Eds.), Respiratory Function of the Upper Airway. M. Dekker, New York, pp. 125–192.

Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14, 540–545.

Khoo, M., Gottschalk, A., Pack, A., 1991. Sleep-induced periodic breathing and apnea: a theorical study. J. Appl. Physiol. 70, 2014–2024.

Krieger, J., 1990. Obstructive sleep apnea: clinical manifestations and pathophysiology. In: Thorpy, M. (Ed.), Handbook of Sleep Disorders, pp. 259–284.

Launois, S., Similowski, T., Fleury, B., Aubier, M., Murciano, D., Housset, B., Pariente, R., Derenne, J.-P., 1990. The transition between apnoea and spontaneous ventilation in patients with coma due to volontary intoxication with barbiturates and carbamates. Eur. Respir. J 1, 573–578.

Lofaso, F., Coste, A., Gilain, L., Harf, A., Guilleminault, C., Goldenberg, F., 1996. Sleep fragmentation as a risk factor for hypertension in middle-aged nonapneic snorers. Chest 109, 896–900.

Loomis, A., Harvey, E., Hobart, G., 1938. Distribution of disturbance-patterns in the human electroencephalogram with special reference to sleep. J. Neurophysiol. 1, 413–430.

Montravers, P., Dureuil, B., Desmonts, J.M., 1992. Effect of IV midazolam on upper airway resistance. Br. J. Anaesth. 68, 27–31.

Munson, E.S., Saidman, L.J., Eger, E.I., 1965. Effect of nitrous oxide and morphine on the minimum anesthetic concentration for fluroxene. Anesthesiology 26, 134–139.

Nishino, T., Takizawa, K., Yokokawa, N., Hiraga, K., 1987. Depression of the swallowing reflex during sedation and/or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen. Anesthesiology 67, 995–998.

Northwood, D., Sapsford, D.J., Jones, J.G., Griffiths, D., Wilkins, C., 1991. Nitrous oxide sedation causes post-hyperventilation apnoea. Br. J. Anaesth. 67, 7–12.

Partinen, M., Telakivi, T., 1992. Epidemiology of obstructive sleep apnea syndrome. Sleep 15, S1–S4.

Rechtschaffen, A., Kales, A., 1968. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Washington DC, US Government Printing Office (NIH publication no. 204).

Remmers, J.E., DeGroot, W.J., Sauerland, E.K., Anch, A.M., 1978. Pathogenesis of upper airway occlusion during sleep. J. Appl. Physiol. 44, 931–938.

Royston, D., Jordan, C., Jones, J., 1983. Effect of subanaesthetic concentrations of nitrous oxide on the regulation of ventilation in man. Br. J. Anaesth. 55, 449–455.

White, D., 1985. Central sleep apnea. Med. Clin. N. Am. 69, 1205–1219.

Xie, A., Wong, B., Phillipson, E.A., Slutsky, A., Bradley, D., 1994. Interraction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. Am. J. Respir. Crit. Care Med. 150, 489–495.