

NITROUS OXIDE SEDATION CAUSES POST-HYPERVENTILATION APNOEA†

D. NORTHWOOD, D. J. SAPSFORD, J. G. JONES, D. GRIFFITHS AND C. WILKINS

SUMMARY

We have studied, in six normal subjects, the effect of nitrous oxide sedation on the ventilatory pattern and oxygen saturation using pulse oximetry (Sp_{O_2}) after hyperventilation to an end-tidal carbon dioxide partial pressure (PE'_{CO_2}) of 3 kPa. This value of PE'_{CO_2} was shown to be less than the apnoeic threshold of all these subjects when their ventilation vs PE'_{CO_2} response curves were plotted. All subjects became apnoeic when told to relax following hyperventilation while breathing 75% nitrous oxide for 90 s. Apnoea was defined as cessation of breathing for 20 s or more. The mean duration of apnoea was 78 s (range 29-130 s). All subjects demonstrated arterial desaturation (mean Sp_{O_2} 75%, range 44-87%). In contrast, following hyperventilation with air, no apnoea was seen in any subject, although there was some evidence of desaturation (mean Sp_{O_2} 92.5%, range 88-98%). It was concluded that subjects who are sedated with nitrous oxide behave similarly to those who are anaesthetized rather than to those who were fully conscious, in that they become apnoeic below the apnoeic threshold point. The reduction in Sp_{O_2} after hyperventilation was explained almost entirely by apnoea and may explain abnormalities of respiratory control and hypoxaemia in patients recovering from general anaesthesia or sedation accompanied by hypocapnia. This mechanism may be of importance in obstetric patients after breathing Entonox, when apnoea and hypoxaemia may reduce oxygen delivery to the fetus.

KEY WORDS

Anaesthetics, gases: nitrous oxide sedation. Carbon dioxide: apnoeic threshold, hypocapnia. Measurement techniques: pulse oximetry. Ventilation: hypoventilation, pattern.

Previous work has demonstrated a reduction in arterial oxygen saturation (Sa_{O_2}) in normal subjects after hyperventilation with Entonox (50% nitrous oxide: 50% oxygen) which was greater than that seen after hyperventilation with 50% oxygen in nitrogen [1]. Suggested mechanisms for this include an effect of nitrous oxide on the ventilatory response to carbon dioxide, the ventilatory response to hypoxia, ventilation/perfusion matching and diffusion hypoxia. It is well known that spontaneously breathing but anaesthetized patients become apnoeic if they undergo hyperventilation to a Pa_{CO_2} less than their apnoeic threshold [2]. In contrast, naive awake subjects continue to breathe if they first voluntarily hyperventilate to a Pa_{CO_2} less than the apnoeic threshold and then relax. It is unknown if patients who are sedated with nitrous oxide or other drugs behave as anaesthetized or awake patients. We have investigated, therefore, the possibility that nitrous oxide sedation produced by a brief period breathing nitrous oxide affects ventilatory control when a subject is breathing at an end-tidal carbon dioxide (PE'_{CO_2}) less than the apnoeic threshold so as to produce both apnoea and hypoxaemia.

SUBJECTS AND METHODS

Six normal healthy volunteers gave informed consent to the study, which was approved by the hospital Ethics Committee. The study was des-

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†This work was presented to the Anaesthetic Research Society at the Nottingham Meeting in July 1990.

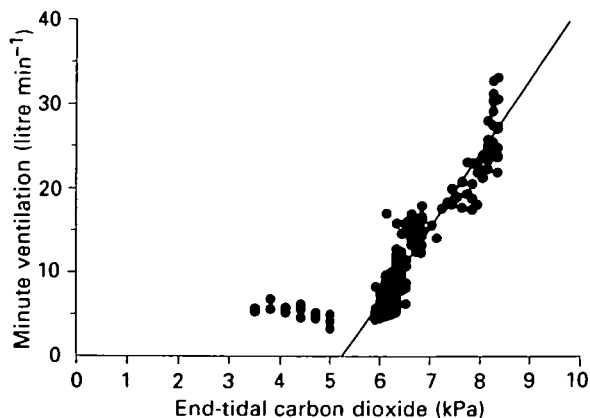


FIG. 1. Quasi steady state carbon dioxide response curve of one subject. Regression line is extrapolated to the X-axis, showing an apnoeic threshold of 5.25 kPa. Note the continuation of ventilation after hyperventilation to a PE'_{CO_2} of 3.5 kPa.

cribed to each subject, but they were not told that apnoea was expected after hyperventilation.

There were three parts to the study: carbon dioxide response curve obtained using a quasi steady state method; hyperventilation with air immediately followed by nitrous oxide; hyperventilation breathing room air. The three parts of the study were obtained in a random fashion on different days.

Subjects were familiarized with the equipment and told that they should comply with orders given during the study periods. These commands would be to commence hyperventilation, to stop hyperventilating and relax completely, or to take a deep breath.

Equipment

The subject was asked to breathe through a mouthpiece whilst wearing a nose-clip. A Fleisch II pneumotachograph was connected to the mouthpiece which led in turn to a low resistance T-piece with one-way valves. The expiratory limb was open to atmosphere and the inspiratory limb was connected to a three-way tap. This allowed delivery of inspired gas to be changed from room air to that held in a 70-litre Douglas bag, which contained a mixture of 75% nitrous oxide in oxygen. The Douglas bag and three-way tap were situated behind the subject. All tubing, including the tap, was low resistance, wide bore. Subjects could not distinguish between inspired gas coming from atmosphere or from the bag. An Ohmeda

6000 multi-gas mass spectrometer, calibrated and used according to the manufacturers' instructions, was used to check the composition of the mixture. The mass spectrometer was used also to sample inspired and end-tidal oxygen, nitrogen, carbon dioxide and nitrous oxide from the mouthpiece. A Validyne CD12 carrier demodulator was used to process the pneumotachograph signal and the output was relayed to a computerized data acquisition system. This enabled tidal volume, ventilatory frequency, inspired and expired times, inspired and expired minute volume and breath number to be measured throughout the study period. An Ohmeda Biox 3700 pulse oximeter was used to monitor arterial oxygen saturation (Sp_{O_2}). All variables monitored were stored on hard disc and displayed contemporaneously by the computer. A copy was obtained on paper using a Brother M-1709 printer.

Carbon dioxide response curves

The breathing system was modified for this part of the study by connecting the pneumotachograph to a Magill circuit fitted with a 6-litre bag. A Boyle anaesthetic machine was used to supply oxygen to the circuit and carbon dioxide was introduced in a stepwise fashion by increasing the flow in 100-ml min^{-1} increments to increase PE'_{CO_2} . Three or four increments were used to generate each curve, each increment taking 4 min.

The same measurements of inspired and expired gas tensions, respiratory variables and Sp_{O_2} were sampled by the computer and stored as before.

Hyperventilation studies

The subject was allowed time to become accustomed to breathing through the apparatus. When PE'_{CO_2} and minute volume were constant, the subject was told to hyperventilate. Large tidal volumes were preferred to rapid rates. When PE'_{CO_2} 3 kPa was reached, that minute volume was maintained for 2 min. PE'_{CO_2} was maintained close to 3 kPa, the subject either increasing or decreasing ventilation appropriately at the command of the observer. At this point, the hyperventilation was continued for a further 90 s with the subject breathing either room air or the 75% nitrous oxide in oxygen mixture.

When this period was complete, the subject was instructed to relax and breathe quietly, the inspired gas being changed to room air if nitrous oxide had been given during hyperventilation.

TABLE I. Duration of apnoea and least Sp_{O₂} in each subject after hyperventilation with air or 75% nitrous oxide. **P* < 0.05 compared with air (Wilcoxon signed rank test)

Subject	Duration of apnoea (s)		Least Sp _{O₂} (%)	
	Air	N ₂ O	Air	N ₂ O
1	—	29	94	81
2	—	130	98	44
3	—	70	88	87
4	—	30	93	77
5	—	120	94	75
6	—	90	88	86
Mean (SD)	—	78 (43)	92.5 (3.9)	75 (15.9)*

The study finished when PE'_{CO_2} , minute ventilation and Sp_{O₂} returned to near normal values. These variables were monitored continuously during the acclimatization period. During the relaxation stage the subject was not disturbed unless Sp_{O₂} decreased to less than 85%, when they were asked to take a single deep breath.

RESULTS

Five males and one female (ages 26–54 yr) took part in the study.

Carbon dioxide response curves

Plots of minute ventilation against PE'_{CO_2} demonstrated a linear relationship, so that a regression line was calculated and the intercept with the *X*-axis was plotted to give the apnoeic threshold (fig. 1).

The mean apnoeic threshold for the six subjects was 5.3 (SD 0.3) kPa (range 4.9–5.4 kPa). Minute ventilation was measured also in each subject after a short period of hyperventilation with air. These values were plotted on the carbon dioxide response curves, producing a “hockey stick” shape to the plot in every subject.

Hyperventilation with nitrous oxide

The inspired mixture was 75% nitrous oxide and 4% nitrogen in oxygen. Subjects breathing nitrous oxide were able to respond to verbal commands given by the observer, although there was impairment of normal cognitive function in all subjects and they later reported a variable period of amnesia which started at the latter stages of breathing nitrous oxide. After hyperventilation, all of the subjects became apnoeic, defined as the cessation of breathing for 20 s or more (table I). Three subjects needed prompting to take deep breaths because of the onset of hypoxaemia (Sp_{O₂}

< 85%). One did not respond immediately to the command to take a breath but removed the mouthpiece and nose-clip, when further prompting restored spontaneous ventilation. The period of apnoea sustained by this subject was 130 s; this was included in the results table.

Plots of minute ventilation and Sp_{O₂} against time (fig. 2) show that arterial desaturation corresponded to periods of hypoventilation which included apnoea. The mean value of the least saturation noted following nitrous oxide breathing was 75 (15.9)% and occurred at the end of apnoea (table I).

The mean PE'_{CO_2} noted when spontaneous ventilation returned was 4.4 (0.4) kPa.

Hyperventilation with air

Although minute ventilation was reduced after hyperventilation, no periods of apnoea were noted.

The decrease in minute ventilation in the 3-min period after hyperventilation with air and nitrous oxide may be seen in figure 3. The presence of nitrous oxide clearly depressed minute ventilation and the values in the first 60 s represent virtual apnoea. The mean reductions in minute ventilation after air or nitrous oxide were significantly different (*P* < 0.05, paired *t* test).

Sp_{O₂} also decreased during the period after hyperventilation. The mean of the smallest values was 92.5 (3.9)%. This was significantly different from the value of 75% obtained after exposure to nitrous oxide (*P* < 0.05, Wilcoxon signed rank test) (table I).

DISCUSSION

During measurements for the carbon dioxide response curves, ventilation increased in a linear manner with increasing concentrations of inspired

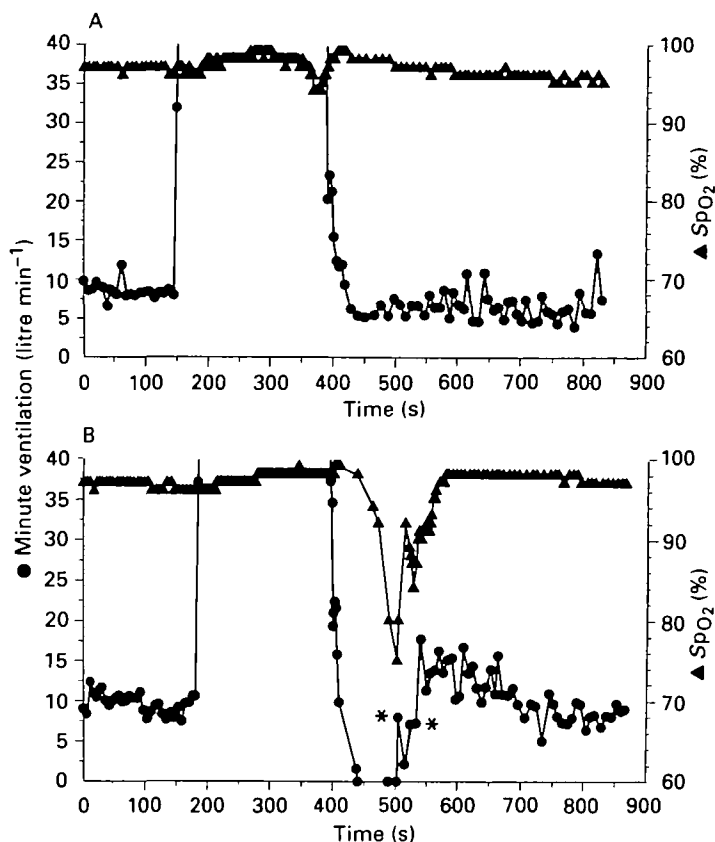


FIG. 2. Plots of minute ventilation (●) and arterial oxygen saturation (▲) against time. Curves show initial acclimatization period, hyperventilation and then relaxation: A following hyperventilation with air; B following hyperventilation first with air then for 90 s with nitrous oxide. *Forced breath.

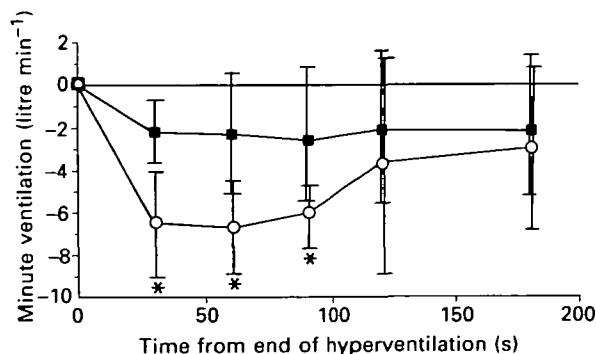


FIG. 3. Change in minute ventilation against time immediately after a period of hyperventilation with air (■) and with nitrous oxide (○). Bars represent 95% confidence limits. * $P < 0.05$ (paired Student's t test).

carbon dioxide over a wide range. Severe hypercapnia is reported to depress ventilation, but this extreme was avoided in this study and

extrapolation of the curve to the abscissa indicates a concentration of carbon dioxide at which ventilation should become zero—the apnoeic threshold. This, of course, assumes that the $\dot{V}_E$ against PE'_{CO_2} response is linear at values less than the normal PE'_{CO_2} .

In the anaesthetized, spontaneously breathing subject, ventilation is studied easily and there is no doubt that hyperventilation to less than the apnoeic threshold induces apnoea in this state [2]. Inducing hypocapnia in awake human subjects and obtaining this threshold experimentally has proved difficult and conflicting results have been reported in the literature. For example, in the awake state hyperventilation was reported to be followed by apnoea [3], a normal ventilatory pattern [4] or hyperventilation [5]. Other studies have experienced all these various responses in their study groups [6, 7]. Some of the work has been criticized because preconceived ideas by the

subjects participating in the study could have influenced the results [8]. Study designs have differed also, especially the degree of hypocapnia reached and the duration for which it was maintained. In Bainton and Mitchell's study [7], three of 16 awake subjects demonstrated apnoea after hyperventilation on the first occasion they were studied, but they reported that 15 of 16 became apnoeic after further trials. However, their definition of apnoea included a "missed breath" and although this period of apnoea was lengthened—by repeating the study on successive days—only three subjects demonstrated apnoea by our criteria.

The results from all the subjects in our study showed no apnoeic periods following hyperventilation with air and all our subjects continued breathing at hypocapnia, which supports the concept of the "hockey stick shaped" carbon dioxide response curve (fig. 1). Nielsen and Smith [9] demonstrated this first with hypoxic hypocapnic breathing, and it suggests that there is a threshold above which carbon dioxide concentration must increase before ventilation is stimulated. Fink [8] has proposed that a "wakefulness stimulus" maintains ventilation below this threshold, but the important transition zone between anaesthesia and normal consciousness has not been investigated. Our results showed that sedation induced by a brief period of hyperventilation with nitrous oxide caused apnoea when the PE'_{CO_2} was less than the apnoeic threshold. At first sight, it is surprising that the mean PE'_{CO_2} value on return of spontaneous breathing following apnoea was 4.4 kPa, which is 0.9 kPa less than our mean measured apnoeic threshold. This could be a result of the appearance of the respiratory stimulant effects of nitrous oxide as it was being eliminated [10]. Alternatively, our estimate of the apnoeic threshold may have been too great because of a shift in the response curve to the right. This may occur using a dynamic method of measurement of the carbon dioxide response (a quasi static method), as a lag in the ventilatory response occurs as a result of circulatory times and the state of the central chemoreceptors and respiratory centres. Carbon dioxide partial pressures here may have been initially smaller than normal at the start of the assessment because of a tendency shown by subjects to increase their minute ventilation when breathing via a mouth-piece and nose-clip [11, 12]. Thus a mild carbon dioxide depletion would have occurred during the

acclimatization period and restoration of carbon dioxide concentrations in the respiratory centres may have moved the curve to the left again.

It is interesting to note that, at the eucapnic region of the curve, a decreased ventilatory sensitivity to a low inspired concentration of carbon dioxide has been reported [13]. This may imply that the response curve may have two "dog legs" in its course not one, and the apnoeic threshold obtained by extrapolation would move again to the left. Nunn [14] has proposed a shift of 0.7 kPa in the carbon dioxide response curve if the discrepancy between the PE'_{CO_2} at the return of spontaneous ventilation and that at the apnoeic threshold is a result of measurement by dynamic methods. This correction would make our mean apnoeic threshold 4.5 kPa, which is close to the mean PE'_{CO_2} at the return of spontaneous breathing.

A reduction in Sp_{O_2} occurred in the period after hyperventilation in almost all subjects. This occurred after air or nitrous oxide breathing, but was most profound after apnoeic periods which occurred only after exposure to nitrous oxide. Although end-tidal oxygen was undoubtedly diluted by the washout of nitrous oxide, its contribution to the production of hypoxaemia has been shown to be very small in normal healthy subjects [15–17]. It is conceivable that, during the period of apnoea, there is no net transfer of nitrous oxide from blood to alveoli, without ventilation to provide a washout gradient. The degree of oxygen desaturation reached by each individual during apnoea is a function of metabolic rate and FRC, which acts as a reservoir of oxygen. Without knowing these two variables, it is not possible to predict accurately the degree of desaturation to expect following a period of apnoea. However, if it is assumed that FRC is 2 litre and oxygen consumption is 200 ml min⁻¹, it can be calculated that during apnoea the Sp_{O_2} would decrease to about 80% after 80 s. Our result, a mean Sp_{O_2} of 75% with a mean duration of apnoea of 78 s, is consistent with this prediction and suggests that apnoea is the predominant cause of the hypoxaemia noted in this study.

In conclusion, we have shown that the reduction of PE'_{CO_2} to less than the apnoeic threshold in normal subjects in the presence of nitrous oxide-induced sedation causes apnoea and hypoxaemia. The influence of other forms of sedation and that of drowsiness or sleep remains to be investigated further. It is worthy of note that Fink

reported two of his subjects "dozed off" whilst hypocapnic and immediately became apnoeic [4]. Spontaneous ventilation was restored when they were awakened by an auditory stimulus. Patients with brain damage also show apnoea after hyperventilation [18].

The study clearly demonstrates the effects of sedation on ventilatory control, predominantly neural control (awake) switching to predominantly chemical control (asleep or sedated). This information may have relevance in the occurrence of apnoea in a wide range of conditions from "cot death" to cardiorespiratory arrest during clinical procedures performed under sedation, especially if the patient is hypocapnic, from fear or pain. It may be a particular problem also in managing obstetric patients with Entonox. Post-hyperventilation apnoea following Entonox may be associated with hypoxaemia and impaired oxygenation of the fetus. It behoves clinicians to observe such patients closely and the use of pulse oximetry would be of benefit in such circumstances. It also supports the continued use of carbon dioxide cylinders on anaesthetic machines, which was the subject of a recent editorial in the Journal [19].

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