Effects of 20% nitrous oxide on the ventilatory response to hypercapnia and sustained isocapnic hypoxia in man

A. Dahan and D. S. Ward

SUMMARY
To examine the effects of a subanaesthetic concentration of nitrous oxide on ventilation, we have studied the ventilatory response to carbon dioxide and isocapnic hypoxia (F\textsubscript{N\textsubscript{2}O} 0.2). In five subjects, we performed step decreases in P\textsubscript{E}CO\textsubscript{2} to 6.7 kPa for 15 min and step increases in P\textsubscript{E}CO\textsubscript{2} (A\textsubscript{P}CO\textsubscript{2} 1.5 kPa). The carbon dioxide responses were partitioned into a fast peripheral and slow central component. All control oxygen responses were biphasic: the acute hypoxic response was 7.2 (4.6) litre min\textsuperscript{-1} and the subsequent decline 4.2 (2.6) litre min\textsuperscript{-1}. With nitrous oxide, the acute hypoxic response was 10.3 (6.7) litre min\textsuperscript{-1}, but was followed by a non-significant decline of 3.8 (3.0) litre min\textsuperscript{-1} because of a progressive increase in breathing frequency in the hypoxic period. None of the variables obtained from the carbon dioxide responses differed between groups. Our data indicate that a subanaesthetic concentration of nitrous oxide did not affect the peripheral chemoreflex loop. The hyperventilatory response to prolonged hypoxia was sustained better with nitrous oxide compared with control. (Br. J. Anaesth. 1994; 72: 17-20)

KEY WORDS

Yacoub and colleagues examined the effects of 40% nitrous oxide on the hypoxic and the hypercapnic ventilatory responses in man [1]. They observed no effect on the hypercapnic ventilatory response, while the hypoxic ventilatory response was depressed by more than 60%. They argued that these findings are best explained by the depressant effect of nitrous oxide on the function of the peripheral chemoreceptors or their afferent nerves. Knill and Clement obtained similar results with 0.1 MAC nitrous oxide [2]. They observed a 40% decrease in carbon dioxide response and hypoxic response. Studies with other anaesthetics produced similar results. Knill's group showed that halothane, enflurane and isoflurane depressed the hypoxic ventilatory response at subanaesthetic concentrations (0.1 MAC) by 50-70% [3-5]. However, Temp, Henson and Ward found no effect of 0.1 MAC isoflurane on the hypoxic ventilatory response [6]. Also, 0.9 MAC isoflurane did not decrease the response to hypoxia [7]. Temp's group argued that these findings differed from those of Knill's group because of the different approach in applying the hypoxic stimulus. In common with Yacoub's group, Knill and colleagues used the progressive hypoxic technique of Weil [1-5, 8], while Temp and co-workers used a rapid decrease in end-tidal P\textsubscript{O\textsubscript{2}} (P\textsubscript{E}O\textsubscript{2}) which was maintained for 20 min [6]. The biphasic nature of the ventilatory response to isocapnic hypoxia is observed only when imposing a sudden decrease in P\textsubscript{E}O\textsubscript{2} and keeping this decreased value constant. This response shows an initial period of hyperventilation (of peripheral origin) followed, after 5 min, by a slow decline in ventilation (\textit{V\textsubscript{I}}) (caused by the central depressant effects of hypoxia) [9, 10]. Therefore, the response to a hypoxic ramp does not discriminate between the peripheral and central effects of hypoxia and hence the influence of a drug might have on these sites.

The main aim of this study was to investigate the influence of a subanaesthetic concentration of nitrous oxide (F\textsubscript{N\textsubscript{2}O} 0.2) on the respiratory control system, by applying square-wave changes in end-tidal P\textsubscript{CO\textsubscript{2}} (P\textsubscript{E}CO\textsubscript{2}) and step decreases in P\textsubscript{E}O\textsubscript{2}. Using a mathematical model, we partitioned the hypercapnic response into two components [11]. This model separates the breath-to-breath response into a fast component from the peripheral and a slow component from the central chemoreflex loop, characterized by a carbon dioxide sensitivity, time constant, time delay and off-set. It has been used successfully to study the respiratory control system in man and animals [11, 12]. To discriminate between the initial hyperventilatory response and the subsequent decline in \textit{V\textsubscript{I}}, the response to hypoxia was examined over a 15-min period.

SUBJECTS AND METHODS
We studied five healthy subjects (male; mean age 24 yr) after receiving approval by the local Ethics Committee. All subjects gave written informed consent. They were asked to refrain from stimulants

ALBERT DAHAN, M.D., PH.D., Department of Anesthesiology, University Hospital Leiden, PO Box 9800, 2300 RC Leiden, The Netherlands. DENHAM S. WARD, M.D., PH.D., Departments of Anesthesiology and Electrical Engineering, UCLA School of Medicine, Los Angeles, CA, U.S.A. Accepted for Publication: August 4, 1993.* Present address: Department of Anesthesiology, University of Rochester School of Medicine, 601 Elmwood Ave, Box 604, Rochester, New York 14642, U.S.A.

Correspondence to A.D.
and depressant substances for at least 12 h before the study. Hypoxic and hypercapnic experiments were performed on different days (sessions). Each session consisted of a 1-h rest period, followed by one control and one nitrous oxide study (run). The time between runs was 60 min, between sessions at least 1 week. To study the ventilatory responses we used the "dynamic end-tidal forcing" technique [11]. This technique enables us to force the end-tidal oxygen and carbon dioxide tensions to follow a specific pattern.

In the hypoxia studies, after a period of steady-state $V_l$ with $P'_cO_2$, 14.5 kPa and $P'_cCO_2$ increased to 0.1–0.2 kPa greater than resting values, $P'_cO_2$ was rapidly decreased to 6.7 kPa and kept constant for 15 min. Thereafter, hypoxia was introduced ($Fi_O_2=0.8$) for 10 min to eliminate the residual effects of hypoxia [13].

In hypercapnia studies, after a period of steady-state $V_l$ ($P'_cCO_2$, 0.1–0.2 kPa greater than resting values, $P'_cCO_2$, was increased by 1.5 kPa within one or two breaths, maintained at this value for 8 min and then returned to its original value for another 8 min.

Before a run, ECG monitoring was started and an ear probe of a pulse oximeter (Ohmeda Biox 3700, U.S.A.) was applied. During the run, both the subject breathed through a mouthpiece and wore a nose clip. Inspired and expired gas flows were measured with a turbine flow meter (Sensor Medics VMM-1, U.S.A.). The oxygen, carbon dioxide and nitrous oxide concentrations of inspired and expired gas were measured with a mass-spectrometer (Perkin Elmer 1100 MGA, U.S.A.). All signals were recorded on a strip-chart recorder and digitized (50 Hz). Tidal volume ($V_t$), ventilatory frequency ($f$), $V_l$, $P'_cCO_2$, $P'_cO_2$, and end-tidal nitrous oxide partial pressure ($P'_cNO_2$) were calculated and stored on a breath-to-breath basis.

The mouthpiece and flowmeter were connected to a mixing chamber. The gas flow to the chamber was controlled by two servo-valves, by which the flow of oxygen and carbon dioxide could be set as desired. The main flow of gas in the mixing chamber consisted of nitrogen, room air, or both. A personal computer (IBM AT, U.S.A.) provided control signals to the servo-valves, so that the composition of the inspiratory gas mixture could be adjusted to allow $P'_cCO_2$ and $P'_cO_2$ to follow a dynamic pattern in time. When appropriate, nitrous oxide was added to the mixing chamber, and the flow adjusted manually to obtain a constant inspired concentration of 20%. In the nitrous oxide runs, the subjects began inhaling the gas 10 min before the data collection started (washin period).

Data analysis

In the hypoxia studies, all runs were evaluated by taking the mean values of the final 3-min period before hypoxia (period A), minutes 3–5 of hypoxia (period B) and minutes 12–15 of hypoxia (period C). We defined the difference in $V_l$ between periods B and A as the "acute hypoxic response" and that between periods B and C as the "hypoxic ventilatory decline".

To partition the ventilatory response into components arising from the central and peripheral chemoreflex loop in hypercapnia studies, we analysed the breath-to-breath data with a two-compartment model (see Introduction) [11,12]. We measured carbon dioxide sensitivity of the central chemoreceptors, central carbon dioxide sensitivity of the peripheral chemoreceptors and the off-set or extrapolated $P'_cCO_2$ of the steady-state $V_t$-PE'CO$_2$ response at zero $V_l$.

To test for a significant difference between control and nitrous oxide studies, a Student's paired $t$ test was performed on the acute hypoxic response, hypoxic ventilatory decline, peripheral carbon dioxide sensitivity ($G'_p$), central carbon dioxide sensitivity ($G'_c$), ratio $G'_p/G'_c$ and off-set. The data from periods A, B and C ($P'_cCO_2$, $P'_cO_2$, $P'_cNO_2$, $V_l$, $V_t$ and $f$) were subjected to (two-way analysis of variance with post-hoc multiple comparisons with Student-Newman-Keuls test. $P \leq 0.05$ was taken as significant. All values are mean (SD).

RESULTS

All subjects completed the two sessions without difficulty or side effects. The end-tidal nitrous oxide tensions measured were between 17.7 and 18.0 kPa in the nitrous oxide studies. This caused the subjects to be lightly sedated and easily arousable.

Hypoxia studies. The mean group responses are shown in figure 1 and mean values of the variables in table I. The relative large SD of $P'_cCO_2$ reflects inter-subject variability. The average change for each subject was less than 0.05 kPa throughout one experiment. During control, all subjects showed the typical biphasic response after exposure to hypoxia. The rapid increase in ventilation (acute hypoxic response: 7.2 (4.6) litre min$^{-1}$) was followed by a significant decline in $V_l$ (hypoxic ventilatory decline):

![Figure 1. Comparison of the mean (SD) ventilatory response of all subjects to sustained hypoxia in control (●) and 30% nitrous oxide (○) studies. Plot represents the ventilation ratio obtained by dividing all breath-to-breath values by the mean $V_l$ of period A. Each point represents a 5-s average of the breath-to-breath $V_l$ ratio. Control: period A (3 min before hypoxia): 100% ; period B (3-min period after the first 2 min of hypoxia): 162 (18%) ; period C (12–15 min of hypoxia): 125 (27%). Nitrous oxide: period A: 100% ; period B: 180 (28%) ; period C: 165 (35%).](image-url)
MAC values of 0.17 in our study and 0.33 in that of about 35 kPa would be obtained, giving respective tidal nitrous oxide values. If we extrapolate our data to an inspiratory fraction of 0.4, an end-tidal value of 0.1 MAC nitrous oxide reported by Yacoub and colleagues [1] and Knill and Clement [2], respectively, are in contrast with our findings of no significant effect on the acute hypoxic response or on the peripheral carbon dioxide sensitivity with 20% nitrous oxide. Yacoub's group did not state the end-tidal nitrous oxide. Yacoub's group did not state the end-tidal nitrous oxide. 

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A drug that does not affect the peripheral chemoreflex loop but increases the magnitude or speed of onset of the central depressive effects of hypoxia produces a depressed response to a hypoxic ramp compared with control. However, our hypoxic runs did not show an effect by nitrous oxide on the magnitude or onset of hypoxic ventilatory decline. Another reason for the difference in results could be that a slow hypoxic ramp by itself gives a dissimilar response compared with a sudden step to hypoxia [15, 16]. To obtain the hypercapnic ventilatory response, we used a steady-state technique. This avoids the methodological problems mentioned above. Furthermore, our technique provided information on the contribution to $V_t$ of the peripheral chemoreflex loop. Although not significant, both the acute hypoxic response and the peripheral carbon dioxide sensitivity showed a tendency to increase with 20% nitrous oxide. Nitrous oxide causes an increase in sympathetic outflow [17]. It is possible that the responses mediated by the peripheral chemoreceptors are enhanced by nitrous oxide through an increase in beta adrenergic activity.

We did not observe any difference in absolute value of hypoxic ventilatory decline between control and nitrous oxide studies. As it seems that the magnitude of the hypoxic ventilatory response is related to the acute hypoxic response [9], it is possible also to express the hypoxic response as a ratio of hypoxic ventilatory decline to acute hypoxic response ($\Delta V_T / \Delta V_{T,c}$). In the control runs, this ratio was 58 (25), compared with 30 (10) in the nitrous oxide runs ($P < 0.05$, paired $t$ test). This indicates that the hyperventilatory response was better sustained with 0.15 MAC nitrous oxide during 15 min of hypoxia.

It is interesting to observe the effects of nitrous oxide on the breathing pattern of the hypoxic response. The hypoxic ventilatory decline observed in the control group was caused by a reduction in $V_t$ with minimal changes in ventilatory frequency. This is typical for the response to sustained hypoxia in man [9, 13]. Although, in the nitrous oxide studies, $V_t$ declined by 200 ml from period B to C, it did not quite reach the level of significance. The breathing frequency was constant in the period before hypoxia, but increased progressively during hypoxia (table I). With respect to breathing pattern, the increase in breathing frequency caused the decrease in the ratio of hypoxic ventilatory decline to acute hypoxic response with nitrous oxide (a better sustained acute hypoxic response via progressive hyperpnoea). In common with other inhalation anaesthetics, nitrous oxide increases breathing frequency by an effect on the respiratory centres in the central nervous system [14]. In the nitrous oxide studies, the breathing

### Table I. Ventilatory response to hypoxia (mean (SD)). A = 3-min period before hypoxia; $B = 3$-min period following the first 2 min of hypoxia; $C = 12$-$15$ min of hypoxia. $P < 0.05$ compared with:

<table>
<thead>
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<th>Period A</th>
<th>Control</th>
<th>N₂O</th>
<th>Control</th>
<th>N₂O</th>
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<tbody>
<tr>
<td>$P_{ET,CO_2}$(kPa)</td>
<td>5.8 (0.3)</td>
<td>5.7 (0.3)</td>
<td>5.7 (0.4)</td>
<td>5.7 (0.2)</td>
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<tr>
<td>$P_{ET,N_2O}$(kPa)</td>
<td>13.8 (0.1)</td>
<td>6.6 (0.03)</td>
<td>6.6 (0.1)</td>
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<tr>
<td>$P_{ET,N_2O}$(kPa)</td>
<td>13.7 (0.1)</td>
<td>6.6 (0.03)</td>
<td>6.7 (0.04)</td>
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4.2 (2.6) litre min⁻¹. These changes occurred through changes in $V_t$, with minimal changes in ventilatory frequency. The small increase in ventilatory frequency after induction of hypoxia was not sustained during sustained hypoxia. In the nitrous oxide group, the sharp increase in $V_t$ (acute hypoxic response: 10.3 (6.7) litre min⁻¹) was followed by a non-significant decline (hypoxic ventilatory decline: 3.8 (3.0) litre min⁻¹). This response was caused by changes in $V_t$ and $f$; ventilatory frequency was constant throughout the pre-hypoxia period and the significant increase of almost 4 b.p.m. occurred only in hypoxia. Between control and nitrous oxide runs, the acute hypoxic response and hypoxic ventilatory decline did not differ.

#### Hypercapnia studies

The peripheral carbon dioxide sensitivities averaged 7.4 (4.3) litre min⁻¹ kPa⁻¹ (control) and 7.9 (3.8) litre min⁻¹ kPa⁻¹ (nitrous oxide) (ns); mean central carbon dioxide sensitivities were 15.0 (5.3) litre min⁻¹ kPa⁻¹ (control) and 18.1 (8.9) litre min⁻¹ kPa⁻¹ (nitrous oxide) (ns). The ratio $G_{AV}/G_{C}$ was 0.49 (0.20) for control and 0.56 (0.36) for nitrous oxide runs (ns). The values of the off-sets for control and nitrous oxide runs were 4.8 (0.3) kPa and 4.9 (0.4) kPa (ns).

#### DISCUSSION

The large reduction in hypoxic ventilatory response by 65% with 40% nitrous oxide and by 40% with 0.1 MAC nitrous oxide reported by Yacoub and colleagues [1] and Knill and Clement [2], respectively, are in contrast with our findings of no significant effect on the acute hypoxic response or on the peripheral carbon dioxide sensitivity with 20% nitrous oxide. Yacoub's group did not state the end-tidal nitrous oxide values. If we extrapolate our data to an inspiratory fraction of 0.4, an end-tidal value of about 35 kPa would be obtained, giving respective MAC values of 0.17 in our study and 0.33 in that of Yacoub's group [14]. It is possible that this explains the large discrepancy in hypoxic responses. In contrast, the data of Knill and Clement were obtained at 0.1 MAC nitrous oxide, clearly less than our MAC value. The speed of application of the hypoxic stimulus must also be considered in explaining these differences. The groups of Yacoub and Knill performed a slow decline in oxygen over 10 min, while we performed a fast reduction in $P_{ET}$.

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frequency during period A did not differ from control. The reason for the lack of increase may be the small concentration used in our procedure. It seems reasonable to attribute the progressive tachypnoea with nitrous oxide to its sympathomimetic effects. The combination of moderate hypoxia and 20% nitrous oxide may have resulted in sufficient beta adrenergic activity to cause progressive tachypnoea and hence preservation of the acute response to hypoxia. Aminophylline and moderate exercise produce similar patterns of breathing during sustained isocapnic hypoxia [18, 19]. This suggests a similar mechanism for the maintenance of the hypoxic response. Further studies are necessary to see if this occurs at the peripheral chemoreceptors or within the central nervous system.

In summary, we found no effect of a subanesthetic concentration of nitrous oxide on the peripheral chemoreflex loop, in contrast with Yacoub and colleagues [1] and Knill and Clement [2]. This discrepancy cannot be ascribed easily to differences in methods. The effects of 0.17 MAC nitrous oxide on the peripheral chemoreflex loop are consistent with the effects of 0.1 MAC isoflurane [6]. Furthermore, the hyperventilatory response to prolonged hypoxia seemed to be sustained better with nitrous oxide, as a result of a progressive increase in breathing frequency during hypoxia.

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