EFFECTS OF NITROUS OXIDE ON THE RESPIRATORY PATTERN OF SPONTANEOUSLY BREATHING CHILDREN

A Re-appraisal

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The effect of the withdrawal of nitrous oxide from the inspired gas mixture in 10 spontaneously breathing children during nitrous oxide–halothane anaesthesia was described in a previous communication (Wren et al., 1984). The principal changes observed in that study were a 32.7% increase in minute ventilation, and an 8.4% decrease in alveolar carbon dioxide concentration. These effects were produced solely by a 42.7% increase in tidal volume, as no significant change in respiratory rate was observed.

That communication suggested that the changes in ventilation were a direct effect of the decrease in alveolar nitrous oxide concentration. In subsequent discussion, however, an alternative mechanism was proposed. As the tidal volume signals recorded were derived by electronic integration (Mercury VP5) of the inspiratory flow signal from a (Fleisch II) pneumotachograph, it was suggested that the large inflow of oxygen which occurs during nitrous oxide elimination would, by producing a large increase in the inspiratory flow signal, result in a false increase in the tidal volume signal. In addition, it was suggested that this possibility could be elucidated by a further study in which the alveolar nitrous oxide concentration would be decreased in two stages, allowing equilibration to occur at each stage. Informed consent was obtained from the parents of all children included in all of these studies, which had the approval of the hospital Ethics Committee.

Half of the children in the first study had received papaveretum 0.4 mg kg⁻¹ i.m. as preoperative medication and the other half received thiopentone per rectum. To avoid bias resulting from the different drugs used in premedication, it was decided that the five children (aged between 7 and 11 yr (mean 9.6 yr); body weight 22–38 kg (mean 30.8 kg)) who had received papaveretum in that study (now designated phase I) should be compared with a new group of comparable children, premedicated in the same way, in whom
the effects of a staged reduction of alveolar nitrous oxide would be studied before surgery commenced. This new study was designated phase II.

PHASE II

PATIENTS AND METHODS

Anaesthetic management

The six healthy children included in this study varied in age from 7 to 12 yr (mean 9.17 yr) and in body weight from 28 to 46.5 kg (mean 36.4 kg). Premedication was with papaveretum 0.4 mg kg\(^{-1}\), and anaesthesia was induced with thiopentone 3–4 mg kg\(^{-1}\) i.v., with tracheal intubation facilitated by suxamethonium 1–2 mg kg\(^{-1}\) i.v. Anaesthesia with spontaneous ventilation was maintained with nitrous oxide and halothane in oxygen, delivered from a standard anaesthetic machine (Penlon Ltd) and standard vaporizers (Dräger Vapor, Fluotec MK III) through a Bain co-axial breathing system.

Throughout each study the dialled halothane concentration was altered as required to maintain a constant end-tidal halothane concentration \((E'_\text{hal})\) of 0.9%.

The fresh gas flows \((V_F)\) used were derived by adding to the flows recommended to prevent rebreathing with the Bain system (Steward, 1979), a volume of 600 ml min\(^{-1}\) to replace the volume extracted from the circuit by the three gas analysers used.

A standard procedure for altering nitrous oxide concentration was used throughout the series. When spontaneous ventilation was established, the inspired mixture was adjusted to maintain a constant end-tidal nitrous oxide concentration \((E'_{\text{N}_2\text{O}})\) of 65% and end-tidal halothane \((E'_{\text{hal}})\) of 0.9%. When these end-tidal values had been stable for 15 min, the data of five sequential breaths were recorded. The \(E'_{\text{N}_2\text{O}}\) was then reduced by approximately 50%, while the original total \(V_F\) was restored with oxygen, and the dialled halothane concentration adjusted to maintain \(E'_{\text{hal}}\) at 0.9%. This procedure involved considerable difficulty, and invariably required an increase in the dialled halothane concentration. Following 15 min of breathing this mixture, a further five sequential breaths were recorded. The nitrous oxide was then withdrawn completely, the total \(V_F\) restored with oxygen, and the dialled halothane concentration again adjusted to maintain a constant \(E'_{\text{hal}}\) of 0.9%. Following 15 min of breathing this mixture, a final five sequential breaths were recorded.

In addition to detailed monitoring of respiratory function, the progress of the children during anaesthesia was monitored clinically by another anaesthetist, with continuous monitoring of electrocardiogram, arterial pressure and inspired oxygen concentration \((F_{1_{\text{O}_2}})\).

Respiratory pattern and gas analysis

The equipment and calibration procedures used for the measurement of respiratory flows and volumes, and the gas analysers were as described by Wren and colleagues (1984).

Computer analysis and recording of data

As in the phase I study, data from the pneumotachograph and the gas analysers were fed into a computer (Apple II) via a high speed analog-to-digital converter (Mountain Computer). However, the computer program used in the phase I study had been significantly upgraded for, in addition to identifying, recording and graphically displaying valid breaths in real time, it performed several other functions.

It applied all necessary correction factors to the data in real time. This was a major advance, since it made possible the display of corrected data in the operating theatre. In addition, the new program produced a composite file of corrected data (in addition to a raw data file). This composite file was formatted in such a way that it could be readily transferred, via the Apple's RS232 interface, to another computer which ran a CP/M operating system (BBC Microcomputer with Z80 second processor). Once in this CP/M environment, all necessary numerical manipulations and statistical analysis could be performed rapidly and accurately using a commercial statistical programme (Microstat, Eco-soft Inc.).

A program has also been written which facilitated the calibration of the analysers and pneumotachograph. In addition to making this process easier and more accurate, it recorded a file with the patient data. This file had two functions: it modified the correction factors so as to compensate for any slight miscalibration and also provided a permanent record of the accuracy and linearity of the analysers and pneumotachograph which could be scrutinized at a later date, should there be doubt about the validity of any recorded data.

An important feature of this system is that it
Table I. The alveolar concentrations of nitrous oxide and halothane and the tidal volumes (mean (SD)) recorded in three comparable groups of children during phase I (nitrous oxide elimination as a single stage procedure); phase II (nitrous oxide elimination in two stages with a constant end-tidal halothane concentration); phase III (a 16% reduction in end-tidal halothane concentration with a constant end-tidal nitrous oxide concentration)

<table>
<thead>
<tr>
<th></th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>65</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>Alveolar concn (%)</td>
<td>1.06</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Tidal volume (ml kg⁻¹)</td>
<td>3.38 (0.32)</td>
<td>4.04 (0.48)</td>
<td>3.63 (1.28)</td>
</tr>
<tr>
<td></td>
<td>3.85 (1.23)</td>
<td>3.88 (1.24)</td>
<td>3.39 (0.62)</td>
</tr>
<tr>
<td></td>
<td>3.88 (0.58)</td>
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records every feature of each breath which it
analyses, in addition to the specific features which
are of interest at the time of acquisition, thereby
permitting their retrieval at a later stage if this
becomes necessary. This facility proved very
useful in the present study. From the data of each
breath, the computer extracted several variables,
including tidal volume per kilogram body weight
\((VT \text{ kg}^{-1})\), minute volume per kilogram body
weight \((V'E \text{ kg}^{-1} \text{ min}^{-1})\), respiratory frequency and
inspired and expired carbon dioxide tension.

**Statistical analysis**

The type of statistical analysis used was similar
for all parts of the study. In the first instance, the
entire data from each part were subjected to a
"normal curve goodness of fit" test, the results of
which did not justify the assumption that the
population from which the samples had been
drawn was normally distributed. Moreover, since
the sample sizes were not large enough to warrant
appeal to the Central Limit Theorem, a non-
parametric test was most appropriate, and the
Kruskal–Wallis one-way Anova by Ranks test was
used. All necessary statistical calculations were
performed by a computer running the Microstat
(Ecosoft Inc.) software package.

**RESULTS**

For clarity of presentation and ease of comparison,
the description of results will be confined to the
variable of major consistent change, tidal volume,
as related to the alveolar nitrous oxide concentration
expressed in the form of the \(FA/FA_0\) \(N_2O\) ratio
(Eger, 1974); that is, the alveolar nitrous oxide
concentrations expressed as a fraction of the
concentration which pertained before the with-
drawal of nitrous oxide.

The decrease in alveolar nitrous oxide concen-
tration was associated with a 7% increase in tidal
volume, mean \(VT\) increased from 3.63 (SD 1.28)
to 3.85 (SD 1.23) ml kg⁻¹ when the \(FA/FA_0\) \(N_2O\)
was decreased to 0.5, and to 3.88 ml kg⁻¹ (SD 1.24)
when \(FA/FA_0\) \(N_2O\) was decreased to zero.

**FIG. 1.** The changes in the tidal volume of three comparable
groups of children produced by altering the alveolar
concentrations of nitrous oxide and halothane. (1) Nitrous
oxide elimination as a single stage procedure with no
adjustment of end-tidal halothane concentration (phase I).
\(VT\) increased from 3.38 ml kg⁻¹ to 4.04 ml kg⁻¹ when nitrous
oxide was eliminated as a single stage procedure. (2)
Elimination as a two-stage procedure with a constant end-
tidal halothane concentration of 0.9% (phase II). \(VT\) increased
from 3.63 ml kg⁻¹ to 3.88 ml kg⁻¹ when nitrous oxide elimina-
tion was performed as a two-stage procedure with a con-
stant end-tidal halothane concentration of 0.9%. (3)
End-tidal halothane concentration decreased from 1.06%
to 0.9%, with a constant end-tidal nitrous oxide concentra-
tion of 65% (phase III). \(VT\) increased from 3.39 ml kg⁻¹ to
3.88 ml kg⁻¹ when the end-tidal halothane concentration was
reduced from 1.06% to 0.9%, with a constant end-tidal nitrous
oxide concentration of 65%.
This increase in tidal volume was not statistically significant.

These findings were compared with those from phase I and the subsequent phase III (described below) in table I and figure 1; and the percentage changes in the three phases are compared in figure 2.

DISCUSSION

The results of the phase II study, in which nitrous oxide was eliminated in two stages, contrasted sharply with the changes seen in the phase I study in which the elimination of nitrous oxide (in a single stage) was associated with a statistically significant \( P < 0.05 \) increase (19%) in mean tidal volume.

The difference in the design of these studies centered around the fact that the decrease in \( E'_{N_2O} \) in the phase II study was performed in two distinct stages with time allowed for equilibration at each stage before data were recorded; whereas the reduction in \( E'_{N_2O} \) in the phase I study was produced in a single stage with continuous recording of data. The phase II study was originally designed to investigate the possible contribution of a “gas effect” to the increase in tidal volume seen in the previous study, but its design also had an additional effect. The staged nature of the study gave adequate time to ensure that the end-tidal halothane concentration remained stable throughout the process. This proved difficult to achieve and it was found necessary to make numerous adjustments to the dialled halothane in order to keep both inspired and expired halothane concentrations constant.

In the phase I study, no adjustments to dialled halothane were made during the nitrous oxide washout. Such minor variations in end-tidal halothane as were observed in that study were regarded as artefactual and it was argued, at that time, that minor changes in end-tidal halothane concentration would not produce significant changes in ventilation within the short time course of nitrous oxide elimination. In any event, it would have been impossible to adjust dialled halothane to compensate for these variations in the short time course of the phase I study (the nitrous oxide washout was complete in 200 s), especially since the computer program in use at that time had not been developed to the point where it was capable of displaying corrected values in real time.

Since the computer recorded all data about each breath in the phase I study, it was possible to review the data from that study and examine the effects of nitrous oxide washout on both inspired and expired halothane. This reappraisal revealed a decrease in both of these concentrations of the order of 16% during nitrous oxide washout. Furthermore, these lower halothane concentrations were sustained after the end of the washout period (fig. 3).

It was decided to examine this phenomenon in greater detail and under more controlled circumstances.

For this purpose the effects of a staged withdrawal of nitrous oxide on the end-tidal halothane concentration were studied in a further five normal children of the same age group and body weight, who were premedicated with papaveretum in the same dose scale, and the dialled concentration of halothane, delivered from the Abingdon vaporizer used in phase I, remained constant at 2% throughout the two-stage nitrous oxide elimination. The results of this study revealed that the true alveolar halothane concentration varied from 1.06% when the \( FA/F_{A_{N_2O}} \) was 1.0, to 0.9% when the \( FA/F_{A_{N_2O}} \) was zero—a 16% reduction in the alveolar halothane concentration. The significance of this change was assessed by a further study designated phase III.
PHASE III

PATIENTS AND METHODS

The five healthy children included in this study, varied in age from 5.5 to 11 yr (mean 7.1 yr) and in body weight from 19.5 to 29 kg (mean weight 24.2 kg); all received papaveretum 0.4 mg kg$^{-1}$ i.m., as preoperative medication.

The methods and equipment used for the induction and maintenance of anaesthesia, and for the recording and analysis of data were the same as those used in phase II.

The data of five sequential breaths were recorded when the end-tidal nitrous oxide and halothane concentrations had been stable, at 65% and 1.06%, respectively, for 15 min; $E'_{hal}$ was then decreased to 0.9%, and when this value had been stable for 15 min, the data of a further five sequential breaths were recorded.

RESULTS

The decrease in alveolar halothane concentration from 1.06% to 0.9%, in the presence of a constant alveolar nitrous oxide concentration of 65%, was associated with a 14% increase in tidal volume; the mean tidal volume of the group increased from 3.39 (±0.62) ml kg$^{-1}$ to 3.88 (±0.58) ml kg$^{-1}$ (table I, figs 1 and 2).

DISCUSSION

The study designated phase I mimics a clinical situation where nitrous oxide is “turned off” without any adjustment of dialled halothane concentration. The results of this procedure are depicted graphically in figure 3. The tidal volume increased over a period of 200 s to reach a maximum value 30% greater than the original $V_T$, and then declined over the following 100 s, to reach a constant “fall-back” value which was 19% higher than the tidal volume immediately before the withdrawal of nitrous oxide. The overall change in tidal volume was statistically significant ($P < 0.05$). During the washout of nitrous oxide, it was found that both inspired and end-tidal halothane concentrations decreased by approximately 16%.

The phase II study, in which the withdrawal of nitrous oxide was accomplished in two stages, with time allowed for equilibration before data recording and in which end-tidal halothane was kept constant, showed an overall increase in tidal
volume of only 7%, which was not statistically significant.

The phase III study which examined the effect on tidal volume of a 16% decrease in end-tidal halothane concentration at constant end-tidal nitrous oxide concentration, showed an overall increase in tidal volume of 14%. If the percentage change recorded in phase II is added to the percentage change recorded in phase III, the result is the stippled line in figure 2, which is virtually identical with the percentage change observed in the phase I studies.

Furthermore, as figure 3 reveals, while the maximum increase in $V_t$ in phase I coincided precisely with the decrease in $F_a/F_{a_0} N_{t0}$ to less than 0.2, it is at this point also, 180 s after the nitrous oxide was "turned off", that the full decrease in the alveolar halothane concentration was established.

This decrease in delivered halothane resulting from the change in the composition of the carrier gas from a nitrous oxide–oxygen mixture to pure oxygen was a consistent finding, but of considerably longer duration than that described in previous reports (Palayiwa, Sanderson and Hahn, 1983).

From the data of these studies it is possible to deduce the mechanism behind the changes in tidal volume observed in the phase I study. The overall 19% increase can be explained primarily by the decrease in the alveolar halothane concentration. The contribution of the decrease in alveolar nitrous oxide concentration is minor; quantitatively about one-half that of halothane. The initial 30% increase in tidal volume, before the establishment of the steady-state "fall back" increase of 19%, is precisely related in time to the nitrous oxide washout and may reflect a "gas effect".

The final comment on the effect of nitrous oxide which arises from the data of these studies can be derived by comparing the end points of phases II and III. As the final tidal volumes recorded in both of these phases were 3.88 ml kg$^{-1}$ and the children in phase II were breathing an alveolar mixture of 0.9% halothane in oxygen, and those in phase III an alveolar mixture of 0.9% halothane in 65% nitrous oxide in oxygen, it is quite clear that nitrous oxide, of itself, has little effect on tidal ventilation in children.

REFERENCES


