Interaction of Isoflurane and Nitrous Oxide Combinations Similar for Median Electroencephalographic Frequency and Clinical Anesthesia

Heiko Röpcke, M.D.* Helmut Schwilden, M.D. Ph.D.†

Background: The volatile anesthetic sparing effect of nitrous oxide in clinical studies is less than might be expected from the additivity of minimum alveolar concentration values. Other studies identify nonadditive interactions between isoflurane and nitrous oxide. The aim of this study was to quantify the interaction of isoflurane and nitrous oxide at a constant median electroencephalographic frequency.

Methods: Twenty-five patients were studied during laparotomies. Nitrous oxide was randomly administered in concentrations of 0, 20, 40, 60, and 75 vol%, to ten patients for each nitrous oxide concentration. Isoflurane vaporizer settings were chosen so that the median electroencephalographic frequency was held between 2 and 3 Hz. The relationship between nitrous oxide concentrations and required isoflurane concentrations was examined with the method of isoboles.

Results: Nitrous oxide linearly decreased the isoflurane requirement. Addition of every 10 vol% of nitrous oxide decreased the isoflurane requirement by approximately 0.04 vol%. The total anesthetic requirement of isoflurane and nitrous oxide, expressed in terms of previously reported minimum alveolar concentration values, increased significantly with increasing nitrous oxide concentrations.

Conclusions: The interaction of isoflurane and nitrous oxide in the dose range 0–75 vol% on median electroencephalographic frequency is compatible with additivity. The potency of nitrous oxide as a substitute for isoflurane is less than on a minimum alveolar concentration basis. Maintaining median electroencephalographic frequency more appropriately reflects the clinical usage of isoflurane and nitrous oxide than does maintaining minimum alveolar concentration. (Key words: Anesthetics, gases; nitrous oxide. Anesthetics, volatile: isoflurane. Brain: electroencephalography. Interactions, drug: isoflurane/nitrous oxide. Monitoring: electroencephalography. Potency: anesthetic.)

THE minimum alveolar concentration (MAC) of a single volatile anesthetic is necessary to suppress movement to skin incision of 50% of patients, serves as a measure to compare the potencies of inhalational anesthetics. Clinical anesthesia most often uses a combination of nitrous oxide and a volatile agent. Nitrous oxide is well documented to decrease the requirement of volatile anesthetics necessary to suppress the response to skin incision.

It has been shown that the interaction between nitrous oxide and volatile agents such as halothane, enflurane, or isoflurane, is additive in the sense that the linear combination of two MAC fractions of nitrous oxide and the volatile agent totaling 1.0 MAC also suppresses skin incision in 50% of the patients.6–9 The additivity of MAC supports the “unitary theory of narcosis” that asserts that all anesthetics act in the same way. This theory suggests an identity of action at a molecular level.5

Recent studies by Cole et al. claimed to have shown a nonlinear contribution to the interaction of nitrous oxide with halothane, enflurane, and isoflurane in rats.6,7 Chortkoff et al. examined the ED50 for suppression of learning and the ability to respond appropriately to verbal command using the combination of isoflurane plus 40 vol% nitrous oxide.8 For both ED50s, a slightly higher value is reported than predicted by assumption of additivity. A study by Yli-Hankala et al. showed that the addition of nitrous oxide to isoflurane decreases the frequency and duration of isoflurane-induced burst suppression in the electroencephalogram (EEG) in a manner indicating a nonadditive interaction.9

The type and degree of interaction between an anesthetics also depend on the clinical end point used. Dcady et al. demonstrated that the ratios of anesthetic concentration to maximum effect are greater for isoflurane than for nitrous oxide. Concentration to maintain a postoperative level of 100% of the preoperative level of electroencephalogram (EEG) activity did not differ for the two agents. Therefore, the tail length to 80% baseline activity is shorter for nitrous oxide than isoflurane. Dcady et al. concluded that the interaction of isoflurane and nitrous oxide is highly dependent on the clinical requirement.

Methods

After approval by the institutional review board and informed consent of patients, ASA physical status I and II or III patients with abdominal surgery were studied. All patients had received dexamethasone before surgery. After induction of anesthesia, alfentanil and 0.5–1.0 mg/kg body weight etomidate was administered for rapidsequence intubation. During surgery, isoflurane and nitrous oxide were administered to maintain an end-tidal carbon dioxide concentration of 35 mmHg. Measurements were performed with a Criticare System 7000 monitor. The arterial blood pressure, cardiac output, and end-tidal carbon dioxide tension were measured with a pulse oximeter. The electrocardiogram was recorded with a 12-lead system. The end-tidal carbon dioxide concentration was continuously monitored with a Nellcor Nonin 9100 disposable capnometer (Nellcor Puritan Bennett, Pleasanton, Calif). The electroencephalogram was recorded with a Monarch monitor (Criticare Systems, Inc, Bothell, Wash).
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concentration to maintain upright position to response to tail-clamp stimulus and the ratios of anesthetic concentration to maintain upright position to heat applied to the tail differs for the anesthetics nitrous oxide, isoflurane, enfurane, and halothane in mice. Their findings do not support a unitary mechanism of anesthetic action. Instead, righting reflex and response to tail-clamp test or heat test seem to be depressed by different mechanisms.

The aim of this study was to quantify the interaction of nitrous oxide and isoflurane while maintaining a constant level of cortical activity as indicated by a median EEG frequency between 2 and 3 Hz during surgery. The rationale for this target range is that earlier work has shown that median EEG frequencies between 2 and 3 Hz are associated with reasonable planes of anesthesia. In addition, it has been shown that during anesthesia with isoflurane and 60% nitrous oxide at 1.3 MAC average median EEG frequency was around 2.5 Hz during surgery.

Methods

After approval by the local Ethics Committee, written informed consent was obtained from 25 female patients. ASA physical status 1 or 2, aged 39 ± 8 yr, scheduled for gynecologic laparotomies. Not included were patients with apparent neurologic deficit, hypothyroidism or hyperthyroidism, pregnancy, or patients who had received drugs affecting central neurotransmitter release. Patients received 7.5 mg oral midazolam 2 h before surgery. Anesthesia was induced with 0.5 mg alfentanil and 3 mg/kg thiopental. Vecuronium was administered for neuromuscular block and no anticholinergic agent was used. Once the trachea had been intubated, anesthesia was maintained with isoflurane and nitrous oxide. In addition to nitrous oxide, patients’ lungs were ventilated with oxygen and air. End-tidal carbon dioxide tension was monitored and kept constant at 35 mmHg. Blood pressure and heart rate were measured noninvasively with a Dinamap Vital Data Monitor (Criticon, Tampa, FL) at intervals of 3 min. Esophageal temperature was monitored. After induction of anesthesia, a 60-min waiting period allowed the effects of the induction doses of thiopental and alfentanil to be reduced.

One EEG lead in F3 and P3 position (international 10–20 system) (Sirecust 404, Siemens, Erlangen, Germany) was used for on-line signal analysis. The raw signal was filtered between 0.5 and 52 Hz and divided into epochs of 8.192 s duration, which were digitized at a rate of 125 Hz. The median EEG frequency (50% quantile of the power spectrum) and the percentage of activity in the frequency bands 0.5–2, 2–5, 5–8, 8–13, and 13–32 Hz were calculated. A moving average over seven epochs was used for data smoothing. End-tidal isoflurane concentrations were measured by a Normac anesthetic gas analyzer (Datex, Copenhagen, Denmark). For each patient, the analyzer was calibrated without any anesthetic and with a standard concentration of volatile anesthetic. For each EEG epoch, the corresponding end-tidal isoflurane concentration was determined.

The target range for median EEG frequency was chosen as 2–3 Hz. If median EEG frequency was greater than 3 Hz isoflurane vaporizer settings were increased by 20%, if median EEG frequency was lower than 2 Hz isoflurane vaporizer settings were decreased by 20%.

Required isoflurane concentration was defined as the mean end-tidal isoflurane concentration over a period of 15 min. During a period of 15 min, we determined 110 values of end-tidal isoflurane concentration (1 value for each 8.192 s EEG epoch). If the corresponding median EEG frequencies were out of the range of 2–3 Hz these values for measured end-tidal isoflurane concentration were rejected.

The mean of the median EEG frequencies of all 110 epochs was used as an indicator of the adequacy of isoflurane dosage. Deviation from the mean of the target range (2.5 Hz) would indicate too high or too low levels of isoflurane administration.

The standard deviation of the 110 values of end-tidal isoflurane concentrations was used as an indicator of the constancy of end-tidal isoflurane concentrations.

Nitrous oxide was randomly administered in concentrations of 0, 20, 40, 60, and 75%, each concentration was given to ten patients (n = 10 for each concentration), each patient received two different nitrous oxide concentrations. The measurement periods were allocated during surgical stimulation between opening and closure of the peritoneum. A period of 30 min for equilibration of nitrous oxide and isoflurane was allowed after the nitrous oxide change and before a second measurement period.

The hypothesis of additivity between the two anesthetic agents was tested with the method of isoboles. For each concentration of nitrous oxide, we measured the required concentration of isoflurane necessary to maintain the median EEG frequency between 2 and 3 Hz. Additivity is present if all pairs of concentrations...
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Table 1. Age, Temperature, Median Electroencephalographic Frequency, Required End-tidal Isoflurane Concentrations, and Total Anesthetic Requirement for Different Nitrous Oxide Concentrations

<table>
<thead>
<tr>
<th>Nitrous Oxide (vol %)</th>
<th>Age (yr)</th>
<th>Temperature (°C)</th>
<th>Median EEG Frequency (Hz)</th>
<th>Mean of Required End-tidal Isoflurane (vol %)</th>
<th>Mean of Standard Deviations of Required End-tidal Isoflurane (vol %)</th>
<th>Total Anesthetic Requirement (MAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38.4 ± 8.0</td>
<td>35.7 ± 0.6</td>
<td>2.51 ± 0.12</td>
<td>1.06 ± 0.24</td>
<td>0.11</td>
<td>0.92 ± 0.21</td>
</tr>
<tr>
<td>20</td>
<td>40.9 ± 9.3</td>
<td>35.7 ± 0.6</td>
<td>2.47 ± 0.08</td>
<td>1.04 ± 0.25</td>
<td>0.07</td>
<td>1.09 ± 0.22</td>
</tr>
<tr>
<td>40</td>
<td>37.3 ± 6.4</td>
<td>35.9 ± 0.5</td>
<td>2.45 ± 0.06</td>
<td>0.87 ± 0.27</td>
<td>0.11</td>
<td>1.14 ± 0.23</td>
</tr>
<tr>
<td>60</td>
<td>38.0 ± 9.4</td>
<td>35.6 ± 0.7</td>
<td>2.48 ± 0.10</td>
<td>0.77 ± 0.15</td>
<td>0.10</td>
<td>1.24 ± 0.13</td>
</tr>
<tr>
<td>75</td>
<td>38.7 ± 9.7</td>
<td>35.7 ± 0.5</td>
<td>2.46 ± 0.07</td>
<td>0.79 ± 0.23</td>
<td>0.10</td>
<td>1.41 ± 0.20</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

of both agents (Ci, iso, Ce, nitrous oxide) that lead to the same effect obey the equation

\[
\alpha \times C_{\text{iso}} + \beta \times C_{\text{nitrous oxide}} = 1
\]

with suitable coefficients \( \alpha > 0 \) and \( \beta > 0 \).

Thus, additive interaction is present if data points lie on a straight line. Deviations from linearity indicate a nonadditive interaction.

Differences in age, temperature, and median EEG frequency in the groups of different nitrous oxide concentrations were tested with analysis of variance. Regression analysis was used to quantify the nature and strength of the relationship between nitrous oxide concentrations and end-tidal isoflurane concentrations, necessary to maintain median EEG frequency between 2 and 3 Hz, and the relationship between blood pressure, heart rate, and nitrous oxide concentrations. Regression analysis was used to determine whether nitrous oxide influenced isoflurane requirement differently at the first and second measurement periods. Statistical significance was assumed at probability levels of \( \leq 0.05 \).

Results

Age and temperature did not differ between the groups receiving the various nitrous oxide concentrations (table 1).

Figure 1 depicts as an example the relationship between isoflurane concentration and median EEG frequency for one subject. The hysteresis between end-tidal isoflurane concentrations and median EEG frequency was eliminated, using the concept of effect compartments.

At a constant median EEG frequency of 2.5 Hz, the nitrous oxide concentrations did not influence the pattern of EEG, as depicted in figure 2. In addition, analysis of variance showed no significant difference in the percentage of activity in the EEG frequency bands between the various nitrous oxide concentrations (table 2).

Discussion

The results of the hemodynamic data for each group are shown in table 2.

Table 2. Hemodynamic Data for Different Nitrous Oxide Concentrations

<table>
<thead>
<tr>
<th>Nitrous Oxide (vol %)</th>
<th>Median BP (mm Hg)</th>
<th>Median HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>40</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>75</td>
<td>100</td>
<td>70</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Fig. 1. Relationship between isoflurane concentration and median electroencephalographic frequency after hysteresis elimination for patient 1 receiving 75 vol% nitrous oxide.

Fig. 2. Raw electroencephalograms of five typical patients with isoflurane/nitrous oxide anesthesia when median electroencephalographic frequency reached 2.5 Hz.
The mean of all median EEG frequencies from the
of ten patients of each nitrous oxide group did not differ
significantly between the various nitrous oxide con-
centrations (table 1).

Figure 3 depicts the isobole of required end-tidal iso-
flurane concentrations to maintain the median EEG fre-
quency between 2 and 3 Hz versus the chosen nitrous
oxide concentrations. Regression analysis was per-
formed by fitting linear and quadratic models relating
isoflurane concentrations to independently chosen ni-
trous oxide concentrations. Lowest standard error of
estimation was found for a linear model. The line of
regression was calculated as:

\[ C_{\text{iso}} = 1.05 \text{ vol}\% - 0.0041 \times C_{\text{nitrous oxide}} \] (1)

The probability level for dependence of the required
isoflurane concentration on nitrous oxide concentration
(slope \( \neq 0 \)) is 0.015. The correlation coefficient is
-0.93, R-squared is 89.6\%, standard error of estimation
is 0.05.

No statistically significant differences were observed
between the nitrous oxide administrations at the first
and second measurement periods.
If the total anesthetic requirement is expressed as the
sum of isoflurane and nitrous oxide MAC-fractions (as-
suming 1.0 MAC of isoflurane to be 1.15 vol\% and 1.0
MAC of nitrous oxide to be 1.04 atm absolute) there is
a significant increase in the total anesthetic MAC multi-
plies with increasing nitrous oxide concentrations (fig. 4).
No significant difference in systolic blood pressure,
diastolic blood pressure, and heart rate between the
various nitrous oxide concentrations could be observed
(table 2).

**Discussion**

The results of this study are limited by the absence
of the concentration of nitrous oxide alone, which leads
to a median EEG frequency of 2–3 Hz during surgery.
Nitrous oxide can be used as the sole anesthetic only
in hyperbaric conditions. This is not practicable under
clinical conditions. However, this study shows that ni-
trous oxide in the dose range 0–75 vol\% linearly de-
creases the isoflurane requirement necessary to main-
tain median EEG frequency between 2 and 3 Hz during
surgical operation. This is compatible with an additive
type of interaction between nitrous oxide and isoflurane
on median EEG frequency.

Cole et al. reported deviations from linearity of the
interaction between nitrous oxide and halothane, en-
flurane, or isoflurane on MAC in rats.\(^6\)\(^,\)\(^7\) The observed
deviations, however, were judged as rather small,\(^1\)\(^3\) so
that clinical relevance may be questioned.

Isoboles do not always consistently exhibit one type
of interaction throughout their course.\(^1\)\(^4\) Therefore, we
cannot conclude that the type of interaction will remain

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**Table 2. Hemodynamic Parameters and Electroencephalographic Frequency Bands for Different Nitrous Oxide Concentrations**

<table>
<thead>
<tr>
<th>Nitrous Oxide (vol %)</th>
<th>BP(_{\text{mmHg}}) (mmHg)</th>
<th>BP(_{\text{mmHg}}) (mmHg)</th>
<th>HR (min(^{-1}))</th>
<th>( \delta_1 ) 0.5–2 Hz (%)</th>
<th>( \delta_2 ) 2–5 Hz (%)</th>
<th>( # ) 5–8 Hz (%)</th>
<th>( # ) 8–13 Hz (%)</th>
<th>( # ) 13–32 Hz (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>112 \pm 4</td>
<td>66 \pm 8</td>
<td>80 \pm 15</td>
<td>47.1 \pm 2.1</td>
<td>14.8 \pm 2.7</td>
<td>13.7 \pm 3.6</td>
<td>8.6 \pm 4.7</td>
<td>1.9 \pm 0.7</td>
</tr>
<tr>
<td>20</td>
<td>113 \pm 14</td>
<td>69 \pm 13</td>
<td>80 \pm 11</td>
<td>46.9 \pm 2.7</td>
<td>15.6 \pm 3.4</td>
<td>13.0 \pm 2.5</td>
<td>7.9 \pm 4.3</td>
<td>2.2 \pm 0.9</td>
</tr>
<tr>
<td>40</td>
<td>112 \pm 15</td>
<td>73 \pm 15</td>
<td>72 \pm 8</td>
<td>46.8 \pm 3.9</td>
<td>15.1 \pm 4.2</td>
<td>12.0 \pm 3.7</td>
<td>9.4 \pm 4.7</td>
<td>3.0 \pm 1.7</td>
</tr>
<tr>
<td>60</td>
<td>112 \pm 11</td>
<td>69 \pm 11</td>
<td>77 \pm 12</td>
<td>46.4 \pm 3.1</td>
<td>16.8 \pm 3.4</td>
<td>11.4 \pm 3.8</td>
<td>8.8 \pm 3.1</td>
<td>3.2 \pm 1.0</td>
</tr>
<tr>
<td>75</td>
<td>114 \pm 15</td>
<td>71 \pm 13</td>
<td>76 \pm 15</td>
<td>46.6 \pm 2.5</td>
<td>16.3 \pm 3.7</td>
<td>10.8 \pm 5.0</td>
<td>4.8 \pm 2.1</td>
<td>3.1 \pm 1.6</td>
</tr>
</tbody>
</table>

Values are mean \( \pm \) SD.
BP\(_{\text{mmHg}}\) = systolic blood pressure; BP\(_{\text{mmHg}}\) = diastolic blood pressure; HR = heart rate.
additive at higher partial pressures of nitrous oxide then corresponding to 75 vol%.

The slope of isoboles can be used as an indicator of the potency of nitrous oxide to decrease the requirement of isoflurane. The potency of nitrous oxide to decrease the requirement of isoflurane necessary to keep median EEG frequency between 2 and 3 Hz is less than the potency of nitrous oxide to decrease the requirement of isoflurane necessary to suppress movement to skin incision in 50% of patients (MAC). Using equation (1), we can estimate that the addition of every 10 vol% of nitrous oxide decreases the isoflurane requirement as defined by the EEG criterion by approximately 0.04 vol%, while, in terms of MAC, each 10% of nitrous oxide decreases the isoflurane requirement by approximately 0.11 vol% (assuming additive interaction and MAC isoflurane, 1.15 vol%; and MAC nitrous oxide, 1.04 atm absolute16, fig. 5).

We cannot exclude the possibility that our results are perturbed by acute tolerance by using subsequent measurement periods for each patient.17–20 However, using regression analysis we could not identify an influence of nitrous oxide at the different measurement periods.

Other recent studies can be used to estimate the interaction of isoflurane and nitrous oxide when the level of clinical judgment or memory functions are considered (fig. 5). Eger et al. compared isoflurane anesthesia with and without 60% nitrous oxide for several kinds of surgeries.21 Without nitrous oxide, the attending anesthesiologist determined an average end-tidal concentration of 0.85 vol% isoflurane to be necessary for clinical anesthesia; 60 vol% nitrous oxide allowed a reduction of isoflurane to 0.64 vol%. Assuming a linear relationship, every 10% of nitrous oxide reduces the isoflurane requirement by 0.035 vol%. Eger et al. used lower levels of isoflurane than in our study. This could be explained by the coadministration of 0.23 mg fentanyl, which was not used in our study. In another study, Dwyer et al. determined the dose of isoflurane and nitrous oxide that suppressed memory by 50% (EDSO).22 The EDSO was 0.2 MAC for isoflurane and 0.5 MAC for nitrous oxide. Assuming linear dependence, every 10% of nitrous oxide decreases the isoflurane requirement by 0.045 vol%.

The differences in the potency of nitrous oxide to substitute isoflurane confirm the results of previous studies: the relative potencies of inhaled anesthetic agents depend on the end point measured.10,23,24 These studies do not support the hypothesis that both anesthetics act in the same way. One possible explanation is that these anesthetics act at different anatomic sites. Whereas the EEG is known to represent the electrical activity of cortical structures, more recent studies suggest that MAC is a test of anesthetic potency that evaluates depression of a spinal reflex. Rampil et al. demonstrated that, with regard to MAC, the anesthetic potency of isoflurane is independent of forebrain structures of the rat.25 They concluded that surgical

![Fig. 4. Sum of fractional minimum alveolar concentration contributions (total minimum alveolar concentration) of nitrous oxide concentrations and required isoflurane concentrations to maintain median electroencephalographic frequency between 2 and 3 Hz. Data points are mean ± SD. Regression line.](image)

unresponsiveness as determined by subcortical stimulation in the dose range of nitrous oxide and isoflurane.

Rampil demonstrated that T1 in rats does not decrease MAC in goats.25 When the brain was stimulated, that subcortical stimulation increased MAC.

Quantitative EEG with isoflurane showed dose-related paroxysmal EEG activity and stimulation showed that isoflurane could be that EEO was actually a noxious stimulation that resulted in the action.

The potency of MAC for clinical isoflurane was almost similar. This study is in the dose range of nitrous oxide and isoflurane. In a study of its interaction, it is indicated that the MAC of isoflurane is lower the MAC of nitrous oxide. Thus, nitrous oxide is an essential anesthetic agent.

In conclusion, the effect of nitrous oxide in the dose range of MAC isoflurane on median electroencephalographic frequency 2–3 Hz (this study). Every point (●) represents the mean of measurements.

![Fig. 5. Comparison of different studies used to estimate the interaction of isoflurane and nitrous oxide. — — — — Minimum alveolar concentration-awake, Dwyer et al.21 — — — — Clinical signs, Eger et al.21 — — — Minimum alveolar concentration, Stevens et al.21 — — — Median electroencephalographic frequency 2–3 Hz (this study). Every point (●) represents the mean of a measurement.](image)

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unresponsiveness appears to be supported and may be determined by subcortical structures. In another study, Rampil demonstrated that acute spinal anesthesia at T1 in rats does not change MAC. Antigonini et al. measured MAC in goats and found a large increase in isoflurane requirement (from 1.2 vol% up to 2.9 vol%) when the brain was preferentially anesthetized. They conclude, that subcortical structures modulate movement in response to painful stimuli during general anesthesia.

Quantitative EEG measurement during anesthesia with isoflurane and nitrous oxide at 1.3 and 1.5 MAC showed dose-related dependence. However, comparison of EEG and movement response to noxious stimulation showed no correlation. One conclusion could be that EEG effects and movement response to noxious stimulation are to be regarded as components of anesthesia that result from separate pharmacologic actions.

The potency of nitrous oxide as a substitute for isoflurane for clinical anesthesia in the study of Eger et al. is approximately equal to the potency found in this study. This suggests that the use of EEG median frequency better reflects what an attending anesthesiologist considers as clinically appropriate anesthesia, than does the addition of MAC fractions of both agents.

In spite of its analgesic properties, nitrous oxide is known to have only weak anesthetic potency. Due to its high MAC value, it cannot be used effectively as a sole anesthetic at normal atmospheric pressure. This study of its interaction with isoflurane on the EEG indicates that the potency of nitrous oxide as a substitute for isoflurane is less than might be expected from its MAC value. Thus, it might be asked whether nitrous oxide is an essential anesthetic component for inhalational anesthesia with isoflurane.

In conclusion, this study has shown that nitrous oxide in the dose range of 0–75 vol% linearly decreases the requirement of isoflurane needed to maintain median EEG frequency between 2 and 3 Hz. The degree of interaction for this endpoint is, however, less than anticipated from MAC studies, but seems to more appropriately reflect the clinical usage of both drugs.

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Background: The brain can be damaged by ischemia and reperfusion. Ischemia has been shown to cause unexpected hemodynamic changes, leading to postoperative complications, such as stroke, injury, and death. The aim of this study was to determine the effects of ischemia and reperfusion on the hemodynamic changes that occur in the brain after surgery.

Methods: Anesthesia was induced with propofol, etomidate, and fentanyl.previous drug therapy: 3 months (ACEI, angiotensin-converting enzyme inhibitor) or 6 months (ACEI, angiotensin-converting enzyme inhibitor, and statin).

Ischemia was induced using aortic occlusion, followed by reperfusion. The hemodynamic changes were measured using a catheter placed in the left carotid artery.

Results: The hemodynamic changes were significantly greater in the ischemia group compared to the control group. After ischemia, the heart rate increased, blood pressure decreased, and cerebral blood flow decreased. These changes were accompanied by a decrease in cerebral oxygen saturation.

Conclusion: Ischemia and reperfusion lead to significant hemodynamic changes in the brain, which can be clinically significant. Further studies are needed to determine the best strategies for managing these changes in order to prevent complications.

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Long-term Treatment without Anesthesia Undergoing Mitral Valve Repair
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Received for publication August 7, 1995. The angiography was performed at Hoffmann-La Roche Inc., and the surgical procedures were performed at the University Hospital of Geneva. The figures were prepared in the Laboratory of Anesthesiology, V 84, No 4, Apr 1996.