TRANSFER OF NITROUS OXIDE INTO BODY AIR CAVITIES

E. S. MUNSON

The characteristic feature of body air cavities is their tendency to decrease in size and ultimately disappear. During air breathing the transfer of gases from a high partial pressure within cavities to a lower partial pressure in blood forms the basis for the resorption of air spaces such as pneumoperitoneum, pneumothorax and subcutaneous emphysema (Piiper, 1965). The formation of atelectasis in closed alveoli also follows these principles. However, during nitrous oxide anaesthesia, the reverse occurs; that is, the tendency of closed body air cavities is to increase in size and/or pressure until equilibrium prevails. This effect is related to the difference in solubility between nitrous oxide and nitrogen, and accounts for a number of potential hazards during the induction, maintenance, and subsequent recovery from nitrous oxide anaesthesia. This indicates that nitrous oxide is not an innocuous agent and, in certain situations, may be contraindicated.

DIFFERENTIAL SOLUBILITY IN BLOOD

Just as nitrous oxide molecules enter alveolar gas from pulmonary blood on recovery from anaesthesia, nitrous oxide enters any closed, gas-containing space within the body when the partial pressure of nitrous oxide within that space is less than the partial pressure of the anaesthetic in the blood. On induction of anaesthesia, air-containing cavities of the body contain principally nitrogen or other relatively insoluble gases, but no nitrous oxide. The rate of gas transfer between blood and air cavity depends on the same factors which control anaesthetic uptake or excretion at the alveolar-capillary interface: solubility in blood, air cavity blood flow, and the blood-to-gas-space anaesthetic partial pressure difference. When nitrous oxide is administered in high concentration (approximately 80%) it may be substituted for nitrogen in any non-collapsible body-gas cavity without influencing the resulting equilibrium pressure. However, the gas space volume before equilibrium is achieved is dependent on the relative rates of molecular transfer of nitrous oxide and the gas within the original body cavity. Although the partial pressure gradients from nitrous oxide and nitrogen numerically are approximately equal, the rates of transfer are proportional to their solubilities in blood. A 34-fold difference in the blood/gas partition coefficients exists between nitrous oxide (0.46) and nitrogen (0.013). Therefore, at the same partial pressure, for every molecule of nitrogen that moves from the gas space to the blood, 34 molecules of nitrous oxide move from the blood into the gas cavity. For practical purposes we can assume that nitrogen absorption by blood is negligible and, therefore, these molecules remain within the original gas. Since the nitrous oxide partial pressure within the gas space eventually must reach equilibrium with the alveolar (arterial) concentration (partial pressure), the increased number of anaesthetic molecules results either in an increase in the gas space volume, if it is compliant, or in the pressure, if the space is non-compliant.

When 50% nitrous oxide is present in the alveoli, the body gas space must be doubled (fig. 1A). Similarly, at an alveolar concentration of 75% nitrous oxide, the gas space must increase fourfold (fig. 1B). This relationship is geometric in nature, so that changes in volume (pressure) are minimal during inhalation of relatively low concentrations of nitrous oxide. However, the administration of anaesthetic in 100% concentration (1 atmosphere pressure), as might occur during hyperbaric conditions, would result in an infinite increase in gas-space volume.

This effect of differential solubility is not limited to nitrous oxide. These relationships hold for any anaesthetic provided that (1) the gas is administered in high concentration, and (2) it is of greater solubility in blood than nitrogen. Other anaesthetics that satisfy these criteria include ethylene (see below) and, theoretically, xenon. Since most of the newer halogenated agents are much more soluble in blood than nitrous oxide, their relative rates of transfer into air cavities would be quite rapid. Fortunately, their greater potencies preclude use at high concentrations. At constant perfusion, the rate of volume change in a gas space is proportional to the degree of blood solubility, while the magnitude of change is dependent on alveolar (arterial) anaesthetic concentration (partial pressure).

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A. ALVEOLAR NITROUS OXIDE CONCENTRATION = 50%

FIG. 1. Volume changes in a body air cavity when the alveolar nitrous oxide concentration is 50% (A) or 75% (B). (Munson and Merrick, 1966; reprinted by permission.)

B. ALVEOLAR NITROUS OXIDE CONCENTRATION = 75%

CLOSED COMPLIANT GAS CAVITIES

Gastrointestinal gas.

The most common body gas space affected by nitrous oxide inhalation is bowel gas. In healthy subjects high concentrations of nitrous oxide present little hazard with the possible exception of aerophagia, but severe distension may occur during obstructive conditions. Normally, the quantity of nitrogen present during bowel obstruction is minimal, but other gases such as hydrogen and methane are present which are even less soluble in blood than nitrogen. Foldes, Kepes and Ship (1965) reported the development of severe abdominal distension in a patient with unrecognized adynamic ileus, following induction of nitrous oxide anaesthesia, which caused severe respiratory and circulatory embarrassment. Another report cited the entry of nitrous oxide into a gas-filled ovarian cyst that had previously communicated with the bowel via a fistulous tract (Whitwam, Scott and Sunshine, 1965).

In dog experiments Eger and Saidman (1965) showed a twofold increase in gastrointestinal gas volume after 2 hours of nitrous oxide inhalation (fig. 2). Cundy, Aldrete and Thomas (1969) also studied the effects of nitrous oxide and ethylene inhalation on isolated air-filled intestinal segments. The lesser blood solubility of ethylene as compared with nitrous oxide (blood/gas partition coefficients 0.14 v. 0.46, respectively) resulted in a slower rate of initial increase and subsequent decrease of bowel gas. These authors also showed the importance of the integrity of both the arterial and venous circulations on the rate of induced gas volume change.

Clinically, the magnitude of volume change possible is related to the initial amount of bowel gas present, the concentration of nitrous oxide administered, and the duration of anaesthetic exposure. The greatest change will occur when the initial gas volume is large and the concentration of nitrous oxide high. Since the onset of gas distension develops relatively slowly (fig. 2), the use of nitrous oxide for induction of anaesthesia should have relatively little consequence in patients with bowel obstruction. However, during maintenance of anaesthesia (after 10 min) nitrous oxide should be discontinued, or at least reduced to less than 50% concentration. It is unlikely that the maximal change possible in gas volume is even achieved, since increase in intraluminal pressure tends to limit tissue perfusion and, therefore, further delivery of anaesthetic to the gas space.

Pneumoperitoneum.

For many years the surgical management of giant
abdominal hernias included preoperative treatment by progressive pneumoperitoneum. An unusual anaesthetic complication of "abdominal tamponade" was reported by Johnson (1971) following the administration of 67% nitrous oxide. The resultant increase in intra-abdominal gas volume and pressure produced severe circulatory depression and decreased pulmonary compliance, which quickly returned to normal on opening the peritoneal cavity.

The use of sulphur hexafluoride, a gas less soluble in blood than nitrogen (blood/gas partition coefficients 0.004 and 0.013, respectively), for the production of pneumoperitoneum results in a phenomenon analogous to that observed with nitrous oxide. Following intraperitoneal injection of sulphur hexafluoride, air breathing results in the transfer of nitrogen from arterial blood into the gas space faster than the sulphur hexafluoride can be absorbed by blood (Tenney, Carpenter and Rahn, 1953). This results in greater volume increase with longer intervals between required refills (2.5 to 4 times as compared with air) for maintenance of therapeutic pneumoperitoneum (fig. 3). Theoretically the use of nitrous oxide in a patient whose peritoneal cavity is filled with sulphur hexafluoride would produce the same effect as if the space contained nitrogen.

Pneumothorax.

The inhalation of nitrous oxide in the presence of a pneumothorax also may have profound consequences on both ventilation and circulation. In animal studies (fig. 4) a twofold increase in intrapleural gas volume occurred within 10 min, and a threefold change after 45 min of nitrous oxide anaesthesia (Eger and Saidman, 1965). Ventilatory inadequacy and hypotension have been reported in a patient with asymptomatic intrapleural air during induction of nitrous oxide anaesthesia (Hunter, 1955; Christian, Munson, and Hamilton, 1969). It is also possible that gas trapping in the lungs in patients with bullous (cystic) lung disease may result in ventilatory depression, pneumothorax, or pulmonary venous gas embolism. Therefore, nitrous oxide anaesthesia in patients with pneumothorax, pneumoperitoneum, or cystic lung disease is best avoided. Stanley and Kawamura (1973) have shown recently that nitrous oxide may affect similarly the endotracheal tube cuff "space", an artificial closed air cavity in the upper airway. However, resultant increases in cuff volume and pressure are related to the differential solubilities of nitrous oxide and nitrogen in rubber rather than in blood.

Venous air embolism.

Air bubbles within the venous circulation are extremely vulnerable to the effect of nitrous oxide. The increase in intravascular gas volume occurs at a far greater rate than with any other gas cavity
because the air is bathed directly in blood containing the anaesthetic, and perfusion is no limitation. Nunn (1959) was the first to report that an air bubble increased several-fold in size when tonometered in venous blood drawn from a patient anaesthetized with nitrous oxide. When rabbits were anaesthetized with halothane and nitrous oxide, the LD$_{50}$ for intravenously injected air was 3.4 times less than when the animals received halothane alone (Munson and Merrick, 1966). The presence of nitrous oxide in the blood makes lethal a small amount of air that might otherwise be innocuous if accidentally aspirated or injected into a vein.

Nitrous oxide also has profound effects on the pulmonary circulation during venous air embolism (Munson, 1971). In dog experiments, air injected directly into the pulmonary artery rapidly produced elevations in right ventricular and pulmonary artery pressures, which caused an increase in wasted ventilation and a decrease in arterial oxygen partial pressure. These changes always were greater during inhalation of nitrous oxide, and could be reproduced 10–20 min later by the resumption of nitrous oxide inhalation (fig. 5). This suggests that nitrous oxide should be avoided where the possibility of air embolism exists. Those who use nitrous oxide in such patients should employ adequate monitoring to ensure early detection of gas embolism. Should venous air embolism occur during nitrous oxide inhalation, the anaesthetic should be discontinued in an effort to reduce the volume of intravascular gas before pulmonary outflow obstruction occurs. Figure 6 shows the relative effects of several gases more and less soluble in blood than nitrous oxide.

![Figure 5](https://academic.oup.com/bja/article-abstract/46/3/202/339407)
VENOUS GAS EMBOLISM

Air

FIG. 6. The presence of intracardiac gas, monitored with a precordial Doppler device, is shown following separate intravenous gas injections in a dog anaesthetized with pentobarbitone and breathing air. The gases appear (from above down) in decreasing order of solubility in blood. In the lowest trace the e.c.g. indicates time (heart rate 120 beats/min).

The fleeting effect of carbon dioxide attests to its acceptance as a contrast gas for various clinical diagnostic procedures.

NON-COMPLIANT GAS CAVITIES

Pneumoencephalography.

Inhalation of nitrous oxide in patients subjected to pneumoencephalography is particularly hazardous. Since the brain is enclosed within a bony framework, transfer of nitrous oxide from blood into air within the intraventricular system results in a rapid and significant increase in cerebrospinal fluid pressure (Bergstrom, Hogstrom, and Lodin, 1967; Gordon and Greitz, 1970; Saidman and Eger, 1965). Analysis of cisternal gas in patients anaesthetized with nitrous oxide during air ventriculography has been reported by Philippart (1969). He showed that the rate of onset, as well as the severity of intracranial pressure rise, was dependent on posture. The proximity of air to the choroid plexus in the upright and prone positions resulted in greater changes than when patients were supine. In the supine position the gas rose to the anterior portion of the ventricular system away from contact with the vascular plexus. This author noted that nitrous oxide inhalation was especially hazardous when the initial pressure was high or when a space-occupying lesion was present.

Saidman (1970) reported that when intrathecal nitrous oxide is used as the contrast gas, no change in cerebrospinal fluid pressure occurs, as the partial pressure of nitrous oxide in blood is nearly equal to that of the intraventricular gas (fig. 7). Since the absorption of intrathecal nitrous oxide is much more rapid than either air or oxygen (Aird, 1937), its use as the contrast medium should be advantageous. More rapid absorption of gas following anaesthesia should result in a decreased incidence of headache and morbidity in the postoperative period. However, the relatively rapid absorption of contrast gas may disappoint the surgeon who desires a delayed radiogram. Collan and Iivanainen (1969) have reported a case of cardiovascular collapse following nitrous oxide encephalography. They believe that the rapid elimination of nitrous oxide may lead to a deleterious decrease in cerebrospinal fluid pressure in patients with large cerebral ventricles. Nitrous oxide anaesthesia is best avoided in patients during air pneumoencephalography.

Fig. 7. Lumbar spinal fluid pressures in six patients following the intrathecal injection of air or nitrous oxide. While all patients were anaesthetized with nitrous oxide, note that increases in subarachnoid pressure occurred when air, but not nitrous oxide, was used as the contrast gas medium. (Saidman, 1970; from Saidman and Moya, Complications of Anesthesia, 1970. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.)


Middle ear and paranasal sinuses.

The middle ear and paranasal sinuses are unique body air cavities since they are present normally, and represent open non-ventilated spaces. Measurements of nitrous oxide emanating from the maxillary sinus in patients anaesthetized with nitrous oxide have been made by Rasmussen (1967). In certain disease states, normal equilibrating mechanisms may be compromised, thereby creating closed cavities which are subject to the same effects of nitrous oxide as other non-compliant spaces. Relatively rapid increases in middle ear pressure have been reported (fig. 8) during nitrous oxide anaesthesia in patients (Thomsen, Terkildsen and Arnfred, 1965) and animals (Matz, Rattenborg and Holaday, 1967).

Clinically, increased middle ear pressure results in a bulging eardrum and may make ear operations difficult, such as replacement of the tympanic membrane or closing a perforation. To avoid this complication nitrous oxide should be eliminated or reduced to at least 50% concentration just prior to surgical closure of the middle ear. The presence of increased middle ear pressure in closed cavities may contribute to some patients' complaints of postoperative pain, delirium, nausea, and vomiting. However, rapid re-absorption of nitrous oxide also may result in sub-ambient middle ear pressures and a conductive-type hearing loss of short duration (Waun, Sweitzer, and Hamilton, 1967).

Recovery from anaesthesia

So far we have considered only closed gas cavities that are influenced by nitrous oxide during induction and maintenance of anaesthesia. Another interesting and differential solubility-related phenomenon occurs in the lung on recovery from nitrous oxide anaesthesia when air is breathed. Fink (1955) originally called this "diffusion anoxia", but a more accurate and descriptive term would be "alveolar dilution effect". Alveolar dilution results from the relatively greater outflow of nitrous oxide from pulmonary blood than uptake of nitrogen by the blood (Rackow, Salanitre and Frumin, 1961). Hypoxaemia and hypoventilation through decreased chemoreceptor

Fig. 8. Changes in middle ear pressure during nitrous oxide inhalation. Note that the rate of pressure rise is proportional to anaesthetic concentration, and that opening of the eustachian canal (at 30 cm water pressure) limits pressure rise on the 40% curve. (Thomsen, Terkildsen and Arnfred, 1965; reprinted by permission of Archives of Otolaryngology, copyright 1965, American Medical Association.)

Fig. 9. Calculated excretion rates of various gases after complete equilibration at the percentages noted. Ventilation was maintained constant at 4 l./min. Note that gas output is greatest with nitrous oxide. Diffusion anoxia, which is related to the dilution of alveolar respiratory gases by nitrous oxide at the end of anaesthesia, has been reported only with this agent. (Munson and Eger, 1971; reprinted by permission of the Williams & Wilkins Co., Baltimore.)
stimulation also may result. Sheffer, Steffenson, and Birch (1972) have shown that during spontaneous breathing of air the maximum depression of levels of arterial oxygen (from 69 to 54 mm Hg) and carbon dioxide (50 to 42 mm Hg) were seen when nitrous oxide outflow was greatest (3–5 min). Calculations of the volumes of various anaesthetics excreted on resumption of air breathing are shown in figure 9. Since the alveoli are open cavities, maintenance of adequate ventilation tends to oppose the development of hypoxaemia from a dilution mechanism (Selim, Markello and Baker, 1970). Frumin and Edelist (1969) believe that the clinical importance of diffusion anoxia is minimal, provided arterial oxygenation and ventilatory reserves are adequate. However, since these prerequisites cannot always be guaranteed, alveolar dilution should be obviated by the inhalation of high concentrations of oxygen during the first few minutes of nitrous oxide elimination.

SUMMARY

The fact that nitrous oxide is transferred into a normally-occurring or artificially-induced body air cavity does not necessarily mean that use of nitrous oxide is contraindicated. In those conditions where volume and/or pressure changes occur rapidly, as with a pneumothorax, pneumoencephalography, or venous air embolism, nitrous oxide inhalation is best avoided. In other situations the advantages of nitrous oxide must be balanced against its disadvantages. For example, the use of nitrous oxide for induction of anaesthesia in patients with bowel obstruction, or for middle ear surgery, has relatively less consequence. Although reports are lacking, the clinician should be alerted to patients with mediastinal and subcutaneous emphysema, arterial gas embolism after cardiopulmonary bypass, and intraocular air as possible conditions where nitrous oxide must be balanced against its disadvantages. The fact that nitrous oxide is transferred into a normally-occurring or artificially-induced body air cavity does not necessarily mean that use of nitrous oxide is contraindicated. In those conditions where volume and/or pressure changes occur rapidly, as with a pneumothorax, pneumoencephalography, or venous air embolism, nitrous oxide inhalation is best avoided. In other situations the advantages of nitrous oxide must be balanced against its disadvantages. For example, the use of nitrous oxide for induction of anaesthesia in patients with bowel obstruction, or for middle ear surgery, has relatively less consequence. Although reports are lacking, the clinician should be alerted to patients with mediastinal and subcutaneous emphysema, arterial gas embolism after cardiopulmonary bypass, and intraocular air as possible conditions where nitrous oxide must be balanced against its disadvantages.

REFERENCES


CORRESPONDENCE

AN ADVERSE REACTION TO ALTHESIN

Sir,—An 18-year-old, healthy male was admitted to hospital for suturing of a lacerated knee under general anaesthesia. Thiopentone 250 mg was used for induction of anaesthesia and anaesthesia was maintained with nitrous oxide, oxygen and halothane given from a mask. There was no adverse reaction. Five years previously he had an operation for removal of a cyst from his clavicle, but no record of the method of anaesthesia was made. At the age of 8, he had two "gas" dental anaesthetics. He had a 5-year history of hay fever.

Ten years after the knee injury he was readmitted for skin grafting. No premedication was given and anaesthesia was induced with Althesin 4 ml given slowly i.v. During the injection he became restless, lifting his head off the pillow on several occasions. Nitrous oxide, oxygen and halothane 1% was given from a face mask. Immediately a confluent red rash was noticed on his chest. Over the next 2 min it spread rapidly to cover completely his trunk, neck and face.

The radial pulse became rapid and barely palpable. In spite of being given 100% oxygen, he was centrally and peripherally cyanosed and he began to sweat. He maintained spontaneous respiratory through all. All these events occurred within 5 min of induction. The patient was given 1 litre of Harrmann's solution over about 20 min and an intravenous injection of hydrocortisone 200 mg. About 10 min after induction his pulse felt stronger. The arterial systolic pressure was 40 mm Hg and the pulse rate was 120 beats/min.

The patient's condition improved gradually. After a further 10 min his arterial systolic pressure had increased to 60 mm Hg and the pulse rate remained at 120 beats/min. He was no longer cyanosed, but had developed facial oedema, which was severe over both upper eyelids. He was conscious but drowsy. One hour after induction he was alert, his arterial systolic pressure was 85 mm Hg and the pulse rate was 120 beats/min. Within 2 hours he had returned to normal apart from some facial oedema. Judged by auscultation his chest remained clear throughout. There were no permanent after-effects.

One of the most useful in-vitro tests for "typical" anaphylactic reactions in man (immunologically mediated by antibodies mainly of the IgE class) or anaphylactoid-like reactions (non-immunologically mediated, the noxious agent directly releasing pharmacological mediators) is the leucocyte histamine release test. Blood leucocytes (particularly basophils) are challenged either with the causative or suspected agents, and if an allergy is to be sought, by anti-IgE, which would release histamine in positive cases.

Table I gives a summary of the sensitivity tests performed on this patient.

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<th>Test material</th>
<th>Weal (mm)</th>
<th>Erythema</th>
<th>Leucocyte histamine release (°L content)</th>
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<td>Control</td>
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<tr>
<td>Vehicle</td>
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<td>10/1000</td>
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<td>30</td>
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Either steroid in Althesin, when used separately, appeared to produce histamine release from skin mast cells but did not release histamine from basophil leucocytes. Each also reduced the response to vehicle by mast cells, and histamine release: both reactions are more likely to be a direct effect in mast cells in the skin and blood basophil leucocytes, respectively.

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| Control       |          |          | 14          |
| Vehicle       |          |          | 10/1000     |
| Cremophor     | 7        | 13       | 30          |
| Althesin      | 7        | 26       | 62          |
| Alphadolone   | 8        | 29       | <4          |
| Alphaxalone   | 8        | 32       | <4          |
| Vehicle       |          |          | 10/µg/ml 5  |
| and           |          |          | <4          |
| alphadolone   |          |          | 10/µg/ml 5  |
| Vehicle       |          |          | <4          |
| and           |          |          | 10/µg/ml 5  |
| alphaxalone   |          |          | <4          |
| Alphadolone   |          |          | 50/µg/ml    |
| Alphaxalone   |          |          | <4          |
| Propanidid in |          |          | <4          |
| Cremophor     | diluted 1/1000 | 7 | 17 | 23 |
| Anti-IgE      |          |          | 61          |

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