We postulated that nitrous oxide transfer into the pleural cavity can occur by diffusion from the alveoli, independent of vascular transport. Under general anaesthesia, six sheep were studied in two phases, a control and an experimental phase. The sheep were anaesthetized, intubated, and received positive pressure mechanical ventilation. A catheter was placed in the right pleural cavity and 150 ml air injected. The animals were ventilated with 100% oxygen. The inspired gas was changed to a mixture of 50% nitrous oxide and 50% oxygen, and the rate of increase of nitrous oxide concentration in the pleural space was measured. The animals were then ventilated with 100% oxygen and then killed by exsanguination while ventilation was continued. The inspired mixture was changed to 50% nitrous oxide and 50% oxygen and the rate of increase in nitrous oxide concentration was measured in the pleural space again. During ventilation with nitrous oxide in the living animals, the concentration of nitrous oxide in the pleural cavity increased rapidly and decreased to zero during ventilation with 100% oxygen. During ventilation without circulation, the rate of increase in the concentration of nitrous oxide in the pleural cavity was the same as in the control phase. This suggests that nitrous oxide enters the pleural space by diffusion, rather than by vascular delivery. This mechanism may explain the rapid increase in the volume of pneumothorax if nitrous oxide is given in the inspired gas.

Previous studies suggest that vascular transport of inhaled nitrous oxide causes the rapid increase in size of a preexisting pneumothorax. Eger and his colleagues studied the time course of volume and concentration changes in two gas-filled cavities: the intestine and the pleural spaces of dogs. When nitrous oxide was administered, a substantial difference was noted in the doubling time of the volume of gas in an artificially created pneumothorax (10 min) compared with an intestinal loop (2 h). Associated with the increase in volume, they noted an initial rapid increase in nitrous oxide concentration in the intrapleural space, followed by a slower progressive change. The difference in the rate of increase in nitrous oxide concentration in the bowel compared with the pleural space was thought to be because of a greater blood flow to the pleura. The difference in the blood gas partition coefficient of nitrous oxide (0.46) and nitrogen (0.014) resulted in the preferential transfer of nitrous oxide into a compliant air filled cavity faster than nitrogen could exit. This is considered responsible for the rapid increase in size of a pneumothorax when a patient inspires a mixture of oxygen and nitrous oxide.

We questioned the ability of blood to deliver the relatively large volumes of nitrous oxide needed to rapidly affect its concentration in a large cavity. We postulated that the delivery of nitrous oxide to the pleural cavity is by direct diffusion from the alveoli rather than by vascular delivery.

Methods
Six sheep were studied in two phases, a control phase followed by an experimental phase. The study design was reviewed and approved by our institutional Animal Studies
Review Committee in accordance with American Physiological Society/National Institute of Health guidelines. Anaesthesia was induced with an i.m. injection of ketamine (1 mg kg⁻¹), and i.v. access secured. Glycopyrrolate (0.2 mg i.v.) was given to decrease secretions. After administration of pancuronium 1 mg kg⁻¹ i.v., the animal was intubated with a size 8.0 cuffed tracheal tube and controlled ventilation was started (Ohmeda 7000 ventilator) using a semiclosed circle system. A 14-gauge catheter was placed in the right femoral artery to measure arterial pressure and allow arterial blood gas sampling. Anaesthesia was maintained with isoflurane (1% inspired) and muscle relaxation maintained (pancuronium 2 mg i.v. every 30–45 min). A gas analyser (Ohmeda RGM 5250) was used to analyse inspired and expired oxygen, carbon dioxide, and nitrous oxide concentrations. Baseline arterial blood gas analysis was performed (Instrumentation Laboratories 16/40 pH, Blood Gas, Electrolytes Analyzer, Lexington, MA, USA) during ventilation with an inspired oxygen concentration of 100%.

A 14-gauge catheter was then placed in the right pleural space for introduction of air and sampling. A chest x-ray was obtained after placement to exclude any pneumothorax caused by lung injury by the catheter. Arterial blood gas analysis was done to assess any change in \( P_{O_2} \), which also would indicate injury to the lung at the time of catheter placement. After lung injury had been excluded, air (150 cc) was injected into the pleural space through the 14-gauge catheter to create a pneumothorax, and the catheter was then closed. Ventilation with 100% oxygen was continued for 5 min (fresh gas flow 4 litre min⁻¹). Animals were then studied in two phases.

During the control phase, the fresh gas flow was changed to oxygen (2 litre min⁻¹) and nitrous oxide (2 litre min⁻¹). Samples of gas (10 ml) were taken from the pleural space catheter, every 1–2 min. The aspirated samples were analysed with an Ohmeda Rascal II anesthetic gas monitor. To prevent loss of volume from sampling each volume of gas taken was replaced with 10 ml of room air. The concentration of nitrous oxide in the pleural space was

![Fig 1](image_url) Change in nitrous oxide concentration with time in the control phase (A) and the experimental phase (ventilation without circulation, B) during administration of 50% nitrous oxide (left side of panel), followed by administration of 100% oxygen (right side of panel).
recorded against time. After the control measurements (normal circulation) animals were ventilated with 100% inspired oxygen until no nitrous oxide was detected in the pleural space (re-equilibration).

Each animal was then exsanguinated via the femoral arterial cannula until cardiac arrest occurred. I.v. pentobarbital was then administered. This may have been ineffective because cardiac arrest had already occurred but was done to ensure death of the animals, as suggested by our institutional animal studies committee. Ventilation was continued, and gas administration repeated as an experimental phase, with no circulation. After re-equilibration with 100% oxygen, animals were again ventilated with a mixture of nitrous oxide (2 litre min⁻¹) and oxygen (2 litre min⁻¹). Samples of pleural gas were taken and analysed as in the control phase.

Data were analysed using repeated measures analysis of variance (Statistica, Tulsa, OK, USA). The null hypothesis was rejected if P<0.05.

Results

Blood gas values did not change after catheter placement

During the control phase (pre-cardiac arrest), a significant (P<0.05) increase in concentration of nitrous oxide in the pleural cavity occurred, with a mean concentration of 39.6% nitrous oxide at 6 min. At the conclusion of the control phase, when the FIO₂ was increased to 1.0, the concentration of nitrous oxide in the pleural space rapidly declined to mean value of 2.83% nitrous oxide (Fig. 1B, P<0.05).

During the experimental phase in the absence of circulation, the concentration of nitrous oxide in the pleural space again increased significantly (P<0.05) from zero to a maximum of 42.6% nitrous oxide (mean). This increase resembled that seen in the control group. When FIO₂ was changed to 1.0, the nitrous oxide concentration in the pleural space rapidly decreased to 1.5% (mean nitrous oxide concentration) (Fig. 1B).

Discussion

This study suggests that nitrous oxide diffuses directly from alveolar gas into the pleural space rather than being transferred by the circulation. Relatively few studies¹³ have examined the mechanism of transfer of an insoluble gas to an air filled cavity. Those reports have stated that introduction of the gas into the cavity is secondary to vascular delivery, proposing that the vascular deliver of a relatively soluble gas such as nitrous oxide into the cavity occurs at a faster rate than the relatively insoluble gas nitrogen can be removed. This has been given as the primary explanation for the rapid increase in volume of a pneumothorax observed clinically. In a landmark paper published in Anesthesiology 1968, Eger and colleagues² proposed that high blood flow to the pleura delivered nitrous oxide to the pleural cavity, resulting in a rapid increase in the concentration of nitrous oxide and in the size of a pneumothorax.

Our study questioned whether the major mechanism of nitrous oxide transfer into the pleural cavities was a result of direct diffusion or vascular delivery. We found a rapid increase in the nitrous oxide concentration in the pleural space in both the control and the experimental animals. We ensured that the samples were not samples from the lung by chest x-ray and blood gas measurement to document absence of pneumothorax caused by lung injury by the pleural catheter.

An increase in nitrous oxide concentration in the control phase could potentially be explained by vascular delivery of nitrous oxide to the cavity. However, the increase in nitrous oxide concentration seen when there was no circulation but continued ventilation can only be explained by direct diffusion of nitrous oxide across the visceral pleural surface.

An increase in the size of a pneumothorax in a patient on positive pressure ventilation receiving a gas mixture containing nitrous oxide, is well known clinically. We did not measure the change in volume of the pneumothorax in this study, but the change in volume of the pneumothorax should parallel the increase in nitrous oxide concentration. Based on the results of this study we believe that the rapid increase of nitrous oxide in a pneumothorax is by direct diffusion from the alveoli, independent of vascular delivery.

Acknowledgements

The authors wish to thank Dr Stephen O. Heard for his critical review of the manuscript. We also wish to thank Kathy Coomey and Susan St Martin for editorial assistance.

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