

The Use of Air in the Inspired Gas Mixture During Two-Lung Ventilation Delays Lung Collapse During One-Lung Ventilation

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BACKGROUND: Collapse of the ipsilateral lung facilitates surgical exposure during thoracic procedures. The use of different gas mixtures during two-lung ventilation (2LV) may improve or impede surgical conditions during subsequent one-lung ventilation (OLV) by increasing or delaying lung collapse. We investigated the effects of three different gas mixtures during 2LV on lung collapse and oxygenation during subsequent OLV: Air/Oxygen (fraction of inspired oxygen [F_{IO_2}] = 0.4), Nitrous Oxide/Oxygen ("N₂O," F_{IO_2} = 0.4) and Oxygen ("O₂," F_{IO_2} = 1.0).
METHODS: Subjects were randomized into three groups: Air/Oxygen (n = 33), N₂O (n = 34) or O₂ (n = 33) and received the designated gas mixture during induction and until the start of OLV. Subjects' lungs in all groups were then ventilated with F_{IO_2} = 1.0 during OLV. The surgeons, who were blinded to the randomization, evaluated the lung deflation using a verbal rating scale at 10 and 20 min after the start of OLV. Serial arterial blood gases were performed before anesthesia induction, during 2LV, and every 5 min, for 30 min, after initiation of OLV.
RESULTS: The use of air in the inspired gas mixture during 2LV led to delayed lung deflation during OLV, whereas N₂O improved lung collapse. Arterial oxygenation was significantly improved in the O₂ group only for the first 10 min of OLV, after which there were no differences in mean P_{aO_2} values among groups.
CONCLUSIONS: De-nitrogenation of the lung during 2LV is a useful strategy to improve surgical conditions during OLV. The use of F_{IO_2} 1.0 or N₂O/O₂ (F_{IO_2} 0.4) during 2LV did not have an adverse effect on subsequent oxygenation during OLV.

The primary indication for one-lung ventilation (OLV) is to facilitate surgical exposure in the chest by collapsing the ipsilateral lung. Thus, anesthetic techniques which delay lung collapse may impede thoracic surgery. Studies of OLV in sheep have demonstrated that two mechanisms are primarily involved in the determination of rate of collapse of the nonventilated lung.¹ The first mechanism is passive exhalation from the inherent elastic recoil of the lung. However, this passive exhalation is usually over within 60 s of lung isolation and any means to further deflate, such as with an increase in pleural pressure or suctioning of the airway, failed due to small airway closure. Uptake of

residual lung gases or absorption atelectasis is a second mechanism of lung collapse during OLV. Thus, efforts to promote lung collapse will primarily occur via changing the rate of gaseous uptake in the alveoli. There have been no human studies that have evaluated the effects of inspired gas mixtures on lung collapse during thoracic surgery.

Nitrogen may delay the development of atelectasis because it is not as easily absorbed into the bloodstream as oxygen (O₂) or nitrous oxide (N₂O).² While potentially delaying lung collapse, the use of air in the inspired gas mixtures during two-lung ventilation (2LV) may improve oxygenation during subsequent OLV by decreasing the rate atelectasis formation in the ventilated lung.³⁻⁵ Indeed, Agarwal et al.⁶ describe improved gas exchange in healthy patients' lungs undergoing general anesthesia when the patients are ventilated with fraction of inspired oxygen (F_{IO_2}) 0.4 instead of F_{IO_2} 1.0 postintubation. There has been a recent trend to replace the conventional use of N₂O/O₂ mixtures with air/oxygen mixtures during general anesthesia.^{7,8}

The hypothesis of this study was that the use of nitrogen-containing air in the inspired gas mixture during 2LV delays lung collapse during subsequent OLV. We also hypothesized that the use of air or N₂O

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in the inspired gas mixture during 2LV would affect arterial oxygenation during subsequent OLV with a $FiO_2 = 1.0$.

METHODS

After hospital Research Ethics Board approval and after obtaining written consent, patients scheduled for elective thoracotomy or thoracoscopic surgery for lung cancer were allocated by random number assignment to one of three study groups: "AIR," "N₂O" or "O₂". Subjects were consecutive consenting adult patients of the two participating thoracic surgeons (GD and TW) scheduled for surgery in the lateral decubitus position, with an expected duration of OLV to exceed 30 min, and who had no contraindications to the study protocol. All patients had preoperative spirometry. Patients were excluded if difficulty in airway management was anticipated on preoperative assessment or they had evidence of bullae on chest radiographs or major medical co-morbidities.

During induction and maintenance of anesthesia, the AIR group received an inspired gas mixture of O₂ and air (FiO_2 0.40), the N₂O group received a gas mixture of O₂ and N₂O (FiO_2 0.40) and the O₂ group received 100% O₂. Patients received total IV anesthesia to avoid the possible confounding effects of inhaled volatile anesthetic concentrations on oxygenation during OLV. The selected inspired gas mixture was titrated to a total fresh gas flow of 8 L per minute. Anesthesia induction was achieved with 2–3 μ g/kg fentanyl, 2 mg/kg propofol, and 1 mg/kg of rocuronium. Anesthesia was maintained with propofol 120–200 μ g \cdot kg⁻¹ \cdot min⁻¹ infusion and intermittent boluses of rocuronium 0.15–0.3 mg/kg based on train-of-four neuromuscular monitoring.

Tidal volumes were 10 mL/kg ideal body weight during both 2LV and OLV without positive end-expiratory pressure (PEEP). The selected gas mixture was introduced by mask during induction and continued during positive pressure ventilation until the start of OLV. The patients' airways were intubated with an appropriate-size left-sided double-lumen endobronchial tube (DLT) and the position of the DLT was confirmed with fiberoptic bronchoscopy (FOB). After induction of anesthesia, the FOB was repeated by the surgeon via the DLT and a cervical mediastinoscopy was performed in the supine position if required for cancer staging. The patients were then turned to the lateral position and the position of the DLT was confirmed and adjusted as needed by FOB. OLV of the dependent lung was begun in the lateral position, immediately before opening the nondependent lung pleura, by inflation of the bronchial cuff of the DLT and clamping the lumen of the DLT to the nonventilated lung proximally. The distal port of the DLT lumen was then opened to atmosphere and the adequacy of lung isolation was confirmed by monitoring the inspired and expired tidal volumes using the side-stream spirometer of the anesthetic machine (ADU-S5,

GE-Datex/Ohmeda, Madison, WI). During OLV, all patients' lungs were ventilated with a $FiO_2 = 1.0$.

Measurements

Arterial blood gases were obtained while the patient was breathing room air prior to anesthesia induction, during 2LV in the lateral position, and every 5 min for the first 30 min of OLV to document the time at which the Pao₂ values became equivalent in the groups. The time, FO₂, arterial O₂ saturation, end-tidal carbon dioxide, heart rate, and arterial blood pressure were also noted for each blood gas determination. If arterial O₂ saturation decreased below 90%, the DLT was checked for malpositioning with FOB and a recruitment maneuver (a sustained inflation of the lung to 25 cm H₂O pressure for 20 s) of the ventilated lung was performed.⁹

The surgeons were blinded to the gas mixtures inspired by the patients. The surgeons did not divide the pulmonary vasculature before the end of 20 min of OLV in order to minimize the surgical effects on lung collapse and shunt fraction. Surgeons were instructed to provide a lung deflation score at 10 and 20 min after the initiation of OLV using a nonparametric verbal rating scale for lung deflation from zero (corresponding to no lung deflation) up to 10 (corresponding to maximal lung deflation). All data were recorded manually by the supervising anesthesiologist on a standardized study case report form and later transferred to a computerized database.

Data Analysis

The sample size of the study was calculated based on previously published data showing a mean Pao₂ during OLV of approximately 220 mm Hg with a SD of 100 mm Hg.¹⁰ Using an assumed clinically relevant difference in mean Pao₂ levels during OLV among groups of 50 mm Hg, a minimum of 33 subjects were required per group to achieve an α of 0.05 with a β of 0.2. The data collected were entered into a Microsoft Access database and then analyzed with SPSS v11.0 statistical software package. Data were analyzed by two-way analysis of variance and significant effects were followed up with separate Mann-Whitney tests for nonparametric variables and Fisher's tests for parametric variables.

RESULTS

One-hundred patients were enrolled into the study (AIR $n = 33$, N₂O = 34, O₂ = 33). Demographic data and other information are listed in Table 1. There were no differences among the three study groups with respect to preoperative lung function, type of surgery, side of surgery or time from induction to OLV.

Lung deflation scores for the three groups at the different study time periods are shown in Figure 1. Lung deflation scores were lower in the AIR group indicating less lung collapse at both 10 and 20 min after initiation of OLV compared with the N₂O and O₂

Table 1. Demographics

	AIR	Nitrous oxide	Oxygen
No. of cases	33	34	33
Gender: male/female	15/18	15/19	18/15
Age (yr)	64 ± 12	65 ± 14	65 ± 11
Weight (kg)	73.5 ± 28.5	77.2 ± 22.0	73.5 ± 23.5
Height (cm)	164 ± 12	168 ± 13	165 ± 18
Time to one lung ventilation (min)	66 ± 40	64 ± 32	65 ± 35
Surgical procedure			
R thoracotomy (wedge/segmentectomy)	1	2	0
R thoracotomy (lobectomy)	16	18	20
R thoracotomy (pneumonectomy)	1	1	3
R VATS	3	0	0
L thoracotomy (wedge/segmentectomy)	0	0	0
L thoracotomy (lobectomy)	12	11	8
L thoracotomy (pneumonectomy)	0	1	0
L VATS	0	1	2
Mediastinoscopy (added to procedure)	6	4	3
Pulmonary function tests			
FEV1 (% of predicted)	83 ± 24	81 ± 22	83 ± 28
FVC (% of predicted)	88 ± 24	82 ± 21	87 ± 25
FEV1/FVC	80 ± 14	78 ± 14	83 ± 15
RV (% of predicted)	133 ± 38	122 ± 33	131 ± 35
FRC (% of predicted)	133 ± 29	123 ± 25	125 ± 26
Arterial blood gas on room air			
pH	7.42 ± 0.03	7.43 ± 0.03	7.43 ± 0.03
Paco ₂ (mm Hg)	39.5 ± 3.5	39.8 ± 3.6	40.2 ± 3.1
Pao ₂ (mm Hg)	88 ± 12	91 ± 10	87 ± 13

There were no significant differences for any of these variables among groups.

VATS = video-assisted thoracoscopic surgery; FEV = forced expiratory volume at 1 s; FVC = forced vital capacity (lung function test); RV = residual volume; FRC = functional residual capacity.

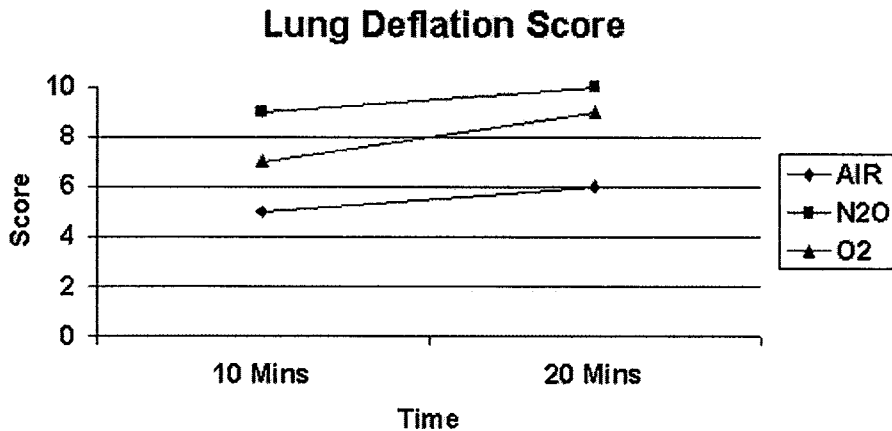


Figure 1. Median Lung Deflation Score vs Time after the start of one-lung ventilation (OLV). A Lung Deflation Score of 0 equals no lung collapse while a score of 10 equals complete lung collapse. Lung deflation scores in the AIR group were significantly lower compared to the nitrous oxide (N₂O) and oxygen (O₂) groups at 10 min and 20 min after initiation of OLV ($P < 0.008$). Lung deflation scores in the N₂O group were higher compared with the O₂ Group 10 min ($P < 0.002$) but not 20 min ($P = 0.32$) after initiation of OLV. AIR ($n = 33$): Air/O₂ Fio₂ 0.4 during two-lung ventilation (2LV); then fraction of inspired oxygen (Fio₂) 1.0 during OLV. N₂O ($n = 34$): N₂O/O₂ Fio₂ 0.4 2LV; then Fio₂ 1.0 OLV. O₂ ($n = 33$): Fio₂ 1.0 2LV; and Fio₂ 1.0 OLV.

groups. The median lung deflation scores at 10 min of OLV were: AIR = 5 versus N₂O = 9 and O₂ = 7 ($P < 0.008$). After 20 min of OLV the median lung deflation scores were: AIR = 6 versus N₂O = 10, O₂ = 9 ($P < 0.008$). Lung deflation scores in the N₂O group were significantly improved compared with the O₂ group after 10 min of OLV ($P < 0.002$), but they were not different after 20 min of OLV ($P = 0.032$).

There were no significant differences in mean Pao₂ values at baseline among the three study groups

(Table 1). Arterial oxygenation at the different study time periods is shown in Figure 2. The O₂ group had a higher Pao₂ during 2LV in the lateral position compared with the AIR and N₂O groups (AIR = 160 mm Hg, N₂O = 188 mm Hg, O₂ = 411 mm Hg; $P < 0.001$). After 5 and 10 min of OLV, the O₂ group still had a higher Pao₂ compared with the other groups (5 min: AIR = 198 mm Hg, N₂O = 213 mm Hg, O₂ = 337 mm Hg; $P < 0.001$; 10 min: AIR = 188 mm Hg, N₂O = 190 mm Hg, O₂ = 264 mm Hg; $P = 0.005$). This

Arterial Oxygenation

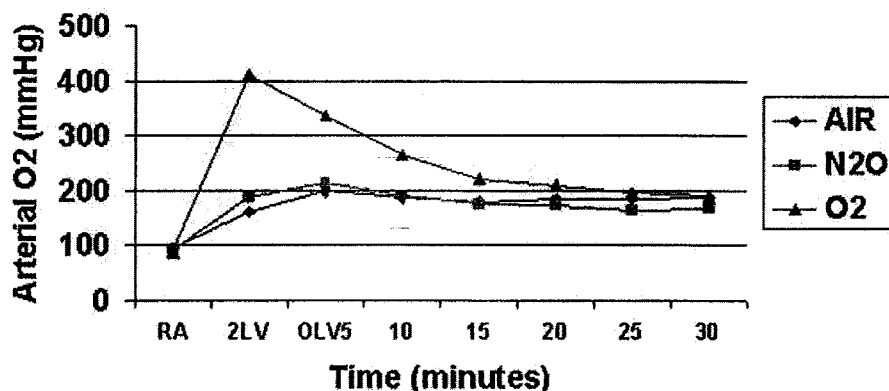


Figure 2. Mean P_{aO_2} at the different study periods for the patients randomized to the AIR, nitrous oxide (N_2O) and oxygen (O_2) groups. There were no differences in oxygenation among groups at baseline while breathing room air (RA, $P = 0.32$). During two-lung ventilation (2LV) just prior to one-lung ventilation (OLV) P_{aO_2} was significantly higher in the O_2 group compared with the N_2O and AIR groups ($P < 0.001$). After 5 min of OLV arterial O_2 was higher in the O_2 group compared with the N_2O and AIR groups ($P < 0.001$). After 10 min of OLV 10 min, arterial O_2 was higher in the O_2 group compared with the N_2O and AIR groups ($P = 0.005$). No significant differences were observed in arterial O_2 between the O_2 vs N_2O and AIR groups after 15, 20, 25 or 30 min OLV.

difference in arterial oxygenation in the O_2 group versus the other groups was still present after 15 min of OLV, but the differences were not significant after correcting for repeated measures ($P = 0.04$). There were no differences among the N_2O and AIR groups. There were no subsequent differences in mean P_{aO_2} values between groups to the end of the study period. Clinically important desaturation ($Sp_{O_2} < 90\%$) requiring alveolar recruitment maneuvers occurred in a small minority of patients with a similar incidence in each study group (AIR $n = 2$, N_2O $n = 2$, O_2 $n = 1$). No patient required discontinuation of OLV.

DISCUSSION

Lung collapse facilitates intrathoracic surgical procedures and is particularly important in minimally invasive thoracoscopic surgery and for patients with chronic obstructive pulmonary disease who have delayed lung deflation secondary to decreased lung elastic recoil. This study was designed to determine whether the type of inspired gas mixture used during two-lung anesthesia had an effect on lung collapse and oxygenation during OLV. Previous studies demonstrating that the use of nitrogen-containing air in the inspired gas mixture delays atelectasis during 2LV suggest that during OLV the nonventilated lung would also be subject to the same effect.^{2,3,5} This would theoretically delay collapse of the operated lung and thus worsen surgical conditions. Indeed, the results of the present study show that the use of air/ O_2 during 2LV was detrimental to lung collapse 10 and 20 min after initiation of OLV.

During OLV with an open chest, the nonventilated lung collapses initially due to elastic recoil, which quickly brings the lung down to its closing capacity. Remaining gas in the lung is then removed by absorption into the pulmonary capillary blood. Reasons for

the poor lung collapse during OLV include slow nitrogen uptake from the alveoli due to its low solubility ($N_2 = 0.015$ mL/dL blood vs $N_2O = 0.47$ mL/dL)⁴ and possibly the effects of hypoxic pulmonary vasoconstriction, which decreases blood flow to the nonventilated lung further limiting gas uptake by the circulation. A modest improvement was noted in lung deflation in the AIR group from the 10-min to 20-min time points. Since the study was only performed to 20 min, the time at which the AIR group would have similar lung deflation scores to the other two study groups is unknown. Surgical exposure in the chest is dependent on the collapse of the nonventilated lung. Delaying lung collapse will impair surgical exposure and prolong the procedure. Facilitating lung collapse is particularly important in minimally invasive thoracoscopic surgery and in patients with smoking-related lung disease who may demonstrate gas trapping and reduced elastic recoil.

There was a significant difference between the N_2O and O_2 groups in lung deflation scores after 10 min of OLV (median collapse scores: $N_2O = 9/10$, $O_2 = 7/10$). Both are gases with relatively rapid uptake from the alveoli. Pfitzner et al.¹ suggest that a 50% N_2O/O_2 inspired gas mixture leads to earlier collapse during OLV than a pure O_2 mixture. This may be related, in part, to a "second gas" effect, whereby the rapid absorption of N_2O would facilitate O_2 uptake, or to a concentration effect or to the gas solubility. Similarly, Joyce et al.^{11,12} suggest that increasing the concentration of N_2O in mixtures of N_2O/O_2 will lead to a faster rate of collapse. The results of this current study corroborate this hypothesis based on our finding of more rapid lung collapse when N_2O is included in the inspired gas mixture during 2LV prior to initiation of OLV. However, after 20 min of OLV, there

was no significant difference in lung deflation scores between the two gases.

In the setting of ventilation with tidal volumes of 10 mL/kg, an F_{IO_2} of 1.0 and without PEEP, there were no significant differences in the arterial oxygenation in any of the three study groups beyond 10 min of OLV. The significantly higher levels of P_{aO_2} in the O_2 group before this are of no clinical benefit. Upon initiation of OLV, the O_2 group had a higher mean- P_{aO_2} than the other groups, which is not unexpected. However, despite starting from a higher P_{aO_2} , the progressive decline of P_{aO_2} values during OLV suggest that, once OLV is initiated, the arterial O_2 level is determined more by the F_{IO_2} than the pre lung-isolation gas mixture. The gravitational gradient and fall of the mediastinum in the open chest during OLV may be more important factors in the formation of atelectatic regions of the ventilated dependent lung than the gas mixture used during the initial period of 2LV ventilation. It would seem intuitive that the application of PEEP would alter the development of atelectasis in the dependent, ventilated lung. However, during OLV, PEEP may contribute to an increase in shunting of blood flow away from the dependent, ventilated lung in some patients, depending on the individual lung mechanics and the presence of intrinsic or "auto" PEEP.¹³

Limitations of this study include the fact that the study period for lung collapse, before allowing surgical resection to proceed, was limited to 20 min. Thus, it is not clear at what time the lung collapse would become equal among the groups. Another potential criticism is that the method of assessing lung collapse using the surgeon's rating scale was not completely objective and parametric. However, to use a more objective assessment, such as the distance of lung collapse away from the chest wall, would be clinically less relevant due to the differences in sizes of the patients' thoraces. The most clinically relevant assessment of the surgical access in the hemi-thorax is the surgeon's clinical impression, which was documented in this study. The majority of patients in this study had open thoracotomies, and the number of thoracoscopic procedures (AIR = 3, N_2O = 1, O_2 = 2) was too small to analyze as separate subgroups. It is not possible to be certain that these results can be extrapolated equally to patients having minimally invasive procedures, even though the physiology of one-lung anesthesia seems essentially the same for both types of surgery. The specific subgroup of thoracoscopic patients could be studied separately in the future. Another limitation is that the ability of nitrogen to decrease atelectasis in the ventilated lung and improve gas exchange during OLV may have been masked in the AIR group by switching to F_{IO_2} 1.0 during OLV. However, it is our standard clinical practice, and common in many other centers, to use an

F_{IO_2} of 1.0 at the start of OLV to avoid potential hypoxemia.

In summary, deflation of the nonventilated lung during thoracic surgery is delayed if air is used as part of the anesthetic technique during the initial period of 2LV. The use of N_2O during 2LV will increase the initial rate of lung collapse compared with 100% O_2 , but this effect is not significant after 20 min of OLV. Oxygenation during OLV with a F_{IO_2} of 1.0 is independent of the gas mixture used during 2LV. For thoracic procedures in which delayed collapse of the nonventilated lung will impede surgical exposure, the optimal anesthetic technique should include thorough de-nitrogenation of the lung which is to be collapsed, before OLV. Clinically, this can be done simply with ventilation using F_{IO_2} 1.0, unless the patient has a specific contraindication to the use of a high F_{IO_2} , such as previous bleomycin therapy.¹⁴ After the initiation of OLV, techniques to avoid atelectasis in the dependent ventilated lung, such as recruitment, the titration of air in the inspired gas mixture, and possibly PEEP may then be useful.

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