

Combination of nitrous oxide and the modified inflation-deflation method for identifying the intersegmental plane in segmentectomy: A randomized controlled trial

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Abstract

Background: During thoracoscopic segmentectomy, accurately and rapidly identifying the intersegmental plane (ISP) is of great importance. This study aimed to investigate the effect and safety of a nitrous oxide (N₂O)/oxygen (O₂) inspired mixture on the appearance time of the ISP (T_{ISP}) via the modified inflation-deflation method.

Methods: A total of 65 participants who underwent segmentectomy were randomized into three groups: 75% N₂O (n = 24), 50% N₂O (n = 23) or 0% N₂O (n = 18). The 75% N₂O group received a gas mixture of N₂O/O₂ (Fio₂ = 0.25), the 50% N₂O group received N₂O/O₂ (Fio₂ = 0.5), and the 0% N₂O group received 100% oxygen during lung expansion. The appearance time of satisfactory and ideal planes was recorded. Furthermore, arterial blood gas at breathing room air, one-lung ventilation (OLV) before lung expansion, 5 and 15 min after lung expansion were also recorded.

Results: T_{ISP} was significantly shorter in the 75% N₂O group (320.2 ± 65.9 s) compared with that of the 50% N₂O group (552.4 ± 88.9 s, p < 0.001) and the 0% N₂O group (968.3 ± 85.5 s, p < 0.001), while the 50% N₂O group was shorter than that of the 0% N₂O group (p < 0.001). Arterial oxygenation was significantly improved in the 0% N₂O group only after lung expansion, before which there were no differences in mean PaO₂ values among groups.

Conclusions: The use of N₂O in the inspired gas mixture during lung expansion is an applicable strategy to rapidly identify the ISP via the modified inflation-deflation method without any adverse effect on OLV related arterial oxygenation during segmentectomy.

KEYWORDS

intersegmental plane, lung segmentectomy, nitrous oxide

INTRODUCTION

Anatomical segmentectomy is one of many valuable surgical methods because of its many advantages, compared with lobectomy, especially in elderly patients with comorbidities and younger patients with early stage non-small cell lung cancer (NSCLC) or ground-glass opacities (GGOs).^{1, 2} Owing to structural variation, identification of the intersegmental plane

(ISP) still present difficulties for thoracic surgeons. To date, several methods for identifying the ISP have been reported, most of which belong to two categories which aim to develop inflation/deflation lines or inject indocyanine green either intravenously or intrabronchially.³⁻⁶ However, it has been reported that these methods have multiple limitations,⁷ and developing a new simple and practical approach to accurately determine the ISP is therefore urgently required.

The inflation-deflation method has been widely used for distinguishing the ISP in clinical practice without any

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additional auxiliary materials, in order to maintain the resected segment with a more precise physiological shape.⁸ The feasibility of this method has been previously demonstrated but some shortcomings exist such as a long waiting time for emergence of ideal demarcation, an obscure intersegmental border and that it is unsatisfactory in patients with varying degrees of emphysema. In view of these criticisms, a comprehensive understanding of the factors that affect the appearance of the ISP in this procedure is essential to improve this technology. During this process, the speed of the ISP formation is determined by the collapse rate of the preserved segments of nonventilated lung (NVL) after the initiation of one-lung ventilation (OLV).⁹ Furthermore, two distinct mechanisms are primarily involved in determination of the lung collapse. The first is inherent elastic recoil, which occurs immediately after pleural opening. However, this process is usually over within 60 s due to small airway closure. The second mechanism is continuous gaseous diffusion.¹⁰ Thus, effective strategies to promote the second phase of lung collapse are primarily achieved via acceleration of the rate of gaseous absorption in the alveoli.

The rate of gas uptake depends on the inspired gas composition and solubility of inert gas in the inspired mixture.¹¹ Based on this analysis, the inspired gas characterized by oxygen and an inert gas, such as nitrous oxide (N₂O), the rate of gas uptake is relatively fast.

Several lines of evidence have reported that inspired mixture gas containing N₂O could significantly accelerate the rate of gas absorption, thereby rapidly resulting in lung collapse.^{12–14} In this regard, we performed a prospective randomized trial to investigate the efficacy and safety of the combined modified inflation-deflation method with N₂O mixture inspired gas on the appearance time of the ISP (T_{ISP}) during segmentectomy.

METHODS

Study design and eligibility

This was a single-center, prospective, randomized controlled clinical trial. The study was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (approval No. 2019-SR-449), and registered at clinicaltrials.gov (NCT04302350). Written informed consent was obtained from all participants.

Patients with pulmonary nodules scheduled to receive video-assisted segmentectomy between January 15, 2020, and July 15, 2020, at the First Affiliated Hospital of Nanjing Medical University were enrolled. The inclusion criteria were as follows: (i) patients with a persistent (with at least a three-month follow-up) pulmonary nodule (maximum diameter ≤ 2 cm) with 50% or more GGOs on thin-slice computed tomography (CT), indicating an underlying malignancy; (ii) no evidence of lymph nodes or distant metastases; or (iii) patients at high risk owing to poor general condition and unable to tolerate a standard lobectomy

(severe cardiopulmonary insufficiency, coagulation defects and other surgical contraindication), and in expectation of preserving pulmonary function. Patients with evidence of bullae on chest radiography (maximum diameter >1 cm) and patient refusal were excluded. Before surgery, high-resolution lung nodule CTA (iopromide) and three-dimensional CT bronchography and angiography (3D-CTBA) were applied to confirm the location of nodules and associated vessels and bronchi.

Randomization

Eligible individuals were randomly assigned to the 75% N₂O group, 50% N₂O group or 0% N₂O group with a 1:1:1 allocation. Randomization was carried out using computer online software (Research Randomizer Version 4.0 at <https://www.randomizer.org>). Concealment was carried out using opaque envelopes, which were opened after the patients arrived in the operating room. Due to the double-blinded study design, all participants, surgeons, research staff, and statisticians were blinded to treatment allocation. The group situation was known to an anesthesiologist who did not take part in follow-up, data collection/study outcomes analysis, and the outcome assessors who were unaware of the nature of the study.

Sample size calculation

The appearance time of the ISP was the primary outcome. There are no previously published data demonstrating T_{ISP} with N₂O mixed gas. Based on our experience, and data from a similar study using nitrogen-containing air in the inspired gas mixture,⁸ we estimated the mean T_{ISP} to be 180 s. We conducted the preliminary study with nine patients (three in each group), and then sample size calculation was performed with PASS V.11.0 (PASS, NCSS) for Windows. Sample size calculations were based on (i) $\alpha = 0.05$ (two-sided tailed), and (ii) 80% power. On the basis of these data, a power analysis indicated that the required sample size of 16 patients for each group was deemed necessary. Considering the possible protocol dropouts and incomplete follow-up, we ultimately decided to enroll 65 patients in our trial (Figure 1).

Operative procedure

All patients underwent general anesthesia with double-lumen endotracheal intubation, and then OLV of the dependent lung with Fio₂ = 1.0 was commenced in the lateral decubitus position. To eliminate any possible effects of surgical technique, all procedures were performed by the same surgical team. Common three-port technique for video-assisted thoracoscopic surgery (VATS) segmentectomy was used. The utility port (3 cm) was on the fourth or fifth intercostal space (ICS) of the anterior axillary line. The other two

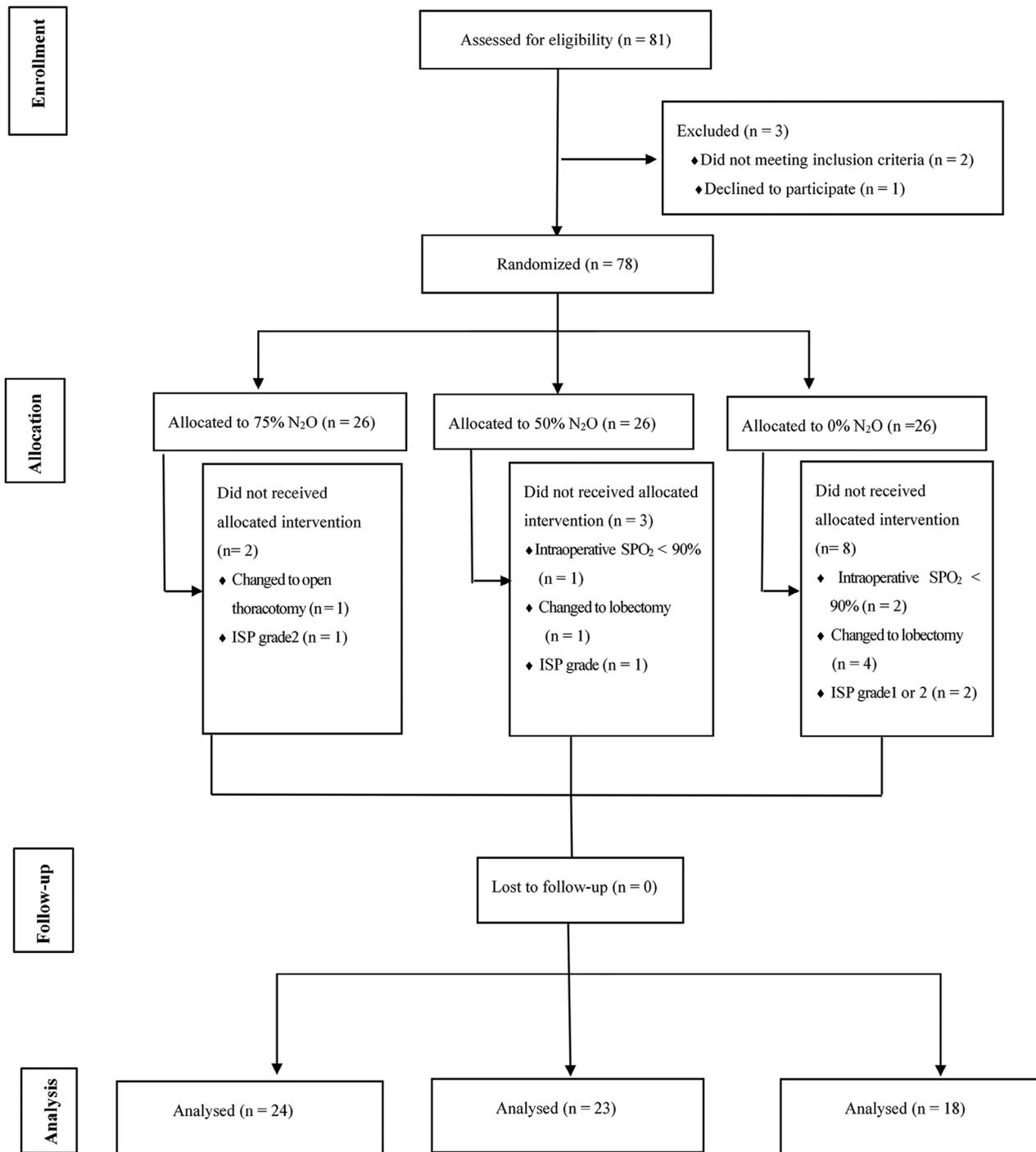


FIGURE 1 The study flow diagram

ports (2 cm) were in the seventh or eighth ICS of the midaxillary and posterior axillary lines. Under the guidance of real-time 3D navigation and simulated navigation technique, the targeted segmental bronchi, arteries, and intrasegmental veins were accurately identified and dissected by ligation or stapler cutting. After the targeted segment structures were successfully dissected, a portable nitrous oxide concentration detector (TD600-SH-B-N₂O, TianDi) was installed by an anesthesiologist to measure N₂O

concentration (vol%). To avoid the interference of the total gas flow, the flow of gas mixture was set to 8 l/min (75% N₂O group N₂O:O₂ = 6:2, 50% N₂O group N₂O:O₂ = 4:4, 0% N₂O group O₂ = 8). When the N₂O concentration detector reached the predetermined gas concentration, the collapsed lung was completely re-expanded with controlled airway pressure under 20 cmH₂O (1 cm H₂O = 0.098 kPa), and then Fio₂ = 1.0 was performed after the initiation of the OLV (Figure 2).

Finally, the preserved segments were deflated, but the targeted segments were kept inflated so that an irregularly curved demarcation was identified naturally. The inside two-thirds of the parenchyma were then separated along the intersegmental veins using electrocautery, and the peripheral one third of the parenchyma was detached along the ISP with endostaplers. The resected segment was taken out in a specimen bag, and perioperative frozen section pathology was then performed. The nodal sampling of N1 and N2 lymph nodes were routinely performed to evaluate for the possibility of occult nodal metastases. If the surgical margin was insufficient, or any lymph node was diseased, lobectomy with systemic lymphadenectomy was performed. The pathological diagnosis staging was determined based on the eighth edition of the Union for International Cancer Control (UICC) tumor node metastasis (TNM) classification.¹⁵

Measurement of clinical outcomes

To evaluate the ISP distribution, we classified the border clarity into four grades at 0–20 min after initiation of the OLV: 1 = poor collapse of the preserved segments and more than half of the border unclear; 2 = partial collapse of the preserved segments; 3 = more than half of the preserved segments had collapsed and border almost clear; 4 = circumferentially clear (Figure 3). Two surgeons (L.C. and Q.Z.) blinded to the randomization evaluated the grades independently, and disagreements were resolved by consensus. A border clarity by a grade of 3 or 4 was considered to be satisfactory and ideal. T_{ISP} was recorded simultaneously, which was also the primary outcome of this trial. Additionally, the start time point of T_{ISP} was when the whole lungs had completely re-expanded. The end point was when the preserved segment was fully deflated, and a boundary had formed between the targeted segment and the reserved lung. This plane does not significantly change over time. When grade 1 or 2 was identified, surgeons divided the targeted segment along the intersegmental/intersubsegmental veins.

Secondary outcomes included peripheral oxygen saturation (SpO_2) and arterial blood gases obtained when the

patient was breathing room air (RA), OLV before lung expansion (OLV), 5 and 15 min after the lung expansion, duration of surgery, the incidence of postoperative complications (including air leak, chylothorax, atelectasis, pulmonary embolism, and pulmonary infection), total thoracic drainage, duration of drainage and postoperative hospital stay.

Statistical analysis

All data were analyzed using SPSS software version 24 (IBM SPSS). Continuous variables analysis was performed by one-way analysis of variance (ANOVA), and post-hoc was analyzed by least significant difference (LSD) comparison. Continuous descriptive variables were reported as mean \pm standard deviation (SD). Categorical variables expressed in percentage were analyzed using Chi-square. A two-tailed p -value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 81 patients with pulmonary nodules for segmentectomy were eligible for enrollment into the study. Three patients were excluded (one refused to participate in the trial, and two did not meet the inclusion criteria). Finally, 78 patients were randomly divided into the 75% N_2O group ($n = 26$), the 50% N_2O group ($n = 26$), and the 0% N_2O group ($n = 26$). During the surgical procedure, 13 patients were excluded in the final analysis (one case was changed to open thoracotomy, five cases were changed to lobectomy, three cases had intraoperative $SPO_2 < 90\%$, and four cases were grades 1/2). The final analysis included 24 patients in the 75% N_2O group, 23 patients in the 50% N_2O group, and 18 patients in the 0% N_2O group (Figure 1). Patient characteristics were equal among the three groups and are shown in Table 1. The location of the resected segments was well balanced among groups (Table S1).

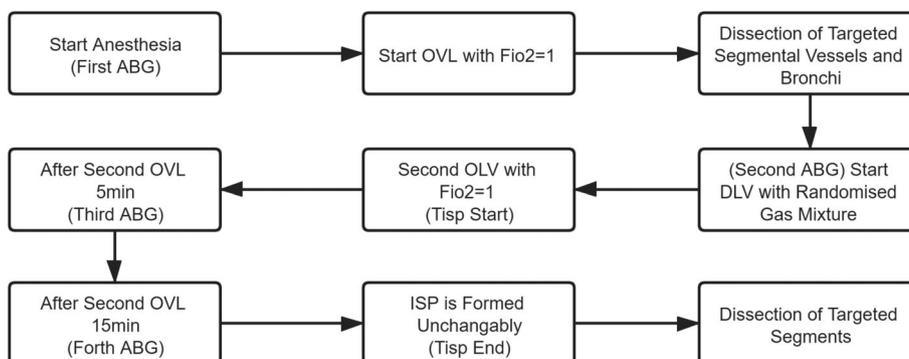


FIGURE 2 Experimental strategy. ABG, arterial blood gases; OLV, one-lung ventilation; DLV, double lungs ventilation; T_{ISP} , the appearance time of intersegmental plane

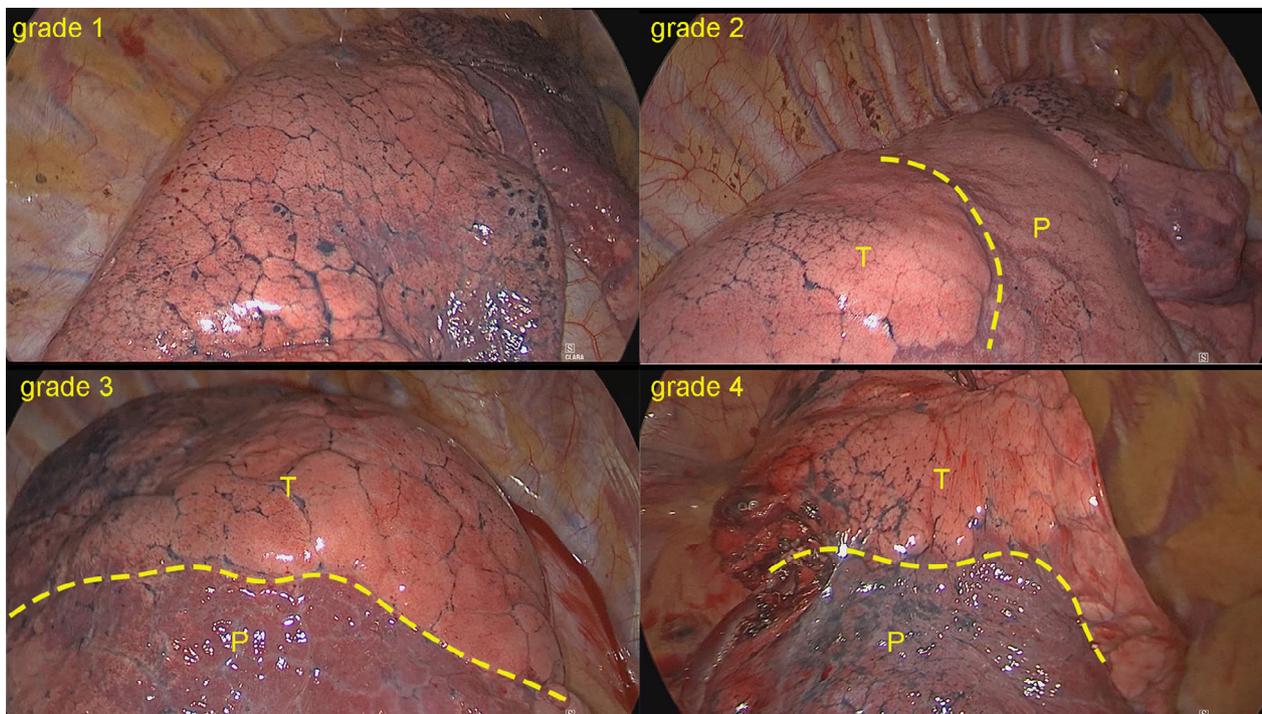


FIGURE 3 Inflation-deflation line clarity evaluation: 1 = poorly collapse of the preserved segments and more than half of border unclear; 2 = partial collapse of the preserved segments; 3 = more than half preserved segments collapsed and border almost clear; 4 = circumferentially clear. T, targeted segment; P, preserved segment; dotted line: intersegmental boundary (based on intersegmental veins)

Treatment outcomes

One-way ANOVA indicated a significant difference in the T_{ISP} among the three groups ($F = 338.6$, $p < 0.001$). Post hoc analysis showed that T_{ISP} was significantly shorter in the 75% N_2O group (320.2 ± 65.9 s), as compared with the 50% N_2O group (552.4 ± 88.9 s, $p < 0.001$) and the 0% N_2O group (968.3 ± 85.5 s, $p < 0.001$) with a significant difference between the latter two groups ($p < 0.001$) (Figure 4). Additionally, N_2O exerted a concentration-dependent change on T_{ISP} .

There were no significant differences in average values of SpO_2 and PaO_2 at baseline among groups (Table 1). The 0% N_2O group (392.1 ± 94.4 mmHg) had a higher PaO_2 after 5 min of lung expansion as compared with the 75% N_2O group (204.7 ± 59.3 mmHg, $p < 0.001$) and the 50% N_2O group (260.2 ± 86.6 mmHg, $p < 0.001$), and the 50% N_2O group was higher than in the 75% N_2O group ($p = 0.021$). This difference in arterial oxygenation in 0% N_2O (301.7 ± 67.0 mmHg) versus the other groups was still present after 15 min of lung expansion (75% N_2O group = 233.3 ± 81.0 mmHg, $p = 0.006$; 50% N_2O group = 251.4 ± 78.2 mmHg, $p = 0.042$), whereas there was no difference between the latter two groups (Figure 5 (a)). No significant differences in mean SpO_2 values were seen between groups at the different study periods (Figure 5(b)).

Surgical outcomes

The duration of surgery, total thoracic drainage volume after the operation, duration of drainage, postoperative hospital

stay, and the incidence of postoperative complications did not differ among the three groups (Table 2). Furthermore, 13 cases had postoperative complications: two cases developed air leak, one case developed chylothorax, two cases developed atrial fibrillation, three cases developed pneumothorax after chest tube withdrawal, and eight cases developed pneumonia, and all patients recovered after conservative management. The postoperative pathological diagnoses exhibited in situ adenocarcinoma (27 cases), invasive adenocarcinoma (26 cases), minimally invasive adenocarcinoma (eight cases), sclerosing pneumocytoma (one case), cryptococcal infection (one case), atypical adenomatous hyperplasia (one case), and metastatic carcinoma (one case) (Table S2).

DISCUSSION

Thoracoscopic segmentectomy is increasingly becoming a popular procedure in thoracic surgery, and is utilized as a more prominent option for the treatment of small-sized early-stage lung cancers.¹⁶ Recently, many studies have demonstrated that VATS segmentectomy for early-stage lung cancers provides equivalent oncologic outcomes and greater preservation of lung function compared with lobectomy.^{2, 17, 18} Moreover, compared with wedge resection, an adequate surgical margin can be achieved with segmentectomy, and intrapulmonary lymph node sampling performed, which reduces local recurrence and metastasis of malignant tumors.^{19–21} There has therefore been an increased interest in VATS segmentectomy for the treatment of early-stage lung

TABLE 1 Demographic and baseline characteristics

	75% N ₂ O	50% N ₂ O	0% N ₂ O	p-value
No. of cases	24	23	18	
Age (year)	54.0 ± 9.6	52.5 ± 10.9	50.5 ± 13.1	0.598
Gender n (%)				0.297
Male	9 (37.5)	4 (17.4)	6 (33.3)	
Female	15 (62.5)	19 (82.6)	12 (66.7)	
Weight (kg)	60.5 ± 11.1	57.4 ± 11.0	60.8 ± 7.9	0.242
Body mass index (kg/m ²)	22.9 ± 3.0	21.6 ± 3.3	22.3 ± 2.4	0.317
Smoking history n (%)	1 (4.2)	3 (13.0)	2 (11.1)	0.190
ASA n (%)				0.680
I	17 (70.8)	15 (65.2)	14 (77.8)	
II	7 (29.2)	8 (34.8)	4 (22.2)	
COPD n (%)	2 (8.33)	3 (13.0)	3 (16.7)	0.712
Pulmonary function				
FEV-1 (%)	80.9 ± 4.7	84.0 ± 6.4	80.2 ± 6.8	0.090
RV/TLC (%)	40.9 ± 6.5	41.6 ± 6.7	39.1 ± 7.3	0.499
DLCO (%)	94.1 ± 15.9	90.6 ± 10.9	88.1 ± 11.4	0.353
MVV (%)	91.7 ± 22.2	97.2 ± 18.6	98.7 ± 16.1	0.466
Arterial blood gas and SpO ₂ on room air				
SpO ₂ (%)	98.0 ± 1.5	97.5 ± 1.2	97.7 ± 1.2	0.443
PaO ₂ (mmHg)	90.0 ± 12.9	93.2 ± 14.7	93.8 ± 10.1	0.587

Note: Data are expressed in mean ± SD or number (%).

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV, forced expiratory volume; MVV, maximal voluntary ventilation; RV, residual volume; TLC, total lung capacity.

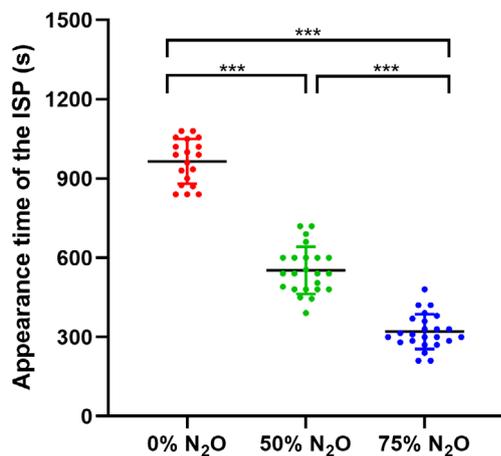


FIGURE 4 The appearance time of the intersegmental plane (T_{ISP}) among three groups. *** $p < 0.001$

cancer. Nevertheless, whilst segmentectomy has interesting superiorities, distinguishing the ISP remains a crucial technical challenge.

A clear and adequate demarcation of the ISP is a crucial factor during segmentectomy, as it is necessary to obtain sufficient resection margins and complete removal of the segment containing the nodules.²² Multiple methods have been proposed to identify the ISP, with each approach

having various pros and cons.⁷ The technique based on near-infrared (NIR) fluorescence imaging with intravenous indocyanine green (ICG) to identify lung resection borders has recently advanced considerably, and its application has been reported in several studies.^{4, 5, 9} This method limits fluorescence visualization to only a few minutes, and the boundary line gradually becomes obscure due to initial non-uniform distribution of ICG and distribution of ICG into adjacent areas. Additionally, this method is not suitable for patients allergic to ICG. Rubenstein et al. proposed a traditional lung inflation–deflation method, which induced the collapse of the segment to be resected and inflation of the remaining lung. However, with this method, the plane became blurred due to the influence of collateral ventilation and the inflation of the segment limits the thoracoscopic working space.²³ To overcome these problems, Tsubota et al. reported a “reverse technique” which is the complete opposite of the conventional inflation–deflation technique mentioned above which clamps the targeted segmental bronchus after the lung has been fully inflated, thereby leaving the targeted segment inflated.³ Okada et al. conducted a prospective study of a method to distinguish the ISP using selective jet ventilation under intraoperative bronchofiberscopy through the hybrid VATS. This approach provided a quick and easy identification of the ISP, while the positioning operation of the bronchi, especially the subsegmental bronchi, is extremely demanding.²⁴ Based on this analysis, Wang et al. described a

FIGURE 5 Mean SpO₂ (a) and PaO₂ (b) values for the patients randomized to 75% N₂O group, 50% N₂O group and 0% N₂O group, measured while breathing room air (RA), one-lung ventilation before lung expansion (OLV), 5 min and 15 min after the lung expansion. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

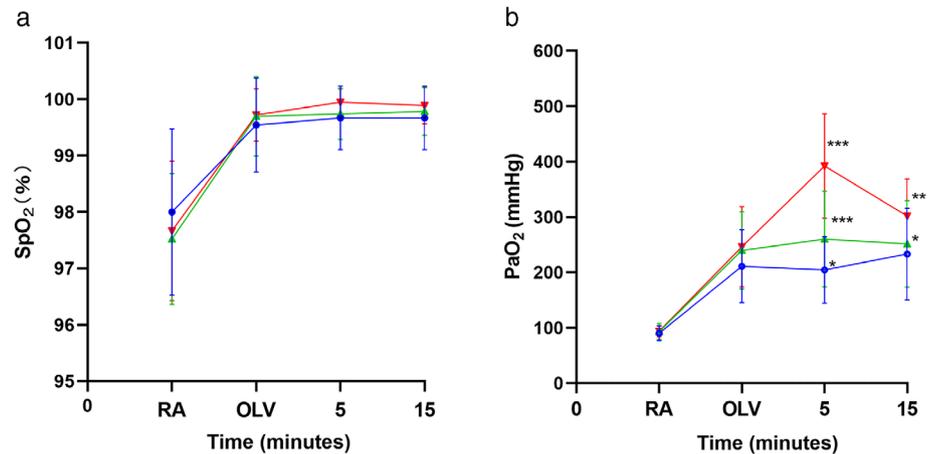


TABLE 2 Perioperative characteristics

	75% N ₂ O	50% N ₂ O	0% N ₂ O	<i>p</i> -value
Duration of surgery (min)	148.8 ± 28.4	134.4 ± 23.8	139.4 ± 22.6	0.157
Total drainage (ml)	525.0 ± 392.4	596.9 ± 406.6	461.9 ± 254.4	0.508
Duration of drainage (days)	2.5 ± 0.9	3.3 ± 2.3	2.4 ± 0.9	0.347
Postoperative hospital stay (days)	4.5 ± 0.9	4.3 ± 2.2	3.8 ± 1.4	0.098
Postoperative complications (n[%])	5(20.8)	4(17.4)	7(38.9)	0.304
Air leakage	1(4.2)	0	0	0.420
Chylothorax	0	1(4.4)	1(5.6)	0.533
Pneumothorax	1(4.2)	0	2(11.1)	0.241
Pneumonia	2(8.3)	3(13.0)	3(16.7)	0.712
Atrial fibrillation	1(4.2)	0	1(5.6)	0.550

Note: Data are expressed in mean ± SD or number (%).

“modified inflation–deflation method” for tailoring complex demarcations in segments using 100% oxygen to expand the lung;⁸ however, it usually takes about 15–20 min to visibly identify the ISP after inflation. Accordingly, we now report a novel method based on a modified lung inflation–deflation method using N₂O mixed gas inhalation which determines the ISP rapidly and has been shown to be safe and efficient.

The specific procedure of the method is that after accurately dissecting the targeted segmental bronchi, arteries, and intrasegmental veins, under the guidance of 3D navigation, the whole lung is re-expanded using N₂O mixture gas. Additionally, the suggested transpulmonary pressure should not exceed 20 cmH₂O, to avoid re-expansion and reduce possible pressure-associated lung trauma.⁸ Recently, Yao et al. demonstrated the validity and accuracy of a collateral ventilation method for ISP identification, which provided the basis for our novel method.²⁵ When a lung segment is inflated by positive ventilation, the pressure gradient makes the gas flow through collateral pathways into the adjacent segments, which makes the targeted segment fully inflate. After resuming the OLV, the preserved segments gradually collapsed by the circulation and gaseous exchange, while

the targeted segment was still in an inflated state, thus naturally demarcating an irregular and reliable inflation–deflation line, and this does not change over time.

Numerous published studies have demonstrated that the use of N₂O in the inspired mixture gas could accelerate the rate of atelectasis.^{12, 13} In theory, the rapid uptake of N₂O is due to low solubility in the blood (blood/gas distribution coefficient of 0.47) along with an inability to bind to hemoglobin, leads to a further uptake by the circulation. Moreover, after initiation of OLV with 100% oxygen, the ongoing exhalation of N₂O from the ventilated lung will increase the pressure gradient of N₂O in the NVL resulting in a faster uptake of N₂O. On the other hand, if ventilation is with pure oxygen, gaseous uptake is limited by the magnitude of the shunt and the oxygen-carrying capacity of hemoglobin.¹³ Indeed, the results of this study support the hypothesis that N₂O-O₂ inhaled gas mixture hastens preserved lung collapse after initiation of the OLV, and then accelerates the appearance of intersegmental demarcation. Furthermore, time to the ISP appearance was significantly shorter in the 75%N₂O group by approximately 4 min, as compared to the 50% N₂O group, which could avoid the waiting time required

for the inflated lung to deflate, thereby reducing the operating time.

There is no doubt that the 0% N₂O group had a higher average PaO₂ value after the initiation of OLV, although the significantly higher levels of PaO₂ were of no clinical benefit. There were no significant differences in the value of SpO₂ among the three groups. Indeed, the changes in SpO₂ were less dramatic than PaO₂ due to the slope of the oxygen dissociation curve at the high PaO₂ levels.²⁶ Considering the specific contraindication of N₂O in patients with bullae, for example, the method of using the N₂O mixture should be approached with caution. In addition, there has been concern about using highly concentrated N₂O, which potentially has a risk of causing diffusion hypoxia and surgical wound infection. However, these adverse effects are not consistent with some other studies and are probably as a result of low Fio₂ and long duration exposure.^{27, 28} Accordingly, the procedure of our method, which only used 75% N₂O in a short period of time, should have minimal adverse oxygenation effects, and the patients could tolerate a “touch of” diffusion hypoxia. Also, after applying with high concentrated N₂O to expand lungs, the OLV of the dependent lung was started with a Fio₂ = 1.0, which could reverse potential hypoxia to some extent.

The factors influencing the visualization of the ISP are accurate intersegmental identification and difficulty in dissection.²⁹ As a result of the preoperative 3D-CTBA model not fully coinciding with the actual anatomy intraoperatively, four cases did not initially develop a satisfactory border. More interestingly, we found these cases were almost all patients with smoking-related lung diseases or chronic pulmonary emphysema. Indeed, in patients with emphysematous lungs who may demonstrate gas trapping and reduced elastic recoil it is not easy to visualize the plane and may prolong waiting time for demarcation to appear. Thus, the formation of an available demarcation is closely related to precise reconstruction results and pulmonary parenchyma quality. Moreover, Sun et al. have verified that the modified inflation-deflation method and the NIR fluorescence imaging with intravenous ICG method are totally concordant, which is highly concordant with the real intersegmental demarcation.⁹

The prominent advantages of our method in VATS segmentectomy are as follows: (1) N₂O is an agent which is easy to use, and easy to monitor. (2) N₂O mixture inhaled for a short time does not lead to a risk of potential hypoxia. (3) The appearance of the ISP is fast and efficient. (4) The demarcation persists during surgery and does not become blurred with the passage of time. (5) It provides a satisfactory surgical field of vision because only the targeted segment is inflated, allowing the surgeon to achieve curative resections with free surgical margins, (6) No morbidity and mortality related to this method have been previously observed in research. However, this method still has some limitations: (1) Because of structural variation of the targeted segment, an adjacent segmental pulmonary artery feeds a part of the targeted segment, and if the feed vessels cannot be identified and divided, this can lead to partial

collapse of the targeted segment, thus making the inflation-deflation line inaccurate. (2) In elderly patients with emphysema, which is a problem in almost all the lung ventilation methods, the formation of the ISP is inefficient and takes longer, thereby causing a reduction in the quality of surgical guidance. (3) This method additionally requires engagement of specialized anesthesiologists who are experts in the procedures and are familiar with the protocols.

However, this study has several limitations. First, the method of judging the ISP was not entirely parametric and objective. However, there is no objective and universal way to measure the ISP thus far. The most clinically relevant assessment of surgical access is the surgeon's clinical impression, which was documented in this study. Second, we only analyzed successful cases, while those cases which failed were excluded. Third, the study period for arterial blood gas was limited to 15 min after lung expansion due to the restrictions of the surgical procedure. Thus, it is not clear at what time PaO₂ values would become equal among the groups. Fourth, the study did not include details on postoperative pulmonary function, which made it difficult to assess the long-term effects of this method on postoperative pulmonary function recovery. Fifth, this was a small-size, single-center study with short-term follow-up; indeed, further larger and multi-center studies are greatly needed.

In conclusion, the combination of N₂O mixed gas inhalation and a modified inflation-deflation method is available to quickly identify the ISP without further impairments in subsequent arterial oxygenation during OLV. However, the concrete physiological mechanisms and factors that N₂O affecting inflation-deflation development time still require further detailed studies.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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