Apneic oxygen insufflation decreases the incidence of hypoxemia during one-lung ventilation in open and thoracoscopic pulmonary lobectomy: A randomized controlled trial

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ABSTRACT

Objective: Hypoxemia is common during one-lung ventilation (OLV) for thoracic surgery. When hypoxemia occurs, surgery is interrupted for rescue ventilation. Apneic oxygen insufflation (AOI), which provides O₂ without applying pressure, may prevent hypoxemia and does not interrupt surgery. The aim of this study was to determine the effectiveness of the AOI technique for preventing hypoxemia during OLV in thoracic surgery.

Methods: Patients undergoing open or thoracoscopic pulmonary lobectomy from September to December 2015 were included. Patients were assigned randomly to a non-AOI group or an AOI group (n = 45 each). OLV was initiated and at the 15-minute mark (OLV15), patients in the AOI group received oxygen insufflation at 3 L/min to the nonventilated lung for 30 minutes (OLV45). The primary endpoint was the occurrence of hypoxemia (SaO₂ <90%) during OLV.

Results: The demographic and operative data were similar between the 2 groups. The incidence of hypoxemia was greater in the non-AOI than the AOI group (18% vs 0%; *P* = .009). ΔPaO₂ (the difference in partial pressure of oxygen in arterial blood between OLV 45 and 15 minutes) was smaller in the AOI than the non-AOI group (−29 mm Hg vs −69 mm Hg; *P* = .005). Duration of surgery and incidence of complications did not vary between groups.

Conclusions: AOI decreases the incidence of hypoxemia and improves arterial oxygenation during OLV for open and thoracoscopic surgery. AOI may be a valuable option to prevent hypoxemia. It can be used before relying on continuous positive airway pressure or intermittent two-lung ventilation and result in fewer interruptions in surgery. (*J Thorac Cardiovasc Surg* 2017;154:360-6)

Apneic oxygen insufflation technique.

Central Message

Apneic oxygen insufflation can prevent hypoxemia during one-lung ventilation.

Perspective

Hypoxemia is common during one-lung ventilation for thoracic surgery. Apneic oxygen insufflation (AOI) can provide oxygen without applying pressure. We evaluated the effectiveness of the AOI technique for preventing hypoxemia without interruption of surgery during one-lung ventilation.

See Editorial Commentaries pages 367 and 369.

Hypoxemia, defined as a decrease in arterial oxygen saturation (SaO₂) < 90%, is not uncommon during one-lung ventilation (OLV), and the reported incidence is in the range of 1% to 24% in thoracic surgery.¹⁻⁴ Because life-threatening situations arise with hypoxemia, various

measures are taken to restore normoxia.⁵ While finding correctable causes such as double-lumen tube (DLT) malposition, attempts to reverse the ventilation/perfusion mismatch are tried.⁵

To improve ventilation/perfusion mismatch, continuous positive airway pressure (CPAP) 5 to 10 cm H₂O is used before resorting to intermittent two-lung ventilation (TLV).⁶ Applying CPAP, however, requires interrupting surgery for a recruitment maneuver, and the subsequent

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Scanning this QR code will take you to a supplemental video for the article.

Abbreviations and Acronyms

AOI	= apneic oxygen insufflation
CPAP	= continuous positive airway pressure
CRP	= C-reactive protein
ΔPaO_2	= partial pressure of oxygen in arterial blood at OLV45 – PaO_2 at OLV15
DLT	= double-lumen tube
HPV	= hypoxic pulmonary vasoconstriction
OLV	= one-lung ventilation
OLV15	= OLV at the 15-minute mark
OLV30	= OLV at the 30-minute mark
OLV45	= OLV at the 45-minute mark
PaO_2	= partial pressure of oxygen in arterial blood
SaO_2	= arterial oxygen saturation
TLV	= two-lung ventilation
WBC	= white blood cell

surgical view is impaired substantially.⁷ Although one report showed that a low level of CPAP is effective at reversing the hypoxemia and provides a good surgical field, the study was confined to open thoracic surgery.⁸

Intermittent positive pressure,⁹ selective segmental lung insufflations,¹⁰ and apneic oxygenation¹¹⁻¹⁴ have been introduced as alternatives to CPAP; however, reports on these methods have limitations because they are preliminary studies,⁹⁻¹⁴ include a small number of cases,⁹⁻¹¹ or are noncontrolled and nonrandomized trials.^{9-11,13,14} Therefore, to date, no generally accepted replacement or supplementary method for CPAP is available in hypoxic situations during OLV. Apneic oxygen insufflation (AOI) is to infuse O_2 through an endotracheal tube without applying pressure.¹⁵ If AOI increases arterial oxygenation without interfering with surgery, it could help prevent hypoxemia and result in an adequate surgical environment during thoracic surgery.

Therefore, we conducted a randomized controlled trial of the AOI technique during OLV. We hypothesized that AOI technique would decrease the incidence of hypoxemia by 20% compared with the control technique in patients undergoing OLV for open or thoracoscopic pulmonary lobectomy.

METHODS

This prospective, randomized study was approved by the local institutional review board (SMC 2015-06-020) and registered with the Clinical Research Information Service (KCT0001629; principal investigator: Hyun Joo Ahn; date of registration: September 15, 2015). Written informed consent was obtained from all eligible patients before enrollment.

Study Population

Adult patients (aged > 19 years) scheduled for elective open or thoracoscopic lobectomy in a single tertiary-care academic hospital were recruited. Exclusion criteria were American Society of Anesthesiologists physical status > III and moderate degree lung disease by our institutional

pulmonary function test guideline (either forced expiratory volume in 1 second/forced vital capacity < 60% and forced expiratory volume in 1 second < 50% or forced vital capacity < 50%).

Patients with cardiac disease (history of angina, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass graft), cerebrovascular disease (history of cerebral infarction, cerebral hemorrhage, and dementia), or liver disease (history of liver cirrhosis and hepatitis) were not excluded, and patients with pulmonary disease (chronic obstructive pulmonary disease, bronchiectasis, asthma, interstitial lung disease) but who did not meet the exclusion criteria were not excluded.

Randomization and Blinding

Consenting study participants were assigned randomly to 1 of 2 arms, a non-AOI group or an AOI group, by the use of computer-generated random numbers with a fixed block size of 4 on a 1:1 ratio. The investigator in charge of randomization wrote the patient's allocation on paper and sealed it in an opaque envelope. Experimental setup was completed before the induction of anesthesia. The principal investigator or coinvestigator opened the envelope to identify the assignment immediately before OLV initiation and turned the oxygen flow meter on or off according to group assignment. The flow meter was covered with an opaque cloth. Surgeon, patients, attending anesthesiologists, data recorder, and analyzer were blinded about group assignment.

FIGURE 1. Apneic oxygen insufflation technique using endobronchial suction catheter and oxygen tubing. The suction catheter connected to oxygen flow meter was inserted into the non-ventilated side of the DLT. The lumen of DLT was open completely, and the catheter went through the full lumen of the tube as opposed to the smaller capped hole on DLT; thus, space between the suction catheter and the DLT lumen enabled free passage of gas. Insertion depth was predetermined and marked on the suction catheter before insertion. Predetermined depths were 1 cm beyond the opening of endobronchial lumen or 2 cm beyond the opening of endotracheal lumen, depending on the nonventilated side.

VIDEO 1. AOI technique. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)30416-6/addons](http://www.jtcvsonline.org/article/S0022-5223(17)30416-6/addons).

Anesthesia and Monitoring

All patients were monitored by 3-lead electrocardiogram, pulse oximetry, and noninvasive blood pressure before induction. Intubation was performed with a DLT (Broncho-Cath; Mallinckrodt Laboratories, Athlone, Ireland), and tube position was confirmed by fiberoptic bronchoscopy. An arterial catheter was placed in the radial artery opposite the surgical site. SaO_2 was measured indirectly on the index finger by the use of an adhesive pulse oximeter (Oxysensor II; Covidien, Minneapolis, Minn). Tidal volume was set to a target of 8 mL/kg predicted body weight during TLV and changed to 6 mL/kg during OLV with 5 cm H_2O of positive end-expiratory pressure. Ventilation rate was adjusted to keep end-tidal carbon

dioxide levels between 30 and 45 mm Hg. A 1.0 fraction of inspired oxygen was applied before OLV to facilitate lung collapse.¹⁶ After the beginning of OLV, fraction of inspired oxygen was decreased to 0.5 and maintained until the end of the study.

Surgery

Seven thoracic surgeons, who performed more than 140 major pulmonary resections per year, conducted operations and were unaware of group assignments. Lobectomies were performed through standard posterolateral thoracotomy or video-assisted thoracoscopic surgery as indicated. Vessels and bronchi of the target lobe were dissected individually. For patients with non-small cell lung cancer, a systematic lymph node dissection was mandatory.

Study Protocol

OLV was initiated and at the 15-minute mark (OLV15), and patients in the AOI group received oxygen insufflation at 3 L/min to the nonventilated lung for 30 minutes (OLV45). Patients not receiving AOI were not supplied with oxygen but otherwise were prepared in the same manner as patients receiving AOI. When SaO_2 decreased to less than 90%, rescue maneuvers (CPAP or TLV) were started.

Arterial blood gas analysis was conducted shortly before the beginning of oxygen insufflation (OLV15) and at 15 minutes (OLV30) and 30 minutes (OLV45) into the study. Hemodynamic and ventilatory variables were recorded at 5-minute intervals during the study period by a blinded recorder.

AOI Technique

We used a Mallinckrodt endobronchial suction catheter (10 Fr; Covidien) and oxygen tubing (7-ft Star Lumen Tubing; Hudson RCI, Morrisville, NC) for the AOI technique. One end of the oxygen tubing was connected to an independent oxygen flow meter of the ventilator, which was covered with an opaque cloth; the other end was connected to a suction

FIGURE 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. AOI, Apneic oxygen insufflation.

TABLE 1. Patient characteristics in non-AOI and AOI groups

Variables	Non-AOI (n = 45)	AOI (n = 45)	P value
Age, y	62 ± 10	62 ± 9	.9
Male	28 (62)	29 (64)	.8
BMI, kg/m ²	24.4 ± 2.4	24.0 ± 2.5	.4
Current smoker	10 (22)	6 (13)	.3
Preoperative lung injury*	10 (22)	11 (24)	.7
Comorbidities			
Charlson comorbidity index score	4.2 ± 1.4	4.4 ± 1.4	.7
Hypertension	19 (42)	16 (36)	.5
Diabetes	11 (24)	7 (16)	.3
Angina/MI/CABG	2 (4)	3 (7)	1
Renal disease	1 (2)	0 (0)	1
Cerebral disease	2 (4)	2 (4)	1
Liver disease	1 (2)	1 (2)	1
Normal EKG	44 (98)	44 (98)	1
FEV1, L	2.7 ± 0.7	2.8 ± 0.5	.6
DLCO, mL/mm Hg/min	3.7 ± 0.9	3.7 ± 0.7	.9
Left/right surgery	27 (60)/18 (40)	28 (62)/17 (38)	.8
VATS/open lobectomy	23 (51)/22 (49)	24 (53)/21 (47)	.8

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed in number (percentage). Group differences were compared by χ^2 or Fisher exact tests for categorical variables and 2-sample *t* tests for continuous variables. There were no differences between groups. *AOI*, Apneic oxygen insufflation; *BMI*, body mass index; *MI*, myocardial infarction; *CABG*, coronary artery bypass graft surgery; *EKG*, electrocardiography; *FEV1*, forced expiratory volume in 1 second; *DLCO*, diffusing capacity of the lung for carbon monoxide; *VATS*, video-assisted thoracoscopic surgery. *Preoperative lung injury includes chronic obstructive pulmonary disease, bronchiectasis, asthma, and interstitial lung disease.

catheter. The opening on the connector of the suction catheter was sealed with surgical silk plaster to prevent air leakage. The suction catheter was introduced into the nonventilated side of the DLT. The lumen of DLT was open completely, and the catheter went through the full lumen of the tube as opposed to the smaller capped hole on DLT; thus, space between the suction catheter and the DLT lumen enabled the free passage of gas. Insertion depth was predetermined and marked on the suction catheter

before insertion. Predetermined depths were 1 cm beyond the opening of endobronchial lumen or 2 cm beyond the opening of endotracheal lumen, depending on the nonventilated side (Figure 1, Video 1).

Outcomes

The primary outcome was incidence of SpO₂ < 90%. Secondary outcome was ΔPaO₂ (partial pressure of oxygen in arterial blood [PaO₂] at OLV45 – PaO₂ at OLV15). Duration the operation, the incidence of postoperative complications and postoperative white blood cell (WBC) and C-reactive protein (CRP) also were recorded. Categories of postoperative complications were pulmonary, cardiovascular, urologic, neurologic, and wound problems.

Statistical Analysis

In a previous study, the incidence of SpO₂ < 90% was 24%.⁴ χ^2 tests with a one-sided alpha of 5% for 20% decrease in incidence of hypoxemia required 80 patients for 80% power. Given up to 10% dropout or ineligibility, we planned to recruit 90 patients (45 each for the AOI and non-AOI groups).

χ^2 or Fisher exact tests were used to compare categorical variables, and 2-sample *t* tests were used to compare continuous variables. Durations of SpO₂ less than 95% and 90% were compared by log-rank tests. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC).

RESULTS

A total of 104 patients were evaluated for eligibility between September and December 2015. Of these, 14 were excluded (4 did not meet inclusion criteria, 6 declined to participate, and 4 had a change in anesthetic or surgical procedure). Therefore, a total of 90 patients were assigned randomly to 1 of 2 groups: non-AOI (n = 45) or AOI (n = 45). In one patient in the non-AOI group, the surgeon asked for manual TLV to test air leakage before completing study; thus, this patient was excluded. As a result, 44 patients in the non-AOI group and 45 in the AOI group were analyzed for our primary endpoint (incidence of SpO₂ < 90%) and for the analysis of operation

FIGURE 3. Probability of SpO₂ (A) <95% and (B) <90% in non-AOI and AOI groups from 15 minutes to 45 minutes after OLV. Probability is depicted as Kaplan-Meier curves. SpO₂, Oxygen saturation; AOI, apneic oxygen insufflation. Dotted lines are 95% the confidence limits.

duration and postoperative complications. Our secondary outcome, ΔPaO_2 analysis, was conducted after we excluded patients who received rescue CPAP or TLV ($n = 8$ in the non-AOI group, $n = 0$ in the AOI group) during the study period because this rescue maneuver increased PaO_2 . The CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the study is shown in Figure 2. Baseline characteristics did not vary between groups (Table 1).

The incidence of $SpO_2 < 95\%$ was greater in the non-AOI group than the AOI group (39% vs 16% ; $P = .015$). The incidence of $SpO_2 < 90\%$ also was greater in the non-AOI group than the AOI group (18% vs 0% ; $P = .009$). The lowest SpO_2 was greater in the AOI group than the non-AOI group (median [95% confidence interval]: 97 [96%-98%] and 96 [94%-97%], $P = .021$). Time to $SpO_2 < 95\%$ and $SpO_2 < 90\%$ was longer in the AOI than the non-AOI group (Figure 3, A and B).

No difference was observed in baseline PaO_2 (OLV15: 151 ± 62 mm Hg vs 154 ± 52 mm Hg in the non-AOI and AOI groups, $P = .8$); however, PaO_2 was greater in the AOI group than the non-AOI group at all subsequent time points. Baseline SpO_2 (OLV15) was not different between groups (98.4% non-AOI vs 98.7% AOI; $P = .7$); however, SpO_2 was greater in the AOI group than the non-AOI group at all subsequent time points (Figure 4).

Duration of operation was 153 ± 62 minutes and 131 ± 44 minutes in the non-AOI and AOI groups ($P = .5$). The incidence of postoperative complications, postoperative WBC, and postoperative CRP was not different between the non-AOI and AOI groups (Table 2).

DISCUSSION

Our study demonstrated that the AOI technique prevents hypoxemia during OLV in both open and video-assisted thoracoscopic surgery lobectomy. Frumin and colleagues¹⁵ first showed that apneic oxygenation maintained normal oxygen saturation for more than 45 minutes in humans by connecting an oxygen-filled circle apparatus to the endotracheal tube. The mechanism was ventilatory mass flow of oxygen, which enables the oxygen absorbed in alveoli to be replaced by passive oxygen movement through gas flow at ambient pressure.¹⁷ Apneic oxygenation has been used successfully in situations such as rigid bronchoscopy,¹⁸ endoscopy,¹⁹ and endotracheal intubation.²⁰ Unlike closed-chest and two-lung apneic oxygenation, however, the technique used in our study has been investigated rarely in open-chest and one-lung situations.

Pfutzner and colleagues²¹ stated that apneic oxygenation would not be useful in OLV because the lung is exposed to atmospheric pressure and collapses to the point of small airway closure. The same group, however, later found that a nonventilated lung collapses slowly and hypoxic pulmonary vasoconstriction (HPV) proceeds slowly when a lung

FIGURE 4. A, PaO_2 and B, SpO_2 in patients with or without AOI from 15 minutes to 45 minutes after OLV. PaO_2 , Partial pressure of oxygen in arterial blood; AOI, apneic oxygen insufflation; SpO_2 , oxygen saturation; OLV, one-lung ventilation. * $P < .05$ between groups.

is insufflated with oxygen and reported that oxygen insufflation may be helpful in preventing hypoxia.²² Delay in both lung collapse and HPV progression by apneic oxygenation also is shown in animal experiments.²³

Rees and Wansbrough¹² showed that AOI increases PaO_2 during OLV. This study enrolled only 12 patients in each the AOI and control groups and started AOI at the beginning of

TABLE 2. Duration of operation and incidence of postoperative complications and postoperative WBC and CRP

Variables	Non-AOI (n = 45)	AOI (n = 45)	P value
Duration of operation, min	153 ± 62	131 ± 44	.5
Postoperative complications	12 (27)	11 (24)	.8
Postoperative WBC, × 10 ³ /μL	10.9 ± 3.5	12.3 ± 3.0	.6
Postoperative CRP, mg/L	3.59 ± 2.28	4.02 ± 2.64	.4

Continuous variables are expressed as mean ± standard deviation. Categorical variables are presented as number (percentage). AOI, Apneic oxygen insufflations; WBC, white blood cell; CRP, C-reactive protein.

OLV. Decreasing the speed of lung collapse and delaying HPV by early application of AOI, however, are not desirable in most clinical OLV circumstances. Therefore, we tested whether AOI is effective when applied after lung collapse is established. In our study, the AOI technique was initiated 15 minutes after the beginning of OLV, so the nonventilated lung was adequately collapsed¹⁶ and HPV was functioning almost at full capacity.²⁴ In addition, operations began approximately 15 minutes into OLV, resulting in further collapse of the nonventilated lung. Therefore, our results suggest that AOI is efficacious even when used after the lung is collapsed. This result indicates the usefulness of the AOI technique to prevent hypoxemia without the interruption of OLV during thoracic surgery.

The rate of insufflation in our study was 3 L/min. In closed-chest, two-lung apneic oxygenation, a gas flow greater than 0.3 L/kg/min is required for adequate CO₂ removal.²⁵ In an OLV situation, however, CO₂ is removed by the ventilated lung. Thus, large gas flows to remove CO₂ are not necessary. According to a study on selective segmental oxygen insufflation, an oxygen flow of 5 L/min generated a pressure of 24 cm H₂O, which is enough to re-inflate collapsed alveoli.¹⁰ In our preliminary study, however, this flow rate was too high and overinflated the lung. Rees and Wansbrough¹² provided oxygen at 1 L/min; however, this flow rate is too low to replace the outward movement of gas from the nonventilated lung and provide the alveoli with oxygen. Therefore, we chose a flow rate of 3 L/min, and it enabled appropriate oxygen delivery and did not impede the surgeon's view.

Catheter depth is another important issue in AOI. We used an animal study to decide depth.²⁶ Deeper placement of the catheter tip can block the lobar bronchial orifice. In contrast, placement above the carina might result in insufficient gas turbulence for diffusion.²⁷ Therefore, we considered 1 cm beyond the opening of the endobronchial lumen or 2 cm beyond the opening of the endotracheal lumen as an appropriate depth.

We saw no differences in duration of operation, incidence of postoperative complications, or postoperative serum WBC and CRP between the non-AOI and AOI groups. In an animal study, indicators of biochemical injury and cellular damage (malondialdehyde and myeloperoxidase)

increased after bronchial occlusion and OLV.²⁸ In this regard, to retain oxygen flow via the AOI technique in the deflated lung may decrease ischemia-reperfusion injury. Our study is low powered for the analysis of complications. A larger scale study may reveal differences in biochemical and clinical outcomes between the groups.

This study has some limitations. First, it was performed for only 45 minutes during OLV. This period is considered to be when hypoxemia occurs most commonly. Nonetheless, AOI for longer periods during OLV would give us more information. In addition, studies applying AOI at various time points during OLV and applying AOI at the time when hypoxemia actually occurred would be necessary. Second, for safety reasons, we excluded patients with severe lung disease. A study design including patients vulnerable to OLV might have been more appropriate to the hypothesis of this study.

In conclusion, our study demonstrated that AOI decreases the incidence of hypoxemia and improves arterial oxygenation during OLV for open and thoracoscopic surgery. AOI may be a valuable option to prevent hypoxemia. It can be used before relying on CPAP or intermittent TLV, resulting in fewer interruptions in surgery.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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