PROtective Ventilation with a low versus high Inspiratory Oxygen fraction(PROVIO) and its effects on postoperative pulmonary complications:protocol for a randomized controlled trial

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Study protocol

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Abstract

Background Postoperative pulmonary complications (PPCs) have been the most common perioperative complication following surgical site infection, which prolongs the hospital stay and increases health care cost. Lung-protective ventilation strategy is considered better practice in abdominal surgery to prevent PPCs. The role of inspiratory oxygen fraction (FiO2) in the strategy is currently not clear and remains disputable, despite liberal oxygen administration and hyperoxia is demonstrated to be associated with respiratory mechanism changes and increased mortality in ventilated patients. The trial aims at exploring the effect of FiO2 in lung-protective ventilation strategy on PPCs. Methods PROtective Ventilation with a low versus high Inspiratory Oxygen fraction trial(PROVIO)is a single-center, prospective, randomized, controlled trial planning to recruit 252 patients under abdominal surgery lasting for at least 2 hours. The patients are randomly assigned to (1) a low FiO2 (30% FiO2) group and (2) a high FiO2 (80% FiO2) in lung-protective ventilation strategy. The primary outcome of the study is the occurrence of PPCs within the first 7 days postoperatively. Secondary outcomes include the severity grade of PPCs, the occurrence of postoperative extrapulmonary complications and all-cause mortality within the first 7 and 30 days postoperatively. Discussion PROVIO trial specially assesses the effect of low versus high FiO2 in lung-protective ventilation strategy on PPCs and the results will provide practical approaches to intraoperative oxygen management. Trial registration number Registered at www.ChiCTR.org.cn on 13 February 2018 with identifier no. ChiCTR18 00014901.

Background

About 2.0% to 5.6% developed postoperative pulmonary complications (PPCs) in more than 234 million patients accepting surgery, up to 40% in general and vascular surgery, which have been the most common perioperative complications following surgical site infection (SSI) [1-6]. PPCs, especially respiratory failure, add to morbidity and mortality risk in hospitalized patients [1, 4, 5]. Moreover, PPCs prolong the hospital stay, increase medical expense and waste resource [2, 5]. Preventing the PPCs has been a major indicator to evaluate the safety and quality of healthcare. A possible explanation for increasing morbidity of PPCs is that mechanical ventilation under general anesthesia results in gas exchange impairment, local inflammatory response and circulation disorder [7, 8]. Thus, decreased lung volumes, ventilator-induced lung injury and atelectasis are strongly associated with the incidence of PPCs [9].

Prior studies noted that so-called lung-protective ventilation which refers to low tidal volume (VT), appropriate positive end-expiratory pressure (PEEP) level and recruitment maneuvers seems to be the optimum option to surgery and ICU population [10-13]. A decrease of PPCs, mortality and health system costs have been observed in the protective ventilated population. On the basis of the robust evidence available, a combination of low VT (6 to 8 ml per kilogram of predicted body weight) [11, 14], a level of PEEP at 5-8 cmH2O [15] and repeated recruitment maneuvers [16] have been now widely adopted.

The inspiratory oxygen fraction (FiO2), as a significant factor of ventilation parameters, has not been regarded as a clinical standard. Knowledge about hyperoxia caused by high FiO2 is stressed by clinicians over the past few decades. Potentially preventable hyperoxia and substantial oxygen exposure are common in clinical practice to maintain satisfactory oxygenation [17]. However, exposure to oxygen has been shown to be related to adverse effects in critically ill patients [18, 19]. Thus, questions have been raised about the use of oxygen in ventilated patients undergoing elective surgery. Evidence is lacking for a regular application of a high FiO2 in abdominal surgery suggested by a Cochrane review [20]. The proper level of FiO2 in lung-protective ventilation strategy to protect against PPCs and improve clinical outcomes has not been addressed in the perioperative period. Inconsistent with what most of us thought, there's no significant difference in pulse oximetry, oxygenation index and functional residual capacity for several time-points with 30% or 80% FiO2 in a prospective study on FiO2 perioperatively [21].

The relationship between FiO2 and PPCs in surgical patients is mainly affected by hyperoxia-induced respiratory mechanism change. Higher FiO2 seems to be associated with pulmonary complications and adverse clinical outcomes, but the existing evidence is insufficient to warrant its effect to promote PPCs. We hypothesize that compared with high FiO2 (80%), a low level of FiO2 (30%) would decrease the incidence of PPCs in patients under abdominal surgery when both are treated with lung-protective ventilation strategy.

Methods And Design

Study design

The PROVIO trial is a single-center, prospective, randomized, controlled, two-arm study and is conducted in accordance with the *Declaration of Helsinki*. Trial will be conduted in West China Hospital of Sichuan University, China. We aim to assess the effect of FiO2 in lung-protective ventilation strategy in an abdominal surgical population of patients on PPCs, extra-pulmonary complications (e.g., SSI, sepsis), hospital stay, and mortality.

The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement. The Consolidated Standards of Reporting Trials (CONSORT) diagram is presented in Figure 1.

Figure 1. CONSORT diagram of the PROVIO trial.

Study population

The inclusion criteria of the study are: American Society of Anesthesiologists (ASA) physical status I to III patients aged 18 years or older, scheduled for elective abdominal surgery with an expected duration of at least 2 hours and planned to be extubated in the operating room. Laparotomy and laparoscopy surgery will not be restricted. Patients are ineligible if they are suffered pneumothorax, acute lung injury or acute respiratory distress syndrome within last three months. Other exclusion criteria include a history of heart

failure (New York Heart Association classes, NYHA), chronic renal failure (glomerular filtration rate < 30 ml/min) and serious hepatic diseases (e.g., hepatic failure). Patients are also excluded if they are need of re-surgery and/or mechanical/ circulatory assistance, consent for other clinical studies, known pregnancy, and with a body mass index (BMI) of 30 kg/m2.

Randomization, blinding and bias minimization

Patients will be recruited from West China Hospital of Sichuan University. Consecutive male or female aged 18 years or older under general anesthesia who accept abdominal surgery are screened for study eligibility. Randomization will be performed using a computer-generated randomization list (SPSS 22.0) with an allocation rate of 1:1. The allocation is concealed in an opaque envelope and will be sent to the attending anesthetist by an investigator without knowing it.

Given the characteristics of the study, the attending anesthetist must know and observe the intervention. Researchers including the data collector and the data analyzer are all blinding to the randomization arm, in addition to the investigator in the operating room. All the surgeons, nurses and anesthetists in post-anesthesia care unit (PACU) do not know the allocation. Postoperative visits and outcome assessment will be taken by a blinded investigator. Emergency unblinding is permissible if hypoxemia occurs.

Standard procedures

There will be an evaluation of risk according to the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score [22] before the randomization (Table 1). An investigator assesses the individual risk of PPCs with the seven predictors of ARISCAT risk score (age, preoperative pulse oxygen saturation (SpO2), respiratory infection in the last month, preoperative anemia, duration of surgery, and emergency procedure). A risk scored ≥ 26 is regarded as an intermediate-high risk.

All randomized participants will accept the general standard care and monitoring including five leads electrocardiogram, SpO2, blood pressure (invasive or noninvasive) and end-tidal carbon dioxide (ETCO2). The attending anesthetist responsible for the patient can choose the bispectral index (BIS), muscle relaxant monitoring and cardiac output monitoring depending on individuals and clinical routines.

Also, they will be managed intraoperatively with the individualized anesthetic plan drew up by the attending anesthetist. There will be no limitation to anesthetic regimen. Use of antiemetics and muscle relaxant antagonist (mainly neostigmine) will be recorded in case report form (CRF).

Table 1. Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score in the logistic regression model

Intraoperative ventilatory management

Pre-oxygenation and induction are prescribed for 5 minutes at 100% FiO2 with a mask. In accordance with the allocation, the participants are randomized to accept low FiO2 (30% FiO2) or high FiO2 (80% FiO2) perioperatively (from intubation to extubation). FiO2 implement through adjusting the air-O2 ratio

when total gas flow remains 2 L/min. FiO2 in our protocol refers to the actual fraction of inspired oxygen presented in the anesthesia machine panel. Table 2 shows the ventilation settings.

Intraoperative ventilation in all participants will be performed via lung protective ventilation strategy. A recruitment maneuver with peak airway pressure (Paw) 30 cmH2O for 30s will be performed after intubation instantly, every 60 min after intubation and before extubation. Other settings are shown in table 1. Ventilatory parameters will be monitored by the anesthesia machine and recorded: tidal volume, minute volume (MV), Paw, plateau pressure (Pplat), fresh gas flow, PEEP and FiO2.
After extubation, patients will be sent to the PACU or ward where they will be oxygenated with 2L/min, pure oxygen via a nasal tube in 24 hours. At the same time, they will accept standard monitoring.

Table 2: Intraoperative ventilation settings for the PROVIO trial

Intraoperative care

After induction, standard intraoperative care will be applied in both groups to reach a target of standard state (Table 3). Vasoactive agent therapy is permitted when the hemodynamics get instability with the discretion of the attending anesthetist.

Table 3: Standard state target

Rescue strategies for intraoperative hypoxemia

In general, surgery patients rarely require adjustment of the FiO2 in 30% FiO2 group according to the previous trials and clinical practice. In cases of hypoxemia, defined as SpO2 < 92% or PaO2 < 60 mmHg, the rescue strategies will be performed immediately to treat.

Finding out the underlying causes of hypoxemia matters. Checking if there exists endotracheal tube displacement, airway secretion blocking, bronchospasm, pneumothorax and hemodynamic change. After excluding the above causes, a rescue recruitment maneuver with Paw 30 cmH2O for 30s will be implemented. If failed, FiO2 and ventilation settings were permitted to alter until acquiring the satisfied oxygenation (SpO2 ≥ 92% or PaO2 ≥ 60 mmHg).

Outcome measurements

The primary outcome is the occurrence of pulmonary complications within the first 7 days postoperatively. Definition of PPCs follows the ARISCAT study (respiratory infection, respiratory failure, bronchospasm, atelectasis, pleural effusion, pneumothorax, or aspiration pneumonitis.) [4].

The secondary outcomes include the occurrence of PPCs in the postoperative 30 days; SSI, postoperative nausea and vomiting (PONV) in the first 7 days; the severity grade of pulmonary complications (Table 4); and death rate in the 7 and 30 postoperative days.

Pulmonary complications will be scored with a grade scale ranging from 0 to 5 adapted from Kroenke et al, Hulzebos et al, Fernandez-Bustamante et al and Canet et al [4, 5, 23, 24]. Grade 0 in scale represents no

PPCs, grades 1 to 4 represent increasing severity levels of pulmonary complications, and grade 5 represents death before discharge. SSI will be defined with the criteria from the Centers for Disease Control and Prevention (CDC) [25].

Table 4. The grade of pulmonary complications

Tertiary outcomes in the first 7 and 30 days postoperatively are as follows:

1. Sepsis: the infection-centric systemic response which needs to meet two or more criteria of the Systemic Inflammatory Response Syndrome (SIRS) [26].

2. Septic shock: defined as a composite of sepsis-induced response, perfusion abnormalities and hypotension despite adequate fluid resuscitation [26].

3. Myocardial ischemia [27].

4. Heart failure [27].

5. Urinary system infection [27].

6. Acute kidney injury: defined according to the KDIGO [28].

7. Anastomosis fistula.

8. Reintubation.

9. Unplanned admission to ICU.

10. Hospital length of stay postoperatively.

Data collection and follow-up

The study is conducted in the operating room and visits are restricted during the screening period, hospitalization period and follow-up period. The primary and secondary outcomes will be measured on postoperative 1, 2, 3, 5, 7 or at discharge by interview. On postoperative day 30, participants are visited by phone (Figure 2). Demographic and baseline data will be collected preoperatively, which include age, sex, weight, body mass index, ASA physical status, ARISCAT risk score, smoking status, pulmonary status (COPD, atelectasis, asthma respiratory infection within the last three months, use of ventilatory support) routine laboratory tests (hemoglobin, white blood cell count, platelet count, neutrophil count) and medical history.

Figure 2. Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments

Both intraoperative surgery- and anesthesia-associated data are recorded, including type of surgery, surgical incision or approach, duration of surgery and ventilation, blood loss, transfusion of blood products, fluid balance (calculated by subtracting the measurable fluid losses from measurable fluid intake during anesthesia.), anesthetic procedure, drugs during anesthesia (e.g., anesthetics and antiemetics), adjustment of ventilatory parameters or FiO2, hypoxemia event, the need for rescue strategy, number of emergency recruitment maneuvers, and unplanned admission to ICU.

Postoperative visits are conducted daily and clinical data required to assess PPCs grade includes body temperature, lung auscultation, symptoms (e.g., cough, expectoration, and dyspnea.), chest imaging manifestations, and laboratory tests. Surgical incision assessment, PONV, and other outcomes will also be measured and collected daily according to the evaluation criterion mentioned above.

Data and Safety Monitoring Board (DSMB) which is composed of five independent individuals is set to watch over the overall conduct of the study (the screening, recruitment and conforming to the protocol). DSMB is responsible for checking and ensuring the completeness and validity of data recording. The interim analysis will be conducted when the first 120 participants are recruited and visited completely.

Study drop-out

Participants have the right to withdraw from the study at any time without any consequences for further treatment. Investigators have the right to terminate the study at any time in consideration of best interests of participants. Both two situations will be recorded in CRF and discussed.

Any adverse events and treatments will be send to DSMB and discussed if the participant should drop out according to this.

Statistical considerations

The sample size required was estimated based on the investigative data in our medical center. The pilot study showed that PPCs (respiratory infection, respiratory failure, bronchospasm, atelectasis, pleural effusion, pneumothorax, or aspiration pneumonitis) occurred in 50.4% patients received 80% FiO2 after abdominal surgery (sample size: 100). And assuming a rounded 50% rate of PPCs in the high FiO2 group, we calculated that a total sample size of 252 patients (126 in each group) will have 80% power to detect a relative risk reduction of 35% in PPCs between groups, at a two-sided alpha level of 0.05 and 5% dropout. We will conduct a sample size reassessment after recruiting half of patients for safety consideration.

All statistics will be analyzed by SPSS 22.0 statistical software through the intention-to-treat principle, which covers all randomized patients receiving surgery. Participants with adjusted FiO2 are still treated as low FiO2 population when analyzed. In a descriptive analysis to population, mean and standard deviation (SD) will be used for normally distributed variables, medians and interquartile ranges used for non-normally distributed variables and percentages used for categorical variables. Stratified description will be used as appropriate.

There will be a baseline comparison of age, gender, BMI, type of surgery, surgical approach, duration of surgery and ARISCAT score between groups and logistic regression analysis will be done if an imbalance between groups exists. Student t-test will be used for continuous normally distributed variables and the Mann-Whitney U test will be used for continuous non-normally distributed data. The primary and secondary outcomes will be compared using the χ^2 test or Fisher's exact test, while multiple logistic-regression analysis used to identify hazards. A 2-sided P value < 0.05 was considered statistically significant.

A custom-made folder is made to store the participants' data, which consists of documents and forms. Only blinded researchers have access to the folder. Only when study completes, the investigators can get the data.

All original data (mainly recorded in CRF) will be handled according to China law and archived for at least 3 years and cleaned with asking permission of hospital after that.

Discussion

Any ventilatory settings play a critical role in clinical outcomes of surgery population under general anesthesia and intraoperative oxygen supply strategy must not be underestimated. Many physicians consider excessive oxygen supplement a salutary pattern which is now widely applied in the routine practice of simplicity and easy availability [29]. Despite the controversy, the majority of published randomized trials comparing 30% and 80% FiO2 mainly in SSI and PONV find that intraoperative high FiO2 decreases the risk of both [30-32]. Furthermore, new WHO recommendations on intraoperative and postoperative measures for SSI prevention in 2016 suggest that patients undergoing general anesthesia with endotracheal intubation for surgical procedures should receive 80% FiO2 intraoperatively [33]. What remains controversial is whether the intraoperative use of high FiO2 is essential to surgery population without hypoxemia, although 30% and 80% FiO2 provide similar oxygenation [21]. A multicenter observational trial collecting the ventilator data 1h after induction finds that most patients (83%) in Japan were exposed to potentially preventable hyperoxia, especially in one-lung ventilation and the elder [17].

The "benefit" of this pervasive liberal oxygen management has recently been questioned. There is a growing concern about oxygen affecting lung capillary endothelial function and facilitating oxidative stress [34-36][34]. Endothelial activation may initiate progressive hyperoxic lung injury when hyperoxic ventilated at 70% FiO2 persistently [37]. Besides, excessive oxygen can lead to pulmonary endothelial cells damage through mitochondrial fragmentation [38]. This can be explained by the formation of reactive oxygen species (ROS) and pro-inflammatory cytokines in endothelial cells which were found in an animal study [37, 39]. Romagnoli et al. demonstrated that protective ventilation with the lowest level of FiO2 to keep SpO2≥95% weaken oxygen toxicity by less ROS production [40]. However, there is still contradiction not confirming high FiO2's detrimental effect on endothelial dysfunction in healthy volunteers solely [41]. Another interpretation is high FiO2 may change pulmonary gas exchange in

surgical patients. Ventilation with high FiO2 (80%-100%) increases intrapulmonary shunt [42] and impairs gas exchange [43]. In addition, resorption atelectasis results from a phenomenon which nitrogen is displaced by O2 that can diffuse more rapidly into the blood. Resorption atelectasis can also promote the pulmonary shunt and cause hypoxemia [44]. Ventilation for induction of anesthesia with 100% FiO2 leads to significantly larger atelectasis areas than with 60% FiO2 [45]. Atelectasis area tends towards being low ventilation/perfusion-ratio (VA/Q) which poorly ventilated relatively to perfusion. Hyperoxia is also an important factor contributing to the apoptosis of alveolar epithelial cells and lower the level of surfactant proteins which indicate the damage of lung tissue [46]. The synthetic action of above factors increases the risk of lung injury and pulmonary complications.

Indeed, supplemental oxygen results in hyperoxia, as reported an independent risk factor for ventilator-associated pneumonia in an observational study [47]. Liberal oxygen use is considered detrimental in mechanically ventilated patients in the aspect of lung function [48] and clinical outcomes [19]. The PROXI trial demonstrates that the incidence of PPCs, PONV, and SSI after abdominal surgery were not significantly different in patients receiving 80% or 30% FiO2 [49]; nevertheless, the former suffers higher long-term mortality (23.3% vs. 18.3%) [50]. And an observational trial has suggested a dose-dependent manner about FiO2 and 30 days mortality. The incidence of PPCs has declined by half in low FiO2 group with a median of 31% (range 16%-34%) [51].

Yet no direct evidence revealed the relationship of FiO2 in lung-protective ventilation and PPCs, and existing data reported postoperative pulmonary function is better protected with a relative low FiO2 intraoperatively [52]. A systematic review found that the included trials only focused on postoperative atelectasis, rather than all forms of PPCs [53]. Despite PROXI trial demonstrated that PPCs did not differ after inhalation of 80% vs 30% oxygen, the results are worth discussing. Emergency surgery population were not excluded in PROXI trial, which is an independent risk factor of pulmonary complications [4]. Intubation time is also a key element of causing pneumonia and atelectasis. Moreover, complications measures of PROXI lacked a standard and comprehensive judgment, which only assessed the three types of PPCs (atelectasis, pneumonia and respiratory failure) according to CDC criteria. And above all, the ventilation strategy to patients was not specified, which plays a key role in the incidence of pulmonary complications. The iPROVE-O2 trial is an ongoing randomized controlled trial (clinicaltrials.gov identifier NCT02776046) comparing the efficacy of 80% and 30% FiO2 with individualized open-lung ventilatory strategy in reducing the incidence of SSI [54]. The major differences from PROVIO trial are: the appearance of pulmonary complications as one of secondary outcome; individualized open-lung ventilation as ventilatory mode that is a combination of 8ml/kg VT, recruitment maneuver and the optimal individualized PEEP. Recruitment maneuver will be performed by a PEEP-titration trial. Undoubtedly, individualized open-lung ventilation strategy is complex to implement clinically and hard to popularize, when comparing to lung-protective ventilation.

Limitations of our study must be mentioned. We conducted a pilot study to acquire the incidence of PPCs in our medical center referring to the sample size calculation. Hope our results will provide the possible direction and reference to subsequent researches of FiO2. Secondly, the study excludes the patients

scheduled for some types of surgery because of the duration of surgery. The oxygenation index and arterial oxygen pressure, which may reflect the actual oxygenation state will not be measured during the perioperative period.

In the absence of intraoperative lung-protective ventilation strategy, previous studies failed to identify the certain relation of FiO2 and PPCs. We insist that lung-protective ventilation in both groups will reduce bias about the ventilation-associated impact and enhance lung protection. Conclusively, PROVIO trial is the first clinical trial focusing on the effect of FiO2 in lung-protective ventilation on PPCs, whose results may provide guidance of routine oxygen management and an optimal choice of FiO2 application to protect from pulmonary complications.

Trial status

The trial is ongoing from February, 2018, and expected to complete on May, 2019. The protocol version is 3.0 (issue date: 25 December 2018)

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study has been approved by The Ethical Committee of the West China Hospital of Sichuan University (2018 approval NO.8) and informed consent will be obtained from all study patients before participating. Our trial was registered at http://www.chictr.org.cn (ChiCTR1800014901). We will obtain informed consent from all patients in written form who meet all the inclusion criteria and none of the exclusion criteria before arrival to the operating room.

The results of the PRIVIO trial will be published in peer-reviewed journals focused on perioperative medicine and presented at national and international conferences.

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Consent for publication: Not applicable.

Author Contributions: XFL, XYY, and HY (Hai Yu) provided substantial contributions to study conception and design. XFL and HY (Hai Yu) drafted protocol and edited manuscript. DJ, HY (Hong Yu),YLJ, JLJ, LLH anticipated in study design. All the authors read and approved the final manuscript.

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Competing interests: None declared.

Abbreviations

AE: Adverse Event; ARISCAT: Assess Respiratory Risk in Surgical Patients in Catalonia; ASA: American Society of Anesthesiologists; BIS: the bispectral index; BMI: body mass index; CDC: the Centers for Disease Control and Prevention; CONSORT: The Consolidated Standards of Reporting Trials; COPD: chronic obstructive pulmonary disease; CRF: case report form; DSMB: Data and Safety Monitoring Board; ETCO2: end-tidal carbon dioxide; FiO2: inspiratory oxygen fraction; Hb: hemoglobin; HR: Heart rate; MAP: Mean arterial pressure; MV: minute volume; NYHA: New York Heart Association classes; ICU: Intensive Care Unit; I: E: Inspiratory to Expiratory ratio; P plat: plateau pressure; PACU: post-anesthesia care unit; PEEP: positive end-expiratory pressure; PONV: postoperative nausea and vomiting; PPCs: Postoperative pulmonary complications; PROVIO: PROtective Ventilation with a low versus high Inspiratory Oxygen fraction trial; ROS: reactive oxygen species; SD: standard deviation; SIRS: the Systemic Inflammatory Response Syndrome; SPIRIT: the Standard Protocol Items: Recommendations for Interventional Trials; SpO2: pulse oxygen saturation; SSI: surgical site infection; VA/Q: ventilation/perfusion-ratio; VT: tidal volume.

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Tables

Table 1. Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score in the logistic regression model

	βCoefficient	Score *
Age (years)		
≤50	0	0
51-80	0.331	3
> 80	1.619	16
Preoperative SpO2 (%)	0	0
≥96	0.802	8
91-95	2.375	24
≤90	0	0
Respiratory infection in the last month	1.698	17
No	0	0
Yes	1.105	11
Preoperative anemia (Hb ≤10 g/dl)	1.480	15
No	2.431	24
Yes	1.593	16
Surgical incision	2.268	23
Peripheral	0.768	8
Upper abdominal	0	0
Intrathoracic	0.768	8
Duration of surgery (h)		
≤2		
2–3		
>3		
Emergency procedure		
No		
Yes		

*A risk score ≥26 predicts an intermediate to high risk for postoperative pulmonary complications after abdominal surgery. The simplified risk score was the sum of each logistic regression coefficient multiplied by 10, after rounding off its value.

Hb = hemoglobin.

Table 2: Intraoperative ventilation settings for the PROVIO trial

	Low FiO2 group	High FiO2 group
FiO2	0.30	0.80
VT	8 ml/kg	8 ml/kg
PEEP	6-8 cmH2O	6-8 cmH2O
I: E	1:2	1:2
RR	Adjusted according to ETCO2 (35-45 mmHg)	Adjusted according to ETCO2 (35-45 mmHg)
P max	30 cmH2O	30 cmH2O

Table 3: Standard state target

	Parameter	Value
Hemodynamics	Mean arterial pressure (MAP)	70 mmHg < MAP < 100 mmHg
Hemodynamics	Heart rate (HR)	50/min < HR < 100/min
Oxygenation	SpO2	≥92%

Table 4. The grade of pulmonary complications

Postoperative pulmonary complications grade	
Grade 1	-Cough, dry -Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; normal chest radiograph -Dyspnea, not due to other documented cause
Grade 2*	-Cough, productive, not due to other documented cause -Bronchospasm: new wheezing or preexistent wheezing resulting in a change in therapy -Hypoxemia: SpO2 < 90 at room air -Atelectasis: gross radiological confirmation (concordance of 2 independent experts) plus either temperature > 37.5°C or abnormal lung findings -Hypercarbia (PaCO2 > 50mmHg), requiring treatment.
Grade 3	-Pleural effusion, resulting in thoracentesis -Pneumonia: radiological evidence (concordance of 2 independent experts) plus clinical symptoms (two of the following: leucocytosis or leucopenia, abnormal temperature, purulent secretions), plus either a pathological organism (by Gram stain or culture), or a required change in antibiotics -Pneumothorax -Noninvasive ventilation, strictly applied to those with all of the following: a) SpO2 ≤ 92% under supplemental oxygen; b) need of supplemental oxygen > 5L/min; and respiratory rate ≥ 30 bpm -Reintubation postoperative or intubation, period of ventilator dependence does not exceed 48 hours
Grade 4	-Ventilatory failure: postoperative ventilator dependence exceeding 48 hours, or reintubation with subsequent period of ventilator dependence exceeding 48 hours
Grade 5	-Death

*We only classified as grade 2 if two or more items in the grade 2 were present.

Figures

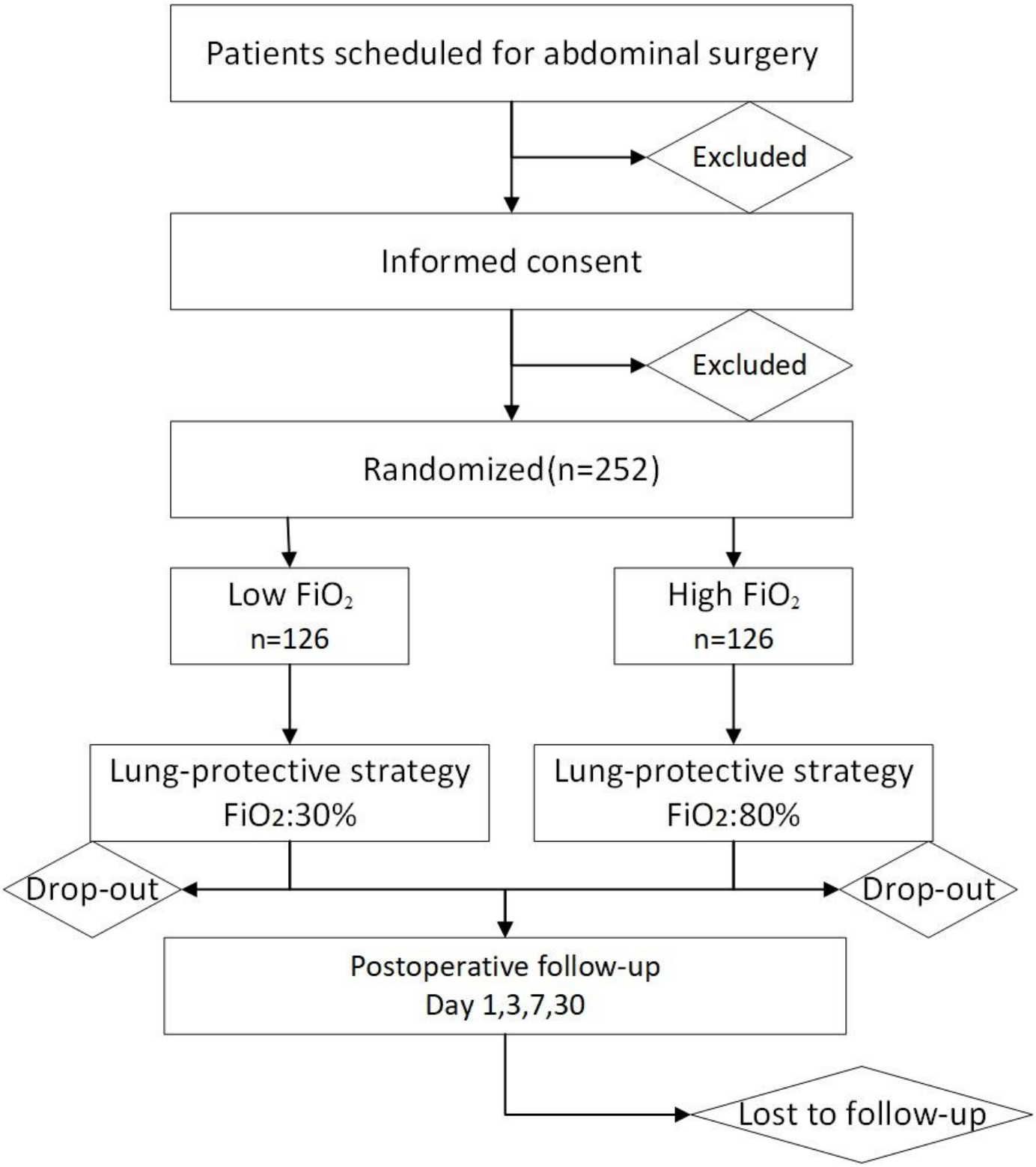

Figure 1

CONSORT diagram of the PROVIO trial.

	STUDY PERIOD									
	Enrolment	Allocation / Intervention			Post-intervention					
TIMEPOINT	Preoperative visit	Allocation	During surgery	End of surgery	POD 1	POD 2	POD 3	POD 5	POD 7	POD 8-30
ENROLMENT										
Eligibility screen	×									
Informed consent	×									
Demographic data	×									
Allocation		×								
INTERVENTIONS										
Low FiO_2 with PLV			×							
High FiO_2 with PLV			×							
Adverse events			×							
Surgery and anesthesia data				×						
ASSESSMENTS										
PPCs					×	×	×	×	×	×
Grade of PPCs					×	×	×	×	×	×
Extrapulmonary complications					×	×	×	×	×	×
Adverse invents					×	×	×	×	×	×
In-hospital stay								×	×	×
Reintubation					×	×	×	×	×	×
Unplanned admission to ICU					×	×	×	×	×	×
Mortality					×	×	×	×	×	×

Figure 2

Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments.

Supplementary Files

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