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

Xue-Fei Li
Sichuan University West China Hospital
Dan Jiang
Sichuan University West China Hospital
Yu-Lian Jiang
Sichuan University West China Hospital
Hong Yu
Sichuan University West China Hospital
Jia-Li Jiang
Sichuan University West China Hospital
Lei-Lei He
Sichuan University West China Hospital
Xiao-Yun Yang
Sichuan University West China Hospital
Hai Yu (yuhaishan117@yahoo.com)
Sichuan University West China Hospital https://orcid.org/0000-0003-2465-0801

Study protocol

Keywords: Postoperative pulmonary complications, Lung-protective ventilation, Fraction of inspired oxygen, Abdominal surgery

Posted Date: June 17th, 2019

DOI: https://doi.org/10.21203/rs.2.477/v2

Version of Record: A version of this preprint was published on November 1st, 2019. See the published version at https://doi.org/10.1186/s13063-019-3668-x.

Abstract

Background: Postoperative pulmonary complications (PPCs) is the most common perioperative complication following surgical site infection (SSI), which prolongs the hospital stay and increases health care cost. Lung-protective ventilation strategy is considered as better practice in abdominal surgery to prevent PPCs. However, the role of inspiratory oxygen fraction (FiO₂) in the strategy remains disputable. Previous trials have focused on reducing SSI by increasing inhaled oxygen concentration but higher FiO₂ (80%) was found to be associated with a greater incidence of atelectasis and mortality in recent researches. The trial aims at comparing the effect of FiO₂ added to lung-ventilation strategy on reducing the incidence of PPCs during general anesthesia for abdominal surgery. 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 will be 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 postoperative 7 days. Secondary outcomes include the severity grade of PPCs, the occurrence of postoperative extrapulmonary complications and all-cause mortality within the postoperative 7 and 30 days. Discussion: PROVIO trial assesses the effect of low versus high FiO₂ in lung-protective ventilation strategy on PPCs for abdominal surgery patients 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% of more than 234 million patients undergoing surgery developed postoperative pulmonary complications (PPCs), especially after general and vascular surgery (approximately 40%), which makes PPCs 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 resources utilization [2, 5]. Reduction of pulmonary complications is a very important evaluation index of medical quality management. A possible explanation for increasing morbidity in patients who develop 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 (V_T), 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 V_T (6 to 8 ml per kilogram of predicted body weight) [11, 14], a level of PEEP at 5-8 cmH_2O [15] and repeated recruitment maneuvers [16] are now widely adopted.

Setting FiO_2 intraoperatively is a significant task of anesthetists, but has not based on evidence-based guidelines. Obtaining comprehensive knowledge about hyperoxia caused by high FiO_2 has been 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, there's no significant difference in pulse oximetry, oxygenation index and functional residual capacity for several time-points with 30% or 80% FiO_2 intraoperatively [18]. Exposure to oxygen is related to adverse effects in critically ill patients [19, 20]. Thus, questions have been raised about the use of oxygen in ventilated patients undergoing elective surgery. The recent systematic review revealed that the trials of this decade about FiO_2 on SSI have been inconclusive, and we should also focus on clinically relevant pulmonary side-effects and other adverse events [21-24]. The proper level of FiO_2 in lung-protective ventilation strategy to protect against PPCs and improve clinical outcomes has not been addressed in the perioperative period.

The relationship between FiO_2 and PPCs in surgical patients is mainly affected by hyperoxia-induced respiratory mechanism change. Higher FiO_2 seems to be associated with pulmonary complications and adverse clinical outcomes, but the existing evidence is insufficient to warrant its effect to promote PPCs [25-27]. We hypothesize that compared with high FiO_2 (80%), a low level of FiO_2 (30%) would decrease the incidence of PPCs in patients undergoing 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 and two-arm study and is conducted in accordance with the *Declaration of Helsinki*. The trial will be conducted in West China Hospital of Sichuan University, China. We aim to assess the effect of FiO_2 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 the last three months. Other exclusion criteria are: diagnosis of heart failure (New York Heart Association classes, NYHA Ⅲ), chronic renal failure (glomerular filtration rate < 30 ml/min), serious hepatic diseases (e.g., hepatic failure), scheduled for reoperation or postoperative mechanical circulatory support, known pregnancy, participation in another interventional study, and with a body mass index (BMI) of > 30 kg/m^2.

Randomization, blinding and bias minimization

Patients will be recruited from West China Hospital of Sichuan University. Consecutive male or female patients aged 18 years or older under general anesthesia who will undergo 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 investigator in the operating room, the data collector and the data analyzer will all be blinded to the randomization arm. All the surgeons, nurses and anesthetists in post-anesthesia care unit (PACU) do not know the allocation. Postoperative visits and outcome assessment will be performed by a blinded investigator. Emergency unblinding is permissible if hypoxemia occurs (defined as SpO_2 < 92% or PaO_2 < 60 mmHg).

Standard procedures

The risk of PPCs will be assessed with the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score [28] 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 (SpO_2), respiratory infection in the last month, preoperative anemia, duration of surgery, and emergency procedure). The ARISCAT score will help to analyze the effect of FiO_2 to intermediate-high risk patients who get a score of more than 26.

All randomized participants will receive the general standard care and monitoring including five leads electrocardiogram, SpO_2, blood pressure (invasive or noninvasive) and end-tidal carbon dioxide (E_TCO_2). 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.

Moreover, the participants 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 will be prescribed for 5 minutes at 100% FiO_2 with a mask. In accordance with the allocation, the participants will be randomized to receive low FiO_2 (30% FiO_2) or high FiO_2 (80% FiO_2) during mechanical ventilation. FiO_2 implement through adjusting the air-O_2 ratio when total gas flow remains 2 L/min. FiO_2 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 (P_{aw}) 30 cmH_2O for 30s will be performed after intubation instantly, every 60 min after intubation and before extubation. Other settings are shown in table 2. Ventilatory parameters will be monitored by the anesthesia machine and recorded: tidal volume, minute volume (MV), P_{aw}, plateau pressure (P_{plat}), fresh gas flow, PEEP and FiO_2.

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 receive 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 drugs can be used in patients with unstable hemodynamics as appropriate.

Table 3: Standard state target

Rescue strategies for intraoperative hypoxemia

Around 30% FiO_2 has proved to be safe in mechanically ventilated patients and rarely causes hypoxemia [18]. We design a rescue strategy for patients in whom SpO_2 measured by pulse oximetry fell to less than 92% or PaO_2 less than 60 mmHg for more than one minute.

Checking if there exists endotracheal tube displacement, airway secretion blocking, bronchospasm, pneumothorax, and hemodynamic change. After excluding the underlying causes, a rescue recruitment maneuver with P_{aw} 30 cmH_2O for 30s will be implemented [12, 16, 29]. If failed, FiO_2 and ventilation settings are permitted to alter until acquiring the satisfied oxygenation ($SpO_2 \geq 92\%$ or $PaO_2 \geq 60$ 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 ostoperative 7 days; the severity grade of pulmonary complications in the postoperative 7 and 30 days (Table 4); and death rate in the postoperative 7 and 30 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, 30, 31]. 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) [32].

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) [33].

2. Septic shock: defined as a composite of sepsis-induced response, perfusion abnormalities, and hypotension despite adequate fluid resuscitation [33].

3. Myocardial ischemia [34].

4. Heart failure [34].

5. Urinary system infection [34].

6. Acute kidney injury: defined according to the KDIGO [35].

7. Anastomosis fistula.

8. Reintubation.

9. Unplanned admission to ICU.

10. Hospital length of stay postoperatively.

Data collection and follow-up

The study will be 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 will be 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 will be 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 FiO_2, hypoxemia event, the need for rescue strategy, number of emergency recruitment maneuvers, and unplanned admission to ICU.

Postoperative visits will be 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 supervise the overall conduct of the study (the screening, recruitment and adherence 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. DSMB have access to patient allocation, but the results of interim analysis will be treated as strictly confidential.

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 sent 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% FiO_2 after abdominal surgery (sample size: 100). And assuming around 50% rate of PPCs in the high FiO_2 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 (IBM Corporation, USA) through the intention-to-treat principle, which covers all randomized patients receiving surgery. Participants with adjusted FiO_2 are still treated as low FiO_2 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 performed 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 the study completes, the investigators can get the data.

Discussion

The optimal intraoperative FiO_2 is more highly debated. Many physicians consider excessive oxygen supplement a salutary pattern which is now widely applied in the routine practice of simplicity and easy availability [36]. Despite the controversy, the majority of published randomized trials comparing 30% and 80% FiO_2 mainly in SSI and PONV find that intraoperative high FiO_2 decreases the risk of both [37-39]. 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% FiO_2 intraoperatively [40]. What remains controversial is whether the intraoperative use of an elevated FiO_2 is essential to all intubated patients without hypoxemia, although 30% and 80% FiO_2 provide similar oxygenation [18]. 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 [41].

The “benefit” of this pervasive liberal oxygen management has recently been questioned. Concerns on potential detrimental effects such as impairing lung capillary endothelial function and facilitating oxidative stress due to the use of high FiO_2 were raised[42-44][34]. Endothelial activation may initiate progressive hyperoxic lung injury when hyperoxic ventilated at 70% FiO_2 persistently [45]. In addition, excessive oxygen can lead to pulmonary endothelial cells damage through mitochondrial fragmentation [46]. 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 [45, 47]. Romagnoli et al. demonstrated that protective ventilation with the lowest level of FiO_2 to keep $SpO_2 \geq 95\%$ weaken oxygen toxicity by less ROS production [48]. However, there is still contradiction not confirming high FiO_2’s detrimental effect on endothelial dysfunction in healthy volunteers solely [49]. Another interpretation is that high FiO_2 may change pulmonary gas exchange in surgical patients. Ventilation with high FiO_2 (80%-100%) increases intrapulmonary shunt [50] and impairs gas exchange [51]. In addition, resorption atelectasis results from a phenomenon which nitrogen is displaced by O_2 that can diffuse more rapidly into the blood. Resorption atelectasis can also promote pulmonary shunt and cause hypoxemia [52]. Ventilation for induction of anesthesia with 100% FiO_2 leads to significantly larger atelectasis areas than with 60% FiO_2 [53]. Atelectasis area tends towards being low ventilation/perfusion-ratio (V_A/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 [54]. 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 [55]. Liberal oxygen use is considered detrimental in mechanically ventilated patients in the aspect of lung function [56] and clinical outcomes [20]. The PROXI trial demonstrated that the incidence of PPCs, PONV, and SSI after abdominal surgery were not significantly different in patients receiving 80% or 30% FiO_2 [57]; nevertheless, the former suffers higher long-term mortality (23.3% vs. 18.3%) [58]. And an observational trial has suggested a dose-dependent manner about FiO_2 and 30 days mortality. The incidence of PPCs has declined by half in low FiO_2 group with a median of 31% (range 16%-34%) [27].

Yet no direct evidence revealed the relationship of FiO_2 in lung-protective ventilation and PPCs, and existing data reported postoperative pulmonary function is better protected with a relative low FiO_2 intraoperatively [59]. A systematic review found that the included trials only focused on postoperative atelectasis, rather than all forms of PPCs [60]. 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 is not specified, which plays a key role in the incidence of pulmonary

complications. The iPROVE-O_2 trial is an ongoing randomized controlled trial (clinicaltrials.gov identifier NCT02776046) comparing the efficacy of 80% and 30% FiO_2 with individualized open-lung ventilatory strategy in reducing the incidence of SSI [61]. 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 V_T, recruitment maneuver and the optimal individualized PEEP. Recruitment maneuver will be performed by a PEEP-titration trial [62]. Undoubtedly, individualized open-lung ventilation strategy is more complex to implement clinically, when comparing to lung-protective ventilation [62].

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 FiO_2. 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 FiO_2 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 FiO_2 in lung-protective ventilation on PPCs. The results of the trial will support anesthetists in routine oxygen management during general anesthesia in an attempt to prevent PPCs.

Trial status

The trial is ongoing from February 2018, and expected to complete in 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.

Confidentiality

The personal information of patients will be confidential at all periods of trial. Data will be handled according to China law and archived for at least 5 years. Meanwhile, the database will be anonymized and kept for 5 years. Then, data will be destroyed according to the hospital standards concerning destruction of confidential information.

Funding

This research received a funding grant from 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University (project number: 2018HXFH052). 1·3·5 project will in no way intervene in any aspect of trial, including its design, data collection, analysis or presentation.

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.

Acknowledgments

We thank patients for participating in trial dissemination. We also thank the authors of primary studies and our colleagues supporting the study.

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; E_TCO_2: end-tidal carbon dioxide; FiO_2: 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; SpO_2: pulse oxygen saturation; SSI: surgical site infection; V_A/Q: ventilation/perfusion-ratio; V_T: tidal volume.

References

1. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. Mortality after surgery in Europe: a 7 day cohort study. The Lancet. 2012;380:1059-65.

2. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of Long-Term Survival After Major Surgery and the Adverse Effect of Postoperative Complications. Transactions of the Meeting of the American Surgical Association. 2005;123:32-48.

3. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. Annals of surgery. 2000;232:242-53.

4. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010;113:1338.

5. Fernandez-Bustamante A, Frendl G, Sprung J, Kor DJ, Subramaniam B, Martinez Ruiz R, et al. Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery: A Multicenter Study by the Perioperative Research Network Investigators. JAMA surgery. 2017;152:157-66.

6. Gupta H, Gupta PK, Fang X, Miller WJ, Cemaj S, Forse RA, et al. Development and Validation of a Risk Calculator Predicting Postoperative Respiratory Failure. Chest. 2011;140:1207-15.

7. Wolthuis EK, Choi G, Dessing MC, Bresser P, Lutter R, Dzoljic M, et al. Mechanical Ventilation with Lower Tidal Volumes and Positive End-expiratory Pressure Prevents Pulmonary Inflammation in Patients

without Preexisting Lung Injury. Anesthesiology. 2006;105:689.

8. Hedenstierna G, Edmark L. The effects of anesthesia and muscle paralysis on the respiratory system. Intensive care medicine. 2005;31:1327-35.

9. Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005;102:838-54.

10. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013;118:1307-21.

11. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. The New England journal of medicine. 2013;369:428-37.

12. Güldner A, Kiss T, Serpa NA, Hemmes SN, Canet J, Spieth PM, et al. Intraoperative Protective Mechanical Ventilation for Prevention of Postoperative Pulmonary Complications: A Comprehensive Review of the Role of Tidal Volume, Positive End-expiratory Pressure, and Lung Recruitment Maneuvers. Anesthesiology. 2015;123:692.

13. Yang D, Grant MC, Stone A, Wu CL, Wick EC. A Meta-analysis of Intraoperative Ventilation Strategies to Prevent Pulmonary Complications: Is Low Tidal Volume Alone Sufficient to Protect Healthy Lungs? Annals of surgery. 2016;263:881-7.

14. Serpa NA, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci MO, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. Jama. 2012;58:1651-9.

15. Ladha K, Melo MFV, Mclean DJ, Wanderer JP, Grabitz SD, Kurth T, et al. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. Bmj. 2015;351:h3646.

16. Costa LA, Hajjar LA, Volpe MS, Fukushima JT, Rr DSS, Osawa EA, et al. Effect of Intensive vs Moderate Alveolar Recruitment Strategies Added to Lung-Protective Ventilation on Postoperative Pulmonary Complications: A Randomized Clinical Trial. Journal of the American Medical Association. 2017;317:1422.

17. Suzuki S, Mihara Y, Hikasa Y, Okahara S, Ishihara T, Shintani A, et al. Current Ventilator and Oxygen Management during General Anesthesia: A Multicenter, Cross-sectional Observational Study. Anesthesiology. 2018;129:67-76.

18. Staehr AK, Meyhoff CS, Henneberg SW, Christensen PL, Rasmussen LS. Influence of perioperative oxygen fraction on pulmonary function after abdominal surgery: a randomized controlled trial. Bmc

Research Notes. 2012;5:383.

19. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, De JE. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Metaanalysis, and Meta-Regression of Cohort Studies. Critical Care Medicine. 2015;43:1508-19.

20. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet. 2018;391:1693–705.

21. Meyhoff CS. Perioperative hyperoxia: why guidelines, research and clinical practice collide. British journal of anaesthesia. 2019;122:289-91.

22. de Jonge S, Egger M, Latif A, Loke YK, Berenholtz S, Boermeester M, et al. Effectiveness of 80% vs 30-35% fraction of inspired oxygen in patients undergoing surgery: an updated systematic review and meta-analysis. British journal of anaesthesia. 2019;122:325-34.

23. Mattishent K, Thavarajah M, Sinha A, Peel A, Egger M, Solomkin J, et al. Safety of 80% vs 30-35% fraction of inspired oxygen in patients undergoing surgery: a systematic review and meta-analysis. British journal of anaesthesia. 2019;122:311-24.

24. Wetterslev J, Meyhoff CS, Jorgensen LN, Gluud C, Lindschou J, Rasmussen LS. The effects of high perioperative inspiratory oxygen fraction for adult surgical patients. The Cochrane database of systematic reviews. 2015:CD008884.

25. Martin DS, Grocott MP. III. Oxygen therapy in anaesthesia: the yin and yang of O2. British journal of anaesthesia. 2013;111:867-71.

26. Ball L, Lumb AB, Pelosi P. Intraoperative fraction of inspired oxygen: bringing back the focus on patient outcome. British journal of anaesthesia. 2017;119:16-8.

27. Staehr-Rye AK, Meyhoff CS, Scheffenbichler FT, Vidal Melo MF, Gatke MR, Walsh JL, et al. High intraoperative inspiratory oxygen fraction and risk of major respiratory complications. British journal of anaesthesia. 2017;119:140-9.

28. Mazo V, Sabatã© S, Canet J, Gallart L, de Abreu MG, Belda J, et al. Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology. 2014;121:219-31.

29. Spieth PM, Guldner A, Uhlig C, Bluth T, Kiss T, Schultz MJ, et al. Variable versus conventional lung protective mechanical ventilation during open abdominal surgery: study protocol for a randomized controlled trial. Trials. 2014;15:155.

30. Kroenke K, Lawrence VA, Theroux JF, Tuley MR. Operative Risk in Patients With Severe Obstructive Pulmonary Disease. Archives of Internal Medicine. 1992;152:967.

31. Hulzebos EHJ, Helders PJM, Favié NJ, Bie RAD, Riviere ABDL, Meeteren NLUV. Preoperative Intensive Inspiratory Muscle Training to Prevent Postoperative Pulmonary Complications in High-Risk Patients Undergoing CABG Surgery. Digest of the World Core Medical Journals. 2006;296:1851.

32. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control. 2008;36:309.

33. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Jama the Journal of the American Medical Association. 1992;101:1644-55.

34. Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measure. European journal of anaesthesiology. 2015;32:88.

35. Wanner C, Tonelli M. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney International. 2014;85:1303-9.

36. Kabon B, Kurz A. Optimal perioperative oxygen administration. Current Opinion in Anaesthesiology. 2006;19:11-8.

37. Allen G. Supplemental Perioperative Oxygen to Reduce the Incidence of Surgical-Wound Infection. (Brief Article). New England Journal of Medicine. 2000;342:161-7.

38. Goll V, Akça O, Greif R, Freitag H, Arkiliç CF, Scheck T, et al. Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. Anesthesia & Analgesia. 2001;92:112-7.

39. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. Jama. 2005;294:2035-42.

40. Allegranzi B, Zayed B, Bischoff P, Kubilay NZ, De JS, De VF, et al. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infectious Diseases. 2016;16:e288-e303.

41. Suzuki S, Mihara Y, Hikasa Y, Okahara S, Ishihara T, Shintani A, et al. Current Ventilator and Oxygen Management during General Anesthesia:A Multicenter, Cross-sectional Observational Study | Anesthesiology | ASA Publications. Anesthesiology. 2018:1.

42. Martin DS, Mckenna HT, Morkane CM. Intraoperative Hyperoxemia: An Unnecessary Evil? Anesthesia & Analgesia. 2016;123:1643.

43. Romagnoli S, Becatti M, Bonicolini E, Fiorillo C, Zagli G. Protective ventilation with low fraction of inspired oxygen and radicals of oxygen production during general anaesthesia. British journal of anaesthesia. 2015;115:143-4.

44. Nagato AC, Bezerra FS, Manuella L, Lopes AA, Silva MAS, Luís Cristóv?O P, et al. Time course of inflammation, oxidative stress and tissue damage induced by hyperoxia in mouse lungs. International Journal of Experimental Pathology. 2012;93:269-78.

45. Brueckl C, Kaestle S, Kerem A, Habazettl H, Krombach F, Kuppe H, et al. Hyperoxia-induced reactive oxygen species formation in pulmonary capillary endothelial cells in situ. Am J Respir Cell Mol Biol. 2006;34:453-63.

46. Ma C, Beyer AM, Durand M, Clough AV, Zhu D, Norwood Toro L, et al. Hyperoxia Causes Mitochondrial Fragmentation in Pulmonary Endothelial Cells by Increasing Expression of Pro-Fission Proteins. Arterioscler Thromb Vasc Biol. 2018;38:622-35.

47. Nagato AC, Bezerra FS, Lanzetti M, Lopes AA, Silva MA, Porto LC, et al. Time course of inflammation, oxidative stress and tissue damage induced by hyperoxia in mouse lungs. International Journal of Experimental Pathology. 2012;93:269-78.

48. Romagnoli S, Becatti M, Bonicolini E, Fiorillo C, Zagli G. Protective ventilation with low fraction of inspired oxygen and radicals of oxygen production during general anaesthesia. British journal of anaesthesia. 2015;115:143-4.

49. Larsen M, Ekeloef S, Kokotovic D, Schoupedersen AM, Lykkesfeldt J, Gögenür I. Effect of High Inspiratory Oxygen Fraction on Endothelial Function in Healthy Volunteers: A Randomized Controlled Crossover Pilot Study. Anesthesia & Analgesia. 2017;125:1.

50. Marntell S, Nyman G, Hedenstierna G. High inspired oxygen concentrations increase intrapulmonary shunt in anaesthetized horses. Veterinary Anaesthesia & Analgesia. 2005;32:338-47.

51. Staffieri F, Monte VD, Marzo CD, Grasso S, Crovace A. Effects of two fractions of inspired oxygen on lung aeration and gas exchange in cats under inhalant anaesthesia. Veterinary Anaesthesia & Analgesia. 2010;37:483-90.

52. Akça O, Podolsky A, Eisenhuber E, Panzer O, Hetz H, Lampl K, et al. Comparable postoperative pulmonary atelectasis in patients given 30% or 80% oxygen during and 2 hours after colon resection. Anesthesiology. 1999;91:991-8.

53. Edmark L, Kostovaaherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during induction of general anesthesia. Anesthesiology. 2003;98:28-33.

54. Jin Y, Peng LQ, Zhao AL. Hyperoxia induces the apoptosis of alveolar epithelial cells and changes of pulmonary surfactant proteins. Eur Rev Med Pharmacol Sci. 2018;22:492-7.

55. Six S, Jaffal K, Ledoux G, Jaillette E, Wallet F, Nseir S. Hyperoxemia as a risk factor for ventilator-associated pneumonia. Critical care. 2016;20:195.

56. Rachmale S. The authors respond to: Practice of excessive FIO2 and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. Respiratory Care. 2013;58:83-4.

57. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Høgdall C, Lundvall L, et al. Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: the PROXI randomized clinical trial. Jama. 2009;302:1543.

58. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. Anesthesia & Analgesia. 2012;115:849-54.

59. Zoremba M, Dette F, Hunecke T, Braunecker S, Wulf H. The influence of perioperative oxygen concentration on postoperative lung function in moderately obese adults. European journal of anaesthesiology. 2010;27:501-7.

60. Hovaguimian F, Lysakowski C, Elia N, Tramèr MR. Effect of Intraoperative High Inspired Oxygen Fraction on Surgical Site Infection, Postoperative Nausea and Vomiting, and Pulmonary FunctionSystematic Review and Meta-analysis of Randomized Controlled Trials. Anesthesiology. 2013;119:303-16.

61. Ferrando C, Soro M, Unzueta C, Canet J, Tusman G, Suarez-Sipmann F, et al. Rationale and study design for an individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) and its effects on surgical site infection: study protocol for a randomised controlled trial. 2017;7:e016765.

62. Acosta J, Aguilar G, Alberola MJ, Alcón A, Alonso JM, Alonso MD, et al. Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial. Lancet Respir Med. 2018;6:S2213260018300249.

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

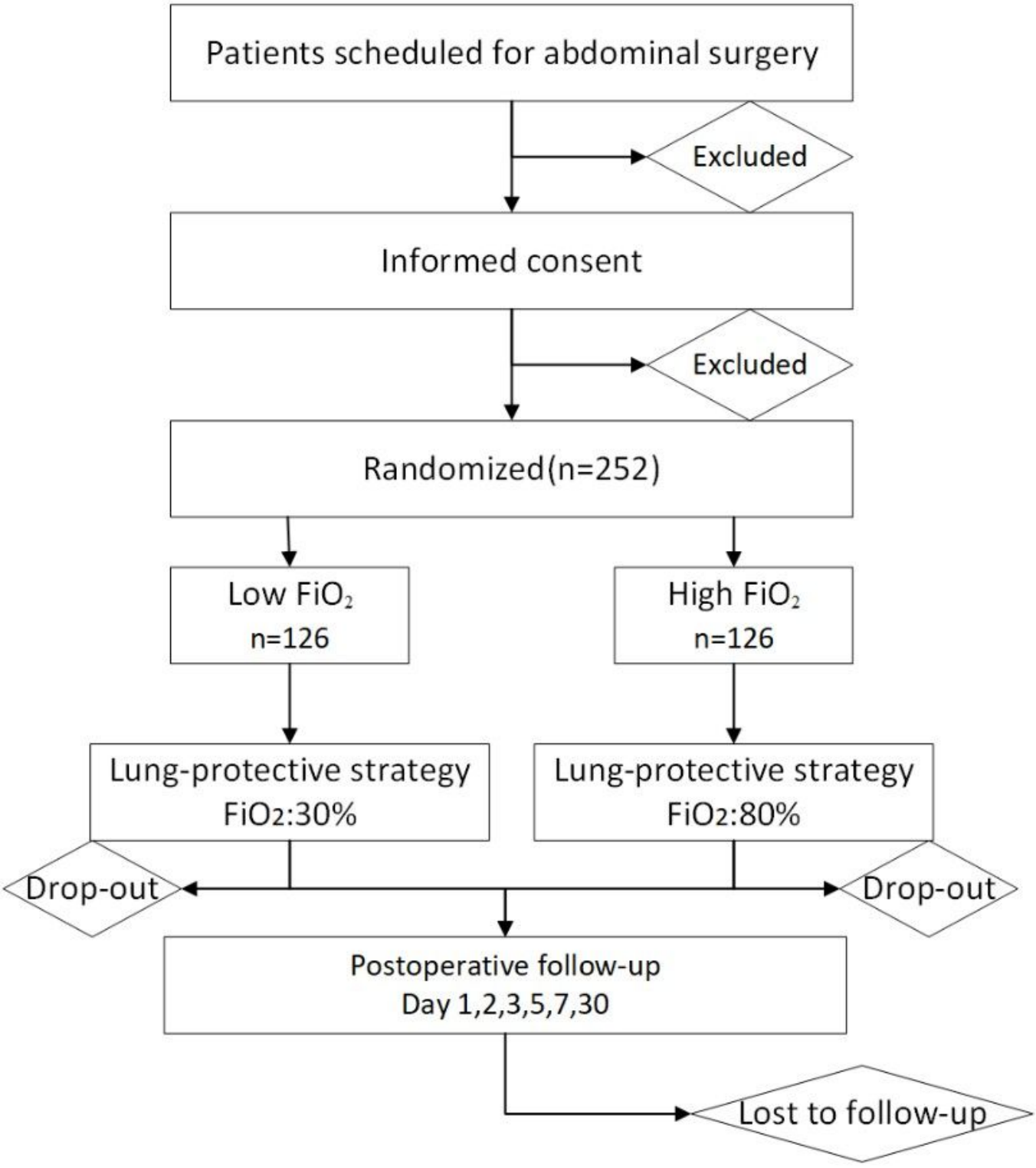

Figure 1

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

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.docx