BMJ Open

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028464
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2018
Complete List of Authors:	ZHOU, zhen-feng; Zhejiang Provincial People's Hospital FANG, Jun-biao; Zhejiang Provincial People,s Hospital WANG, Hong-fa; Zhejiang Provincial People,s Hospital HE, Ying; Zhejiang Provincial People,s Hospital YU, Yong-jian; Zhejiang Provincial People,s Hospital XU, Qiong; Zhejiang Provincial People,s Hospital GE, Yun-fen; Zhejiang Provincial People,s Hospital ZHANG, Miao-zun; Ningbo Medical center Lihuili Hospital, General Surgery HU, Shuang-fei; Zhejiang Provincial People's Hospital, Anesthesiology
Keywords:	Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Author details

Zhen-feng ZHOU, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: zhenfeng9853@163.com

Jun-biao FANG, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: drfangjb@126.com

Hong-fa WANG.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: whf033@163.com

Ying HE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: heyingzju@163.com

Yong-jian YU

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: yyj731227@163.com

Qiong XU.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: happyjoan@163.com

Yun-fen GE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: gyunfen@sina.com

Miao-zun ZHANG , M.D.

- Affiliation: Department of General Surgery, Ningbo Medical center Lihuili Hospital,Ningbo, 325000,China;

Email: idreamof333@126.com

Shuang-fei HU , M.D.

- Corresponding Author
- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: hushuangfei77@sina.com

Abstract

Introduction: PPCs will develop in even 58% of patients undergoing abdominal surgery and PPCs is strongly associated with higher risk of mortality. There are increasing studies shown that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the role of PEEP during the intraoperative period in preventing PCC for laparoscopic surgery is not clearly defined.

Methods and Analysis: A total number of 208 patients with high-risk of postoperative pulmonary complications patients undergoing laparoscopic abdominal surgery will be enrolled and randomized into a standard PEEP (6-8 cmH_2O) group and a low PEEP (≤ 2 cm H_2O) group. Both groups will receive an inspired oxygen fraction (FiO_2) of 0.50 and a tidal volume of 8 ml/kg ideal body weight (IBW). Standard perioperative fluid management standardization and analgesic treatments will be applied in both groups. The primary endpoint was postoperative pulmonary complications within 7 days after surgery. Secondary endpoints will be: the modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, postoperative surgical complications, intensive care unit (ICU) length of stay, hospital length of stay, thirty-day mortality.

Ethics and Dissemination: The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (KY2018026) on 22 October 2018. The first participant is expected to be recruited within 6 months and the estimated completion date of the study is October 2021. The results of this trial will be submitted to a peer-reviewed journal and will inform clinical practice.

TRIAL REGISTRATION NUMBER: http://www.chictr.org.cn, ID: ChiCTR1800019865. Registered on 2 December 2018 ; Pre-results.

Keywords: Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Strengths and limitations of this study:

Intervention is blinded.

Standard perioperative fluid management standardization and analgesic treatments are applied in both groups.

Primary outcome measure is patient centred.

It is not multicentre randomised trial.

Background

Every year around the world, approximately 230 million patients require surgery with general anesthesia and mechanical ventilation [1]. Laparoscopic surgery has been widely accepted because it is associated with less blood loss, less postoperative pain and rapid recovery [2, 3]. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5% [4], and 12% to 58% of patients undergoing abdominal surgery will develop a PPC [4, 5]. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality [6-8].

Nearly 30% of surgery patients undergoing general anesthesia and mechanical ventilation are at intermediate to high risk for PPCs according to large cohort studies [5, 9]. Both alveolar overstretching and atelectasis induce the release of inflammatory mediators, leading to lung and systemic organ damage [10]. Lung-protective ventilation including the use of low tidal volumes and positive endexpiratory pressure (PEEP) aims to prevent atelectasis and improve gas exchange [11, 12]. Furthermore, PEEP has been found to reduce mortality in patients with the acute respiratory distress syndrome and in critically ill patients [13].

Adopting an appropriate PEEP may prevent PPCs. When high

PEEP is applied, alveolar may overinflate and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis [10]. Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducings the incidence of PPC [14, 15]. Despite all these studies recommending the use of low tidal volume [10,14-18], the appropriate PEEP has not yet been defined. A multicenter observational study showed that approximately 20% of patients did not receive PEEP during routine anesthetic practice [17]. In the Intraoperative Protective Ventilation (IMPROVE) trial that included patients undergoing major abdominal surgery with intermediate-risk and high-risk of PPCs, compared to a practice of nonprotective mechanical ventilation including higher tidal volumes without PEEP, a lung-protective ventilation strategy with lower tidal volumes and PEEP of 6 cm H_2O was associated with improved clinical outcomes [14]. Furthermore, in another study including patients undergoing abdominal nonlaparoscopic surgery lasting more than 2 h, compared to a standard ventilation strategy, a protective ventilation strategy with 10 cm H_2O PEEP improved respiratory function and reduced the modified clinical pulmonary infection score (mCPIS) [15].

However, another study showed that low tidal volume combined low PEEP (3 cm H_2O) ventilation may induce postoperative inflammation and may increase the risk of PCC during major surgery such as hepatectomy [18]. In an international multicenter trial, Protective Ventilation using high vs. low PEEP (PROVHILO), including patients undergoing open abdominal surgery with high risk for PPCs, compared with low PEEP (≤ 2 cm H_2O), a ventilation strategy of high PEEP (12 cm H_2O) did not reduce the incidence of PPCs, but more likely caused haemodynamic instability [16]. Therefore, the authors suggested a ventilation strategy of low tidal volume combined with low PEEP (≤ 2 cm H_2O) [16].

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo laparoscopic surgery. Some studies have suggested that laparoscopic-assisted gastrectomy (LAG) is beneficial for postoperative respiratory function recovery. Nevertheless, it is also necessary to consider the effects of pneumoperitoneum (PnP) on airway pressure and pulmonary function. The role of PEEP during the intraoperative period in preventing PCC for laparoscopic surgery has not been clearly defined. We hypothesized that, when compared to low PEEP, standard PEEP may prevent the incidence of PCC and may reduce

the occurrence of organ dysfunction. These anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and; in-hospital stays in patients undergoing laparoscopic surgery.

Methods/design

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH_2O) to those of low PEEP (≤ 2 cm H_2O) in patients at risk for complications undergoing laparoscopic surgery during general anesthesia in terms of: (1) PPCs, (2) modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, changes in chest X-ray findings and oxygenation; (3). intraoperative complications including hypoxemia and hypotension, massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

Study endpoints

Primary outcome measure

The primary endpoint was PPCs including new atelectasis or infiltrates on a chest X-ray, respiratory failure defined as the need for noninvasive or invasive ventilation or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 300 within 7 days after surgery [19].

Secondary outcome measures

Secondary outcome variables were any pulmonary complications and extrapulmonary complications as follows:

1. Postoperative pulmonary complications (PPCs) within 30 days after surgery. Those PPCs are scored according to a grading scale ranging from 0 to 4 [20] (grade 0 representing no PPCs and grades 1 to 4 representing gradually worse forms of PPCs) within 7 and 30 days after surgery (Table 1).

Table 1. Grade scale for postoperative pulmonary complications.

Grade scale	Detailed description
Grade 1	- Cough, dry - Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; results of chest radiograph either normal - Dyspnea, not due to other documented cause
Grade 2	- Cough, productive, not due to other documented cause - Bronchospasm: new wheezing or pre-existent wheezing resulting in change therapy - Hypoxemia - Atelectasis: radiological confirmation plus either temperature > 37.5°C or abnormal lung findings - Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation
Grade 3	- Pleural effusion, resulting in thoracentesis - Pneumonia, suspected: radiological evidence without bacteriological confirmation -Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture - Pneumothorax - Re-intubation postoperative or intubation, period of ventilator dependence (non-invasive or invasive ventilation) ≤ 48 hours
Grade 4	Ventilatory failure: postoperative non-invasive ventilation dependence ≥ 48 hours, or re-intubation with subsequent period of ventilator dependence ≥ 48 hours

2. Postoperative pulmonary complications will also be analyzed separately.

Pneumonia is defined according to Centers for Disease Control

(CDC) criteria [21] as follows: patients with altered or new pulmonary opacities on chest X-ray; patients should also meet at least two of the following criteria: (1) temperature ≥ 38.5°C or < 36°C, (2) white blood cell (WBC) count > 12 x10^9/L or < 4 x10^9/L; (3) purulent sputum: new cough or difficulty breathing or previous coughing or difficulty breathing is further aggravated.

Postoperative hypoxemia and severe hypoxemia [22]: hypoxemia is defined as PaO_2 < 60 mmHg or oxygen saturation (SpO_2) < 90% on room air, but responding to oxygen treatment (hypoventilation should be excluded). Severe hypoxemia is recorded in cases where the patient requires non-invasive or invasive mechanical ventilation.

Suspected pulmonary infection is described in a previous study [16]: the patient takes antibiotics and should meet at least one of the following criteria: (1) changed or new sputum, (2) changed or new pulmonary opacities on chest X–ray, (3) temperature greater than 38.3°C, and (4) WBC count > 12 x10^9/L.

Pulmonary infiltrate is defined according to consensus guidelines: unilateral or bilateral infiltrate with development of ALI (acute lung injury)/ARDS (acute respiratory distress syndrome) on chest X-ray [23].

Atelectasis, pleural effusion or pneumothorax are identified by

chest X-ray.

The modified clinical pulmonary infection score (mCPIS) is calculated as previously described [24] (Table 2).

Suspected pulmonary complications[15] are defined in cases where

Table 2. The definition of modified Clinical Pulmonary Infection Score (mCPIS).

Items	CPIS Points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (℃)	36.5- 38.4	38.5- 38.9	≤ 36.5 or ≥ 39.0
Leukocytes count (per mm^3)	4,000-11,000	<4,000 or >11,000	< 4,000 or > 11,000 + band forms ≥ 500
PaO_2/FiO_2,(mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

PaO_2 =Partial pressure of arterial oxygen; FiO_2 =Fraction of inspired oxygen; ARDS =Acute respiratory distress syndrome

patients display at least three of the following new findings: (1) cough, (2) increased secretions, (3) dyspnea, (4) chest pain, (5) temperature> 38°C, and (6) pulse rate> 100 beats per minute.

Requirement for postoperative ventilation (respiratory failure that requires noninvasive and/or invasive ventilation) for at any time after surgery according to standard criteria and clinical practice guidelines[20].

3. Postoperative extrapulmonary complications within 30 days after surgery:

Systemic inflammatory response syndrome (SIRS) criteria are

defined when meeting the following four criteria by the most deranged value recorded after surgery[13]: (1) rectal or tympanic temperature > 38°C or <36°C (0.5°C will be added to the measured value when oral or other temperatures are used); (2) ventricular rate > 90 beats/min (excluding those who have a known medical condition or are receiving treatment that would prevent tachycardia); (3) respiratory rate> 20 breaths/min or a $PaCO_2$< 32 mmHg or requiring mechanical ventilation; (4) WBC count >12 x 10^9/L or < 4 x 10^9/L.

Sepsis and severe sepsis [13]: sepsis is recorded when meeting at least two SIRS criteria with a defined focus of infection. Defined infection is indicated in patients when they meet at least one of the following criteria: (1) an organism grown in blood or sterile site, (2) an abscess, (3) infected tissue (e.g., pneumonia, urinary tract, peritonitis, soft tissue, vascular infection, etc.) Severe sepsis is recorded in a patient with sepsis who has at least one organ failure, hypotension or hypoperfusion.

Septic shock [13]: regardless of how adequate fluid resuscitation has been administered, the patient is still remains with sepsis-induced hypotension with the presence of perfusion abnormalities.

Other extrapulmonary infection including surgical site infection (SSI) and intraabdominal abscess: SSI [26] defined as surgical site

infection within 30 days after surgery; at least the incision has a purulent effluent; the incision drainage fluid or tissue culture results are positive, with pain or tenderness, local swelling, redness or fever.

Need for postoperative blood transfusion.

Postoperative surgical complications: anastomotic leakage and need for surgical reintervention, defined according to consensus criteria [28].

Unexpected intensive care unit (ICU) admission or readmission.

ICU length of stay and hospital length of stay.

Hospital free-days at follow-up day 30.

In-hospital mortality and thirty-day mortality (all-cause mortality 30 days after randomization).

Intraoperative complications: pneumothorax confirmed by chest X-ray and any other complications.

Study design: This is an unfunded, parallel-group, double-blinded, prospective, randomized controlled clinical trial was registered at http://www.chictr.org.cn (ChiCTR1800019865) and was conducted at the Department of Anesthesiology and Intensive Care of P Zhejiang Provincial People's Hospital. The first patient will be randomized in January 2019. This trail protocol is conducted according to the Consolidated Standards of Reporting Trials

(CONSORT) guidelines (Figure 1). The SPIRIT 2013 Checklist is given in Additional file 1.

Blinding, data collection, randomization and record keeping

Selection of the participants

Researchers will be trained prior to investigation. Study data including patient clinical characteristics, intraoperative respiratory parameters, postoperative outcomes, and laboratory test will be collected onto case report forms (CRF) (Additional file 2).

An independent researcher will randomize the participants into the study group (standard group PEEP) and control group (low PEEP group) in a ratio of 1:1. The random sequence will be computer-generated and participants will be allocated in numerical order with sealed opaque envelopes. The attending anesthesiologist will perform anesthesia strictly according to the research protocol, and will be responsible for data during the preoperative, intraoperative and PACU period. The chief surgeon performs the postoperative laboratory testing. An independent researcher will be involved in postoperative follow-up and data collection. Statistical analysis will be performed by a statistician who does not participate in the data collection. Patients, research staff, surgeons, intensive care physicians and the statistician will be unaware of the group allocation. Some preoperative characteristics

and laboratory results will automatically derived from a computer data base.

The original data (CRF and relevant records) will be maintained for 10 years and then destroyed according to hospital standards.

Selection of the participants

Patients scheduled for elective laparoscopic abdominal surgery under general anesthesia will be screened and recruited during preoperative assessment. Patients meeting inclusion criteria will be required to provide their written informed consent. The participant can withdraw from the trial at any time.

Inclusion criteria are patients older than 18 y, American Society of Anesthesiologists (ASA) physical status II or III, body mass index (BMI) between 18-35 kg/m^2, general anesthesia expected to last more than 3 h, an intermediate or high preoperative index for PPCs risk by the Assess Respiratory Risk in Surgical Patients in Catalonia study (ARISCAT score ≥ 26, the Additional file 3).

Exclusion criteria are emergency surgery or history of previous lung surgery, history of mechanical ventilation within the 2 weeks before recruitment, non–invasive ventilation or oxygen therapy at home, acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome), history of chronic obstructive pulmonary disease (COPD), persistent hemodynamic instability or

severe cardiac disease (New York Heart Association class III or IV, or persistent ventricular tachyarrhythmia's, or acute coronary syndrome), sepsis or septic shock, need renal replacement therapy (CRRT), progressive neuromuscular illness, pregnancy, participation in another study or refusal to participate.

Time course of the study

Preoperative admission

Medical history, ASA physical status, BMI, 12-lead ECG, laboratory results , chest X-ray or computed tomography (CT) scan, ARISCAT score and nutritional risk screening (NRS 2002 tool), the results of echocardiography and spirometry (in cases of history of coronary artery disease or smoking) will be recorded.

Intraoperative care

A central venous catheter and an arterial cannula will be placed before induction of anesthesia. Peripheral oxygen saturation (SpO_2), arterial blood pressure, heart rate (HR), ECG, end-tidal carbon dioxide tension ($EtCO_2$) and bispectral index (BIS) will be monitored continuously. Pneumoperitoneum (PnP), tidal volume, PEEP, airway pressures including peak pressure and plateau pressure, airway resistance (Raw), Vds/Vt, core temperature, and arterial blood gas analysis data will be recorded.

Crystalloid (12-15ml/kg/h) was infused to maintain hemodynamic

stability and central venous pressure 5-12 cm H_2O. Blood loss and vasodilation was supplemented by colloidal fluid.

Routine anesthesia was induced with intravenous dexmedetomidine(1 ug/kg) or midazolam (0.05-0.075mg/kg), cisatracurium (2 mg/kg), propofol (2-3 mg/kg) and fentanyl (1-3 μ/kg) for tracheal intubation. Anesthesia was maintained with propofol, sevoflurane and remifentanil infusion to maintain the BIS 40-50 until skin suturing was completed. Cisatracurium (1.0-1.5 mg/kg) was administered every hour and the last dose was at least 1 hour before the end of operation.

Ropivacaine was administrated as local anesthetic before and at the end of operation respectively. Fentanyl (1-3 μg/kg) and flurbiprofenaxetil 50 mg was required before remifentanil was stop.

Postoperative care

Patients will be transferred to the post-anesthesia care unit (PACU) after surgery regardless of whether they are still intubated. Postoperative pain management will be suggested to achieve a visual analogue scale (VAS) pain score of < 3/10 using a patient-controlled intravenous analgesia pump including fentanyl (0.3-0.5 μg/kg), flurbiprofenaxetil (100 mg) and palonosetron hydrochloride (0.25 mg) palazidine.

The ICU physician and surgeon will independently monitor clinical

progress and all endpoints by daily physical examinations. Appropriate prophylactic antibiotics and antithrombotic treatments will be administered as required during the postoperative period. A chest X-ray will be performed by an independent, trained radiologist on POD 5. Arterial blood gas analysis will be performed on POD 1 and POD 3 and other laboratory tests will performed on POD 1, POD 3, POD 5 and POD 7. The examinations will be repeated and microbiology tests will be performed when the development of pulmonary complications are suspected.

Study arms and intraoperative ventilation protocol

Patients will be randomly assigned to the low PEEP ventilation group (PEEP ≤ 2 cm H_2O) or the standard PEEP group (PEEP = 6-8 cm H_2O) using a volume-controlled ventilation strategy (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) with a tidal volume of 8 ml/kg ideal body weight (IBW), an inspired oxygen fraction (FiO_2) of 0.50 and inspiratory to expiratory ratio of 1:2. Respiratory rate should be adjusted to maintain $ETCO_2$ between 35 and 45 mmHg) and plateau pressure should be no more than 30 cmH_2O. IBW is calculated with formulas as follows [14]: 45.5 + 0.91 x (centimeters of height - 152.4) for females and 50 + 0.91 x (centimeters of height - 152.4) for males. Recruitment maneuvers (RMs)[19] will be performed immediately after tracheal intubation

and every time when the ventilator is interrupted until the end of surgery in each group. The compliance of the respiratory system was calculated with the formulas of V_T/ (plateau pressure of the respiratory system - PEEP).

Recruitment maneuvers will be performed as follows:

(1). Pressure support ventilation (PSV) mode

(2). Positive end-expiratory pressure (PEEP) set to 30 cm of water

(3). Inspiratory gas flow set to the highest value

(4). Duration of the maneuver = 30 sec

A rescue therapy will be applied in case of desaturation (defined as a peripheral SpO_2 of less than 92%), consisting of increasing FiO_2 to 100% in each group and increased PEEP in the low PEEP group (Additional file 4).

From postoperative day 7 (POD 7 to POD 30, follow-up)

Secondary endpoints and any mortality will also be evaluated during the follow-up period. The CONSORT flowchart of the trial is shown in Figure 2.

Data monitoring and Handling of implausible values or missing values: A clinical investigator will identify implausible values. Missing continuous variables should be less than 10% and will be replaced by median. Data monitoring is managed by an independent investigator who is not involved in the study. The

progress of the study will be evaluated and the completeness and accuracy of the data (Informed Consent Forms, source data, CRF and outcome variables) will be verified.

Statistics:

Normally distributed variables will be expressed as the mean ± standard deviation (SD) and will be compared with Student's t-test. Categorical variables will be compared using the chi-square test or the Fisher's exact test. Abnormal continuous variables will be expressed as median (interquartile range (IQR)) and evaluated with the Mann-Whitney U-test. Analysis will be by intention-to-treat comparing the composite outcome measure at 7 days in the two groups by the chi-squared test (or Fisher's exact test as appropriate) and multiple logistic regression analysis adjusting will be performed to identify various risk factors (for the primary outcome and the pulmonary complications at postoperative Day 30). *P* <0.05 will be considered statistically significant and all reported *p* values will be 2-sided. Interim analysis of safety will be conducted after enrolment of the first 200 patients. All analyses will be conducted using the SPSS Version 18.0 (SPSS, Chicago, IL, USA) software.

Sample size calculation

The incidence rate of postoperative pulmonary complications was

0.39 in the low PEEP group [16]. Two tailed chi-squared test was performed and we estimated that 188 patients were required to provide 90% power to detect a 50% relative difference between the two groups, with a type I error probability of 0.05. Assuming that follow-up lost rate was 10 %, and then a total of 208 cases are needed. Analysis was computed using G-Power (version 3.1; Informer Technologies, Inc.).

Adverse events and interruption of the trial:

All patients will be continuously monitored during the study including daily visits during in-hospital and daily phone-call visits during the out of hospital follow-up period (until POD 30). All serious adverse, unexpected or possibly related events will be recorded in the CRF and will be reported to the data monitoring and safety committee (DMSC). DMSC will recommend that the study must to be stopped if it is found that the continued conduct of the study compromises patient safety (a between-group difference in serious adverse events or in 30- day mortality is found).

Discussion:

In this pragmatic, prospective, randomized controlled trial of high-risk patients undergoing laparoscopic surgery, our aim will not be only to assess possible single effects of PEEP levels on major PPCs from those of lower tidal volumes and RM but also to assess relevant clinical parameters associated with alterations in pulmonary function such as chest X-ray, abnormalities, mCPIS, arterial oxygenation/peripheral oxygen saturation in air and changes in dyspnea/cough/secretions. Our findings might change current practice of mechanical ventilation in high-risk patients undergoing laparoscopic surgery.

There are some potential strengths of the present trial protocol. First, this ARISCAT score will be used to predict PPCs and we selected only a high-risk PPC population that will potentially receive maximum benefit from intraoperative PEEP strategy. Although various scores have been developed for predicting PPC incidence based on various countries and surgical populations, the ARISCAT score is considered to be the most valuable tool [10]. Second, this trial design includes instructions for fluid management standardization and analgesic treatments during the perioperative period. Third, the included patients will undergo elective abdominal laparoscopic surgical procedures with more than 3h of general

anesthesia. Previous studies have reported that both abdominal surgery and longer anesthesia duration are potential risk factors for PPCs [8].

Notably, mechanical ventilation itself is one of major contributors to PPCs [29]. PnP is also an important risk factor for PPCs [30]. Intraabdominal pressure is frequently higher than airway pressure during PnP with carbon dioxide (CO_2) for laparoscopic surgery. This pressure gradient usually causes cephalad displacement of the diaphragm and collapses adjacent pulmonary tissues. PnP also decreases respiratory compliance and arterial oxygenation [31] .All these influences on PnP lead finally to atelectasis [32].

On the other hand, PEEP is thought to prevent the development of atelectasis by keeping the airways open and maintaining adequate gas exchange at the end of the expiratory period during PnP [10]. Certainly, the level of PEEP should be adopted according to the patient's and surgical characteristics, as well as to the patient's positioning.

Previous studies reported that very low levels of PEEP are potentially associated with atelectasis by promoting repeated opening and closing of small airways [33]. However, higher levels of PEEP may increase mean airway pressure of the respiratory system and likely even impair hemodynamics.

There is an increasing number of highly qualitative Randomized Controlled Trials (RCTs) regarding intraoperative mechanical ventilation and PPCs, whereas direct assessment of the effect in high-risk patients undergoing laparoscopic surgery remains lacking. The potential significance of this trial is that it may provide evidence of the effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic surgery.

Trial status

The trial is currently ongoing. The first participant is expected to be recruited within 6 months and the estimated completion date of the study is October 2021.

Additional file

Abbreviations

ABGa: Arterial blood gas analysis; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; AMI: Acute myocardial infarction; ASA: American Society of Anesthesiologists; BIS: bispectral index; BMI: Body Mass Index; CDC: Centers for Disease Control; CO_2: carbon dioxide; COPD: Chronic obstructive pulmonary disease; CRF: Case Report Form; CRRT: renal replacement therapy; CT: Computer tomography; DMSC: data monitoring and safety committee; DIC: Disseminated intravascular coagulation; ECG: Electrocardiogram; $EtCO_2$: End-tidal carbon dioxide tension; FiO_2: Fraction of inspired oxygen; HR: Heart rate; IBW: Ideal bodyweight; ICU: Intensive care unit; IQR: interquartile range; LAG: laparoscopic surgery; mCPIS: modified clinical pulmonary infection score; PACU: Post-anesthesia Care Unit;PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PnP: pneumoperitoneum; POD: Postoperative day; PPC:

Postoperative pulmonary complications; PSV: Pressure Support Ventilation; Raw: Airway resistance; RM: Recruitment maneuver; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome; SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials; SpO_2: Oxygen saturation; SSI: surgical site infection; Vds/Vt: Dead space fraction; VAS: visual analogue scale; WBC: White Blood Cell.

Acknowledgements

We want to thank all the contributors and collaborators for their support in this study. We also thank all the participating patients.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

Zhen-feng ZHOU and Shuang-fei HU designed the study protocol and wrote the paper. Hong-fa WANG and Miao-zun ZHANG designed the statistical method. The work of patient recruitment

and data collecting will be done by Jun- biao FANG, Yong-jian YU, Qiong XU, Ying HE and Yun-fen GE. Shuang-fei HU is the study director and Jun- biao FANG is the principal investigator of this study. All authors have read the manuscript and approved to submitting the final paper.

Authors' information

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) (registration number KY2018026) on 22 October 2018. Any subsequent protocol and informed consent document amendments must be approved by the responsible of Ethics Committee. All communications with the regulatory authorities and the Ethics Committee must be recorded.

All recruited patients will be informed of the trial purposes and their duties within the trial before randomization. Recruited patients can withdraw from the study at any time without providing any specific reason. The patient data will be stored in a separate, safe place but that it may be reviewed by the relevant investigator.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

[1] Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008. 372(9633): 139-44.

[2] Lee CM, Park S. Laparoscopic techniques and strategies for gastrointestinal GISTs. J Vis Surg. 2017. 3: 62.

[3] Patel B, Leung U, Lee J, Bryant R, O'Rourke N, Cavallucci D. Laparoscopic pancreaticoduodenectomy in Brisbane, Australia: an initial experience. ANZ J Surg. 2017 .

[4] Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010. 113(6): 1338-50.

[5] Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med. 2001. 135(10): 847-57.

[6] Shander A, Fleisher LA, Barie PS, Bigatello LM, Sladen RN, Watson CB. Clinical and economic burden of postoperative pulmonary complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies. Crit Care Med. 2011. 39(9): 2163-72.

[7] 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. Ann Surg. 2005. 242(3): 326-41; discussion 341-3.

[8] Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006. 144(8): 581-95.

[9] 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. Ann Surg. 2000. 232(2): 242-53.

[10] Güldner A, Kiss T, Serpa NA, 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(3): 692-713.

[11] Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the non-injured lung: review and meta-analysis. Crit Care. 2014. 18(2): 211.

[12] Futier E, Constantin JM, Pelosi P, et al. Intraoperative recruitment maneuver reverses detrimental pneumoperitoneum-induced respiratory effects in healthy weight and obese patients undergoing laparoscopy. Anesthesiology. 2010. 113(6): 1310-9.

[13] Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000. 342(18): 1301-8.

[14] Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013. 369(5): 428-37.

[15] Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013. 118(6): 1307-21.

[16] Hemmes SN, de Abreu M G, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet. 2014. 384(9942): 495-503.

[17] Jaber S, Coisel Y, Chanques G, et al. A multicentre observational study of intra-operative ventilatory

management during general anaesthesia: tidal volumes and relation to body weight. Anaesthesia. 2012. 67(9): 999-1008.

[18] Sato H, Nakamura K, Baba Y, Terada S, Goto T, Kurahashi K. Low tidal volume ventilation with low PEEP during surgery may induce lung inflammation. BMC Anesthesiol. 2016. 16(1): 47.

[19] Ruszkai Z, Kiss E, László I, et al. Effects of intraoperative PEEP optimization on postoperative pulmonary complications and the inflammatory response: study protocol for a randomized controlled trial. Trials. 2017. 18(1): 375.

[20] Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, de la Riviere A B, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA. 2006. 296(15): 1851-7.

[21] Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. Methods Inf Med. 2007. 46(5): 595-600.

[22] Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011. 183(3): E195-214.

[23] Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994. 20(3): 225-32.

[24] Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003. 168(2): 173-9.

[25] Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009. 145(1): 24-33.

[26] Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992. 13(10): 606-8.

[27] Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation. 2007. 116(22): 2634-53.

[28] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004. 240(2): 205-13.

[29] Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA. 2010. 304(23): 2620-7.

[30] Reinius H, Jonsson L, Gustafsson S, et al. Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. Anesthesiology. 2009. 111(5): 979-87.

[31] Hazebroek EJ, Haitsma JJ, Lachmann B, Bonjer HJ. Mechanical ventilation with positive end-expiratory pressure preserves arterial oxygenation during prolonged pneumoperitoneum. Surg Endosc. 2002. 16(4): 685-9.

[32] Park SJ, Kim BG, Oh AH, Han SH, Han HS, Ryu JH. Effects of intraoperative protective lung ventilation on postoperative pulmonary complications in patients with laparoscopic surgery: prospective, randomized and controlled trial. Surg Endosc. 2016. 30(10): 4598-606.

[33] Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005. 102(4): 838-54.

[34] Lindberg P, Gunnarsson L, Tokics L, et al. Atelectasis and lung function in the postoperative period. Acta

Anaesthesiol Scand. 1992. 36(6): 546-53.

[35] Nguyen NT, Anderson JT, Budd M, et al. Effects of pneumoperitoneum on intraoperative pulmonary mechanics and gas exchange during laparoscopic gastric bypass. Surg Endosc. 2004. 18(1): 64-71.

[36] Meininger D, Byhahn C, Mierdl S, Westphal K, Zwissler B. Positive end-expiratory pressure improves arterial oxygenation during prolonged pneumoperitoneum. Acta Anaesthesiol Scand. 2005. 49(6): 778-83.

[37] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012. 120(4): c179-84.

[38] Reintam A, Parm P, Kitus R, Starkopf J, Kern H. Gastrointestinal failure score in critically ill patients: a prospective observational study. Crit Care. 2008. 12(4): R90.

Figure legends:

Figure 1. Standard Protocol Items.

Figure 2. The CONSORT flowchart of the trial.

Standard Protocol Items

	Study period								
	Enrolment		Allocation		Post-allocation				
Timepoint	-1 week	-t1	0	DOS	POD1	POD3	POD5	POD7	POD8-30
Enrolment:									
Perioperative assessment	√								
Eligibility screen		√							
Informed consent		√							
Allocation			√						
Interventions:									
Study Group(Low PEEP)				√					
Control Group(Standard PEEP)				√					
Assessments:									
Intraoperative complications				√					
Postoperative pulmonary complications					√	√	√	√	√
Physical examinations					√	√	√	√	√
Blood gas analysis					√	√	√	√	√
chest X-ray							√		
Postoperative extra-pulmonary complications					√	√	√	√	√
Postoperative surgical complications					√	√	√	√	√
ICU length of stay									
Hospital length of stay									
In-hospital mortality									
Thirty-day mortality					◄———	———	———	———	———►

Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. DOS: day of surgery; POD: postoperative day; ICU: Intensive care unit.

Figure 1. Standard Protocol Items

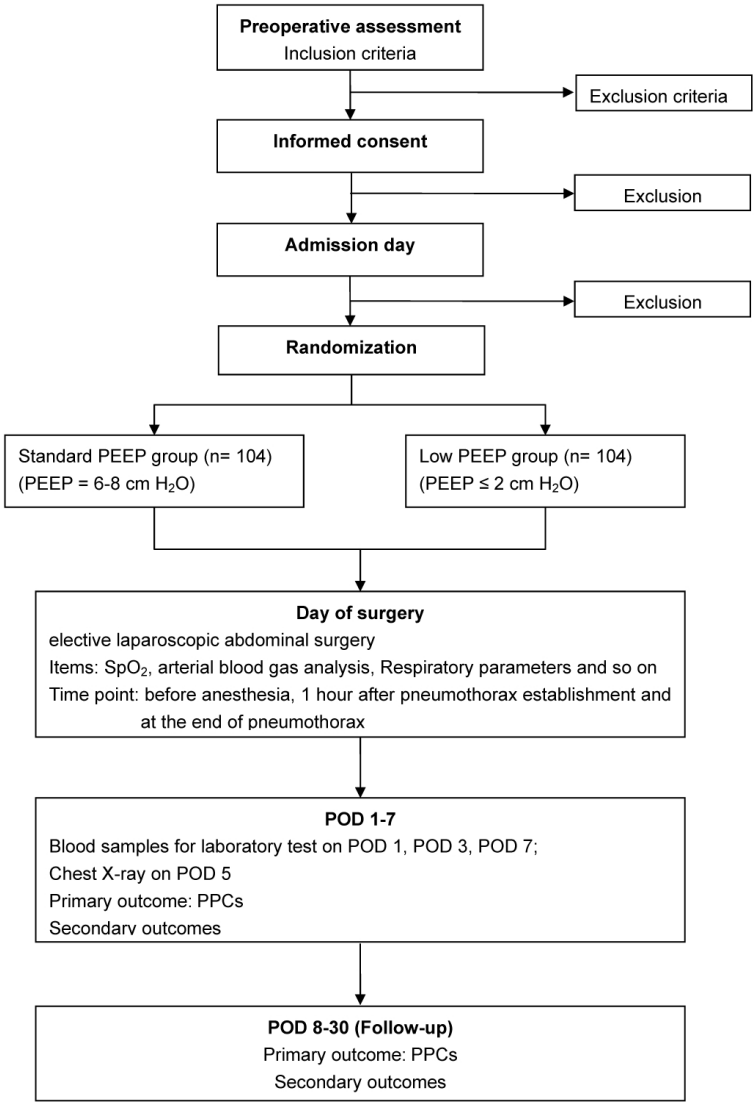

Figure 2. The CONSORT flowchart of the trial

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page, 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5, 14
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	29
Funding	4	Sources and types of financial, material, and other support	28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 28, 29
	5b	Name and contact information for the trial sponsor	1-3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	28, 29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	29

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, 7
	6b	Explanation for choice of comparators	7, 8
Objectives	7	Specific objectives or hypotheses	4, 5, 8, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17,18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-21
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	21, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	19-22
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18-21 Fig.1, Fig.2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22, 23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16, 17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16, 17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	23
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18, 21, 22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21, 22

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17, 21, 22
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17, 22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16,17, 21, 22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22, 23
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	29
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21, 22, 29
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Effects of intraoperative Low-PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic surgery: study protocol for a randomized controlled trial

Case report form

Checklist

Please check the checklist carefully when completed the questionnaire.

□Perioperative assessment: Informed patient details of the study and obtained informed consent from the patient.

Date of signing informed consent: _____

Admission date: _____

□Perioperative data Surgery date: _____

□Completed the above registrations

Completed date: _____

Quality control personnel：_____

Case registration form

Basic information

Case number:

Patient case number:

Random number:

Randomized group：☐ Low-PEEP group (Study Group)

☐ Standard PEEP group (Control Group)

Gender male/female

Height _____cm

Ideal weight _____kg

Actual weight _____kg

Calculation formula of ideal weight：

male= 50 + 0.91×(Height - 152.4)；

female= 45.5±0.91×(Height - 152.4)

Age (years) _____

Contact staff _____

Phone number _____

Address _____

Chief surgeon _____

Baseline Characteristics of the Patients

1. Inclusion and exclusion criteria (Please √ if there is any situation as listed below)

Item	Inclusion criteria	
	yes	no
Age：≥ 18 year		
Scheduled for elective laparoscopic abdominal surgery		
ASA physical status I-III		
BMI: 18-35 kg/m^2		
General anesthesia expected to last more than 3 h		
Had a intermediate or high preoperative index for PPCs risk (ARISCAT score ≥ 26, Supplementary Appendix Table 1)		
	Exclusion criteria	
Emergency surgery		
Mechanical ventilation of > 1 hour within the last 2 weeks before surgery		
History of previous severe (COPD)		
Acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome)		
Previous lung surgery		
Persistent hemodynamic instability or Severe cardiac disease		
Sepsis or septic shock		
Need renal replacement therapy		
Progressive neuromuscular illness		
Pregnancy		
Consented for another interventional study or refusal to participate		
Have a stake in the researcher		
Researchers conside that they are not suitable for clinical trials		

2. Perioperative data (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Preoperative		**One hour after pneumothorax establishment**		**at the end of pneumothorax**	
Temperature		arterial blood gas analysis			
ASA status		FiO_2			
ARISCAT score		Pneumoperal pressure			
NYHA III-IV		Tidal volume			
History of smoking		Respiratory rate			
Drinking		PT-CO_2			
Combined diseases		PEEP			
History of Medication		Platform / peak pressure			
Respiratory infection within one month		Blood pressure			
Weight change in the past one month		Heart rate			
Blood routine examination		Temperature			
Coagulation spectrum					
Biochemical tests		**Intra-operative**			
Chest X-ray or CT		Times of RM			
Pulmonary function test		Adverse events during RM			
mCPIS score		Antibiotic			
		Infusion volume			
		Blood transfusion			
Before anesthesia		Amount of bleeding			
SpO_2 without inhaling oxygen		Urine volume			
Arterial blood gas analysis		Vasoactive drug use			
		Operation time			
		Mechanical ventilation time			
		Other complications			

The amount of each day and duration for smoking and drinking; describe the specific disease and current medication and doses for columns of combined disease and medication history; only check if there is laboratory test or chest X-ray. etal; arterial blood gas analysis should performed after10 min of air adaptation before anesthesia;

Intraoperative complications were recorded and defined as follows: 1. peripheral oxygen saturation less than 90% and/or end-tidal fractions of carbon dioxide more than 45 mmHg for more than 1 min, 2. need to change the ventilation setting (tidal volume and/or respiratory rate), 3. heart rate more than 100 beats/min or less than 60 beats/min, 4. systolic arterial pressure more than 150 mmHg or less than 90 mmHg.

Blood gas analysis during postoperative recovery room should done meet the following 2 points at the same time: 1. 30 minutes after the tracheal tube is removed; 2. after10 min of air adaptation. If peripheral oxygen saturation dropped below 88% during the 10 min of adaptation, the maneuver was stopped and arterial blood gas analysis immediately obtained.

3. Postoperative pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	**POD 1**	**POD 3**	**POD 5**	**POD 7**	**POD 8-30**
SpO_2 after10 min of air adaptation					/
FiO_2 after10 min of air adaptation					/
Arterial blood gas analysis			/	/	/
Heart rate					
Respiratory rate					
Chest X-ray	/	/		/	
Blood routine test					
CRP					
Biochemical tests					
Microbiology test					
Mechanical Ventilation					
Whether tracheal secretions was increased; the nature and quantity of secretions					
Cough					
Difficulty breathing					
Chest pain					
Postoperative hypoxemia					
Postoperative severe hypoxemia					
Suspected lung infection					
Pneumonia					
Exudation of the lungs					
Aspiration pneumonia					
Pulmonary embolism					
Atelectasis					
ALI/ARDS					
Pneumothorax					
Pleural effusion					

ALI: Acute lung injury; ARDS: acute respiratory distress syndrome.

3. Postoperative extra-pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	**POD 1**	**POD 3**	**POD 5**	**POD 7**	**POD 8-30**
SIRS					
Sepsis					
Severe sepsis					
Sepsis shock					
Extrapulmonary infection					
Acute myocardial infarction					
Pulmonary edema caused by heart failure					
Coma					
AKI					
DIC					
Blood transfusion					
Anastomotic leak					
Secondary surgery rate					

SIRS: Systemic inflammatory response syndrome; AKI: acute kidney injury; DIC: disseminated intravascular coagulation.

Additional file 3: preoperative risk index of postoperative pulmonary complications by ARISCAT score

Preoperative risk factor	Point Valve
Age (year)	
≤ 50	
51–80	3
> 80	16
50-59	4
Preoperative SpO_2 (%)	
≥ 96	
91–95	8
≤ 90	24
Respiratory infection in the last month	17
Preoperative anemia (≤ 100 g/L)	11
Surgical incision	
Peripheral	
Upper abdominal	15
Intrathoracic	24
Duration of surgery (h)	
≤ 2	
2 - 3	16
> 3	23
Emergency procedure	8

Intermediate Risk= 26–44 Points; High Risk= ⩾45 Points; SpO_2= oxyhemoglobin saturation by pulse oximetry breathing air in supine position.

Additional file 4. Strategy for SpO_2 decreasing

step	1	2	3	4	5	6	7	8	9
FiO_2	0.5	0.6	0.6	0.7	0.7	0.8	0.8	1.0	RM
standard PEEP group (cm H_2O)	5	5	4	4	3	3	2	2	2
low PEEP ventilation group (cm H_2O)	3	3	4	4	5	5	6	6	6

FiO_2= Fraction of inspired oxygen; PEEP= Positive end-expiratory pressure; RM= Recruitment maneuver

BMJ Open

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028464.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Jun-2019
Complete List of Authors:	ZHOU, zhen-feng; Zhejiang Provincial People's Hospital FANG, Jun-biao; Zhejiang Provincial People,s Hospital WANG, Hong-fa; Zhejiang Provincial People,s Hospital HE, Ying; Zhejiang Provincial People,s Hospital YU, Yong-jian; Zhejiang Provincial People,s Hospital XU, Qiong; Zhejiang Provincial People,s Hospital GE, Yun-fen; Zhejiang Provincial People,s Hospital ZHANG, Miao-zun; Ningbo Medical center Lihuili Hospital, General Surgery HU, Shuang-fei; Zhejiang Provincial People's Hospital, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Medical management
Keywords:	Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Author details

Zhen-feng ZHOU, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: zhenfeng9853@163.com

Jun-biao FANG, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: drfangjb@126.com

Hong-fa WANG.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: whf033@163.com

Ying HE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: heyingzju@163.com

Yong-jian YU

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: yyj731227@163.com

Qiong XU.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: happyjoan@163.com

Yun-fen GE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: gyunfen@sina.com

Miao-zun ZHANG , M.D.

- Affiliation: Department of General Surgery, Ningbo Medical center Lihuili Hospital,Ningbo, 325000,China;

Email: idreamof333@126.com

Shuang-fei HU , M.D.

- Corresponding Author
- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: hushuangfei77@sina.com

Abstract

Introduction: Postoperative pulmonary complications (PPCs) will develop in even 58% of patients undergoing abdominal surgery and PPCs is strongly associated with higher risk of mortality. More and more evidence shows that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the role of positive endexpiratory pressure (PEEP) during the intraoperative period in preventing PCC for laparoscopic surgery is not clearly defined.

Methods and Analysis: A total number of 208 patients with high-risk of postoperative pulmonary complications patients undergoing laparoscopic abdominal surgery will be enrolled and randomized into a standard PEEP (6-8 cmH_2O) group and a low PEEP (≤ 2 cm H_2O) group. Both groups will receive an inspired oxygen fraction (FiO_2) of 0.50 and a tidal volume of 8 ml/kg ideal body weight (IBW). Standard perioperative fluid management standardization and analgesic treatments are applied in both groups. The primary endpoint is postoperative pulmonary complications within 7 days after surgery. Secondary endpoints are: the modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, postoperative surgical complications, intensive care unit (ICU) length of stay, hospital length of stay, thirty-day mortality.

Ethics and Dissemination: The study is approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (KY2018026) on 22 October 2018. The first participant is expected to be recruited within 6 months and the estimated completion date of the study is October 2021. The results of this trial will be submitted to a peer-reviewed journal and will inform clinical practice.

TRIAL REGISTRATION NUMBER: http://www.chictr.org.cn, ID: ChiCTR1800019865. Registered on 2 December 2018 **;** Pre-results.

Keywords: Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Strengths and limitations of this study:

- Intervention is blinded.
- Standard perioperative fluid management standardization and analgesic treatments are applied in both groups.
- Primary outcome measure is patient centred.
- It is not multicentre randomised trial.

Background

Every year around the world, approximately 230 million patients require surgery with general anesthesia and mechanical ventilation [1]. Laparoscopic surgery has been widely accepted because it is associated with less blood loss, less postoperative pain and rapid recovery [2, 3]. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5% [4], and 12% to 58% of patients undergoing abdominal surgery will develop a PPC [4, 5]. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality [6-8].

Nearly 30% of surgery patients undergoing general anesthesia and mechanical ventilation are at intermediate to high risk for PPCs according to large cohort studies [5, 9]. Both alveolar overstretching and atelectasis induce the release of inflammatory mediators, leading to lung and systemic organ damage [10]. Lung-protective ventilation including the use of low tidal volumes and positive endexpiratory pressure (PEEP) aims to prevent atelectasis and improve gas exchange [11, 12]. Furthermore, PEEP has been found to reduce mortality in patients with the acute respiratory distress syndrome and in critically ill patients [13].

Adopting an appropriate PEEP may prevent PPCs. When high PEEP is applied, alveolar may overinflate and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis [10]. Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC [14, 15]. Despite all these studies recommending the use of low tidal volume [10], the appropriate PEEP has not yet been defined. A multicenter observational study has shown that approximately 20% of patients do not receive PEEP during routine anesthetic practice [16]. In the Intraoperative Protective Ventilation (IMPROVE) trial that includes patients undergoing major abdominal surgery with intermediate-risk

and high-risk of PPCs, compares to a practice of nonprotective mechanical ventilation including higher tidal volumes without PEEP, a lung-protective ventilation strategy with lower tidal volumes and PEEP of 6 cm H_2O is associated with improved clinical outcomes [14]. Furthermore, in another study including patients undergoing abdominal nonlaparoscopic surgery lasting more than 2 h, compares to a standard ventilation strategy, a protective ventilation strategy with 10 cm H_2O PEEP improves respiratory function and reduces the modified clinical pulmonary infection score (mCPIS) [15]. However, another study has shown that low tidal volume combined low PEEP (3 cm H_2O) ventilation may induce postoperative inflammation and may increase the risk of PCC during major surgery such as hepatectomy [17]. In an international multicenter trial, Protective Ventilation using high vs. low PEEP (PROVHILO), including patients undergoing open abdominal surgery with high risk for PPCs, compares with low PEEP (≤ 2 cm H_2O), a ventilation strategy of high PEEP (12 cm H_2O) do not reduce the incidence of PPCs, but more likely causes haemodynamic instability [18]. Therefore, the authors suggest a ventilation strategy of low tidal volume combined with low PEEP (≤ 2 cm H_2O) [18].

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they do not include patients planning to undergo laparoscopic surgery. Some studies have suggested that laparoscopic-assisted gastrectomy (LAG) is beneficial for postoperative respiratory function recovery. Nevertheless, it is also necessary to consider the effects of pneumoperitoneum (PnP) on airway pressure and pulmonary function. The role of PEEP during the intraoperative period in preventing PCC for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PCC and may reduce the occurrence of organ dysfunction. These anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and; in-hospital stays in patients undergoing laparoscopic surgery.

Methods/design

Objectives of the study:

This trial aims to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH_2O) to those of low PEEP (≤ 2 cm H_2O) in patients at risk for complications undergoing laparoscopic surgery during general anesthesia in terms of: (1) PPCs, (2) modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, changes in chest X-ray findings and oxygenation; (3). intraoperative complications including hypoxemia and hypotension, massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

Study endpoints

Primary outcome measure

The primary endpoint of PPCs is defined according to a previous report [19] including any new atelectasis or infiltrates on a chest X-ray, respiratory failure (defined as the need for noninvasive or invasive ventilation) or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 300 within 7 days after surgery.

Secondary outcome measures

Secondary outcome variables are any pulmonary complications and extrapulmonary complications as follows:

1. Postoperative pulmonary complications (PPCs) within 30 days after surgery. Those PPCs are scored according to a grading scale ranging from 0 to 4 [20] (grade 0 representing no PPCs and grades 1 to 4 representing gradually worse forms of PPCs) within 7 and 30 days after surgery (Table 1).

Table 1. Grade scale for postoperative pulmonary complications.

Grade scale	Detailed description
Grade 1	- Cough, dry - Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; results of chest radiograph either normal - Dyspnea, not due to other documented cause
Grade 2	- Cough, productive, not due to other documented cause - Bronchospasm: new wheezing or pre-existent wheezing resulting in change therapy - Hypoxemia - Atelectasis: radiological confirmation plus either temperature > 37.5°C or abnormal lung findings - Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation
Grade 3	- Pleural effusion, resulting in thoracentesis - Pneumonia, suspected: radiological evidence without bacteriological confirmation -Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture - Pneumothorax - Re-intubation postoperative or intubation, period of ventilator dependence (non-invasive or invasive ventilation) ≤ 48 hours
Grade 4	Ventilatory failure: postoperative non-invasive ventilation dependence ≥ 48 hours, or re-intubation with subsequent period of ventilator dependence ≥ 48 hours

2. Postoperative pulmonary complications will also be analyzed separately. Pneumonia is defined according to Centers for Disease Control (CDC) criteria [21] as follows: patients with altered or new pulmonary opacities on chest X-ray; patients should also meet at least two of the following criteria: (1) temperature ≥ 38.5°C or < 36°C, (2) white blood cell (WBC) count > 12 x10^9/L or < 4 x10^9/L; (3) purulent sputum: new cough or difficulty breathing or previous coughing or difficulty breathing is further aggravated.

Postoperative hypoxemia and severe hypoxemia [22]: hypoxemia is defined as PaO_2 < 60 mmHg or oxygen saturation (SpO_2) < 90% on room air, but responding to oxygen treatment (hypoventilation should be excluded). Severe hypoxemia is recorded in cases when the patient requires non-invasive or

invasive mechanical ventilation.

Suspected pulmonary infection is described in a previous study [18]: the patient takes antibiotics and should meet at least one of the following criteria: (1) changed or new sputum, (2) changed or new pulmonary opacities on chest X–ray, (3) temperature greater than 38.3°C, and (4) WBC count > 12 x10^9/L.

Pulmonary infiltrate is defined according to consensus guidelines: Chest X–ray demonstrating monolateral or bilateral infiltrate[23].

Atelectasis, pleural effusion or pneumothorax are identified by chest X-ray.

The modified clinical pulmonary infection score (mCPIS) is calculated as previously described [24] (Table 2).

Table 2. The definition of modified Clinical Pulmonary Infection Score (mCPIS).

Items	CPIS Points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (℃)	36.5- 38.4	38.5- 38.9	≤ 36.5 or ≥ 39.0
Leukocytes count (per mm^3)	4,000-11,000	<4,000 or >11,000	< 4,000 or > 11,000 + band forms ≥ 500
PaO_2/FiO_2,(mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

PaO_2 =Partial pressure of arterial oxygen; FiO_2 =Fraction of inspired oxygen; ARDS =Acute respiratory distress syndrome

The Berlin Definition of ARDS(cute Respiratory Distress Syndrome) [25].Suspected pulmonary complications[15] are defined in cases where patients display at least three of the following new findings: (1) cough, (2) increased secretions, (3) dyspnea, (4) chest pain, (5) temperature> 38°C, and (6) pulse rate> 100 beats per minute.

Requirement for postoperative ventilation (respiratory failure that requires noninvasive and/or invasive ventilation) for at any time after surgery according to standard criteria and clinical practice guidelines[20].

3. Postoperative extrapulmonary complications within 30 days after surgery:

Systemic inflammatory response syndrome (SIRS) criteria are defined when

meeting the following two or more criteria by the most deranged value recorded after surgery [26]: (1) rectal or tympanic temperature > 38°C or <36°C (0.5°C will be added to the measured value when oral or other temperatures are used); (2) Heart rate > 90 beats/min (excluding those who have a known medical condition or are receiving treatment that would prevent tachycardia); (3) respiratory rate> 20 breaths/min or a $PaCO_2$< 32 mmHg or requiring mechanical ventilation. White blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands.

Sepsis and Septic shock [26]: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA(Sequential [Sepsis-related] Organ Failure Assessment) score $\geqslant$ 2 points consequent to the infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

Other extrapulmonary infection including surgical site infection (SSI) and intraabdominal abscess: SSI [27] is defined as surgical site infection within 30 days after surgery; at least the incision has a purulent effluent; the incision drainage fluid or tissue culture results are positive, with pain or tenderness, local swelling, redness or fever.

Need for postoperative blood transfusion.

Postoperative surgical complications: anastomotic leakage and need for surgical reintervention, defined according to consensus criteria [28].

Unexpected intensive care unit (ICU) admission or readmission.

ICU length of stay and hospital length of stay.

Hospital free-days at follow-up day 30.

In-hospital mortality and thirty-day mortality (all-cause mortality 30 days after randomization).

Intraoperative complications: pneumothorax is confirmed by chest X-ray and any other complications.

Study design: This is an unfunded, parallel-group, double-blinded, prospective, randomized controlled clinical trial that is registered at http://www.chictr.org.cn (ChiCTR1800019865) and will be conducted at the Department of Anesthesiology and Intensive Care of Zhejiang Provincial People's Hospital. The first patient will be randomized in January 2019. This trail protocol is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1). The SPIRIT 2013 Checklist is given in Additional file 1.

Blinding, data collection, randomization and record keeping

Selection of the participants

Researchers will be trained prior to investigation. Study data including patient clinical characteristics, intraoperative respiratory parameters, postoperative outcomes, and laboratory test will be collected onto case report forms (CRF) (Additional file 2).

An independent researcher will randomize the participants into the study group (standard group PEEP) and control group (low PEEP group) in a ratio of 1:1. The random sequence will be computer-generated and participants will be allocated in numerical order with sealed opaque envelopes. The attending anesthesiologist performs anesthesia strictly according to the research protocol and is also responsible for data during the preoperative, intraoperative and PACU period. The chief surgeon performs the postoperative laboratory testing. An independent researcher will be involved in postoperative follow-up and data collection. Statistical analysis will be performed by a statistician who does not participate in the data collection. Patients, research staff, surgeons, intensive care physicians and the statistician will be unaware of the group allocation. Some preoperative characteristics and laboratory results will automatically derived from a computer data base.

The original data (CRF and relevant records) will be maintained for 10 years and then destroyed according to hospital standards.

Selection of the participants

Patients scheduled for elective laparoscopic abdominal surgery under general anesthesia will be screened and recruited during preoperative assessment. Patients meeting inclusion criteria will be required to provide their written informed consent. The participant can withdraw from the trial at any time. Inclusion criteria are patients older than 18 y, American Society of Anesthesiologists (ASA) physical status II or III, body mass index (BMI) between 18-35 kg/m^2, general anesthesia expected to last more than 3 h, an intermediate or high preoperative index for PPCs risk by the Assess Respiratory Risk in Surgical Patients in Catalonia study (ARISCAT score ≥ 26, the Additional file 3).

Exclusion criteria are emergency surgery or history of previous lung surgery, history of mechanical ventilation within the 2 weeks before recruitment, non–invasive ventilation or oxygen therapy at home, acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome), history of chronic obstructive pulmonary disease (COPD), persistent hemodynamic instability or severe cardiac disease (New York Heart Association class III or IV, or persistent ventricular tachyarrhythmia's, or acute coronary syndrome), sepsis or septic shock, need renal replacement therapy (CRRT), progressive neuromuscular illness, pregnancy, participation in another study or refusal to participate.

Time course of the study

Preoperative admission

Medical history, ASA physical status, BMI, 12-lead ECG, laboratory results , chest X-ray or computed tomography (CT) scan, ARISCAT score and nutritional risk screening (NRS 2002 tool), the results of echocardiography and spirometry (in cases of history of coronary artery disease or smoking) will be recorded.

Intraoperative care

A central venous catheter and an arterial cannula will be placed before induction of anesthesia. Peripheral oxygen saturation (SpO_2), arterial blood

pressure, heart rate (HR), ECG, end-tidal carbon dioxide tension ($EtCO_2$) and bispectral index (BIS) will be monitored continuously. Pneumoperitoneum (PnP), tidal volume, PEEP, airway pressures including peak pressure and plateau pressure, airway resistance (Raw), Vds/Vt, core temperature, and arterial blood gas analysis data will be recorded.

Crystalloid (12-15ml/kg/h) is infused to maintain hemodynamic stability and central venous pressure 5-12 cm H_2O. Blood loss and vasodilation are supplemented by colloidal fluid.

Routine anesthesia is induced with intravenous dexmedetomidine(1 ug/kg) or midazolam (0.05-0.075mg/kg), cisatracurium (2 mg/kg), propofol (2-3 mg/kg) and fentanyl (1-3 μ/kg) for tracheal intubation. Anesthesia is maintained with propofol, sevoflurane and remifentanil infusion to maintain the BIS 40-50 until skin suturing is completed. Cisatracurium (1.0-1.5 mg/kg) is administered every hour and the last dose is at least 1 hour before the end of operation. Ropivacaine is administrated as local incision infiltration anesthesia before and at the end of operation respectively. Fentanyl (1-3 μg/kg) and flurbiprofenaxetil 50 mg are required before remifentanil is stop.

Postoperative care

Patients will be transferred to the post-anesthesia care unit (PACU) after surgery regardless of whether they are still intubated.

Postoperative pain management will be suggested to achieve a visual analogue scale (VAS) pain score of < 3/10 using a patient-controlled intravenous analgesia pump including fentanyl (0.3-0.5 μg/kg), flurbiprofenaxetil (100 mg) and palonosetron hydrochloride (0.25 mg) palazidine.

The ICU physician and surgeon will independently monitor clinical progress and all endpoints by daily physical examinations. Appropriate prophylactic antibiotics and antithrombotic treatments will be administered as required during the postoperative period. A chest X-ray will be performed by an independent, trained radiologist on POD 5. Arterial blood gas analysis will be

performed on POD 1 and POD 3 and other laboratory tests will be performed on POD 1, POD 3, POD 5 and POD 7. The examinations will be repeated and microbiology tests will be performed when the development of pulmonary complications are suspected.

Study arms and intraoperative ventilation protocol

Patients will be randomly assigned to the low PEEP ventilation group (PEEP ≤ 2 cm H_2O) or the standard PEEP group (PEEP = 6-8 cm H_2O) using a volume-controlled ventilation strategy (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) with a tidal volume of 8 ml/kg ideal body weight (IBW), an inspired oxygen fraction (FiO_2) of 0.50 and inspiratory to expiratory ratio of 1:2. Respiratory rate should be adjusted to maintain $ETCO_2$ between 35 and 45 mmHg) and plateau pressure should be no more than 30 cmH_2O. IBW is calculated with formulas as follows [14]: 45.5 + 0.91 x (centimeters of height - 152.4) for females and 50 + 0.91 x (centimeters of height - 152.4) for males. Recruitment maneuvers (RMs)[19] will be performed immediately after tracheal intubation and every time when the ventilator is interrupted until the end of surgery in each group. The compliance of the respiratory system was calculated with the formulas of V_T/ (plateau pressure of the respiratory system - PEEP).

Recruitment maneuvers will be performed as follows:

(1). Pressure support ventilation (PSV) mode

(2). Positive end-expiratory pressure (PEEP) set to 30 cm of water

(3). Inspiratory gas flow set to the highest value

(4). Duration of the maneuver = 30 sec

A rescue therapy will be applied in case of desaturation (defined as a peripheral SpO_2 of less than 92%), consisting of increasing FiO_2 to 100% in each group and increased PEEP in the low PEEP group (Additional file 4).

From postoperative day 7 (POD 7 to POD 30, follow-up)

Secondary endpoints and any mortality will also be evaluated during the follow-up period. The CONSORT flowchart of the trial is shown in Figure 2.

Data monitoring and Handling of implausible values or missing values: A clinical investigator will identify implausible values. Missing continuous variables should be less than 10%. Missing values will be replaced by the mean of all plausible data (both groups) of the respective endpoint. Data monitoring is managed by an independent investigator who is not involved in the study. The progress of the study will be evaluated and the completeness and accuracy of the data (Informed Consent Forms, source data, CRF and outcome variables) will be verified.

Statistics:

Normally distributed variables will be expressed as the mean ± standard deviation (SD) and will be compared with Student's t-test. Categorical variables will be compared using the chi-square test or the Fisher's exact test. Non-normal continuous variables will be expressed as median (interquartile range (IQR)) and evaluated with the Mann-Whitney U-test. The primary outcome and secondary outcomes will be all handled. Intention-to-treat (ITT) analyses are performed to compare the composite outcome measure at 7 days in the two groups by the chi-squared test (or Fisher's exact test as appropriate) and multiple logistic regression analysis adjusting will be performed to identify various risk factors (for the primary outcome and the pulmonary complications at postoperative Day 30). P <0.05 will be considered statistically significant and all reported p values will be 2-sided. Interim analysis of safety will be conducted after enrolment of the first 200 patients. All analyses will be conducted using the SPSS Version 18.0 (SPSS, Chicago, IL, USA) software.

Sample size calculation

The incidence rate of postoperative pulmonary complications was 39% in the low PEEP group [18]. Two tailed chi-squared test was performed and we estimated that 188 patients were required to provide 90% power to detect a 50% relative difference between the two groups, with a type I error probability of 0.05. Assuming that follow-up lost rate was 10 %, and then a total of 208 cases are needed. Analysis is computed using G-Power (version 3.1; Informer

Technologies, Inc.).

Adverse events and interruption of the trial:

All patients will be continuously monitored during the study including daily visits during in-hospital and daily phone-call visits during the out of hospital follow-up period (until POD 30). All serious adverse, unexpected or possibly related events will be recorded in the CRF and will be reported to the data monitoring and safety committee (DMSC). DMSC will recommend that the study must to be stopped unless there is evidence that patient will safety (a between-group difference in serious adverse events or in 30- day mortality is found).

Discussion:

In this pragmatic, prospective, randomized controlled trial of high-risk patients undergoing laparoscopic surgery, our aim will not be only to assess possible single effects of PEEP levels on major PPCs from those of lower tidal volumes and RM but also to assess relevant clinical parameters associated with alterations in pulmonary function such as chest X-ray, abnormalities, mCPIS, arterial oxygenation/peripheral oxygen saturation in air and changes in dyspnea/cough/secretions. Our findings might change current practice of mechanical ventilation in high-risk patients undergoing laparoscopic surgery.

There are some potential strengths of the present trial protocol. First, this ARISCAT score will be used to predict PPCs and we selected only a high-risk PPC population that will potentially receive maximum benefit from intraoperative PEEP strategy. Although various scores have been developed for predicting PPC incidence based on various countries and surgical populations, the ARISCAT score is considered to be the most valuable tool [10]. Second, this trial design includes instructions for fluid management standardization and analgesic treatments during the perioperative period. Third, the included patients will undergo elective abdominal laparoscopic surgical procedures with more than 3h of general anesthesia. Previous studies have reported that both abdominal surgery and longer anesthesia duration are potential risk factors for PPCs [8].

Notably, mechanical ventilation itself is one of major contributors to PPCs [29]. PnP is also an important risk factor for PPCs [30]. Intraabdominal pressure is frequently higher than airway pressure during PnP with carbon dioxide (CO_2) for laparoscopic surgery. This pressure gradient usually causes cephalad displacement of the diaphragm and collapses adjacent pulmonary tissues. PnP also decreases respiratory compliance and arterial oxygenation [31] .All these influences on PnP lead finally to atelectasis [32].

On the other hand, PEEP is thought to prevent the development of atelectasis by keeping the airways open and maintaining adequate gas exchange at the

end of the expiratory period during PnP [10]. Certainly, the level of PEEP should be adopted according to the patient's and surgical characteristics, as well as to the patient's positioning.

Previous studies reported that very low levels of PEEP are potentially associated with atelectasis by promoting repeated opening and closing of small airways [33]. However, higher levels of PEEP may increase mean airway pressure of the respiratory system and likely even impair hemodynamics. There is an increasing number of highly qualitative Randomized Controlled Trials (RCTs) regarding intraoperative mechanical ventilation and PPCs, whereas direct assessment of the effect in high-risk patients undergoing laparoscopic surgery remains lacking. The potential significance of this trial is that it may provide evidence of the effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic surgery.

Trial status

The trial is currently ongoing. The first participant is expected to be recruited within 6 months and the estimated completion date of the study is October 2021.

Additional file

Abbreviations

ABGa: Arterial blood gas analysis; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; AMI: Acute myocardial infarction; ASA: American Society of Anesthesiologists; BIS: bispectral index; BMI: Body Mass Index; CDC: Centers for Disease Control; CO_2: carbon dioxide; COPD: Chronic obstructive pulmonary disease; CRF: Case Report Form; CRRT: renal replacement therapy; CT: Computer tomography; DMSC: data monitoring and safety committee; DIC: Disseminated intravascular coagulation; ECG: Electrocardiogram; $EtCO_2$: End-tidal carbon dioxide tension; FiO_2: Fraction of inspired oxygen; HR: Heart rate; IBW: Ideal bodyweight; ICU: Intensive care unit; IQR: interquartile range; LAG: laparoscopic surgery; mCPIS: modified clinical pulmonary infection score; PACU: Post-anesthesia Care Unit;PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PnP: pneumoperitoneum; POD: Postoperative day; PPC: Postoperative pulmonary complications; PSV: Pressure Support Ventilation; Raw: Airway resistance; RM: Recruitment maneuver; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome; SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials; SpO_2: Oxygen saturation; SSI: surgical site infection; Vds/Vt: Dead space fraction; VAS: visual analogue scale; WBC: White Blood Cell.

Acknowledgements

We want to thank all the contributors and collaborators for their support in this study. We also thank all the participating patients.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

Zhen-feng ZHOU and Shuang-fei HU designed the study protocol and wrote the paper. Hong-fa WANG and Miao-zun ZHANG designed the statistical method. The work of patient recruitment and data collecting will be done by Jun- biao FANG, Yong-jian YU, Qiong XU, Ying HE and Yun-fen GE. Shuang-fei HU is the study director and Jun- biao FANG is the principal investigator of this study. All authors have read the manuscript and approved to submitting the final paper.

Authors' information

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) (registration number KY2018026) on 22 October 2018. Any subsequent protocol and informed consent document amendments must be approved by the responsible of Ethics Committee. All communications with the regulatory authorities and the Ethics Committee must be recorded.

All recruited patients will be informed of the trial purposes and their duties within the trial before randomization. Recruited patients can withdraw from the study at any time without providing any specific reason. The patient data will be stored in a separate, safe place but that it may be reviewed by the relevant

investigator.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Patient and Public Involvement:

No patient involved.

References

[1] Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008. 372(9633): 139-44.

[2] Lee CM, Park S. Laparoscopic techniques and strategies for gastrointestinal GISTs. J Vis Surg. 2017. 3: 62.

[3] Patel B, Leung U, Lee J, Bryant R, O'Rourke N, Cavallucci D. Laparoscopic pancreaticoduodenectomy in Brisbane, Australia: an initial experience. ANZ J Surg. 2017 .

[4] Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010. 113(6): 1338-50.

[5] Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med. 2001. 135(10): 847-57.

[6] Shander A, Fleisher LA, Barie PS, Bigatello LM, Sladen RN, Watson CB. Clinical and economic burden of postoperative pulmonary complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies. Crit Care Med. 2011. 39(9): 2163-72.

[7] 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. Ann Surg. 2005. 242(3): 326-41; discussion 341-3.

[8] Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006. 144(8): 581-95.

[9] 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. Ann Surg. 2000. 232(2): 242-53.

[10] Güldner A, Kiss T, Serpa NA, 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(3): 692-713.

[11] Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the non-injured lung: review and meta-analysis. Crit Care. 2014. 18(2): 211.

[12] Futier E, Constantin JM, Pelosi P, et al. Intraoperative recruitment maneuver reverses detrimental pneumoperitoneum-induced respiratory effects in healthy weight and obese patients undergoing laparoscopy. Anesthesiology. 2010. 113(6): 1310-9.

[13] Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000. 342(18): 1301-8.

[14] Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013. 369(5): 428-37.

[15] Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013. 118(6): 1307-21.

[16] Jaber S, Coisel Y, Chanques G, et al. A multicentre observational study of intra-operative ventilatory management during general anaesthesia: tidal volumes and relation to body weight. Anaesthesia. 2012. 67(9): 999-1008.

[17] Sato H, Nakamura K, Baba Y, Terada S, Goto T, Kurahashi K. Low tidal volume ventilation with low PEEP during surgery may induce lung inflammation. BMC Anesthesiol. 2016. 16(1): 47.

[18] Hemmes SN, de Abreu M G, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet. 2014. 384(9942): 495-503.

[19] Ruszkai Z, Kiss E, László I, et al. Effects of intraoperative PEEP optimization on postoperative pulmonary complications and the inflammatory response: study protocol for a randomized controlled trial. Trials. 2017. 18(1): 375.

[20] Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, de la Riviere A B, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA. 2006. 296(15): 1851-7.

[21] Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. Methods Inf Med. 2007. 46(5): 595-600.

[22] Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011. 183(3): E195-214.

[23] Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994. 20(3): 225-32.

[24] Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003. 168(2): 173-9.

[25] Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012. 307(23): 2526-33.

[26] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016. 315(8): 801-10.

[27] Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992. 13(10): 606-8.

[28] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004. 240(2): 205-13.

[29] Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA. 2010. 304(23): 2620-7.

[30] Reinius H, Jonsson L, Gustafsson S, et al. Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. Anesthesiology. 2009. 111(5): 979-87.

[31] Hazebroek EJ, Haitsma JJ, Lachmann B, Bonjer HJ. Mechanical ventilation with positive end-expiratory pressure preserves arterial oxygenation during prolonged pneumoperitoneum. Surg Endosc. 2002. 16(4): 685-9.

[32] Park SJ, Kim BG, Oh AH, Han SH, Han HS, Ryu JH. Effects of intraoperative protective lung ventilation on postoperative pulmonary complications in patients with laparoscopic surgery: prospective, randomized and controlled trial. Surg Endosc. 2016. 30(10): 4598-606.

[33] Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005. 102(4): 838-54.

Figure legends:

Figure 1. Standard Protocol Items.

Figure 2. The CONSORT flowchart of the trial.

Standard Protocol Items

	Study period								
	Enrolment		Allocation		Post-allocation				
Timepoint	-1 week	-t1	0	DOS	POD1	POD3	POD5	POD7	POD8-30
Enrolment:									
Perioperative assessment	√								
Eligibility screen		√							
Informed consent		√							
Allocation			√						
Interventions:									
Study Group(Low PEEP)				√					
Control Group(Standard PEEP)				√					
Assessments:									
Intraoperative complications				√					
Postoperative pulmonary complications					√	√	√	√	√
Physical examinations					√	√	√	√	√
Blood gas analysis					√	√	√	√	√
chest X-ray							√		
Postoperative extra-pulmonary complications					√	√	√	√	√
Postoperative surgical complications					√	√	√	√	√
ICU length of stay									
Hospital length of stay									
In-hospital mortality									
Thirty-day mortality					◄———	———	———	———	———►

Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. DOS: day of surgery; POD: postoperative day; ICU: Intensive care unit.

Figure 1. Standard Protocol Items

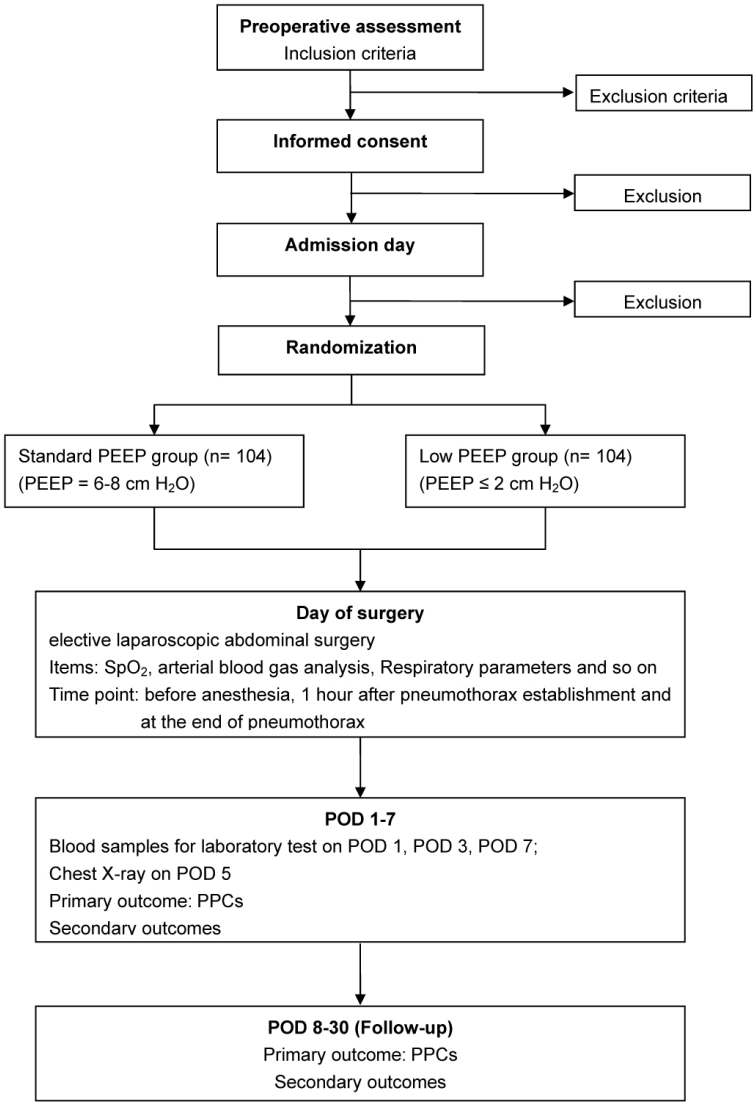

Figure 2. The CONSORT flowchart of the trial

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page, 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5, 14
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	29
Funding	4	Sources and types of financial, material, and other support	28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 28, 29
	5b	Name and contact information for the trial sponsor	1-3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	28, 29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	29

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, 7
	6b	Explanation for choice of comparators	7, 8
Objectives	7	Specific objectives or hypotheses	4, 5, 8, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17,18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-21
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	21, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	19-22
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18-21 Fig.1, Fig.2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22, 23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16, 17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16, 17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	23
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18, 21, 22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21, 22

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17, 21, 22
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17, 22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16,17, 21, 22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22, 23
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	29
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21, 22, 29
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Effects of intraoperative Low-PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic surgery: study protocol for a randomized controlled trial

Case report form

Checklist

Please check the checklist carefully when completed the questionnaire.

□Perioperative assessment: Informed patient details of the study and obtained informed consent from the patient.

Date of signing informed consent: _____

Admission date: _____

□Perioperative data Surgery date: _____

□Completed the above registrations

Completed date: _____

Quality control personnel：_____

Case registration form

Basic information

Case number:

Patient case number:

Random number:

Randomized group：☐ Low-PEEP group (Study Group)

☐ Standard PEEP group (Control Group)

Gender male/female

Height _____cm

Ideal weight _____kg

Actual weight _____kg

Calculation formula of ideal weight：

male= 50 + 0.91×(Height - 152.4)；

female= 45.5±0.91×(Height - 152.4)

Age (years) _____

Contact staff _____

Phone number _____

Address _____

Chief surgeon _____

Baseline Characteristics of the Patients

1. Inclusion and exclusion criteria (Please √ if there is any situation as listed below)

Item	Inclusion criteria	
	yes	no
Age：≥ 18 year		
Scheduled for elective laparoscopic abdominal surgery		
ASA physical status I-III		
BMI: 18-35 kg/m^2		
General anesthesia expected to last more than 3 h		
Had a intermediate or high preoperative index for PPCs risk (ARISCAT score ≥ 26, Supplementary Appendix Table 1)		
	Exclusion criteria	
Emergency surgery		
Mechanical ventilation of > 1 hour within the last 2 weeks before surgery		
History of previous severe (COPD)		
Acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome)		
Previous lung surgery		
Persistent hemodynamic instability or Severe cardiac disease		
Sepsis or septic shock		
Need renal replacement therapy		
Progressive neuromuscular illness		
Pregnancy		
Consented for another interventional study or refusal to participate		
Have a stake in the researcher		
Researchers conside that they are not suitable for clinical trials		

2. Perioperative data (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Preoperative		**One hour after pneumothorax establishment**		**at the end of pneumothorax**	
Temperature		arterial blood gas analysis			
ASA status		FiO_2			
ARISCAT score		Pneumoperal pressure			
NYHA III-IV		Tidal volume			
History of smoking		Respiratory rate			
Drinking		PT-CO_2			
Combined diseases		PEEP			
History of Medication		Platform / peak pressure			
Respiratory infection within one month		Blood pressure			
Weight change in the past one month		Heart rate			
Blood routine examination		Temperature			
Coagulation spectrum					
Biochemical tests		**Intra-operative**			
Chest X-ray or CT		Times of RM			
Pulmonary function test		Adverse events during RM			
mCPIS score		Antibiotic			
		Infusion volume			
		Blood transfusion			
Before anesthesia		Amount of bleeding			
SpO_2 without inhaling oxygen		Urine volume			
Arterial blood gas analysis		Vasoactive drug use			
		Operation time			
		Mechanical ventilation time			
		Other complications			

The amount of each day and duration for smoking and drinking; describe the specific disease and current medication and doses for columns of combined disease and medication history; only check if there is laboratory test or chest X-ray. etal; arterial blood gas analysis should performed after10 min of air adaptation before anesthesia;

Intraoperative complications were recorded and defined as follows: 1. peripheral oxygen saturation less than 90% and/or end-tidal fractions of carbon dioxide more than 45 mmHg for more than 1 min, 2. need to change the ventilation setting (tidal volume and/or respiratory rate), 3. heart rate more than 100 beats/min or less than 60 beats/min, 4. systolic arterial pressure more than 150 mmHg or less than 90 mmHg.

Blood gas analysis during postoperative recovery room should done meet the following 2 points at the same time: 1. 30 minutes after the tracheal tube is removed; 2. after10 min of air adaptation. If peripheral oxygen saturation dropped below 88% during the 10 min of adaptation, the maneuver was stopped and arterial blood gas analysis immediately obtained.

3. Postoperative pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	**POD 1**	**POD 3**	**POD 5**	**POD 7**	**POD 8-30**
SpO_2 after10 min of air adaptation					/
FiO_2 after10 min of air adaptation					/
Arterial blood gas analysis			/	/	/
Heart rate					
Respiratory rate					
Chest X-ray	/	/		/	
Blood routine test					
CRP					
Biochemical tests					
Microbiology test					
Mechanical Ventilation					
Whether tracheal secretions was increased; the nature and quantity of secretions					
Cough					
Difficulty breathing					
Chest pain					
Postoperative hypoxemia					
Postoperative severe hypoxemia					
Suspected lung infection					
Pneumonia					
Exudation of the lungs					
Aspiration pneumonia					
Pulmonary embolism					
Atelectasis					
ARDS					
Pneumothorax					
Pleural effusion					

ARDS: acute respiratory distress syndrome.

3. Postoperative extra-pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	**POD 1**	**POD 3**	**POD 5**	**POD 7**	**POD 8-30**
SIRS					
Sepsis					
Severe sepsis					
Sepsis shock					
Extrapulmonary infection					
Pulmonary edema caused by heart failure					
Blood transfusion					
Anastomotic leak					
Secondary surgery rate					

SIRS: Systemic inflammatory response syndrome; AKI: acute kidney injury; DIC: disseminated intravascular coagulation.

Additional file 3: preoperative risk index of postoperative pulmonary complications by ARISCAT score

Preoperative risk factor	Point Valve
Age (year)	
≤ 50	
51–80	3
> 80	16
50-59	4
Preoperative SpO_2 (%)	
≥ 96	
91–95	8
≤ 90	24
Respiratory infection in the last month	17
Preoperative anemia (≤ 100 g/L)	11
Surgical incision	
Peripheral	
Upper abdominal	15
Intrathoracic	24
Duration of surgery (h)	
≤ 2	
2 - 3	16
> 3	23
Emergency procedure	8

Intermediate Risk= 26–44 Points; High Risk= ⩾45 Points; SpO_2= oxyhemoglobin saturation by pulse oximetry breathing air in supine position.

Additional file 4. Strategy for SpO_2 decreasing

step	1	2	3	4	5	6	7	8	9
FiO_2	0.5	0.6	0.6	0.7	0.7	0.8	0.8	1.0	RM
standard PEEP group (cm H_2O)	5	5	4	4	3	3	2	2	2
low PEEP ventilation group (cm H_2O)	3	3	4	4	5	5	6	6	6

FiO_2= Fraction of inspired oxygen; PEEP= Positive end-expiratory pressure; RM= Recruitment maneuver

BMJ Open

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028464.R2
Article Type:	Protocol
Date Submitted by the Author:	21-Aug-2019
Complete List of Authors:	ZHOU, zhen-feng; Zhejiang Provincial People's Hospital FANG, Jun-biao; Zhejiang Provincial People,s Hospital WANG, Hong-fa; Zhejiang Provincial People,s Hospital HE, Ying; Zhejiang Provincial People,s Hospital YU, Yong-jian; Zhejiang Provincial People,s Hospital XU, Qiong; Zhejiang Provincial People,s Hospital GE, Yun-fen; Zhejiang Provincial People,s Hospital ZHANG, Miao-zun; Ningbo Medical center Lihuili Hospital, General Surgery HU, Shuang-fei; Zhejiang Provincial People's Hospital, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Medical management
Keywords:	Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Author details

Zhen-feng ZHOU, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: zhenfeng9853@163.com

Jun-biao FANG, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: drfangjb@126.com

Hong-fa WANG.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: whf033@163.com

Ying HE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: heyingzju@163.com

Yong-jian YU

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: yyj731227@163.com

Qiong XU.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: happyjoan@163.com

Yun-fen GE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: gyunfen@sina.com

Miao-zun ZHANG , M.D.

- Affiliation: Department of General Surgery, Ningbo Medical center Lihuili Hospital,Ningbo, 325000,China;

Email: idreamof333@126.com

Shuang-fei HU , M.D.

- Corresponding Author
- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: hushuangfei77@sina.com

Abstract

Introduction: Postoperative pulmonary complications (PPCs) will develop in even 58% of patients undergoing abdominal surgery and PPCs is strongly associated with higher risk of mortality. More and more evidence shows that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the role of positive endexpiratory pressure (PEEP) during the intraoperative period in preventing PPCs for laparoscopic surgery is not clearly defined.

Methods and Analysis: A total number of 208 patients with high-risk of postoperative pulmonary complications patients undergoing laparoscopic abdominal surgery will be enrolled and randomized into a standard PEEP (6-8 cmH_2O) group and a low PEEP (≤ 2 cm H_2O) group. Both groups will receive an inspired oxygen fraction (FiO_2) of 0.50 and a tidal volume of 8 ml/kg ideal body weight (IBW). Standard perioperative fluid management standardization and analgesic treatments are applied in both groups. The primary endpoint is postoperative pulmonary complications within 7 days after surgery. Secondary endpoints are the modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, postoperative surgical complications, intensive care unit (ICU) length of stay, hospital length of stay, 30-day mortality.

Ethics and Dissemination: The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (KY2018026) on 22 October 2018. The first participant was recruited in 15th April 2019 and the estimated completion date of the study is October 2021. The results of this trial will be submitted to a peer-reviewed journal and will inform clinical practice.

TRIAL REGISTRATION NUMBER: http://www.chictr.org.cn, ID: ChiCTR1800019865. Registered on 2 December 2018 **;** Pre-results.

Keywords: Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Strengths and limitations of this study:

- Intervention is blinded.
- Standard perioperative fluid management standardization and analgesic treatments are applied in both groups.
- Primary outcome measure is patient centred.
- It is not multicentre randomised trial.

Background

Every year around the world, approximately 230 million patients require surgery with general anesthesia and mechanical ventilation [1]. Laparoscopic surgery has been widely accepted because it is associated with less blood loss, less postoperative pain and rapid recovery [2, 3]. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5% [4], and 12% to 58% of patients undergoing abdominal surgery will develop a PPC [4, 5]. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality [6-8].

Nearly 30% of surgery patients undergoing general anesthesia and mechanical ventilation are at intermediate to high risk for PPCs according to large cohort studies [5, 9]. Both alveolar overstretching and atelectasis induce the release of inflammatory mediators, leading to lung and systemic organ damage [10]. Lung-protective ventilation including the use of low tidal volumes and positive end-expiratory pressure (PEEP), aims to prevent atelectasis and improve gas exchange [11, 12]. Furthermore, PEEP has been found to reduce mortality in patients with the acute respiratory distress syndrome and in critically ill patients [13].

Adopting an appropriate PEEP may prevent PPCs. When high PEEP is applied, alveolar may be overinflate and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis [10]. Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC [14, 15]. Despite all these studies recommend the use of low tidal volume [10], the appropriate PEEP has not yet been defined. A multicenter observational study has shown that approximately 20% of patients do not receive PEEP during routine anesthetic practice [16]. In the Intraoperative Protective Ventilation (IMPROVE) trial that included patients undergoing major abdominal surgery with intermediate-risk

and high-risk of PPCs, compared to a practice of nonprotective mechanical ventilation including higher tidal volumes without PEEP, a lung-protective ventilation strategy with lower tidal volumes and PEEP of 6 cm H_2O was associated with improved clinical outcomes [14]. Furthermore, in another study including patients undergoing abdominal nonlaparoscopic surgery lasting more than 2 h, compared to a standard ventilation strategy, a protective ventilation strategy with 10 cm H_2O PEEP improved respiratory function and reduced the modified clinical pulmonary infection score (mCPIS) [15]. However, another study has shown that low tidal volume combined low PEEP (3 cm H_2O) ventilation may induce postoperative inflammation and may increase the risk of PPCs during major surgery such as hepatectomy [17]. In an international multicenter trial, Protective Ventilation using high vs. low PEEP (PROVHILO), including patients undergoing open abdominal surgery with high risk for PPCs, compared with low PEEP (≤ 2 cm H_2O), a ventilation strategy of high PEEP (12 cm H_2O) did not reduce the incidence of PPCs, but more likely caused haemodynamic instability [18]. Therefore, the authors suggested a ventilation strategy of low tidal volume combined with low PEEP (≤ 2 cm H_2O) [18].

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo laparoscopic surgery. Some studies have suggested that laparoscopic-assisted gastrectomy (LAG) was beneficial for postoperative respiratory function recovery. Nevertheless, it is also necessary to consider the effects of pneumoperitoneum (PnP) on airway pressure and pulmonary function. The role of PEEP during the intraoperative period in preventing PPCs for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PPCs and may reduce the occurrence of organ dysfunction. These anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and; in-hospital stays in patients undergoing laparoscopic surgery.

Methods/design

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH_2O) with those of low PEEP (≤ 2 cm H_2O) in patients at risk for complications undergoing laparoscopic surgery during general anesthesia in terms of: (1) PPCs, (2) modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, changes in chest X-ray findings, and oxygenation; (3). intraoperative complications including hypoxemia, massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

Study endpoints

Primary outcome measure

The primary endpoint of PPCs is defined according to a previous report [19] including any new atelectasis or infiltrates on a chest X-ray, respiratory failure (defined as the need for noninvasive or invasive ventilation) or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 300 within 7 days after surgery.

Secondary outcome measures

Secondary outcome variables are any pulmonary complications and extrapulmonary complications as follows:

1. Postoperative pulmonary complications (PPCs) within 30 days after surgery. Those PPCs are scored according to a grading scale ranging from 0 to 4 [20] (grade 0 representing no PPCs and grades 1 to 4 representing gradually worse forms of PPCs) within 7 and 30 days after surgery (Table 1).

Table 1. Grade scale for postoperative pulmonary complications.

Grade scale	Detailed description
Grade 1	- Cough, dry - Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; results of chest radiograph either normal - Dyspnea, not due to other documented cause
Grade 2	- Cough, productive, not due to other documented cause - Bronchospasm: new wheezing or pre-existent wheezing resulting in change therapy - Hypoxemia - Atelectasis: radiological confirmation plus either temperature > 37.5°C or abnormal lung findings - Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation
Grade 3	- Pleural effusion, resulting in thoracentesis - Pneumonia, suspected: radiological evidence without bacteriological confirmation -Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture - Pneumothorax - Re-intubation postoperative or intubation, period of ventilator dependence (non-invasive or invasive ventilation) ≤ 48 hours
Grade 4	Ventilatory failure: postoperative non-invasive ventilation dependence ≥ 48 hours, or re-intubation with subsequent period of ventilator dependence ≥ 48 hours

2. PPCs will also be analyzed separately.

a. Pneumonia is defined according to Centers for Disease Control (CDC) criteria [21] as follows: patients with altered or new pulmonary opacities on chest X-ray; patients should also meet at least two of the following criteria: (1) temperature ≥ 38.5°C or < 36°C, (2) white blood cell (WBC) count > 12 x10^9/L or < 4 x10^9/L; (3) purulent sputum: new cough or difficulty breathing or previous coughing or difficulty breathing is further aggravated.

b. Postoperative hypoxemia and severe hypoxemia [22]: hypoxemia is defined as PaO_2 < 60 mmHg or oxygen saturation (SpO_2) < 90% on room air, but responding to oxygen treatment (hypoventilation should be excluded). Severe hypoxemia is recorded in cases when the patient requires non-invasive or invasive mechanical ventilation.

c. Suspected pulmonary infection is described in a previous study [18]: the patient takes antibiotics and should meet at least one of the following criteria: (1) changed or new sputum, (2) changed or new pulmonary opacities on chest X–ray, (3) temperature greater than 38.3°C, and (4) WBC count > 12 x10^9/L.

d.Pulmonary infiltrate is defined according to consensus guidelines: Chest X–ray demonstrating monolateral or bilateral infiltrate[23].

e. Atelectasis, pleural effusion or pneumothorax are identified by chest X-ray.

f. The modified clinical pulmonary infection score (mCPIS) is calculated as previously described [24] (Table 2).

Table 2. The definition of modified Clinical Pulmonary Infection Score (mCPIS).

Items	CPIS Points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (℃)	36.5- 38.4	38.5- 38.9	≤ 36.5 or ≥ 39.0
Leukocytes count (per mm^3)	4,000-11,000	<4,000 or >11,000	< 4,000 or > 11,000 + band forms ≥ 500
PaO_2/FiO_2,(mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

PaO_2 =Partial pressure of arterial oxygen; FiO_2 =Fraction of inspired oxygen; ARDS =Acute respiratory distress syndrome

g. ARDS (Acute Respiratory Distress Syndrome) is defined according to the Berlin criteria [25].

h. Suspected pulmonary complications[15] are defined in cases where patients display at least three of the following new findings: (1) cough, (2) increased secretions, (3) dyspnea, (4) chest pain, (5) temperature> 38°C, and (6) pulse rate> 100 beats per minute.

i. Requirement for postoperative ventilation (respiratory failure that requires noninvasive and/or invasive ventilation) for at any time after surgery according to standard criteria and clinical practice guidelines[20].

3. Postoperative extrapulmonary complications within 30 days after surgery:

a. Systemic inflammatory response syndrome (SIRS) criteria are defined when

meeting the following two or more criteria by the most deranged value recorded after surgery [26]: (1) rectal or tympanic temperature > 38°C or <36°C (0.5°C will be added to the measured value when oral or other temperatures are used); (2) Heart rate > 90 beats/min (excluding those who have a known medical condition or are receiving treatment that would prevent tachycardia); (3) respiratory rate> 20 breaths/min or a $PaCO_2$< 32 mmHg or requiring mechanical ventilation. White blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands.

b. Sepsis and Septic shock [26]: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA(Sequential [Sepsis-related] Organ Failure Assessment) score $\geqslant$ 2 points consequent to the infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

c. Other extrapulmonary infection including surgical site infection (SSI) and intraabdominal abscess: SSI [27] is defined as surgical site infection within 30 days after surgery; at least the incision has a purulent effluent; the incision drainage fluid or tissue culture results are positive, with pain or tenderness, local swelling, redness or fever.

d. Need for postoperative blood transfusion.

e. Postoperative surgical complications: anastomotic leakage and need for surgical reintervention, defined according to consensus criteria [28].

f. Unexpected intensive care unit (ICU) admission or readmission.

g. ICU length of stay and hospital length of stay.

h. Hospital free-days at follow-up day 30.

i. In-hospital mortality and thirty-day mortality (all-cause mortality 30 days after randomization).

j. Intraoperative complications: pneumothorax is confirmed by chest X-ray and any other complications.

Study design: This unfunded, parallel-group, double-blinded, prospective, randomized controlled clinical trial was registered at http://www.chictr.org.cn (ChiCTR1800019865) and was conducted at the Department of Anesthesiology and Intensive Care of Zhejiang Provincial People's Hospital. The first participant was recruited in 15th April 2019. This trail protocol is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1). The SPIRIT 2013 Checklist is given in Additional file 1.

Ethics and Dissemination:

The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) (registration number KY2018026) on 22 October 2018. Any subsequent protocol and informed consent document amendments must be approved by the responsible of Ethics Committee. All communications with the regulatory authorities and the Ethics Committee must be recorded.

All recruited patients will be informed of the trial purposes and their duties within the trial before randomization. Recruited patients can withdraw from the study at any time without providing any specific reason. The patient data will be stored in a separate, safe place but that it may be reviewed by the relevant investigator.

Blinding, data collection, randomization and record keeping

Selection of the participants

Researchers will be trained prior to investigation. Study data including patient clinical characteristics, intraoperative respiratory parameters, postoperative outcomes, and laboratory test, will be collected onto case report forms (CRF) (Additional file 2).

An independent researcher will randomize the participants into the study group (standard group PEEP) and control group (low PEEP group) in a ratio of 1:1. The random sequence will be computer-generated and participants will be allocated in numerical order with sealed opaque envelopes. The attending

anesthesiologist performs anesthesia strictly according to the research protocol and is also responsible for data during the preoperative, intraoperative and PACU period. The chief surgeon performs the postoperative laboratory testing. An independent researcher will be involved in postoperative follow-up and data collection. Statistical analysis will be performed by a statistician who does not participate in the data collection. Patients, research staff, surgeons, intensive care physicians and the statistician will be unaware of the group allocation. Some preoperative characteristics and laboratory results will automatically derived from a computer data base.

The original data (CRF and relevant records) will be maintained for 5 years and then destroyed according to hospital standards.

Selection of the participants

Patients scheduled for elective laparoscopic abdominal surgery under general anesthesia will be screened and recruited during preoperative assessment. Patients meeting inclusion criteria will be required to provide their written informed consent (Additional file 3 and 4). The participant can withdraw from the trial at any time.

Inclusion criteria are patients older than 18 y, American Society of Anesthesiologists (ASA) physical status II or III, body mass index (BMI) between 18-35 kg/m^2, general anesthesia expected to last more than 3 h, an intermediate or high preoperative index for PPCs risk by the Assess Respiratory Risk in Surgical Patients in Catalonia study (ARISCAT score ≥ 26, the Additional file 5).

Exclusion criteria are listed as following: emergency surgery or history of previous lung surgery, history of mechanical ventilation within the 2 weeks before recruitment, non–invasive ventilation or oxygen therapy at home, acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome), history of chronic obstructive pulmonary disease (COPD), persistent hemodynamic instability or severe cardiac disease (New York Heart Association class III or IV, or persistent ventricular tachyarrhythmia's, or acute

coronary syndrome), sepsis or septic shock, need renal replacement therapy (CRRT), progressive neuromuscular illness, pregnancy, participation in another study or refusal to participate.

Time course of the study

Preoperative admission

Medical history, ASA physical status, BMI, 12-lead ECG, laboratory results , chest X-ray or computed tomography (CT) scan, ARISCAT score and nutritional risk screening (NRS 2002 tool), the results of echocardiography and spirometry (in cases of history of coronary artery disease or smoking) will be recorded.

Intraoperative care

A central venous catheter and an arterial cannula will be placed before induction of anesthesia. Peripheral oxygen saturation (SpO_2), arterial blood pressure, heart rate (HR), ECG, end-tidal carbon dioxide tension ($EtCO_2$) and bispectral index (BIS) will be monitored continuously. Pneumoperitoneum (PnP), tidal volume, PEEP, airway pressures including peak pressure and plateau pressure, airway resistance (Raw), Vds/Vt, core temperature, and arterial blood gas analysis data will be recorded.

Crystalloid (12-15ml/kg/h) is infused to maintain hemodynamic stability and central venous pressure 5-12 cm H_2O. Blood loss and vasodilation are supplemented by colloidal fluid.

Routine anesthesia is induced with intravenous dexmedetomidine(1 ug/kg) or midazolam (0.05-0.075mg/kg), cisatracurium (2 mg/kg), propofol (2-3 mg/kg) and fentanyl (1-3 μ/kg) for tracheal intubation. Anesthesia is maintained with propofol, sevoflurane and remifentanil infusion to maintain the BIS 40-50 until skin suturing is completed. Cisatracurium (1.0-1.5 mg/kg) is administered every hour and the last dose is at least 1 hour before the end of operation. Ropivacaine is administrated as local incision infiltration anesthesia before and at the end of operation respectively. Fentanyl (1-3 μg/kg) and flurbiprofenaxetil 50 mg are required before remifentanil is stop.

Postoperative care

Patients will be transferred to the post-anesthesia care unit (PACU) after surgery regardless of whether they are still intubated.

Postoperative pain management will be suggested to achieve a visual analogue scale (VAS) pain score of < 3/10 using a patient-controlled intravenous analgesia pump including fentanyl (0.3-0.5 μg/kg), flurbiprofenaxetil (100 mg) and palonosetron hydrochloride (0.25 mg) palazidine.

The ICU physician and surgeon will independently monitor clinical progress and all endpoints by daily physical examinations. Appropriate prophylactic antibiotics and antithrombotic treatments will be administered as required during the postoperative period. chest X-ray will be performed by an independent, trained radiologist on POD 5. Arterial blood gas analysis will be performed on POD 1 and POD 3 and other laboratory tests will be performed on POD 1, POD 3, POD 5 and POD 7. The examinations will be repeated and microbiology tests will be performed when the development of pulmonary complications is suspected.

Study arms and intraoperative ventilation protocol

Patients will be randomly assigned to the low PEEP ventilation group (PEEP ≤ 2 cm H_2O) or the standard PEEP group (PEEP = 6-8 cm H_2O) using a volume-controlled ventilation strategy (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) with a tidal volume of 8 ml/kg ideal body weight (IBW), an inspired oxygen fraction (FiO_2) of 0.50, and an inspiratory to expiratory ratio of 1:2. Respiratory rate should be adjusted to maintain $ETCO_2$ between 35 and 45 mmHg) and plateau pressure should be no more than 35 cmH_2O. IBW is calculated with formulas as follows [14]: 45.5 + 0.91 x (centimeters of height - 152.4) for females and 50 + 0.91 x (centimeters of height - 152.4) for males. Recruitment maneuvers (RMs)[19] will be performed immediately after tracheal intubation and every time when the ventilator is interrupted until the end of surgery in each group. The compliance of the

respiratory system is calculated with the formulas of V_T/ (plateau pressure of the respiratory system - PEEP).

Recruitment maneuvers will be performed as follows:

(1). Pressure support ventilation (PSV) mode

(2). Positive end-expiratory pressure (PEEP) set to 30 cm of water

(3). Inspiratory gas flow set to the highest value

(4). Duration of the maneuver = 30 sec

A rescue therapy will be applied in case of desaturation (defined as a peripheral SpO_2 of less than 92%), consisting of increasing FiO_2 to 100% in each group and increased PEEP in the low PEEP group (Additional file 6).

From postoperative day 7 (POD 7 to POD 30, follow-up)

Secondary endpoints and any mortality will also be evaluated during the follow-up period. The CONSORT flowchart of the trial is shown in Figure 2.

Data monitoring and Handling of implausible values or missing values:

A clinical investigator will identify implausible values. Missing continuous variables should be less than 10% and will be replaced by the mean of all plausible data (both groups) of the respective endpoint. Data monitoring is managed by an independent investigator who is not involved in the study. The progress of the study will be evaluated and the completeness and accuracy of the data (Informed Consent Forms, source data, CRF and outcome variables) will be verified.

Statistics:

Normally distributed variables will be expressed as the mean ± standard deviation (SD) and will be compared with Student's t-test. Categorical variables will be compared using the chi-square test or the Fisher's exact test. Non-normal continuous variables will be expressed as median (interquartile range (IQR)) and evaluated with the Mann-Whitney U-test. The primary outcome and secondary outcomes will be all handled. Intention-to-treat (ITT) analyses are performed to compare the composite outcome measure at 7 days in the two groups by the chi-squared test (or Fisher's exact test as appropriate)

and multiple logistic regression analysis adjusting will be performed to identify various risk factors (for the primary outcome and the pulmonary complications at postoperative Day 30). *P* <0.05 will be considered statistically significant and all reported *p* values will be 2-sided. Interim analysis of safety will be conducted after enrolment of the first 104 patients. All analyses will be conducted using the SPSS Version 18.0 (SPSS, Chicago, IL, USA) software.

Sample size calculation

The incidence rate of postoperative pulmonary complications was 39% in the low PEEP group [18]. Two tailed chi-squared test was performed and we estimated that 188 patients were required to provide 80% power to detect a 50% relative difference between the two groups, with a type I error probability of 0.05. Assuming that follow-up lost rate was 10 %, and then a total of 208 cases are needed. Analysis is computed using G-Power (version 3.1; Informer Technologies, Inc.).

Adverse events and interruption of the trial:

All patients will be continuously monitored during the study including daily visits during in-hospital and daily phone-call visits during the out of hospital follow-up period (until POD 30). All serious adverse, unexpected or possibly related events will be recorded in the CRF and will be reported to the data monitoring and safety committee (DMSC). DMSC will recommend that the study should be stopped unless there is evidence that patient is safety (a between-group difference in serious adverse events or in 30- day mortality is found).

Discussion:

In this pragmatic, prospective, randomized controlled trial of high-risk patients undergoing laparoscopic surgery, our aim is to assess not only possible single effects of PEEP levels on major PPCs from those of lower tidal volumes and RM but also to assess relevant clinical parameters associated with alterations in pulmonary function such as chest X-ray, abnormalities, mCPIS, arterial oxygenation/peripheral oxygen saturation in air and changes in dyspnea/cough/secretions. Our findings might change current practice of mechanical ventilation in high-risk patients undergoing laparoscopic surgery.

There are some potential strengths of the present trial protocol. First, this ARISCAT score will be used to predict PPCs and we select only the high-risk PPC population that will potentially receive maximum benefit from intraoperative PEEP strategy. Although various scores have been developed for predicting PPC incidence based on various countries and surgical populations, the ARISCAT score is considered to be the most valuable tool [10]. Second, this trial design includes instructions for fluid management standardization and analgesic treatments during the perioperative period. Third, the included patients will undergo elective abdominal laparoscopic surgical procedures with more than 3h of general anesthesia. Previous studies have reported that both abdominal surgery and longer anesthesia duration are potential risk factors for PPCs [8].

Notably, mechanical ventilation itself is one of major contributors to PPCs [29]. PnP is also an important risk factor for PPCs [30]. Intraabdominal pressure is frequently higher than airway pressure during PnP with carbon dioxide (CO_2) for laparoscopic surgery. This pressure gradient usually causes cephalad displacement of the diaphragm and collapses adjacent pulmonary tissues. PnP also decreases respiratory compliance and arterial oxygenation [31] .All these influences on PnP lead finally to atelectasis [32].

On the other hand, PEEP is thought to prevent the development of atelectasis

by keeping the airways open and maintaining adequate gas exchange at the end of the expiratory period during PnP [10]. Certainly, the level of PEEP should be adopted according to the patient's and surgical characteristics as well as to the patient's positioning.

Previous studies reported that very low levels of PEEP were potentially associated with atelectasis by promoting repeated opening and closing of small airways [33]. However, higher levels of PEEP may increase mean airway pressure of the respiratory system and likely even impair hemodynamics. There is an increasing number of highly qualitative Randomized Controlled Trials (RCTs) regarding intraoperative mechanical ventilation and PPCs, whereas direct assessment of the effect in high-risk patients undergoing laparoscopic surgery remains lacking. The potential significance of this trial is that it may provide evidence of the effects of intraoperative PEEP on PPCs in high-risk patients undergoing laparoscopic surgery.

Trial status

The first participant was recruited in 15th April 2019 and the estimated completion date of the study is October 2021.

Additional file

Abbreviations

ABGa: Arterial blood gas analysis; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; AMI: Acute myocardial infarction; ASA: American Society of Anesthesiologists; BIS: bispectral index; BMI: Body Mass Index; CDC: Centers for Disease Control; CO_2: carbon dioxide; COPD: Chronic obstructive pulmonary disease; CRF: Case Report Form; CRRT: renal replacement therapy; CT: Computer tomography; DMSC: data monitoring and safety committee; DIC: Disseminated intravascular coagulation; ECG: Electrocardiogram; $EtCO_2$: End-tidal carbon dioxide tension; FiO_2: Fraction of inspired oxygen; HR: Heart rate; IBW: Ideal bodyweight; ICU: Intensive care unit; IQR: interquartile range; LAG: laparoscopic surgery; mCPIS: modified clinical pulmonary infection score; PACU: Post-anesthesia Care Unit;PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PnP: pneumoperitoneum; POD: Postoperative day; PPC: Postoperative pulmonary complications; PSV: Pressure Support Ventilation; Raw: Airway resistance; RM: Recruitment maneuver; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome; SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials; SpO_2: Oxygen saturation; SSI: surgical site infection; Vds/Vt: Dead space fraction; VAS: visual analogue scale; WBC: White Blood Cell.

Acknowledgements

We want to thank all the contributors and collaborators for their support in this study. We also thank all the participating patients.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

Zhen-feng ZHOU and Shuang-fei HU designed the study protocol and wrote the paper. Hong-fa WANG and Miao-zun ZHANG designed the statistical method. The work of patient recruitment and data collecting will be done by Jun- biao FANG, Yong-jian YU, Qiong XU, Ying HE and Yun-fen GE. Shuang-fei HU is the study director and Jun- biao FANG is the principal investigator of this study. All authors have read the manuscript and approved to submitting the final paper.

Authors' information

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Patient and Public Involvement:

Patients and the public were not involved in the design or planning of the study.

References

[1] Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008. 372(9633): 139-44.

[2] Lee CM, Park S. Laparoscopic techniques and strategies for gastrointestinal GISTs. J Vis Surg. 2017. 3: 62.

[3] Patel B, Leung U, Lee J, Bryant R, O'Rourke N, Cavallucci D. Laparoscopic pancreaticoduodenectomy in Brisbane, Australia: an initial experience. ANZ J Surg. 2017 .

[4] Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010. 113(6): 1338-50.

[5] Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med. 2001. 135(10): 847-57.

[6] Shander A, Fleisher LA, Barie PS, Bigatello LM, Sladen RN, Watson CB. Clinical and economic burden of postoperative pulmonary complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies. Crit Care Med. 2011. 39(9): 2163-72.

[7] 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. Ann Surg. 2005. 242(3): 326-41; discussion 341-3.

[8] Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006. 144(8): 581-95.

[9] 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. Ann Surg. 2000. 232(2): 242-53.

[10] Güldner A, Kiss T, Serpa NA, 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(3): 692-713.

[11] Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the non-injured lung: review and meta-analysis. Crit Care. 2014. 18(2): 211.

[12] Futier E, Constantin JM, Pelosi P, et al. Intraoperative recruitment maneuver reverses detrimental pneumoperitoneum-induced respiratory effects in healthy weight and obese patients undergoing laparoscopy. Anesthesiology. 2010. 113(6): 1310-9.

[13] Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000. 342(18): 1301-8.

[14] Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013. 369(5): 428-37.

[15] Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013. 118(6): 1307-21.

[16] Jaber S, Coisel Y, Chanques G, et al. A multicentre observational study of intra-operative ventilatory management during general anaesthesia: tidal volumes and relation to body weight. Anaesthesia. 2012. 67(9): 999-1008.

[17] Sato H, Nakamura K, Baba Y, Terada S, Goto T, Kurahashi K. Low tidal volume ventilation with low PEEP during surgery may induce lung inflammation. BMC Anesthesiol. 2016. 16(1): 47.

[18] Hemmes SN, de Abreu M G, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet. 2014. 384(9942): 495-503.

[19] Ruszkai Z, Kiss E, László I, et al. Effects of intraoperative PEEP optimization on postoperative pulmonary complications and the inflammatory response: study protocol for a randomized controlled trial. Trials. 2017. 18(1): 375.

[20] Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, de la Riviere A B, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA. 2006. 296(15): 1851-7.

[21] Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. Methods Inf Med. 2007. 46(5): 595-600.

[22] Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011. 183(3): E195-214.

[23] Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994. 20(3): 225-32.

[24] Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003. 168(2): 173-9.

[25] Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012. 307(23): 2526-33.

[26] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016. 315(8): 801-10.

[27] Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992. 13(10): 606-8.

[28] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004. 240(2): 205-13.

[29] Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA. 2010. 304(23): 2620-7.

[30] Reinius H, Jonsson L, Gustafsson S, et al. Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. Anesthesiology. 2009. 111(5): 979-87.

[31] Hazebroek EJ, Haitsma JJ, Lachmann B, Bonjer HJ. Mechanical ventilation with positive end-expiratory pressure preserves arterial oxygenation during prolonged pneumoperitoneum. Surg Endosc. 2002. 16(4): 685-9.

[32] Park SJ, Kim BG, Oh AH, Han SH, Han HS, Ryu JH. Effects of intraoperative protective lung ventilation on postoperative pulmonary complications in patients with laparoscopic surgery: prospective, randomized and controlled trial. Surg Endosc. 2016. 30(10): 4598-606.

[33] Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005. 102(4): 838-54.

Figure legends:

Figure 1. Standard Protocol Items.

Figure 2. The CONSORT flowchart of the trial.

Supporting Information

S1 Additional file 1. SPIRIT 2013 Checklist1.

S2 Additional file 2. Case report form.

S3 Additional file 3: Patient consent form in English.

S4 Additional file 4. Patient consent form in original language.

S5 Additional file 5. Preoperative risk index of postoperative pulmonary complications by ARISCAT score.

S6 Additional file 6. Strategy for SpO_2 decreasing.

Standard Protocol Items

	Study period								
	Enrolment		Allocation		Post-allocation				
Timepoint	-1 week	-t1	0	DOS	POD1	POD3	POD5	POD7	POD8-30
Enrolment:									
Perioperative assessment	√								
Eligibility screen		√							
Informed consent		√							
Allocation			√						
Interventions:									
Study Group(Low PEEP)				√					
Control Group(Standard PEEP)				√					
Assessments:									
Intraoperative complications				√					
Postoperative pulmonary complications					√	√	√	√	√
Physical examinations					√	√	√	√	√
Blood gas analysis					√	√	√	√	√
chest X-ray							√		
Postoperative extra-pulmonary complications					√	√	√	√	√
Postoperative surgical complications					√	√	√	√	√
ICU length of stay									
Hospital length of stay									
In-hospital mortality									
Thirty-day mortality					◄———	———	———	———	———►

Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. DOS: day of surgery; POD: postoperative day; ICU: Intensive care unit.

Figure 1. Standard Protocol Items

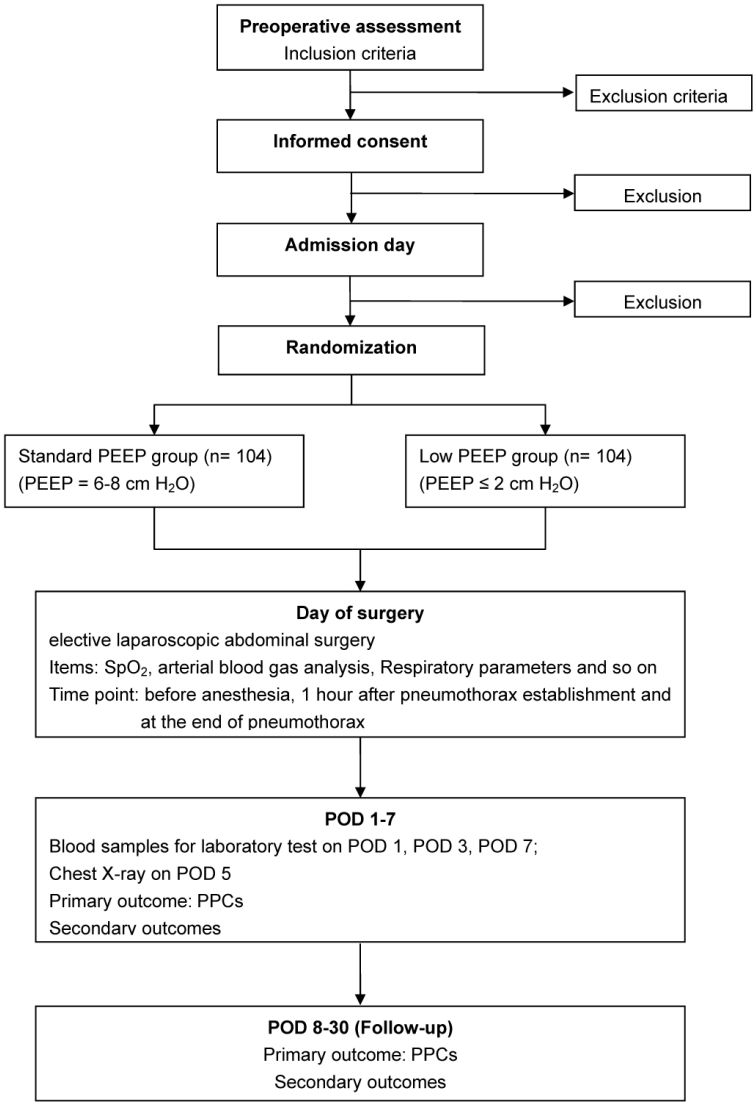

Figure 2. The CONSORT flowchart of the trial

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page, 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5, 14
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	29
Funding	4	Sources and types of financial, material, and other support	28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 28, 29
	5b	Name and contact information for the trial sponsor	1-3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	28, 29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	29

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, 7
	6b	Explanation for choice of comparators	7, 8
Objectives	7	Specific objectives or hypotheses	4, 5, 8, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17,18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-21
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	21, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	19-22
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18-21 Fig.1, Fig.2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22, 23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16, 17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16, 17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	23
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18, 21, 22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21, 22

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17, 21, 22
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17, 22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16,17, 21, 22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22, 23
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	29
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21, 22, 29
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Effects of intraoperative Low-PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic surgery: study protocol for a randomized controlled trial

Case report form

Checklist

Please check the checklist carefully when completed the questionnaire.

□Perioperative assessment: Informed patient details of the study and obtained informed consent from the patient.

Date of signing informed consent: _____

Admission date: _____

□Perioperative data Surgery date: _____

□Completed the above registrations

Completed date: _____

Quality control personnel：_____

Case registration form

Basic information

Case number:

Patient case number:

Random number:

Randomized group：☐ Low-PEEP group (Study Group)

☐ Standard PEEP group (Control Group)

Gender male/female

Height _____cm

Ideal weight _____kg

Actual weight _____kg

Calculation formula of ideal weight：

male= 50 + 0.91×(Height - 152.4)；

female= 45.5±0.91×(Height - 152.4)

Age (years) _____

Contact staff _____

Phone number _____

Address _____

Chief surgeon _____

Baseline Characteristics of the Patients

1. Inclusion and exclusion criteria (Please √ if there is any situation as listed below)

Item	Inclusion criteria	
	yes	no
Age：≥ 18 year		
Scheduled for elective laparoscopic abdominal surgery		
ASA physical status I-III		
BMI: 18-35 kg/m^2		
General anesthesia expected to last more than 3 h		
Had a intermediate or high preoperative index for PPCs risk (ARISCAT score ≥ 26, Supplementary Appendix Table 1)		
	Exclusion criteria	
Emergency surgery		
Mechanical ventilation of > 1 hour within the last 2 weeks before surgery		
History of previous severe (COPD)		
Acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome)		
Previous lung surgery		
Persistent hemodynamic instability or Severe cardiac disease		
Sepsis or septic shock		
Need renal replacement therapy		
Progressive neuromuscular illness		
Pregnancy		
Consented for another interventional study or refusal to participate		
Have a stake in the researcher		
Researchers conside that they are not suitable for clinical trials		

2. Perioperative data (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Preoperative		**One hour after pneumothorax establishment**		**at the end of pneumothorax**	
Temperature		arterial blood gas analysis			
ASA status		FiO_2			
ARISCAT score		Pneumoperal pressure			
NYHA III-IV		Tidal volume			
History of smoking		Respiratory rate			
Drinking		PT-CO_2			
Combined diseases		PEEP			
History of Medication		Platform / peak pressure			
Respiratory infection within one month		Blood pressure			
Weight change in the past one month		Heart rate			
Blood routine examination		Temperature			
Coagulation spectrum					
Biochemical tests		**Intra-operative**			
Chest X-ray or CT		Times of RM			
Pulmonary function test		Adverse events during RM			
mCPIS score		Antibiotic			
		Infusion volume			
		Blood transfusion			
Before anesthesia		Amount of bleeding			
SpO_2 without inhaling oxygen		Urine volume			
Arterial blood gas analysis		Vasoactive drug use			
		Operation time			
		Mechanical ventilation time			
		Other complications			

The amount of each day and duration for smoking and drinking; describe the specific disease and current medication and doses for columns of combined disease and medication history; only check if there is laboratory test or chest X-ray. etal; arterial blood gas analysis should performed after10 min of air adaptation before anesthesia;

Intraoperative complications were recorded and defined as follows: 1. peripheral oxygen saturation less than 90% and/or end-tidal fractions of carbon dioxide more than 45 mmHg for more than 1 min, 2. need to change the ventilation setting (tidal volume and/or respiratory rate), 3. heart rate more than 100 beats/min or less than 60 beats/min, 4. systolic arterial pressure more than 150 mmHg or less than 90 mmHg.

Blood gas analysis during postoperative recovery room should done meet the following 2 points at the same time: 1. 30 minutes after the tracheal tube is removed; 2. after10 min of air adaptation. If peripheral oxygen saturation dropped below 88% during the 10 min of adaptation, the maneuver was stopped and arterial blood gas analysis immediately obtained.

3. Postoperative pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	**POD 1**	**POD 3**	**POD 5**	**POD 7**	**POD 8-30**
SpO_2 after10 min of air adaptation					/
FiO_2 after10 min of air adaptation					/
Arterial blood gas analysis			/	/	/
Heart rate					
Respiratory rate					
Chest X-ray	/	/		/	
Blood routine test					
CRP					
Biochemical tests					
Microbiology test					
Mechanical Ventilation					
Whether tracheal secretions was increased; the nature and quantity of secretions					
Cough					
Difficulty breathing					
Chest pain					
Postoperative hypoxemia					
Postoperative severe hypoxemia					
Suspected lung infection					
Pneumonia					
Exudation of the lungs					
Aspiration pneumonia					
Pulmonary embolism					
Atelectasis					
ARDS					
Pneumothorax					
Pleural effusion					

ARDS: acute respiratory distress syndrome.

3. Postoperative extra-pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	**POD 1**	**POD 3**	**POD 5**	**POD 7**	**POD 8-30**
SIRS					
Sepsis					
Severe sepsis					
Sepsis shock					
Extrapulmonary infection					
Pulmonary edema caused by heart failure					
Blood transfusion					
Anastomotic leak					
Secondary surgery rate					

SIRS: Systemic inflammatory response syndrome; AKI: acute kidney injury; DIC: disseminated intravascular coagulation.

Clinical Research Informed Consent Form of Zhejiang Provincial People's Hospital (Version 1, September 3, 2018)

Dear patient:

You are already diagnosed as _____. We will invite you to participate in a Clinical study Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery. This study is a self-financing project, research number:_____. This study protocol has been reviewed by the Ethics Committee of Zhejiang Provincial People's Hospital and was agreed to conduct this clinical research.

Please carefully read the following items before you decided to participate in this study. It can help you understand the meaning and objectives of this research, the procedures and duration of this study, the benefits, risks and discomforts that you may be meat after participating in this study. You can also discuss with your kins or friends, or ask for an explanation from your doctor to help you make a decision.

I. Introduction:

Every year around the world, approximately 230 million patients require surgery with general anesthesia and mechanical ventilation. Laparoscopic surgery has been widely accepted because it is associated with less blood loss, less postoperative pain and rapid recovery. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5%, and 12% to 58% of patients undergoing abdominal surgery will develop a PPC. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality.

Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC. Despite all these studies recommend the use of low tidal volume, the appropriate PEEP has not yet been defined.. When high PEEP is applied, alveolar may be overinflate and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis.

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo laparoscopic surgery. Some studies have suggested that laparoscopic-assisted gastrectomy (LAG) was beneficial for

postoperative respiratory function recovery. Nevertheless, it is also necessary to consider the effects of pneumoperitoneum (PnP) on airway pressure and pulmonary function.

The role of PEEP during the intraoperative period in preventing PPCs for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PPCs and may reduce the occurrence of organ dysfunction. These anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and; in-hospital stays in patients undergoing laparoscopic surgery.

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH2O) with those of low PEEP (≤ 2 cm H_2O) in patients at risk for complications undergoing laparoscopic surgery during general anesthesia in terms of: (1) PPCs, (2) modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, changes in chest X-ray findings, and oxygenation; (3). intraoperative complications including hypoxemia, massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

II. The process in participating this study:

1) You should cooperate with the medical staff to complete the relevant preoperative preparation according to the clinical routine requirements.

2) You should truly provide the information of related examination and treatment, so that the researcher can accurately carry out the research-related assessment.

3) If you meet inclusion criteria, you can voluntarily choose to participate in this study and sign the informed consent form, and you may be randomly assigned to the standard PEEP group (control group) and low PEEP group (processing group).

4) We will test and record your blood routine and blood gas analysis during the research in the first, the third and he 7th postoperative day. We will take 3 ml of blood for laboratory tests each time.

III. The possible benefits of this study

1. Personal benefit: the setting of intraoperative mechanical ventilation parameters has

a significant impact on postoperative pulmonary complications, hospital stay and mortality in patients undergoing abdominal surgery. Airway pressure monitoring and blood gas analysis are clinically commonly used to reflect lung function during surgery period, however, lung compliance measurement is not routinely performed. We will all do the above measurements to monitor your lung function no matter which group you are assigned to during the study. The responsible clinician will take steps according to the examination results, even he can terminate the clinical research at any time. In this study, patients experienced PPCs may be detected out early and the rate of PPCs may be reduced, and it might improve your recovery. Furthermore, 3 ml of the blood sample required for each test will not affect your health.

2. Social benefits: Current studies shows that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the role of positive endexpiratory pressure (PEEP) during the intraoperative period in preventing PPCs for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PPCs and may reduce the occurrence of organ dysfunction.

IV. **Risks and measures of this study:** (probable adverse reactions, coping solution, compensation measures, treatment costs, claims and etc.)

Many studies have confirmed that the use of low tidal volume combined with PEEP can reduce PPCs in patients undergoing abdominal surgery. We also routinely use PEEP to prevent lung collapse and PPCs. You have about 50% chance of being assigned to the standard PEEP group, and you may be in a risk of potentially high airway pressure. However, we will monitor the airway pressure, blood gas and lung compliance measurement analysis throughout the operation to fully analyze your lung function. The responsible clinician will take steps according to the examination results, even he can terminate the clinical research at any time.

Prevention measures for the risk of intraoperative high airway pressure:

1 sucking; 2 increase inhalation anesthesia; 3 reduce tidal volume to 6 ml/kg (PBW); 4 gradually reduce PEEP to 0; 5 changed to pressure control mode ventilation. Any

research investigator will immediately notify the moderator if there is any suspected adverse event or any ethical issues regarding the study (Liaison: Zhou zhen-feng: 13685856148; PI: Hu Shuang-fei: 13777858909).

V. Relevant expenses:

Our research group is responsible for the cost of blood gas testing, but this study does not increase the cost of other drugs as compared to the clinical routine. Patients and health insurance or third-party payers will not pay for research-related medical care. Research institutions will be responsible for research-related support (including central laboratories). Subjects and health insurance or third-party payers are required to pay for routine or non-study-related medical care. These routine medical treatments include hospitalization and other medical care at discharge.

This study did not increase the cost of drugs and increased the risk of clinical treatment as compared to clinical routine treatment. You can voluntarily choose to participate in this study without relevant economic compensation. We will afford relevant economic compensation after consultation with the patients if adverse events are happened including information leakage, infringement of life rights, certain damage and other events..

VI.Your power:

You will be completely voluntary to participation in this study. You can withdraw from the study at any time without any reason. It will not affect your relationship with the medical staff, future diagnosis and treatment. All your personal data and observation records will be kept in confidential and will be only used for this study. You can obtain any relevant information during this study. You can contact the responsible physician when there is a any problem or you just need to consult the relevant questions.

VII. The ethics committee

This study has been reported to the People's Hospital of Zhejiang Province Human Research Ethics Committee and it has been approved after comprehensive review and assessment the risk of this study. You can contact the Ethics Committee about any

relevant ethics and rights issues during the study. Telephone for 08:00-17:00 is 0571-85893643 and 15671110068 for other time. Email address: zryllwyh@163.com.

Informed consent form. the agreement signature page

Agreement statement

As a patient, I have understand the purpose, methodology, possible treatment benefits and possible adverse effects of this study. I will receive a copy of the signed informed consent form with my name and signed time .

I am willing to participate in this study and ensure that I will follow the doctor's advice as much as possible.

Patient signature:_____ Date:_____

Telephone number: _____

I confirm that I have explained the details of this study to the patient including his powers, possible benefits and risks. I have afforded him a copy of the signed informed consent.

Doctor signature:_____ Date:_____

Doctor Telephone number: _____

浙江省人民医院临床科研知情同意书（版本一，2018 年 09 月 03 日）

亲爱的患者：

医生已经确诊您为_____。我们将邀请您参加一项不同 PEEP 对高风险患者行腹腔镜腹部手术后肺部并发症的影响 研究, 本研究为___自筹___项目，课题编号：_____。本研究方案已经得到_____浙江省人民医院_____伦理委员会审核，同意进行临床研究。

在您决定是否参加这项研究之前，请尽可能仔细阅读以下内容。它可以帮助您了解该项研究以及为何要进行这项研究，研究的程序和期限，参加研究后可能给您带来的益处、风险和不适。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请医生给予解释，帮助您做出决定。

一、研究项目简介：

全世界每年有 2.3 亿以上的手术患者需要全身麻醉和机械通气，腹腔镜手术以其失血量少、术后疼痛轻和恢复快等优点得到广泛应用。接受普通外科手术的患者中约有 5%会发生肺部并发症(post- operative pulmonary complications,PPC)，并且发生 PPC 的患者中约 20%在术后 30 天内死亡。据报道，接受腹部手术的患者术后肺并发症(PPC)发生率在 12%至 58%之间。肺部并发症(post- operative pulmonary complications,PPC)是手术后住院时间延长和死亡主要原因之一。

相比高潮气量结合无 PEEP 的通气模式，近来越来越多的研究显示 LPV 在健康肺部患者全身麻醉下行腹部手术具有肺保护作用，降低 PPC 发生率。目前研究均建议对这部分患者采用低潮气量，但目前研究尚未明确合适的 PEEP 值。PEEP 过高可能引起肺泡过度膨胀、肺血管阻力增高和循环抑制，PEEP 过低又不能起到防止肺不张改善氧合的作用，均可造成不良后果[10]。因此制定最佳的 PEEP 显得尤为重要。

还有一点需要注意的是，以上这些研究手术类型为开腹手术或各种腹部手术类型，有研究认为腹腔镜手术(LAG)有利术后呼吸功能恢复，因为它需要相对较小的皮肤切口，但也需要同时考虑气腹对气道压和肺功能的影响。

综上所述，目前研究证实肺保护性通气策略可以改善腹部手术后肺部并发症，但尚未确定合适的 PEEP 值。鉴于以上原因，目前不同 PEEP 对高风险患者行腹腔镜腹部手术后肺部并发症的影响还未得到证实，有待进一步研究。

研究目的：

1 明确不同 PEEP 值对高风险患者行腹腔镜腹部手术后肺部并发症的影响，评价不同 PEEP 值与术后肺部并发症的关系。

2 明确不同 PEEP 值对高风险患者行腹腔镜腹部手术后其它指标的影响：（1）改良的临床肺部感染评分（mCPIS），术后肺外并发症，胸部 X 线表现变化和氧合作用；（2）术中并发症包括低氧血症，大量输血；（3）术后手术并发症，重症监护病房（ICU）住院时间，住院

时间和 30 天死亡率。

二、参与试验的内容和过程：

1）按照临床常规要求，配合医护人员完成相关的术前准备；

2）如实提供自身疾病和相关检查治疗情况，以利于研究人员准确地进行研究相关的评估；

3) 如果您符合研究纳入标准，您可自愿参加研究，并签署知情同意书，您可能会被随机分配到标准 PEEP 值肺保护性通气策略模式组(对照组)或低 PEEP 值肺保护性通气策略模式组(处理组)，术中按照 2 种不同方案给予处理。

4）因在研究过程中我们将观察记录您的血常规、血气分析情况，需要术后第 1 天、术后第 3 天和术后第 7 天这几个时间点进行血常规、血气分析检查，每次需要采血 3 ml 进行化验检查。

三、参加研究可能的受益

1. 个人受益：因术中机械通气参数的设置对腹部手术后肺部并发症、住院时间和死亡率有明显影响。手术过程中监测气道压和血气分析是临床上常用反应肺功能的指标，但是肺顺应性测量并未在临床中常规开展检测。故不论您在本次从研究中被分到哪一组，都可以采用全面的肺功能检测技术进行监测，临床医生根据检查结果进行相应处理，并可随时终止临床研究。参加本研究，患者肺功能障碍可能早期发现，围术期肺部并发症可能减少。在一定程度上可以促进您的恢复，提高您的舒适性。而且每次化验所需血样本 3 ml 并不会对的健康造成影响。

2. 社会受益：目前研究证实肺保护性通气策略可以改善腹部手术后肺部并发症，但尚未确定合适的 PEEP 值，而且也未明确肺保护性通气策略对腹腔镜下腹部手术患者的保护性。本研究立足于术中 PEEP 值对腹腔镜腹部手术后肺部并发症的影响，为预防腹腔镜下腹部手术患者术后肺部并发症的发生提供依据。

四、参加本项目的风险及处理措施：（可能出现的不良反应及其程度、应对的处理方案、补偿措施：治疗费用、赔付等）

很多研究实验都证实腹部手术中应用低潮气量联合 PEEP 能减少术后肺部并发症，目前我们临床上也是常规应用 PEEP 以预防肺部萎陷和肺部并发症。您有约 50%的机会被分到标准 PEEP 组，可能存在潜在高气道压的风险，但我们在术中全程进行有效的气道压、肺顺应性和血气分析检查，全面分析肺功能，临床医生根据检查结果进行相应处理，并可随时终止临床研究。术中高气道压风险预防措施：①吸痰；②增加吸入麻醉药比；③减少潮气量为 6 ml/kg(PBW)；④逐步减少 PEEP 值至 0；⑤改为压力控制模式通气。任何研究调查者任何时

间发现怀疑有不良事件或对继续实验有任何伦理问题会立即通知主持者（课题联络员：周振锋：13685856148；负责人：胡双飞：13777858909）。

五、有关费用：

本课题组负责血气检测费用，较临床常规未增加其它药物费用。受试者和医疗保险部门或第三方支付者将不会为研究相关医疗付费。研究机构支付研究相关支持（包括中心实验室）。受试者和医疗保险部门或第三方支付者需要为常规医疗或与研究无关的医疗进行付费。这些常规医疗包括住院医疗和出院时带药或其它医疗。

本研究较临床常规未增加药物费用和增加临床治疗风险，自愿参加研究，无相关经济补偿。如因为本研究所造成受试者的相关信息泄露、侵害人生权益等事件，对受试者造成一定损害的，我们将与受试者协商后给予相关经济补偿。

六、您的权力：

您参与试验是完全自愿的，您可以随时退出试验而无需理由，绝不会影响您和医务人员的关系及今后的诊治；您的所有个人资料和观察记录均属保密，仅供本研究使用；试验期间，您可随时了解有关的信息资料，如在试验中发生问题或需要咨询有关问题时，可与主管医师联系。

七、伦理委员会

本研究已向浙江省人民医院人体研究伦理委员会报告，经委员会的全面审查和包括对受试者的风险评估，并获得了批准。在研究中过程中，有关伦理和权益事宜可联系浙江省人民医院人体研究伦理委员会，电话：白天 08:00-17:00， 0571-85893643； 晚上（总值班）：15967110068；邮箱地址： zryllwyh@163.com

知情同意书. 同意签字页

同意声明

作为一名患者，我在了解了本项试验的目的、方法、可能获得的治疗利益和可能发生的不良反应后，我将获得一份经过签名并注明日期的知情同意书副本。

愿意参加此项研究，并保证尽量遵从医嘱。

患者签名：_____ __ __ __ __ 年 __ __ 月 __ __ 日

联系电话：_____

我确认已向患者解释了本试验的详细情况，包括其权力以及可能的受益和风险，并给其一份签署过的知情同意书副本。

医生签名：_____ __ __ __ __ 年 __ __ 月 __ __ 日

医生的工作电话：_____

Additional file 5: preoperative risk index of postoperative pulmonary complications by ARISCAT score

Preoperative risk factor	Point Valve
Age (year)	
≤ 50	
51–80	3
> 80	16
50-59	4
Preoperative SpO_2 (%)	
≥ 96	
91–95	8
≤ 90	24
Respiratory infection in the last month	17
Preoperative anemia (≤ 100 g/L)	11
Surgical incision	
Peripheral	
Upper abdominal	15
Intrathoracic	24
Duration of surgery (h)	
≤ 2	
2 - 3	16
> 3	23
Emergency procedure	8

Intermediate Risk= 26–44 Points; High Risk= ⩾45 Points; SpO_2= oxyhemoglobin saturation by pulse oximetry breathing air in supine position.

Additional file 6. Strategy for SpO_2 decreasing

step	1	2	3	4	5	6	7	8	9
FiO_2	0.5	0.6	0.6	0.7	0.7	0.8	0.8	1.0	RM
standard PEEP group (cm H_2O)	5	5	4	4	3	3	2	2	2
low PEEP ventilation group (cm H_2O)	3	3	4	4	5	5	6	6	6

FiO_2= Fraction of inspired oxygen; PEEP= Positive end-expiratory pressure; RM= Recruitment maneuver

BMJ Open

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-028464.R3
Article Type:	Protocol
Date Submitted by the Author:	14-Sep-2019
Complete List of Authors:	ZHOU, zhen-feng; Zhejiang Provincial People's Hospital FANG, Jun-biao; Zhejiang Provincial People,s Hospital WANG, Hong-fa; Zhejiang Provincial People,s Hospital HE, Ying; Zhejiang Provincial People,s Hospital YU, Yong-jian; Zhejiang Provincial People,s Hospital XU, Qiong; Zhejiang Provincial People,s Hospital GE, Yun-fen; Zhejiang Provincial People,s Hospital ZHANG, Miao-zun; Ningbo Medical center Lihuili Hospital, General Surgery HU, Shuang-fei; Zhejiang Provincial People's Hospital, Anesthesiology
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Medical management
Keywords:	Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery: study protocol for a randomized controlled trial

Author details

Zhen-feng ZHOU, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: zhenfeng9853@163.com

Jun-biao FANG, M.D.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: drfangjb@126.com

Hong-fa WANG.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: whf033@163.com

Ying HE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: heyingzju@163.com

Yong-jian YU

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: yyj731227@163.com

Qiong XU.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: happyjoan@163.com

Yun-fen GE.

- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;

Email: gyunfen@sina.com

Miao-zun ZHANG , M.D.

- Affiliation: Department of General Surgery, Ningbo Medical center Lihuili Hospital,Ningbo, 325000,China;

Email: idreamof333@126.com

Shuang-fei HU , M.D.

- Corresponding Author
- Affiliation: Department of Anesthesiology, Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College), Hangzhou 315000,China;
- Email: hushuangfei77@sina.com

Abstract

Introduction: Postoperative pulmonary complications (PPCs) will develop in even 58% of patients undergoing abdominal surgery and PPCs is strongly associated with higher risk of mortality. More and more evidence shows that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the role of positive endexpiratory pressure (PEEP) during the intraoperative period in preventing PPCs for laparoscopic surgery is not clearly defined.

Methods and Analysis: A total number of 208 patients with high-risk of postoperative pulmonary complications patients undergoing laparoscopic abdominal surgery will be enrolled and randomized into a standard PEEP (6-8 cmH_2O) group and a low PEEP (≤ 2 cm H_2O) group. Both groups will receive an inspired oxygen fraction (FiO_2) of 0.50 and a tidal volume of 8 ml/kg ideal body weight (IBW). Standard perioperative fluid management standardization and analgesic treatments are applied in both groups. The primary endpoint is postoperative pulmonary complications within 7 days after surgery. Secondary endpoints are the modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, postoperative surgical complications, intensive care unit (ICU) length of stay, hospital length of stay, 30-day mortality.

Ethics and Dissemination: The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (KY2018026) on 22 October 2018. The first participant was recruited in 15th April 2019 and the estimated completion date of the study is October 2021. The results of this trial will be submitted to a peer-reviewed journal.

TRIAL REGISTRATION NUMBER: http://www.chictr.org.cn, ID: ChiCTR1800019865. Registered on 2 December 2018 **;** Pre-results.

Keywords: Positive end-expiratory pressure, Postoperative pulmonary complications, laparoscopic surgery

Strengths and limitations of this study:

- Intervention is blinded.
- Standard perioperative fluid management standardization and analgesic treatments are applied in both groups.
- Primary outcome measure is patient centred.
- It is not multicentre randomised trial.

Background

Every year around the world, approximately 230 million patients require surgery with general anesthesia and mechanical ventilation [1]. Laparoscopic surgery has been widely accepted because it is associated with less blood loss, less postoperative pain and rapid recovery [2, 3]. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5% [4], and 12% to 58% of patients undergoing abdominal surgery will develop a PPC [4, 5]. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality [6-8].

Nearly 30% of surgery patients undergoing general anesthesia and mechanical ventilation are at intermediate to high risk for PPCs according to large cohort studies [5, 9]. Both alveolar overstretching and atelectasis induce the release of inflammatory mediators, leading to lung and systemic organ damage [10]. Lung-protective ventilation including the use of low tidal volumes and positive end-expiratory pressure (PEEP), aims to prevent atelectasis and improve gas exchange [11, 12]. Furthermore, PEEP has been found to reduce mortality in patients with the acute respiratory distress syndrome and in critically ill patients [13].

Adopting an appropriate PEEP may prevent PPCs. When high PEEP is applied, alveolar may be overinflate and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis [10]. Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC [14, 15]. Despite all these studies recommend the use of low tidal volume [10], the appropriate PEEP has not yet been defined. A multicenter observational study has shown that approximately 20% of patients do not receive PEEP during routine anesthetic practice [16]. In the Intraoperative Protective Ventilation (IMPROVE) trial that included patients undergoing major abdominal surgery with intermediate-risk

and high-risk of PPCs, compared to a practice of nonprotective mechanical ventilation including higher tidal volumes without PEEP, a lung-protective ventilation strategy with lower tidal volumes and PEEP of 6 cm H_2O was associated with improved clinical outcomes [14]. Furthermore, in another study including patients undergoing abdominal nonlaparoscopic surgery lasting more than 2 h, compared to a standard ventilation strategy, a protective ventilation strategy with 10 cm H_2O PEEP improved respiratory function and reduced the modified clinical pulmonary infection score (mCPIS) [15]. However, another study has shown that low tidal volume combined low PEEP (3 cm H_2O) ventilation may induce postoperative inflammation and may increase the risk of PPCs during major surgery such as hepatectomy [17]. In an international multicenter trial, Protective Ventilation using high vs. low PEEP (PROVHILO), including patients undergoing open abdominal surgery with high risk for PPCs, compared with low PEEP (≤ 2 cm H_2O), a ventilation strategy of high PEEP (12 cm H_2O) did not reduce the incidence of PPCs, but more likely caused haemodynamic instability [18]. Therefore, the authors suggested a ventilation strategy of low tidal volume combined with low PEEP (≤ 2 cm H_2O) [18].

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo laparoscopic surgery. Some studies have suggested that laparoscopic-assisted gastrectomy (LAG) was beneficial for postoperative respiratory function recovery. Nevertheless, it is also necessary to consider the effects of pneumoperitoneum (PnP) on airway pressure and pulmonary function. The role of PEEP during the intraoperative period in preventing PPCs for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PPCs and may reduce the occurrence of organ dysfunction. These anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and; in-hospital stays in patients undergoing laparoscopic surgery.

Methods/design

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH_2O) with those of low PEEP (≤ 2 cm H_2O) in patients at risk for complications undergoing laparoscopic surgery during general anesthesia in terms of: (1) PPCs, (2) modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, changes in chest X-ray findings, and oxygenation; (3). intraoperative complications including hypoxemia, massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

Study endpoints

Primary outcome measure

The primary endpoint of PPCs is defined according to a previous report [19] including any new atelectasis or infiltrates on a chest X-ray, respiratory failure (defined as the need for noninvasive or invasive ventilation) or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) < 300 within 7 days after surgery.

Secondary outcome measures

Secondary outcome variables are any pulmonary complications and extrapulmonary complications as follows:

1. Postoperative pulmonary complications (PPCs) within 30 days after surgery. Those PPCs are scored according to a grading scale ranging from 0 to 4 [20] (grade 0 representing no PPCs and grades 1 to 4 representing gradually worse forms of PPCs) within 7 and 30 days after surgery (Table 1).

Table 1. Grade scale for postoperative pulmonary complications.

Grade scale	Detailed description
Grade 1	- Cough, dry - Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; results of chest radiograph either normal - Dyspnea, not due to other documented cause
Grade 2	- Cough, productive, not due to other documented cause - Bronchospasm: new wheezing or pre-existent wheezing resulting in change therapy - Hypoxemia - Atelectasis: radiological confirmation plus either temperature > 37.5°C or abnormal lung findings - Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation
Grade 3	- Pleural effusion, resulting in thoracentesis - Pneumonia, suspected: radiological evidence without bacteriological confirmation -Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture - Pneumothorax - Re-intubation postoperative or intubation, period of ventilator dependence (non-invasive or invasive ventilation) ≤ 48 hours
Grade 4	Ventilatory failure: postoperative non-invasive ventilation dependence ≥ 48 hours, or re-intubation with subsequent period of ventilator dependence ≥ 48 hours

2. PPCs will also be analyzed separately.

a. Pneumonia is defined according to Centers for Disease Control (CDC) criteria [21] as follows: patients with altered or new pulmonary opacities on chest X-ray; patients should also meet at least two of the following criteria: (1) temperature ≥ 38.5°C or < 36°C, (2) white blood cell (WBC) count > 12 x10^9/L or < 4 x10^9/L; (3) purulent sputum: new cough or difficulty breathing or previous coughing or difficulty breathing is further aggravated.

b. Postoperative hypoxemia and severe hypoxemia [22]: hypoxemia is defined as PaO_2 < 60 mmHg or oxygen saturation (SpO_2) < 90% on room air, but responding to oxygen treatment (hypoventilation should be excluded). Severe hypoxemia is recorded in cases when the patient requires non-invasive or invasive mechanical ventilation.

c. Suspected pulmonary infection is described in a previous study [18]: the patient takes antibiotics and should meet at least one of the following criteria: (1) changed or new sputum, (2) changed or new pulmonary opacities on chest X–ray, (3) temperature greater than 38.3°C, and (4) WBC count > 12 x10^9/L.

d.Pulmonary infiltrate is defined according to consensus guidelines: Chest X–ray demonstrating monolateral or bilateral infiltrate[23].

e. Atelectasis, pleural effusion or pneumothorax are identified by chest X-ray.

f. The modified clinical pulmonary infection score (mCPIS) is calculated as previously described [24] (Table 2).

Table 2. The definition of modified Clinical Pulmonary Infection Score (mCPIS).

Items	CPIS Points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (℃)	36.5- 38.4	38.5- 38.9	≤ 36.5 or ≥ 39.0
Leukocytes count (per mm^3)	4,000-11,000	<4,000 or >11,000	< 4,000 or > 11,000 + band forms ≥ 500
PaO_2/FiO_2,(mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

PaO_2 =Partial pressure of arterial oxygen; FiO_2 =Fraction of inspired oxygen; ARDS =Acute respiratory distress syndrome

g. ARDS (Acute Respiratory Distress Syndrome) is defined according to the Berlin criteria [25].

h. Suspected pulmonary complications[15] are defined in cases where patients display at least three of the following new findings: (1) cough, (2) increased secretions, (3) dyspnea, (4) chest pain, (5) temperature> 38°C, and (6) pulse rate> 100 beats per minute.

i. Requirement for postoperative ventilation (respiratory failure that requires noninvasive and/or invasive ventilation) for at any time after surgery according to standard criteria and clinical practice guidelines[20].

3. Postoperative extrapulmonary complications within 30 days after surgery:

a. Systemic inflammatory response syndrome (SIRS) criteria are defined when

meeting the following two or more criteria by the most deranged value recorded after surgery [26]: (1) rectal or tympanic temperature > 38°C or <36°C (0.5°C will be added to the measured value when oral or other temperatures are used); (2) Heart rate > 90 beats/min (excluding those who have a known medical condition or are receiving treatment that would prevent tachycardia); (3) respiratory rate> 20 breaths/min or a $PaCO_2$< 32 mmHg or requiring mechanical ventilation. White blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands.

b. Sepsis and Septic shock [26]: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA(Sequential [Sepsis-related] Organ Failure Assessment) score $\geqslant$ 2 points consequent to the infection. Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

c. Other extrapulmonary infection including surgical site infection (SSI) and intraabdominal abscess: SSI [27] is defined as surgical site infection within 30 days after surgery; at least the incision has a purulent effluent; the incision drainage fluid or tissue culture results are positive, with pain or tenderness, local swelling, redness or fever.

d. Need for postoperative blood transfusion.

e. Postoperative surgical complications: anastomotic leakage and need for surgical reintervention, defined according to consensus criteria [28].

f. Unexpected intensive care unit (ICU) admission or readmission.

g. ICU length of stay and hospital length of stay.

h. Hospital free-days at follow-up day 30.

i. In-hospital mortality and thirty-day mortality (all-cause mortality 30 days after randomization).

j. Intraoperative complications: pneumothorax is confirmed by chest X-ray and any other complications.

Study design: This unfunded, parallel-group, double-blinded, prospective, randomized controlled clinical trial was registered at http://www.chictr.org.cn (ChiCTR1800019865) and was conducted at the Department of Anesthesiology and Intensive Care of Zhejiang Provincial People's Hospital. The first participant was recruited in 15th April 2019. This trail protocol is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1). The SPIRIT 2013 Checklist is given in Additional file 1.

Blinding, data collection, randomization

Researchers will be trained prior to investigation. Study data including patient clinical characteristics, intraoperative respiratory parameters, postoperative outcomes, and laboratory test, will be collected onto case report forms (CRF) (Additional file 2).

An independent researcher will randomize the participants into the study group (standard group PEEP) and control group (low PEEP group) in a ratio of 1:1. The random sequence will be computer-generated and participants will be allocated in numerical order with sealed opaque envelopes. The attending anesthesiologist performs anesthesia strictly according to the research protocol and is also responsible for data during the preoperative, intraoperative and PACU period. The chief surgeon performs the postoperative laboratory testing. An independent researcher will be involved in postoperative follow-up and data collection. Statistical analysis will be performed by a statistician who does not participate in the data collection. Patients, research staff, surgeons, intensive care physicians and the statistician will be unaware of the group allocation. Some preoperative characteristics and laboratory results will automatically derived from a computer data base.

Selection of the participants

Patients scheduled for elective laparoscopic abdominal surgery under general anesthesia will be screened and recruited during preoperative assessment. Patients meeting inclusion criteria will be required to provide their written

informed consent (Additional file 3 and 4). The participant can withdraw from the trial at any time.

Inclusion criteria are patients older than 18 y, American Society of Anesthesiologists (ASA) physical status II or III, body mass index (BMI) between 18-35 kg/m^2, general anesthesia expected to last more than 3 h, an intermediate or high preoperative index for PPCs risk by the Assess Respiratory Risk in Surgical Patients in Catalonia study (ARISCAT score ≥ 26, the Additional file 5).

Exclusion criteria are listed as following: emergency surgery or history of previous lung surgery, history of mechanical ventilation within the 2 weeks before recruitment, non–invasive ventilation or oxygen therapy at home, acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome), history of chronic obstructive pulmonary disease (COPD), persistent hemodynamic instability or severe cardiac disease (New York Heart Association class III or IV, or persistent ventricular tachyarrhythmia's, or acute coronary syndrome), sepsis or septic shock, need renal replacement therapy (CRRT), progressive neuromuscular illness, pregnancy, participation in another study or refusal to participate.

Time course of the study

Preoperative admission

Medical history, ASA physical status, BMI, 12-lead ECG, laboratory results , chest X-ray or computed tomography (CT) scan, ARISCAT score and nutritional risk screening (NRS 2002 tool), the results of echocardiography and spirometry (in cases of history of coronary artery disease or smoking) will be recorded.

Intraoperative care

A central venous catheter and an arterial cannula will be placed before induction of anesthesia. Peripheral oxygen saturation (SpO_2), arterial blood pressure, heart rate (HR), ECG, end-tidal carbon dioxide tension ($EtCO_2$) and bispectral index (BIS) will be monitored continuously. Pneumoperitoneum

(PnP), tidal volume, PEEP, airway pressures including peak pressure and plateau pressure, airway resistance (Raw), Vds/Vt, core temperature, and arterial blood gas analysis data will be recorded.

Crystalloid (12-15ml/kg/h) is infused to maintain hemodynamic stability and central venous pressure 5-12 cm H_2O. Blood loss and vasodilation are supplemented by colloidal fluid.

Routine anesthesia is induced with intravenous dexmedetomidine(1 ug/kg) or midazolam (0.05-0.075mg/kg), cisatracurium (2 mg/kg), propofol (2-3 mg/kg) and fentanyl (1-3 μ/kg) for tracheal intubation. Anesthesia is maintained with propofol, sevoflurane and remifentanil infusion to maintain the BIS 40-50 until skin suturing is completed. Cisatracurium (1.0-1.5 mg/kg) is administered every hour and the last dose is at least 1 hour before the end of operation. Ropivacaine is administrated as local incision infiltration anesthesia before and at the end of operation respectively. Fentanyl (1-3 μg/kg) and flurbiprofenaxetil 50 mg are required before remifentanil is stop.

Postoperative care

Patients will be transferred to the post-anesthesia care unit (PACU) after surgery regardless of whether they are still intubated.

Postoperative pain management will be suggested to achieve a visual analogue scale (VAS) pain score of < 3/10 using a patient-controlled intravenous analgesia pump including fentanyl (0.3-0.5 μg/kg), flurbiprofenaxetil (100 mg) and palonosetron hydrochloride (0.25 mg) palazidine.

The ICU physician and surgeon will independently monitor clinical progress and all endpoints by daily physical examinations. Appropriate prophylactic antibiotics and antithrombotic treatments will be administered as required during the postoperative period. chest X-ray will be performed by an independent, trained radiologist on POD 5. Arterial blood gas analysis will be performed on POD 1 and POD 3 and other laboratory tests will be performed on POD 1, POD 3, POD 5 and POD 7. The examinations will be repeated and

microbiology tests will be performed when the development of pulmonary complications is suspected.

Study arms and intraoperative ventilation protocol

Patients will be randomly assigned to the low PEEP ventilation group (PEEP ≤ 2 cm H_2O) or the standard PEEP group (PEEP = 6-8 cm H_2O) using a volume-controlled ventilation strategy (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) with a tidal volume of 8 ml/kg ideal body weight (IBW), an inspired oxygen fraction (FiO_2) of 0.50, and an inspiratory to expiratory ratio of 1:2. Respiratory rate should be adjusted to maintain $ETCO_2$ between 35 and 45 mmHg) and plateau pressure should be no more than 35 cmH_2O. IBW is calculated with formulas as follows [14]: 45.5 + 0.91 x (centimeters of height - 152.4) for females and 50 + 0.91 x (centimeters of height - 152.4) for males. Recruitment maneuvers (RMs)[19] will be performed immediately after tracheal intubation and every time when the ventilator is interrupted until the end of surgery in each group. The compliance of the respiratory system is calculated with the formulas of V_T/ (plateau pressure of the respiratory system - PEEP).

Recruitment maneuvers will be performed as follows:

(1). Pressure support ventilation (PSV) mode

(2). Positive end-expiratory pressure (PEEP) set to 30 cm of water

(3). Inspiratory gas flow set to the highest value

(4). Duration of the maneuver = 30 sec

A rescue therapy will be applied in case of desaturation (defined as a peripheral SpO_2 of less than 92%), consisting of increasing FiO_2 to 100% in each group and increased PEEP in the low PEEP group (Additional file 6).

From postoperative day 7 (POD 7 to POD 30, follow-up)

Secondary endpoints and any mortality will also be evaluated during the follow-up period. The CONSORT flowchart of the trial is shown in Figure 2.

Data monitoring and Handling of implausible values or missing values:

A clinical investigator will identify implausible values. Missing continuous

variables should be less than 10% and will be replaced by the mean of all plausible data (both groups) of the respective endpoint. Data monitoring is managed by an independent investigator who is not involved in the study. The progress of the study will be evaluated and the completeness and accuracy of the data (Informed Consent Forms, source data, CRF and outcome variables) will be verified.

Statistics:

Normally distributed variables will be expressed as the mean ± standard deviation (SD) and will be compared with Student's t-test. Categorical variables will be compared using the chi-square test or the Fisher's exact test. Non-normal continuous variables will be expressed as median (interquartile range (IQR)) and evaluated with the Mann-Whitney U-test. The primary outcome and secondary outcomes will be all handled. Intention-to-treat (ITT) analyses are performed to compare the composite outcome measure at 7 days in the two groups by the chi-squared test (or Fisher's exact test as appropriate) and multiple logistic regression analysis adjusting will be performed to identify various risk factors (for the primary outcome and the pulmonary complications at postoperative Day 30). P <0.05 will be considered statistically significant and all reported p values will be 2-sided. Interim analysis of safety will be conducted after enrolment of the first 104 patients. All analyses will be conducted using the SPSS Version 18.0 (SPSS, Chicago, IL, USA) software.

Sample size calculation

The incidence rate of postoperative pulmonary complications was 39% in the low PEEP group [18]. Two tailed chi-squared test was performed and we estimated that 188 patients were required to provide 80% power to detect a 50% relative difference between the two groups, with a type I error probability of 0.05. Assuming that follow-up lost rate was 10 %, and then a total of 208 cases are needed. Analysis is computed using G-Power (version 3.1; Informer Technologies, Inc.).

Adverse events and interruption of the trial:

All patients will be continuously monitored during the study including daily visits during in-hospital and daily phone-call visits during the out of hospital follow-up period (until POD 30). All serious adverse, unexpected or possibly related events will be recorded in the CRF and will be reported to the data monitoring and safety committee (DMSC). DMSC will recommend that the study should be stopped unless there is evidence that patient is safety (a between-group difference in serious adverse events or in 30- day mortality is found).

Ethics and Dissemination:

The study was approved by the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) (registration number KY2018026) on 22 October 2018. Any subsequent protocol and informed consent document amendments must be approved by the responsible of Ethics Committee. All communications with the regulatory authorities and the Ethics Committee must be recorded.

All recruited patients will be informed of the trial purposes and their duties within the trial before randomization. Recruited patients can withdraw from the study at any time without providing any specific reason. The patient data will be stored in a separate, safe place but that it may be reviewed by the relevant investigator.

The original data (CRF and relevant records) will be maintained for 5 years and then destroyed according to hospital standards.

Discussion:

In this pragmatic, prospective, randomized controlled trial of high-risk patients undergoing laparoscopic surgery, our aim is to assess not only possible single effects of PEEP levels on major PPCs from those of lower tidal volumes and RM but also to assess relevant clinical parameters associated with alterations in pulmonary function such as chest X-ray, abnormalities, mCPIS, arterial oxygenation/peripheral oxygen saturation in air and changes in dyspnea/cough/secretions. Our findings might change current practice of mechanical ventilation in high-risk patients undergoing laparoscopic surgery.

There are some potential strengths of the present trial protocol. First, this ARISCAT score will be used to predict PPCs and we select only the high-risk PPC population that will potentially receive maximum benefit from intraoperative PEEP strategy. Although various scores have been developed for predicting PPC incidence based on various countries and surgical populations, the ARISCAT score is considered to be the most valuable tool [10]. Second, this trial design includes instructions for fluid management standardization and analgesic treatments during the perioperative period. Third, the included patients will undergo elective abdominal laparoscopic surgical procedures with more than 3h of general anesthesia. Previous studies have reported that both abdominal surgery and longer anesthesia duration are potential risk factors for PPCs [8].

Notably, mechanical ventilation itself is one of major contributors to PPCs [29]. PnP is also an important risk factor for PPCs [30]. Intraabdominal pressure is frequently higher than airway pressure during PnP with carbon dioxide (CO_2) for laparoscopic surgery. This pressure gradient usually causes cephalad displacement of the diaphragm and collapses adjacent pulmonary tissues. PnP also decreases respiratory compliance and arterial oxygenation [31] .All these influences on PnP lead finally to atelectasis [32].

On the other hand, PEEP is thought to prevent the development of atelectasis by keeping the airways open and maintaining adequate gas exchange at the

end of the expiratory period during PnP [10]. Certainly, the level of PEEP should be adopted according to the patient's and surgical characteristics as well as to the patient's positioning.

Previous studies reported that very low levels of PEEP were potentially associated with atelectasis by promoting repeated opening and closing of small airways [33]. However, higher levels of PEEP may increase mean airway pressure of the respiratory system and likely even impair hemodynamics.

There is an increasing number of highly qualitative Randomized Controlled Trials (RCTs) regarding intraoperative mechanical ventilation and PPCs, whereas direct assessment of the effect in high-risk patients undergoing laparoscopic surgery remains lacking. The potential significance of this trial is that it may provide evidence of the effects of intraoperative PEEP on PPCs in high-risk patients undergoing laparoscopic surgery.

References

[1] Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008. 372(9633): 139-44.

[2] Lee CM, Park S. Laparoscopic techniques and strategies for gastrointestinal GISTs. J Vis Surg. 2017. 3: 62.

[3] Patel B, Leung U, Lee J, Bryant R, O'Rourke N, Cavallucci D. Laparoscopic pancreaticoduodenectomy in Brisbane, Australia: an initial experience. ANZ J Surg. 2017 .

[4] Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010. 113(6): 1338-50.

[5] Arozullah AM, Khuri SF, Henderson WG, Daley J. Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med. 2001. 135(10): 847-57.

[6] Shander A, Fleisher LA, Barie PS, Bigatello LM, Sladen RN, Watson CB. Clinical and economic burden of postoperative pulmonary complications: patient safety summit on definition, risk-reducing interventions, and preventive strategies. Crit Care Med. 2011. 39(9): 2163-72.

[7] 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. Ann Surg. 2005. 242(3): 326-41; discussion 341-3.

[8] Smetana GW, Lawrence VA, Cornell JE. Preoperative pulmonary risk stratification for noncardiothoracic surgery: systematic review for the American College of Physicians. Ann Intern Med. 2006. 144(8): 581-95.

[9] 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. Ann Surg. 2000. 232(2): 242-53.

[10] Güldner A, Kiss T, Serpa NA, 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(3): 692-713.

[11] Sutherasan Y, Vargas M, Pelosi P. Protective mechanical ventilation in the non-injured lung: review and meta-analysis. Crit Care. 2014. 18(2): 211.

[12] Futier E, Constantin JM, Pelosi P, et al. Intraoperative recruitment maneuver reverses detrimental pneumoperitoneum-induced respiratory effects in healthy weight and obese patients undergoing laparoscopy. Anesthesiology. 2010. 113(6): 1310-9.

[13] Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000. 342(18): 1301-8.

[14] Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013. 369(5): 428-37.

[15] Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 2013. 118(6): 1307-21.

[16] Jaber S, Coisel Y, Chanques G, et al. A multicentre observational study of intra-operative ventilatory management during general anaesthesia: tidal volumes and relation to body weight. Anaesthesia. 2012. 67(9): 999-1008.

[17] Sato H, Nakamura K, Baba Y, Terada S, Goto T, Kurahashi K. Low tidal volume ventilation with low PEEP during surgery may induce lung inflammation. BMC Anesthesiol. 2016. 16(1): 47.

[18] Hemmes SN, de Abreu M G, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet. 2014. 384(9942): 495-503.

[19] Ruszkai Z, Kiss E, László I, et al. Effects of intraoperative PEEP optimization on postoperative pulmonary complications and the inflammatory response: study protocol for a randomized controlled trial. Trials. 2017. 18(1): 375.

[20] Hulzebos EH, Helders PJ, Favié NJ, De Bie RA, de la Riviere A B, Van Meeteren NL. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA. 2006. 296(15): 1851-7.

[21] Schumacher M, Wangler M, Wolkewitz M, Beyersmann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. Methods Inf Med. 2007. 46(5): 595-600.

[22] Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ. 2011. 183(3): E195-214.

[23] Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. Intensive Care Med. 1994. 20(3): 225-32.

[24] Fartoukh M, Maitre B, Honoré S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. Am J Respir Crit Care Med. 2003. 168(2): 173-9.

[25] Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012. 307(23): 2526-33.

[26] Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016. 315(8): 801-10.

[27] Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. Infect Control Hosp Epidemiol. 1992. 13(10): 606-8.

[28] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004. 240(2): 205-13.

[29] Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. JAMA. 2010. 304(23): 2620-7.

[30] Reinius H, Jonsson L, Gustafsson S, et al. Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. Anesthesiology. 2009. 111(5): 979-87.

[31] Hazebroek EJ, Haitsma JJ, Lachmann B, Bonjer HJ. Mechanical ventilation with positive end-expiratory pressure preserves arterial oxygenation during prolonged pneumoperitoneum. Surg Endosc. 2002. 16(4): 685-9.

[32] Park SJ, Kim BG, Oh AH, Han SH, Han HS, Ryu JH. Effects of intraoperative protective lung ventilation on postoperative pulmonary complications in patients with laparoscopic surgery: prospective, randomized and controlled trial. Surg Endosc. 2016. 30(10): 4598-606.

[33] Duggan M, Kavanagh BP. Pulmonary atelectasis: a pathogenic perioperative entity. Anesthesiology. 2005. 102(4): 838-54.

Trial status

The first participant was recruited in 15th April 2019 and the estimated completion date of the study is October 2021.

Additional file

Abbreviations

ABGa: Arterial blood gas analysis; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; AMI: Acute myocardial infarction; ASA: American Society of Anesthesiologists; BIS: bispectral index; BMI: Body Mass Index; CDC: Centers for Disease Control; CO_2: carbon dioxide; COPD: Chronic obstructive pulmonary disease; CRF: Case Report Form; CRRT: renal replacement therapy; CT: Computer tomography; DMSC: data monitoring and safety committee; DIC: Disseminated intravascular coagulation; ECG: Electrocardiogram; $EtCO_2$: End-tidal carbon dioxide tension; FiO_2: Fraction of inspired oxygen; HR: Heart rate; IBW: Ideal bodyweight; ICU: Intensive care unit; IQR: interquartile range; LAG: laparoscopic surgery; mCPIS: modified clinical pulmonary infection score; PACU: Post-anesthesia Care Unit;PaO_2: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PnP: pneumoperitoneum; POD: Postoperative day; PPC: Postoperative pulmonary complications; PSV: Pressure Support Ventilation; Raw: Airway resistance; RM: Recruitment maneuver; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome; SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials; SpO_2: Oxygen saturation; SSI: surgical site infection; Vds/Vt: Dead space fraction; VAS: visual analogue scale; WBC: White Blood Cell.

Acknowledgements

We want to thank all the contributors and collaborators for their support in this study. We also thank all the participating patients.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

Zhen-feng ZHOU and Shuang-fei HU designed the study protocol and wrote the paper. Hong-fa WANG and Miao-zun ZHANG designed the statistical method. The work of patient recruitment and data collecting will be done by Jun- biao FANG, Yong-jian YU, Qiong XU, Ying HE and Yun-fen GE. Shuang-fei HU is the study director and Jun- biao FANG is the principal investigator of this study. All authors have read the manuscript and approved to submitting the final paper.

Authors' information

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Patient and Public Involvement:

Patients and the public were not involved in the design or planning of the study.

Figure legends:

Figure 1. Standard Protocol Items.

Figure 2. The CONSORT flowchart of the trial.

Supporting Information

S1 Additional file 1. SPIRIT 2013 Checklist1.

S2 Additional file 2. Case report form.

S3 Additional file 3: Patient consent form in English.

S4 Additional file 4. Patient consent form in original language.

S5 Additional file 5. Preoperative risk index of postoperative pulmonary complications by ARISCAT score.

S6 Additional file 6. Strategy for SpO_2 decreasing.

Standard Protocol Items

	Study period								
	Enrolment		Allocation		Post-allocation				
Timepoint	-1 week	-t1	0	DOS	POD1	POD3	POD5	POD7	POD8-30
Enrolment:									
Perioperative assessment	√								
Eligibility screen		√							
Informed consent		√							
Allocation			√						
Interventions:									
Study Group(Low PEEP)				√					
Control Group(Standard PEEP)				√					
Assessments:									
Intraoperative complications				√					
Postoperative pulmonary complications					√	√	√	√	√
Physical examinations					√	√	√	√	√
Blood gas analysis					√	√	√	√	√
chest X-ray							√		
Postoperative extra-pulmonary complications					√	√	√	√	√
Postoperative surgical complications					√	√	√	√	√
ICU length of stay									
Hospital length of stay									
In-hospital mortality									
Thirty-day mortality					◄———	———	———	———	———►

Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. DOS: day of surgery; POD: postoperative day; ICU: Intensive care unit.

Figure 1. Standard Protocol Items

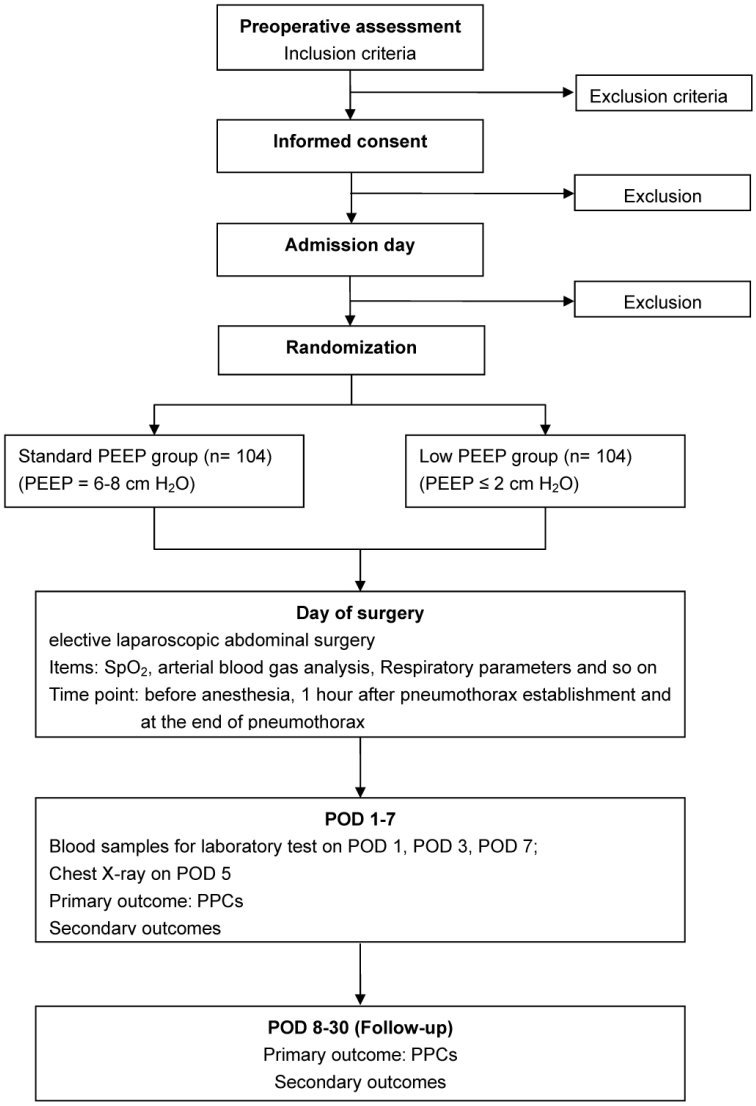

Figure 2. The CONSORT flowchart of the trial

Additional file 1: SPIRIT 2013 Checklist, Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title Page, 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5, 14
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	29
Funding	4	Sources and types of financial, material, and other support	28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3, 28, 29
	5b	Name and contact information for the trial sponsor	1-3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	28, 29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	29

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6, 7
	6b	Explanation for choice of comparators	7, 8
Objectives	7	Specific objectives or hypotheses	4, 5, 8, 9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17,18
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	18-21
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	23
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	21, 22
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	19-22
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18-21 Fig.1, Fig.2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22, 23
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16, 17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16, 17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16, 17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	23
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18, 21, 22
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	21, 22

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	16, 17, 21, 22
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16, 17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16, 17, 22
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16,17, 21, 22
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	23
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22, 23
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	23
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	29
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21, 22, 29
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	30
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	-
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	-
	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Additional file 2: case report forms (CRF)

Effects of intraoperative Low-PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic surgery: study protocol for a randomized controlled trial

Case report form

Checklist

Please check the checklist carefully when completed the questionnaire.

□Perioperative assessment: Informed patient details of the study and obtained informed consent from the patient.

Date of signing informed consent: _____

Admission date: _____

□Perioperative data Surgery date: _____

□Completed the above registrations

Completed date: _____

Quality control personnel：_____

Case registration form

Basic information

Case number:

Patient case number:

Random number:

Randomized group：☐ Low-PEEP group (Study Group)

☐ Standard PEEP group (Control Group)

Gender male/female

Height _____cm

Ideal weight _____kg

Actual weight _____kg

Calculation formula of ideal weight：

male= 50 + 0.91×(Height - 152.4)；

female= 45.5±0.91×(Height - 152.4)

Age (years) _____

Contact staff _____

Phone number _____

Address _____

Chief surgeon _____

Baseline Characteristics of the Patients

1. Inclusion and exclusion criteria (Please √ if there is any situation as listed below)

Item	Inclusion criteria	
	yes	no
Age：≥ 18 year		
Scheduled for elective laparoscopic abdominal surgery		
ASA physical status I-III		
BMI: 18-35 kg/m^2		
General anesthesia expected to last more than 3 h		
Had a intermediate or high preoperative index for PPCs risk (ARISCAT score ≥ 26, Supplementary Appendix Table 1)		
	Exclusion criteria	
Emergency surgery		
Mechanical ventilation of > 1 hour within the last 2 weeks before surgery		
History of previous severe (COPD)		
Acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome)		
Previous lung surgery		
Persistent hemodynamic instability or Severe cardiac disease		
Sepsis or septic shock		
Need renal replacement therapy		
Progressive neuromuscular illness		
Pregnancy		
Consented for another interventional study or refusal to participate		
Have a stake in the researcher		
Researchers conside that they are not suitable for clinical trials		

2. Perioperative data (Please √ or Write down specific situation or if there is any situation as listed below and

please / If there is no corresponding situation)

Preoperative		One hour after pneumothorax establishment		at the end of pneumothorax	
Temperature		arterial blood gas analysis			
ASA status		FiO_2			
ARISCAT score		Pneumoperal pressure			
NYHA III-IV		Tidal volume			
History of smoking		Respiratory rate			
Drinking		PT-CO_2			
Combined diseases		PEEP			
History of Medication		Platform / peak pressure			
Respiratory infection within one month		Blood pressure			
Weight change in the past one month		Heart rate			
Blood routine examination		Temperature			
Coagulation spectrum					
Biochemical tests		Intra-operative			
Chest X-ray or CT		Times of RM			
Pulmonary function test		Adverse events during RM			
mCPIS score		Antibiotic			
		Infusion volume			
		Blood transfusion			
Before anesthesia		Amount of bleeding			
SpO_2 without inhaling oxygen		Urine volume			
Arterial blood gas analysis		Vasoactive drug use			
		Operation time			
		Mechanical ventilation time			
		Other complications			

The amount of each day and duration for smoking and drinking; describe the specific disease and current medication and doses for columns of combined disease and medication history; only check if there is laboratory test or chest X-ray. etal; arterial blood gas analysis should performed after10 min of air adaptation before anesthesia;

Intraoperative complications were recorded and defined as follows: 1. peripheral oxygen saturation less than 90% and/or end-tidal fractions of carbon dioxide more than 45 mmHg for more than 1 min, 2. need to change the ventilation setting (tidal volume and/or respiratory rate), 3. heart rate more than 100 beats/min or less than 60 beats/min, 4. systolic arterial pressure more than 150 mmHg or less than 90 mmHg.

Blood gas analysis during postoperative recovery room should done meet the following 2 points at the same time: 1. 30 minutes after the tracheal tube is removed; 2. after10 min of air adaptation. If peripheral oxygen saturation dropped below 88% during the 10 min of adaptation, the maneuver was stopped and arterial blood gas analysis immediately obtained.

3. Postoperative pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	POD 1	POD 3	POD 5	POD 7	POD 8-30
SpO_2 after10 min of air adaptation					/
FiO_2 after10 min of air adaptation					/
Arterial blood gas analysis			/	/	/
Heart rate					
Respiratory rate					
Chest X-ray	/	/		/	
Blood routine test					
CRP					
Biochemical tests					
Microbiology test					
Mechanical Ventilation					
Whether tracheal secretions was increased; the nature and quantity of secretions					
Cough					
Difficulty breathing					
Chest pain					
Postoperative hypoxemia					
Postoperative severe hypoxemia					
Suspected lung infection					
Pneumonia					
Exudation of the lungs					
Aspiration pneumonia					
Pulmonary embolism					
Atelectasis					
ARDS					
Pneumothorax					
Pleural effusion					

ARDS: acute respiratory distress syndrome.

3. Postoperative extra-pulmonary complications within 30 days after surgery (Please √ or Write down specific situation or if there is any situation as listed below and please / If there is no corresponding situation)

Items/times	POD 1	POD 3	POD 5	POD 7	POD 8-30
SIRS					
Sepsis					
Severe sepsis					
Sepsis shock					
Extrapulmonary infection					
Pulmonary edema caused by heart failure					
Blood transfusion					
Anastomotic leak					
Secondary surgery rate					

SIRS: Systemic inflammatory response syndrome; AKI: acute kidney injury; DIC: disseminated intravascular coagulation.

Additional file 3: patient consent form in English

Clinical Research Informed Consent Form of Zhejiang Provincial People's Hospital (Version 1, September 3, 2018)

Dear patient:

You are already diagnosed as _____. We will invite you to participate in a Clinical study Effects of intraoperative PEEP on postoperative pulmonary complications in high-risk patients undergoing laparoscopic abdominal surgery. This study is a self-financing project, research number:_____. This study protocol has been reviewed by the Ethics Committee of Zhejiang Provincial People's Hospital and was agreed to conduct this clinical research.

Please carefully read the following items before you decided to participate in this study. It can help you understand the meaning and objectives of this research, the procedures and duration of this study, the benefits, risks and discomforts that you may be meat after participating in this study. You can also discuss with your kins or friends, or ask for an explanation from your doctor to help you make a decision.

I. Introduction:

Every year around the world, approximately 230 million patients require surgery with general anesthesia and mechanical ventilation. Laparoscopic surgery has been widely accepted because it is associated with less blood loss, less postoperative pain and rapid recovery. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5%, and 12% to 58% of patients undergoing abdominal surgery will develop a PPC. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality.

Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC. Despite all these studies recommend the use of low tidal volume, the appropriate PEEP has not yet been defined.. When high PEEP is applied, alveolar may be overinflate and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis.

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo laparoscopic surgery. Some studies have suggested that laparoscopic-assisted gastrectomy (LAG) was beneficial for postoperative respiratory function recovery. Nevertheless, it is also necessary to consider the effects of pneumoperitoneum (PnP) on airway pressure and pulmonary function.

The role of PEEP during the intraoperative period in preventing PPCs for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PPCs and may reduce the occurrence of organ dysfunction. These anticipated results may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and; in-hospital stays in patients undergoing laparoscopic surgery.

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH2O) with those of low PEEP (≤ 2 cm H_2O) in patients at risk for complications undergoing laparoscopic surgery during general anesthesia in terms of: (1) PPCs, (2) modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, changes in chest X-ray findings, and oxygenation; (3). intraoperative complications including hypoxemia, massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

II. The process in participating this study:

1) You should cooperate with the medical staff to complete the relevant preoperative preparation according to the clinical routine requirements.

2) You should truly provide the information of related examination and treatment, so that the researcher can accurately carry out the research-related assessment.

3) If you meet inclusion criteria, you can voluntarily choose to participate in this study and sign the informed consent form, and you may be randomly assigned to the standard PEEP group (control group) and low PEEP group (processing group).

4) We will test and record your blood routine and blood gas analysis during the research in the first, the third and he 7th postoperative day. We will take 3 ml of blood for laboratory tests each time.

III. The possible benefits of this study

1. Personal benefit: the setting of intraoperative mechanical ventilation parameters has a significant impact on postoperative pulmonary complications, hospital stay and mortality in patients undergoing abdominal surgery. Airway pressure monitoring and blood gas analysis are clinically commonly used to reflect lung function during surgery period, however, lung compliance measurement is not routinely performed. We will all do the above measurements to monitor your lung function no matter which group you are assigned to during the study. The responsible clinician will take steps according to the examination results, even he can terminate the clinical research at any time. In this study, patients experienced PPCs may be detected out early and the rate of PPCs may be reduced, and it might improve your recovery. Furthermore, 3 ml of the blood sample required for each test will not affect your health.

2. Social benefits: Current studies shows that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the role of positive endexpiratory pressure (PEEP) during the intraoperative period in preventing PPCs for laparoscopic surgery has not been clearly defined. We hypothesized that, when compares to low PEEP, standard PEEP may prevent the incidence of PPCs and may reduce the occurrence of organ dysfunction.

IV. **Risks and measures of this study:** (probable adverse reactions, coping solution, compensation measures, treatment costs, claims and etc.)

Many studies have confirmed that the use of low tidal volume combined with PEEP can reduce PPCs in patients undergoing abdominal surgery. We also routinely use PEEP to prevent lung collapse and PPCs. You have about 50% chance of being assigned to the standard PEEP group, and you may be in a risk of potentially high airway pressure. However, we will monitor the airway pressure, blood gas and lung compliance measurement analysis throughout the operation to fully analyze your lung function. The responsible clinician will take steps according to the examination results, even he can terminate the clinical research at any time.

Prevention measures for the risk of intraoperative high airway pressure:

1 sucking; 2 increase inhalation anesthesia; 3 reduce tidal volume to 6 ml/kg (PBW); 4 gradually reduce PEEP to 0; 5 changed to pressure control mode ventilation. Any research investigator will immediately notify the moderator if there is any suspected adverse event or any ethical issues regarding the study (Liaison: Zhou zhen-feng: 13685856148; PI: Hu Shuang-fei: 13777858909).

V. Relevant expenses:

Our research group is responsible for the cost of blood gas testing, but this study does not increase the cost of other drugs as compared to the clinical routine. Patients and health insurance or third-party payers will not pay for research-related medical care. Research institutions will be responsible for research-related support (including central laboratories). Subjects and health insurance or third-party payers are required to pay for routine or non-study-related medical care. These routine medical treatments include hospitalization and other medical care at discharge.

This study did not increase the cost of drugs and increased the risk of clinical treatment as compared to clinical routine treatment. You can voluntarily choose to participate in this study without relevant economic compensation. We will afford relevant economic compensation after consultation with the patients if adverse events are happened including information leakage, infringement of life rights, certain damage and other events..

VI.Your power:

You will be completely voluntary to participation in this study. You can withdraw from the study at any time without any reason. It will not affect your relationship with the medical staff, future diagnosis and treatment. All your personal data and observation records will be kept in confidential and will be only used for this study. You can obtain any relevant information during this study. You can contact the responsible physician when there is a any problem or you just need to consult the relevant questions.

VII. The ethics committee

This study has been reported to the People's Hospital of Zhejiang Province Human

Research Ethics Committee and it has been approved after comprehensive review and assessment the risk of this study. You can contact the Ethics Committee about any relevant ethics and rights issues during the study. Telephone for 08:00-17:00 is 0571-85893643 and 15671110068 for other time. Email address: zryllwyh@163.com.

Informed consent form. the agreement signature page

Agreement statement

As a patient, I have understand the purpose, methodology, possible treatment benefits and possible adverse effects of this study. I will receive a copy of the signed informed consent form with my name and signed time .

I am willing to participate in this study and ensure that I will follow the doctor's advice as much as possible.

Patient signature:_____ Date:_____

Telephone number: _____

I confirm that I have explained the details of this study to the patient including his powers, possible benefits and risks. I have afforded him a copy of the signed informed consent.

Doctor signature:_____ Date:_____

Doctor Telephone number: _____

Additional file 4. patient consent form in original language

浙江省人民医院临床科研知情同意书（版本一，2018 年 09 月 03 日）

亲爱的患者：

医生已经确诊您为_____。我们将邀请您参加一项不同 PEEP 对高风险患者行腹腔镜腹部手术后肺部并发症的影响 研究, 本研究为___自筹___项目，课题编号：_____。本研究方案已经得到_____浙江省人民医院_____伦理委员会审核，同意进行临床研究。

在您决定是否参加这项研究之前，请尽可能仔细阅读以下内容。它可以帮助您了解该项研究以及为何要进行这项研究，研究的程序和期限，参加研究后可能给您带来的益处、风险和不适。如果您愿意，您也可以和您的亲属、朋友一起讨论，或者请医生给予解释，帮助您做出决定。

一、研究项目简介：

全世界每年有 2.3 亿以上的手术患者需要全身麻醉和机械通气，腹腔镜手术以其失血量少、术后疼痛轻和恢复快等优点得到广泛应用。接受普通外科手术的患者中约有 5％会发生肺部并发症(post- operative pulmonary complications,PPC)，并且发生 PPC 的患者中约 20%在术后 30 天内死亡。据报道，接受腹部手术的患者术后肺并发症(PPC)发生率在 12％至 58％之间。肺部并发症(post- operative pulmonary complications,PPC)是手术后住院时间延长和死亡主要原因之一。

相比高潮气量结合无 PEEP 的通气模式，近来越来越多的研究显示 LPV 在健康肺部患者全身麻醉下行腹部手术具有肺保护作用，降低 PPC 发生率。目前研究均建议对这部分患者采用低潮气量，但目前研究尚未明确合适的 PEEP 值。PEEP 过高可能引起肺泡过度膨胀、肺血管阻力增高和循环抑制，PEEP 过低又不能起到防止肺不张改善氧合的作用，均可造成不良后果[10]。因此制定最佳的 PEEP 显得尤为重要。

还有一点需要注意的是，以上这些研究手术类型为开腹手术或各种腹部手术类型，有研究认为腹腔镜手术(LAG)有利术后呼吸功能恢复，因为它需要相对较小的皮肤切口，但也需要同时考虑气腹对气道压和肺功能的影响。

综上所述，目前研究证实肺保护性通气策略可以改善腹部手术后肺部并发症，但尚未确定合适的 PEEP 值。鉴于以上原因，目前不同 PEEP 对高风险患者行腹腔镜腹部手术后肺部并发症的影响还未得到证实，有待进一步研究。

研究目的：

1 明确不同 PEEP 值对高风险患者行腹腔镜腹部手术后肺部并发症的影响，评价不同 PEEP

值与术后肺部并发症的关系。

2 明确不同 PEEP 值对高风险患者行腹腔镜腹部手术后其它指标的影响：（1）改良的临床肺部感染评分（mCPIS），术后肺外并发症，胸部 X 线表现变化和氧合作用；（2）术中并发症包括低氧血症，大量输血；（3）术后手术并发症，重症监护病房（ICU）住院时间，住院时间和 30 天死亡率。

二、参与试验的内容和过程：

1）按照临床常规要求，配合医护人员完成相关的术前准备；

2）如实提供自身疾病和相关检查治疗情况，以利于研究人员准确地进行研究相关的评估；

3) 如果您符合研究纳入标准，您可自愿参加研究，并签署知情同意书，您可能会被随机分配到标准 PEEP 值肺保护性通气策略模式组(对照组)或低 PEEP 值肺保护性通气策略模式组(处理组)，术中按照 2 种不同方案给予处理。

4）因在研究过程中我们将观察记录您的血常规、血气分析情况，需要术后第 1 天、术后第 3 天和术后第 7 天这几个时间点进行血常规、血气分析检查，每次需要采血 3 ml 进行化验检查。

三、参加研究可能的受益

1. 个人受益：因术中机械通气参数的设置对腹部手术后肺部并发症、住院时间和死亡率有明显影响。手术过程中监测气道压和血气分析是临床上常用反应肺功能的指标，但是肺顺应性测量并未在临床中常规开展检测。故不论您在本次从研究中被分到哪一组，都可以采用全面的肺功能检测技术进行监测，临床医生根据检查结果进行相应处理，并可随时终止临床研究。参加本研究，患者肺功能障碍可能早期发现，围术期肺部并发症可能减少。在一定程度上可以促进您的恢复，提高您的舒适性。而且每次化验所需血样本 3 ml 并不会对的健康造成影响。

2. 社会受益：目前研究证实肺保护性通气策略可以改善腹部手术后肺部并发症，但尚未确定合适的 PEEP 值，而且也未明确肺保护性通气策略对腹腔镜下腹部手术患者的保护性。本研究立足于术中 PEEP 值对腹腔镜腹部手术后肺部并发症的影响，为预防腹腔镜下腹部手术患者术后肺部并发症的发生提供依据。

四、参加本项目的风险及处理措施：（可能出现的不良反应及其程度、应对的处理方案、补偿措施：治疗费用、赔付等）

很多研究实验都证实腹部手术中应用低潮气量联合 PEEP 能减少术后肺部并发症，目前我们临床上也是常规应用 PEEP 以预防肺部萎陷和肺部并发症。您有约 50%的机会被分到标

准 PEEP 组，可能存在潜在高气道压的风险，但我们在术中全程进行有效的气道压、肺顺应性和血气分析检查，全面分析肺功能，临床医生根据检查结果进行相应处理，并可随时终止临床研究。术中高气道压风险预防措施：①吸痰；②增加吸入麻醉药比；③减少潮气量为 6 ml/kg(PBW)；④逐步减少 PEEP 值至 0；⑤改为压力控制模式通气。任何研究调查者任何时间发现怀疑有不良事件或对继续实验有任何伦理问题会立即通知主持者（课题联络员：周振锋：13685856148；负责人：胡双飞：13777858909）。

五、有关费用：

本课题组负责血气检测费用，较临床常规未增加其它药物费用。受试者和医疗保险部门或第三方支付者将不会为研究相关医疗付费。研究机构支付研究相关支持(包括中心实验室)。受试者和医疗保险部门或第三方支付者需要为常规医疗或与研究无关的医疗进行付费。这些常规医疗包括住院医疗和出院时带药或其它医疗。

本研究较临床常规未增加药物费用和增加临床治疗风险，自愿参加研究，无相关经济补偿。如因为本研究所造成受试者的相关信息泄露、侵害人生权益等事件，对受试者造成一定损害的，我们将与受试者协商后给予相关经济补偿。

六、您的权力：

您参与试验是完全自愿的，您可以随时退出试验而无需理由，绝不会影响您和医务人员的关系及今后的诊治；您的所有个人资料和观察记录均属保密，仅供本研究使用；试验期间，您可随时了解有关的信息资料，如在试验中发生问题或需要咨询有关问题时,可与主管医师联系。

七、伦理委员会

本研究已向浙江省人民医院人体研究伦理委员会报告，经委员会的全面审查和包括对受试者的风险评估，并获得了批准。在研究中过程中，有关伦理和权益事宜可联系浙江省人民医院人体研究伦理委员会，电话：白天 08:00-17:00， 0571-85893643； 晚上（总值班）：15967110068；邮箱地址： zryllwyh@163.com

知情同意书. 同意签字页

同意声明

作为一名患者，我在了解了本项试验的目的、方法、可能获得的治疗利益和可能发生的不良反应后，我将获得一份经过签名并注明日期的知情同意书副本。

愿意参加此项研究，并保证尽量遵从医嘱。

患者签名：_____ __ __ __ __ 年 __ __ 月 __ __ 日

联系电话：_____

我确认已向患者解释了本试验的详细情况，包括其权力以及可能的受益和风险，并给其一份签署过的知情同意书副本。

医生签名：_____ __ __ __ __ 年 __ __ 月 __ __ 日

医生的工作电话：_____

Additional file 5: preoperative risk index of postoperative pulmonary complications by ARISCAT score

Preoperative risk factor	Point Valve
Age (year)	
≤ 50	
51–80	3
> 80	16
50-59	4
Preoperative SpO_2 (%)	
≥ 96	
91–95	8
≤ 90	24
Respiratory infection in the last month	17
Preoperative anemia (≤ 100 g/L)	11
Surgical incision	
Peripheral	
Upper abdominal	15
Intrathoracic	24
Duration of surgery (h)	
≤ 2	
2 - 3	16
> 3	23
Emergency procedure	8

Intermediate Risk= 26–44 Points; High Risk= ⩾45 Points; SpO_2= oxyhemoglobin saturation by pulse oximetry breathing air in supine position.

Additional file 6. Strategy for SpO_2 decreasing

step	1	2	3	4	5	6	7	8	9
FiO_2	0.5	0.6	0.6	0.7	0.7	0.8	0.8	1.0	RM
standard PEEP group (cm H_2O)	5	5	4	4	3	3	2	2	2
low PEEP ventilation group (cm H_2O)	3	3	4	4	5	5	6	6	6

FiO_2= Fraction of inspired oxygen; PEEP= Positive end-expiratory pressure; RM= Recruitment maneuver