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Intraoperative protective ventilation with or without periodic lung recruitment manoeuvres on pulmonary complications after major abdominal surgery (REMAIN-1): protocol for a randomised controlled trial

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ABSTRACT

Introduction Postoperative pulmonary complications (PPCs) are frequent after abdominal surgery and significantly affect postoperative outcomes. Intraoperative protective ventilation (IPV) has been demonstrated to mitigate PPCs. However, the comparative effectiveness of two common IPV regimens—IPV with or without periodic lung recruitment manoeuvres (PLRM)—in preventing PPCs is unclear. This study aims to compare the effects of these two IPV regimens on PPCs.

Methods and analysis This study is a prospective, double-blinded, randomised controlled trial. A total of 1060 patients at intermediate or high risk for PPCs, scheduled to undergo major abdominal surgery, will be enrolled and randomly assigned to receive either an IPV with PLRM (intensive IPV group) or an IPV without PLRM (moderate IPV group). Patients assigned to the intensive IPV group will receive positive end-expiratory pressure (PEEP) of 6–10 cm H_2O with lung recruitment manoeuvres performed every 30 min. Patients in the moderate IPV group will receive the same level of PEEP without lung recruitment manoeuvres. Both groups will receive a tidal volume of 7 mL/kg predicted body weight and an inspired oxygen fraction of 0.3–0.4. The primary outcome is respiratory failure within the first 7 postoperative days. Secondary outcomes include other PPCs, extrapulmonary complications, unplanned admissions to the intensive care unit, length of postoperative hospital stay and mortality from any cause.

Ethics and dissemination This protocol has been approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. The first participant was recruited on 9 October 2022, with an estimated completion date of 30 May 2025. The results of this trial are expected to be published in peer-reviewed journals.

Trial registration number NCT05556174.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is a prospective, two-arm, double-blind, randomised controlled trial with 1060 participants.
⇒ Both groups are maintained at equivalent positive end-expiratory pressure levels, ensuring methodological consistency to isolate the effects of periodic lung recruitment manoeuvres in intraoperative protective ventilation.
⇒ Another strength is that we adopt a single outcome measure rather than a composite outcome.
⇒ One limitation is that this study is conducted in a single centre, which may affect its external validity.

INTRODUCTION

Postoperative pulmonary complications (PPCs) are the second most frequent postoperative complications.[1] Notably, at least 30% of patients undergoing surgery lasting more than 2 hours with mechanical ventilation are at risk of PPCs.[2 3] PPCs significantly hinder postoperative recovery and increase the length of hospital stay, intensive care unit admissions and even elevate mortality rates.[3 4] Despite being life-saving, mechanical ventilation remains a major contributor to the development of PPCs.[5] Decades of research have assessed strategies to minimise perioperative lung injury and consequent PPCs. An international expert consensus in 2019 indicated that the prevention and reduction of PPCs can be achieved by optimising intraoperative mechanical ventilation strategies, referred to as intraoperative protective ventilation (IPV).[6]

The main mechanisms by which IPV reduces lung injury and consequent PPCs include mitigating excessive alveolar expansion, alleviating pressure and volume injuries by using low tidal volume ventilation, 'opening the lungs' and reducing atelectasis injury through positive end-expiratory pressure (PEEP) and/or lung recruitment manoeuvres (LRM).[7] Several studies

have found that low tidal volume ventilation using moderate PEEP without LRM can reduce PPCs after surgery.[8 9] Meta-analyses further suggested that IPV should use a PEEP of at least 5 cm H_2O.[10–12] Thus, IPV using a PEEP of more than 5 cm H_2O is becoming the most common clinical practice. However, a large study demonstrated that IPV, including low tidal volume ventilation, moderate PEEP (6–8 cm H_2O) and periodic lung recruitment manoeuvres (PLRM, LRM repeated every 30 min), significantly reduced PPCs and extrapulmonary complications compared with high tidal volume ventilation during abdominal surgery.[13] Our previous study also indicated that the same IPV regimen could reduce PPCs more effectively compared with low tidal volume ventilation during laparoscopic colorectal cancer resection.[14] A meta-analysis covering 18 062 patients also showed moderate-quality evidence supporting the combined use of PLRM and PEEP in IPV.[15] Nonetheless, it is still unclear whether there is a difference in the effects of these two IPV regimens.

In this context, we hypothesise that differences may exist in the effects of IPV with or without PLRM on PPCs after major abdominal surgery. We planned this prospective, randomised controlled trial, intraoperative protective ventilation needs periodic lung recruitment manoeuvres (keep REcruitment MAnoeuvres IN intraoperative protective ventilation, study one: REMAIN-1), to compare the effects of the above-mentioned two IPV regimens on respiratory failure, other PPCs, extrapulmonary postoperative complications, length of hospital stay, unplanned intensive care unit admissions and overall death, as well as intraoperative lung function and haemodynamics in patients scheduled for major abdominal surgery and at intermediate or high risk for PPCs.

METHODS AND ANALYSIS

Objective

This trial aims to compare two common IPV regimens: IPV with PLRM (intensive IPV regimen) and IPV without PLRM (moderate IPV regimen) in terms of their effectiveness in preventing PPCs in patients undergoing major abdominal surgery.

Design and setting

The REMAIN-1 trial is an ongoing, investigator-initiated, single-centre, prospective, two-arm, double-blind, randomised controlled trial comparing two regimens—intraoperative protective ventilation with or without periodic lung recruitment manoeuvres —on pulmonary complications after major abdominal surgery. The trial is conducted at the Sixth Affiliated Hospital of Sun Yat-sen University in Guangzhou, China. The trial flow diagram is presented in figure 1.

Inclusion criteria

Patients scheduled for major abdominal surgery will be screened. The inclusion criteria include being older than 18 years, undergoing major abdominal surgery[16] and expected to receive at least 2 hours of mechanical ventilation at intermediate or high risk for PPCs according to the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score (≥26)[17] and having a pulse oxygen saturation (SpO_2) of≥94% when inhaling air.

Non-inclusion criteria

The non-inclusion criteria include having received at least 1 hour of mechanical ventilation within 2 weeks preceding surgery, having pneumonia within 1 month before surgery, having a progressive neuromuscular illness, severe chronic obstructive pulmonary disease or pulmonary bulla or other severe chronic lung diseases, an American Society of Anaesthesiologists (ASA) physical status of ≥IV, intracranial hypertension, pregnancy, providing consent for another trial or declining to participate.

Respiratory management

All participants will receive volume-controlled ventilation with an initial tidal volume of 7 mL/kg (adjustable range: 6–8 mL/kg) predicted body weight (PBW) as previously described.[13] After tracheal intubation, PEEP will initially be set at 6 cm H_2O (or 8 cm H_2O for patients with a body mass index (BMI) exceeding 30 kg/m^2) and increased by 2 cm H_2O in the pneumoperitoneum state or Trendelenburg position. The fraction of inspired oxygen (FiO_2) will be set at 0.3–0.4, inspiratory-to-expiratory ratio (I:E) at 1:1.5, peak inspiratory pressure limit at 45 cm H_2O and inspiratory pause time at 20%; the respiratory rate will be adjusted to maintain normal oxygenation and normocapnia (end-tidal carbon dioxide partial pressure between 35 and 45 mm Hg). A plateau pressure of 30 cm H_2O or less will be the ventilation target for both groups.

Interventions

Control group: moderate IPV group, patients will receive volume-controlled ventilation with PEEP and no PLRM, reflecting the current standard clinical practice.[10] Experimental group: intensive IPV group, patients will receive volume-controlled ventilation consistent with the control group, combined with PLRM, following a protocol adapted from Futier *et al*.[13] LRM will be conducted immediately after tracheal intubation and repeated every 30 min and every time when ventilation is interrupted until the end of surgery. LRM will be postponed if a patient is haemodynamically unstable. A stepwise increment of tidal volume will be used for each LRM, according to the following steps as previously described:[9 18]

1. PEEP will be set at 12 cm H_2O, and respiratory rate at 6 breaths per minute.
2. Tidal volumes will be increased in steps of 4 mL/kg PBW until a plateau pressure of 30–35 cmH_2O is reached.
3. Three to five breaths will be administered under each increased tidal volume.

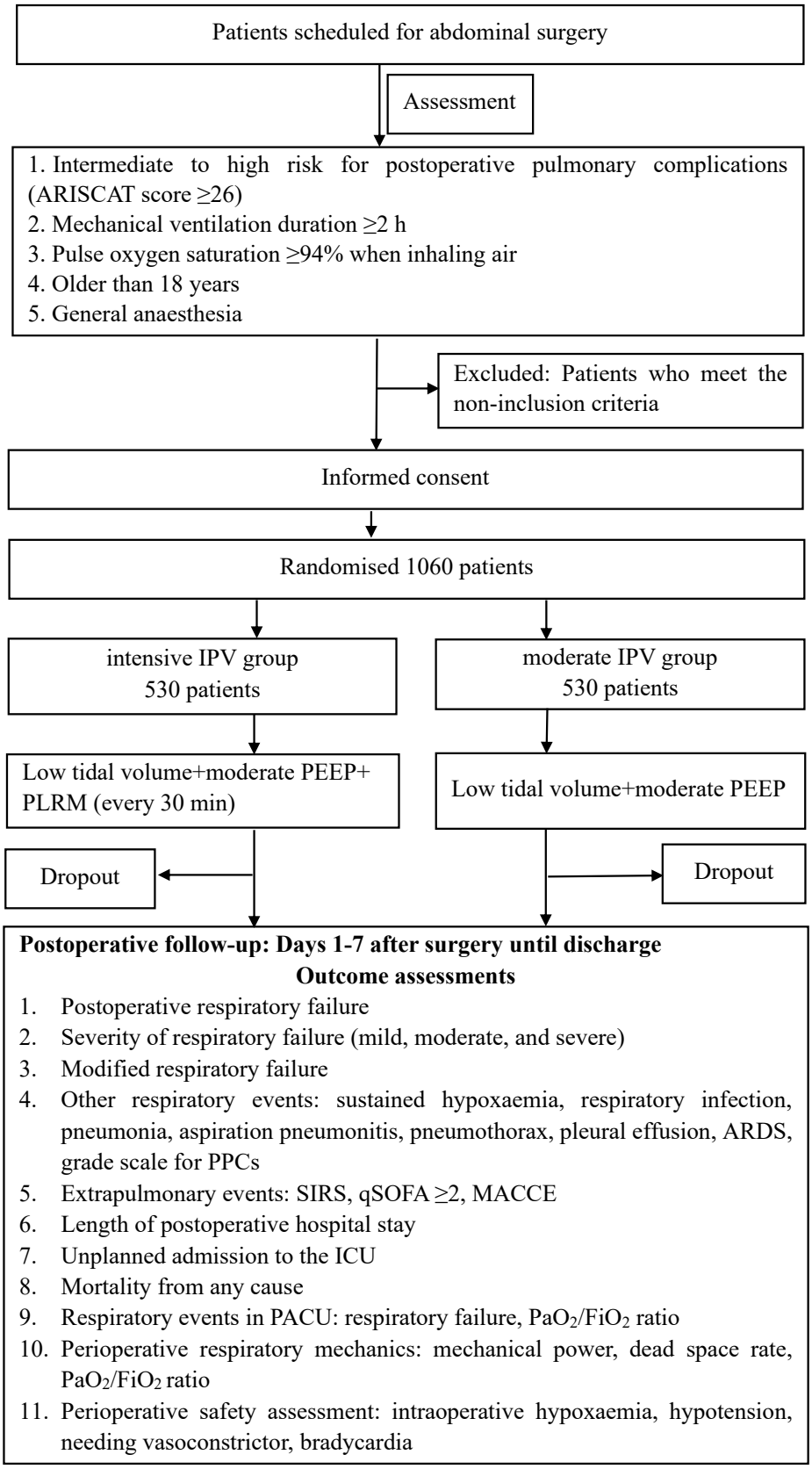

Figure 1 Flow chart of the trial. ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IPV, intraoperative protective ventilation; MACCE, major adverse cardiac and cerebrovascular events; PACU, postanaesthesia care unit; PaO_2, arterial partial pressure of oxygen; PEEP, positive end-expiratory pressure; PLRM, periodic lung recruitment manoeuvres; qSOFA, quick sequential organ failure assessment; SIRS, systemic inflammatory response syndrome.

4. The tidal volume, respiratory rate and PEEP will be set to the original settings after each LRM.

Rescue therapy for intraoperative hypoxaemia

Anaesthesiologists are permitted to modify the ventilation protocol at any time if there are concerns regarding patient safety. If a patient has an SpO_2 of less than 92% during ventilation, a stepwise increase in FiO_2 (by 10–20% each time) will be first applied to improve oxygenation after excluding airway problems, severe haemodynamic impairment and ventilator malfunction. If hypoxaemia persists when the FiO_2 reaches 100%, PEEP will be increased stepwise by 2 cm H_2O increments until reaching 12 cm H_2O. If these measures fail, a single LRM can be applied in the moderate IPV group.

Follow-up

Figure 2 provides details of the enrolment, interventions and assessments. Independent researchers, unaware of the participant allocation, will conduct the follow-ups during the first 7 days after surgery. Intensive follow-up will be performed twice per day on the first two postoperative days (PODs, POD 1 and POD 2) and once per day on the third, fourth, fifth and seventh days (PODs 3, 4, 5 and 7). The follow-up items will include SpO_2 (Masimo Rad-5, Masimo Corporation, Irvine, California, USA) in room

STUDY PERIOD													
	Enrolment	Allocation	Surgery				Postoperative						
TIME POINT	Preoperative visit	Before anaesthesia	During surgery	before the start of surgery	Before extubation	Post-anaesthesia care unit	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7
ENROLMENT:													
Eligibility screen	×												
Informed consent	×												
Allocation		×											
INTERVENTIONS:													
Moderate IPV group: PEEP			×										
Intensive IPV group: PEEP+PLRM(every 30 min)			×										
ASSESSMENTS:													
Demographic data	×												
Medical history	×												
Respiratory variables				×	×								
Haemodynamic variables			×										
Blood gas analysis				×	×								
Anaesthesia/Surgery variables			×										
Adverse events			×										
Need for rescue/Protocol deviation			×										
Recovery status						×	×	×	×	×	×	×	×
Respiratory failure						×	×	×	×	×	×	×	×
Pulmonary complications							×	×	×	×	×	×	×
Extrapulmonary complications						×	×	×	×	×	×	×	×
Unplanned admissions to ICU						×	×	×	×	×	×	×	×
Length of postoperative hospital stay							×	×	×	×	×	×	×
All-cause mortality							×	×	×	×	×	×	×

Figure 2 The schedule of enrolment, interventions and assessment. ICU, intensive care unit; PEEP, positive end-expiratory pressure; PLRM, periodic lung recruitment manoeuvres; POD, postoperative day.

air (if the patients receive oxygen therapy, data will be collected at 10 min after the cessation of oxygen therapy), breathing rate, amount and colour of sputum, degree of cough and dyspnoea, presence or absence of dry and wet rashes, heart rate, blood pressure, ear temperature and numerical rating scores for abdominal pain. Routine blood examination and chest imaging examination will be suggested if PPCs are suspected or clinically indicated.

Outcomes

Primary outcome

The primary outcome is respiratory failure within the first 7 days after surgery. Respiratory failure is defined as a postoperative arterial partial pressure of oxygen (PaO_2) <8 kPa (60 mm Hg) on room air, a PaO_2/FiO_2<40 kPa (300 mm Hg) or SpO_2<90% requiring oxygen therapy.[19 20]

Secondary outcomes

The secondary outcomes include other pulmonary complications, extrapulmonary complications and important clinical events following surgery, which are outlined as follows:

1. Mild respiratory failure, defined as a PaO_2<60 mm Hg or SpO_2<90% in room air, with SpO_2 that can be raised to more than 90% when inhaling oxygen at less than 3 L/min through a nasal catheter.[21]
2. Moderate respiratory failure, defined as a PaO_2<60 mm Hg or SpO_2<90% on oxygen ≤3 L/min through a nasal catheter, with SpO_2 that can be raised to ≥90% when inhaling oxygen >3 L/min through a nasal catheter.
3. Severe respiratory failure, defined as non-invasive or invasive mechanical ventilation, or PaO_2<60 mm Hg or SpO_2<90% despite supplemental oxygen.[21]
4. Sustained hypoxaemia, defined as SpO_2≤92% for 3 consecutive days, or a reduction of SpO_2 (preoperative SpO_2 minus postoperative SpO_2) ≥ 5% for 3 consecutive days in a patient who is awake and inhaling air.
5. Modified respiratory failure, defined as meeting the criteria for moderate or severe respiratory failure in at least one follow-up, mild respiratory failure in at least two follow-ups or mild respiratory failure with sustained hypoxaemia.
6. Respiratory infection, defined as occurring when a patient receives antibiotics for a suspected respiratory infection and meets at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever or leucocyte count >12 000 cells/μL.[17 19]
7. Pneumonia, as previously defined in the literature.[19 22]
8. Aspiration pneumonitis, defined as an acute lung injury after the inhalation of regurgitated gastric contents.[23]
9. Pneumothorax, defined as the presence of air in the pleural space with no vascular bed surrounding the visceral pleura.[19]
10. Pleural effusion, defined as a chest radiograph showing blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in the upright position, evidence of displacement of adjacent anatomical structures or (in the supine position) a hazy opacity in one hemithorax with preserved vascular shadows.[19]
11. Acute respiratory distress syndrome, defined in accordance with the Berlin definition.[19]
12. Grade scale for PPCs. PPCs will be graded on a scale ranging from 0 to 4, with grade 0 representing no pulmonary complications and grades 1 through 4 representing progressively severe forms of complications, as previously described.[13 24]
13. Quick sequential organ failure assessment (qSOFA) score of ≥2. The qSOFA score ranges from 0 to 3 points and consists of three clinical variables: altered mentation (Glasgow Coma Scale ≤13), systolic blood pressure < 100 mm Hg and respiratory rate > 22 breaths per minute. Each positive variable is scored as 1 point.[25]
14. Systemic inflammatory response syndrome, as defined in a previous study.[26]
15. Major adverse cardiac and cerebrovascular events, defined as the occurrence of one or more of the following: non-fatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina or stroke.[19]
16. Length of postoperative hospital stay, defined as the duration from the date of surgery to the date of discharge from the hospital.
17. Unplanned admissions to the intensive care unit (ICU) within 30 days after surgery, excluding the situations in which patients with normal spontaneous breathing, stable circulation and no disturbance of consciousness are transferred to the ICU at the request of surgeons.
18. All-cause mortality from any cause within 30 days after surgery.
19. Intraoperative hypotension, defined as mean arterial pressure <60 mm Hg lasting more than 3 min.
20. Intraoperative administration of vasoconstrictors, defined as the administration of catecholamines when mean arterial pressure is <60 mm Hg.
21. Intraoperative hypoxaemia, defined as SpO_2≤92% lasting more than 3 min.
22. Intraoperative bradycardia, defined as heart rate ≤50 beats per minute and a decrease in heart rate from baseline by ≥20% lasting more than 3 min.
23. Respiratory failure in the postanaesthesia care unit, defined as PaO_2<8 kPa (60 mm Hg) on room air, a PaO_2/FiO_2 ratio <40 kPa (300 mm Hg) or SpO_2<90%, requiring oxygen therapy.[19]
24. Intraoperative mechanical power before the start of surgery (T_1) and before the end of mechanical ventilation (T_2), calculated using the following formula: mechanical power (J/minute) = 0.098 × RR × Vt × (PEEP + ½[Pplat–PEEP] + [Ppeak–Pplat]).[27]

25. PaO_2/FiO_2 ratio measured at T_1 and T_2.
26. Dead space ratio (%), calculated using the formula $([PaCO_2–P_{ET}CO_2]/PaCO_2)$ at T_1 and T_2.

Sample size calculations

We estimate that the incidence of respiratory failure within the first 7 days after surgery is approximately 20.0% in the moderate IPV group according to previous studies.[28–30] Currently, there is no consensus on the minimally important difference in the primary outcome for these patients. Considering a 30% relative reduction in PPCs would be necessary to change clinical practice, we estimate an absolute reduction of 7% in the incidence of respiratory failure for the intensive IPV group. Using a χ^2 test with a type I error of 5%, a power of 85% in a two-sided test and a predicted dropout rate of 5%, we calculate that 530 participants are required in each group.

Recruitment

Participants will be recruited by trained investigators. Eligible patients will receive necessary information regarding the study in the form of both oral explanations and an information sheet. After providing written consent (online supplemental file) to participate in the study, they will undergo screening, which includes completing a medical history, ASA physical status, 12-lead ECG, chest radiography or CT, results of echocardiography or spirometry (for those with a history of heart or lung disease), as well as laboratory results and ARISCAT score. Participants retain the right to withdraw from the trial at any time, without prejudice to their future care.

Randomisation, masking and blinding

Eligible participants will be randomly assigned to either an intensive IPV regimen or a moderate IPV regimen in a 1:1 ratio. A computer-generated randomisation list will be prepared by an independent statistics expert. The allocation sequence will be generated using a permuted-block method with random sizes of 4, 6 or 10, which will be kept in consecutively numbered opaque envelopes, separate from the investigators. The participants, the researchers in charge of participant recruitment, postoperative follow-up, data collection and outcome assessment and the statisticians will all be blinded to the group assignments. However, the intraoperative anaesthesiologists will not be blinded to the group assignments.

Data collection

Researchers will be trained prior to the trial. All study data, including patients' clinical characteristics, intraoperative ventilation and surgery parameters, recovery status in the postanaesthesia care unit and postoperative outcomes will be documented in paper case report forms. One group of researchers will conduct the intraoperative mechanical ventilation regimen strictly in accordance with the study protocol and will be responsible for data collection during both the preoperative and intraoperative periods. Another group of researchers will be responsible for data collection in the postanaesthesia care unit and during postoperative follow-up.

Data management

The data will be initially recorded on a paper sheet, after which a PDF electronic case report form will be created and stored once data recording is complete. The data of all participants will be anonymised and stored in accordance with data protection legislation for further analysis. A data management team will be responsible for blindly reviewing data, dual checking and inputting data, locking databases and exporting data.

Statistical analysis

The baseline characteristics analyses will be performed in the full analysis set (FAS). The outcome analyses will be performed in both the FAS and per-protocol set (PPS). In the intention-to-treat analysis, missing data will be imputed using the method of multiple imputation. In the PPS analysis, missing data will not be imputed. Missing data during follow-up for patients discharged to home earlier than POD7 will be treated using the last observation carried forward.

Both unadjusted and adjusted logistic regression analyses, using a generalised linear model with binomial distribution, will be performed for the binary outcomes. The effects of the intervention on binary outcomes will be estimated as relative risks (RR) with 95% CIs and as well as risk differences with 95% CIs. The adjusted confounders will include surgical position, surgical type, surgical approach, surgical duration, age, BMI, preoperative SpO_2, ARISCAT score and ASA classification. The results of the adjusted analysis will be used for the interpretation of outcomes. In the PPS, the Mann-Whitney-Wilcoxon rank sum test will be used to compare the cumulative number of the observed primary outcome events across all follow-up visits between the two groups.

Treatment effects will be analysed according to the following prespecified subgroups: (1) male versus female; (2) ≥ 75 years versus <75 years; (3) head-up tilt versus Trendelenburg position; (4) laparoscopic surgery versus laparotomy; (5) mechanical ventilation duration ≥3.5 hour versus <3.5 hour; (6) BMI > 24 versus ≤24 kg/m^2; (7) preoperative SpO_2≥97% versus <97%; (8) ARISCAT score ≥45 versus <45; and (9) ASA classification ≥3 versus <3. Analyses of heterogeneity of effects across subgroups will use generalised linear models with a binomial distribution and a logit link, incorporating an interaction between each subgroup and study group as a fixed effect.

For the length of postoperative hospital stay, we will first use the Mann-Whitney-Wilcoxon rank sum test in the PPS to compare the medians between the two groups and then calculate the median difference and 95% CI using the Hodges-Lehman estimation method. It will be further compared using Kaplan-Meier survival curves and represented as hazard ratios (95% CI) calculated from a Cox proportional hazard model. The Schoenfeld residuals

plotted against the transformed time will be used to test the proportional hazard assumptions.

Variables will be expressed as means and SD or medians and interquartile ranges and analysed using a Student's t-test or the Mann-Whitney-Wilcoxon rank sum test as appropriate. Categorical variables will be presented as n (%) and analysed using Fisher's exact test. A two-sided *P* value of less than 0.05 will be considered statistically significant. Statistical analyses will be performed using SPSS statistical software, V.17.0 (SPSS, Chicago, USA).

Data monitoring

All serious adverse, unexpected or possibly related events will be recorded in the CRF and reported to the Data and Safety Monitoring Committee (DSMC). The independent DSMC will monitor and review the ethics or safety issues in accordance with the Declaration of Helsinki.

Protocol dropout

Reasons for withdrawal from the trial include a participant withdrawing consent or refusing further follow-up, resulting in no primary outcome data being obtained.

Patient and public involvement

Patient and public involvement representatives have participated in the study design, including how to protect the rights and interests of patients, determining the rescue therapy and deciding the appropriate follow-up schedule.

DISCUSSION

LRM has been used to reverse atelectasis and improve oxygenation after anaesthetic induction since the 1960s.[31] However, these benefits are short-lived; even when an LRM is performed immediately before extubation, its beneficial effects on oxygenation disappear soon after tracheal extubation,[32] and atelectasis is thought to recur within 40 min.[33] Theoretically, its benefits could be enhanced or prolonged by PLRM.[34] Several studies have shown that IPV with PLRM provides lung protection.[13–15] Nevertheless, IPV with PLRM is still not a common clinical practice.[35 36] This large randomised controlled trial will differentiate the effects of two protective ventilation regimens (IPV with or without PLRM) in preventing PPCs and elucidate the role of PLRM in IPV.

In previous studies on the same topic, PPCs are usually presented as a composite of possible fatal and non-fatal respiratory events with differing pathophysiological mechanisms.[3 19 37] Additionally, the components of these composite PPC outcomes often differ from each other.[3 13 28 29] Unlike previous studies, this study adopts a single outcome, that is, respiratory failure, as the primary outcome. The reasons include (1) respiratory failure is one component of the composite PPC outcomes in most previous studies;[2 13 17 19] (2) it is an objective outcome that is well-defined in previous studies;[17 19] (3) it is a common characteristic of various PPCs when they occur to a more severe degree, thus it also has the advantages of a composite outcome;[38 39] and (4) it has a relatively more stable rate in previous studies[14 40 41] and correlates better with intraoperative lung injury in mechanisms than other PPCs such as bronchospasm, aspiration pneumonia and pulmonary oedema.[42]

One limitation of this study is that it is not conducted across multiple centres, which may affect its external validity. However, this study has a large sample size, covers most types of major abdominal surgeries, adopts flexible anaesthesia plans and is conducted by many anaesthesiologists. Therefore, the conclusions of this study will have a broad applicability in clinical practice.

In summary, REMAIN-1 is an adequately powered prospective randomised controlled trial that elucidates the role of PLRM in IPV. We believe that this study will provide reliable evidence to support the clinical application of IPV.

ETHICS AND DISSEMINATION

This study protocol was reviewed and approved (No. 2022ZSLYEC-398) by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University on 2 September 2022 and registered at ClinicalTrials.gov (NCT05556174) on 14 September 2022. Written informed consent will be obtained from all participants before their recruitment into the trial. The results of this trial will be presented at national and international meetings and published in peer-reviewed journals.

Trial status

The current version of the study protocol is V4.0 (6 February 2023). The time of grant was 19 September 2023. The time of approval from the ethics committee was 2 September 2022. The expected time and duration of inclusions will last from 9 October 2022 to 30 May 2025. The expected time and duration of monitoring will last from 9 October 2022 to 30 June 2025. The expected time and duration of cleaning and closure of the database will last from June 2025 to August 2025. The expected time of data analysis will be in September 2025. The expected time of writing the manuscript and submission for publication will begin in October 2025.

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Contributors HL conceived the study and obtained funding. JL contributed to the data curation and project administration. N-RZ, L-ZZ and YC contributed equally to investigating the study and writing the original draft of this manuscript. SZ, SL and

X-KG contributed in conducting the study and revising the manuscript. All authors have read and approved the final version of the manuscript. HL is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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