



HAL
open science

Intraoperative protective mechanical ventilation in patients requiring emergency abdominal surgery: the multicentre prospective randomised IMPROVE-2 study protocol

Louisa Khaled, Thomas Godet, Samir Jaber, Gerald Chanques, Karim Asehnoune, Justine Bourdier, Lynda Araujo, Emmanuel Futier, Bruno Pereira

► To cite this version:

Louisa Khaled, Thomas Godet, Samir Jaber, Gerald Chanques, Karim Asehnoune, et al.. Intraoperative protective mechanical ventilation in patients requiring emergency abdominal surgery: the multicentre prospective randomised IMPROVE-2 study protocol. *BMJ Open*, 2022, 12 (5), pp.e054823. 10.1136/bmjopen-2021-054823 . hal-03669039

HAL Id: hal-03669039

<https://hal.science/hal-03669039v1>

Submitted on 16 May 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Intraoperative protective mechanical ventilation in patients requiring emergency abdominal surgery: the multicentre prospective randomised IMPROVE-2 study protocol

Louisa Khaled,¹ Thomas Godet,¹ Samir Jaber,² Gerald Chanques,² Karim Asehnoune,³ Justine Bourdier,⁴ Lynda Araujo,⁴ Emmanuel Futier,^{1,5} Bruno Pereira⁴

Introduction Emergency abdominal surgery is associated with a high risk of postoperative complications. One of the most serious is postoperative respiratory failure (PRF), with reported rates up to 20%–30% and attributable 30-day mortality that can exceed 20%.

Lung-protective ventilation, especially the use of low tidal volume, may help reducing the risk of lung injury. The role of positive end-expiratory pressure (PEEP) and recruitment manoeuvre (RM) remains however debated. We aim to evaluate whether a strategy aimed at increasing alveolar recruitment by using higher PEEP levels and RM could be more effective at reducing PRF and mortality after emergency abdominal surgery than a strategy aimed at minimising alveolar distension by using lower PEEP levels without RM.

Methods and analysis The IMPROVE-2 study is a multicentre randomised, parallel-group clinical trial of 680 patients requiring emergency abdominal surgery under general anaesthesia. Patients will be randomly allocated in a 1:1 ratio to receive either low PEEP levels (≤ 5 cm H₂O) without RM or high PEEP levels individually adjusted according to driving pressure in addition to RM, stratified by centre and according to the presence of shock and hypoxaemia at randomisation. The primary endpoint is a composite of PRF and all-cause mortality by day 30 or hospital discharge. Data will be analysed on the intention-to-treat principle and a per-protocol basis.

Ethics and dissemination IMPROVE-2 trial has been approved by an independent ethics committee for all study centres. Participant recruitment began in February 2021. Results will be submitted for publication in international peer-reviewed journals.

Trial registration number NCT03987789.

INTRODUCTION

Emergency abdominal surgery involves several hundred of thousand people worldwide with reported short-term mortality rate up to 20%.^{1–5} Postoperative pulmonary complications occur frequently in patients undergoing major surgery and are associated

Strengths and limitations of this study

- ⇒ This is a large randomised multicentre trial testing the effect of lung-protective ventilation strategy in emergency abdominal surgery.
- ⇒ The multicentre design, broad inclusion criteria, large sample size and follow-up will support external validity.
- ⇒ The primary endpoint is defined according to well-defined and internationally validated criteria.
- ⇒ Allocation will not be concealed to anaesthesiologists, since they must care patients during surgery; however, study outcomes will be assessor blinded, and data analysis will be performed by a blinded statistician.

with perioperative mortality and morbidity.⁶ Postoperative respiratory failure (PRF), usually defined as failure to wean from mechanical ventilation after surgery or the need for unplanned tracheal reintubation after surgery,^{7–8} is one of the most severe pulmonary complication, with a reported incidence up to 20%–30% after emergency abdominal surgery,^{7,9} and attributable 30-day mortality that can exceed 20%.^{6,7}

Mechanical ventilation is an essential supportive therapy to maintain gas exchange during general anaesthesia, but may contribute to lung injury and postoperative pulmonary complications.¹⁰ Recent guidelines recommend use of lung-protective mechanical ventilation, which comprises the use of low tidal volume (VT) and positive end-expiratory pressure (PEEP), in patients undergoing elective surgery.¹¹ Although it is tempting to suppose that lung-protective ventilation might be beneficial in a broader population, the evidence is lacking. Moreover,

Correspondence to

Professor Emmanuel Futier;
efutier@chu-clermontferrand.fr

although there is increasing evidence supporting the use of low VT ventilation to minimise lung stretch during surgery,¹² there remains significant controversy about the efficacy and safety of high PEEP and recruitment manoeuvres (RMs).¹³ Two randomised clinical trials showed lung-protective ventilation with low VT in addition to high PEEP and RM to prevent against postoperative pulmonary complications when compared with ventilation with high VT plus low PEEP without RM.^{14 15} Two other large randomised trials found no benefit of high PEEP with RM compared with low PEEP without RM in this setting,^{16 17} suggesting that beneficial effects arise primarily from the use of low VT ventilation. Concerns have also been raised about possible negative haemodynamic effects of high PEEP and RMs in these studies.

Conversely, a strategy of low VT ventilation using low PEEP, while minimising alveolar distension, may be insufficient to stabilise alveoli and may promote alveolar derecruitment, thereby increasing the likelihood of ventilator-induced lung injury from atelectrauma.^{18–20} An experimental study showed a strategy of low VT ventilation plus low PEEP without RM to promote higher driving pressure and mechanical power delivered to the respiratory system compared with high PEEP levels with RMs.²¹ As such, this raises the question as to whether this strategy can be applied safely in patients at increased risk of PRF.

The driving pressure, calculated as the difference between plateau pressure (Pplat) and PEEP, has been proposed as a means of individualising PEEP setting.¹¹ Data from an individual patient meta-analysis of 17 randomised controlled trials of mechanical ventilation during surgery suggested that increases in PEEP that result in an increase of driving pressure may be associated with increased odds of postoperative pulmonary complications.²² However, to date, data from large randomised clinical trials comparing individualised driving pressure-guided PEEP setting and usual care are lacking.

Objectives

The aim of this study is to compare a strategy aimed at increasing alveolar recruitment by using high PEEP levels individually titrated according to driving pressure and RM with that of a strategy aimed at minimising alveolar distension by using low PEEP levels without RM in patients undergoing emergency abdominal surgery.

Primary objective

To compare the effect of the two ventilation strategies on PRF and mortality in patients receiving low VT lung-protective ventilation during emergency abdominal surgery.

Secondary objectives

To compare the rates of reintubation and use of curative NIV for PRF and the duration of mechanical ventilation between the two ventilation strategies.

To compare the rate of postoperative organ dysfunction between the two ventilation strategies.

To compare the duration of intensive care unit (ICU) and hospital length of stay between the two ventilation strategies.

To compare clinical adverse events between the two ventilation strategies.

METHODS AND ANALYSIS

Trial design and setting

The IMPROVE-2 study is an investigator-initiated, prospective, multicentre, randomised, stratified, parallel-group clinical trial with concealed allocation of patients undergoing emergency abdominal surgery 1:1 to a strategy of increased alveolar recruitment, using high PEEP levels individually titrated according to driving pressure and RMs, or a strategy of minimal alveolar distension, using low PEEP levels without RM (figure 1). The study protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.²³ The trial will take place at 28 university and non-university centres.

Participant eligibility and consent

All patients admitted to a participating clinical trial site will be considered for participation. Patients will be eligible for randomisation if they fulfil all the inclusion criteria and none of the exclusion criteria (table 1).

After patient informed consent has been obtained (or proxy consent has been obtained by the patient's next of kin or legally authorised surrogates), study inclusion will be performed immediately before surgery. Because, in emergency situations, obtaining informed consent prior to participation may not be feasible, the study protocol also provides for a waiver of informed consent from the patient's next of kin if he or she is not present at the time of the patient's inclusion. Deferred informed consent will be obtained as soon as possible from participants or legally authorised surrogates for potential continuation of the research

Randomisation, allocation concealment and blinding

Randomisation

Enrolled patients will be randomised by local investigators using a dedicated, password-protected, SSL-encrypted website (CSONline, Clinsight) accessible 24-hour around-the-clock to allow immediate and concealed allocation. Each patient will be given a unique patient-number and a randomisation number. The allocation sequence will be generated in a 1:1 ratio with the use of a minimisation algorithm, stratified according to study centre, the presence or absence of shock (defined by continuous intravenous infusion of vasoactive drugs) and the presence or absence of hypoxaemia (defined by a partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO₂/FiO₂) ratio ≤300) at randomisation.

Because arterial blood gas use is declining in emergency department and ICU practice, patients may not have arterial blood gas and arterial partial pressure of

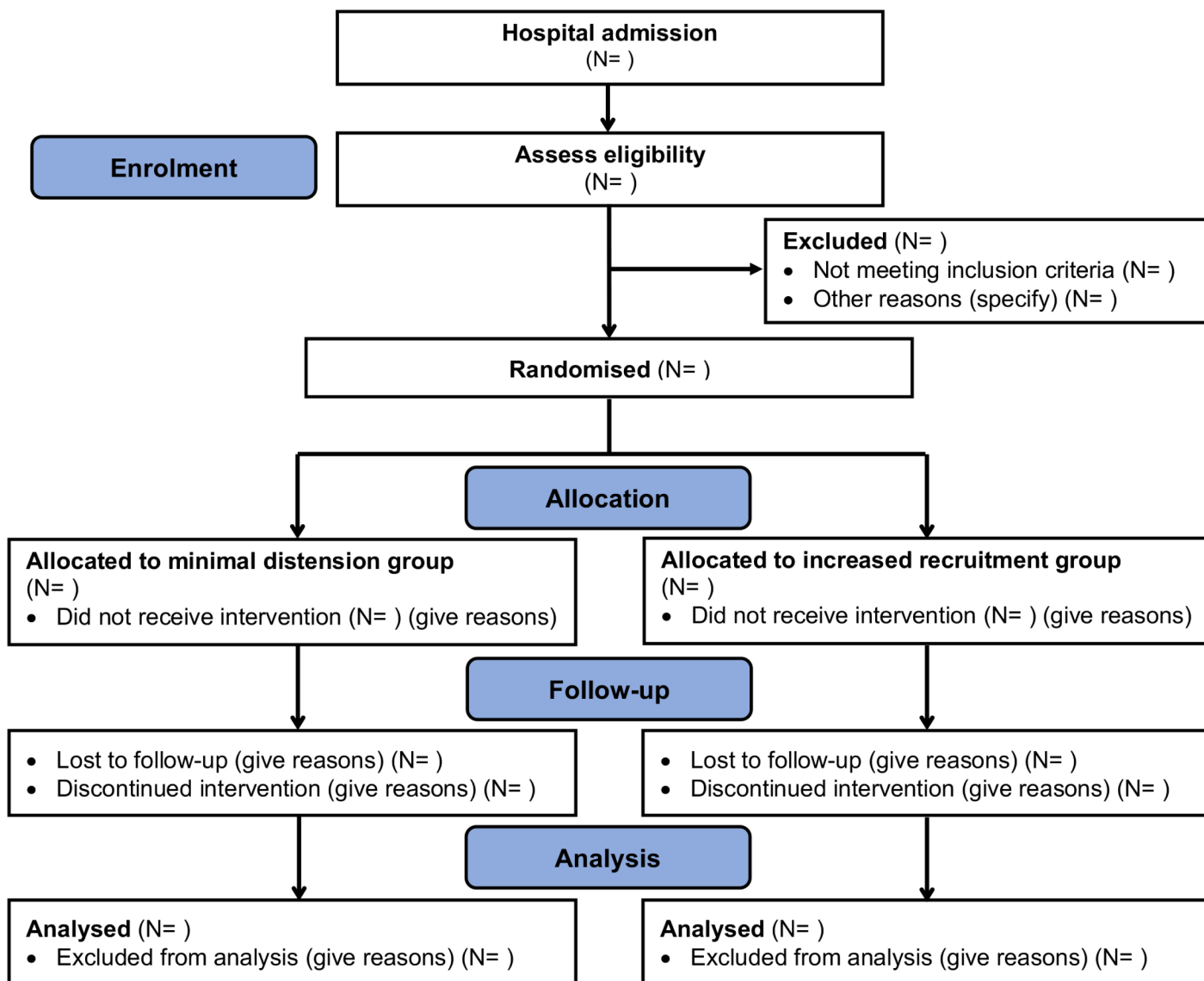


Figure 1 Flow diagram of the IMPROVE-2; Intraoperative Lung Protective Ventilation trial. Flow chart (N=) will be filled during or at the end of the trial.

oxygen (PaO_2) measurement available in the relevant timeframe. Consequently, non-linear imputation based on the Ellis inversion of the Severinghaus equation will be used to impute PaO_2 from oxyhaemoglobin percent saturation measured with pulse oximetry (SpO_2).²⁴ In patients not on a measured FiO_2 , FiO_2 will be estimated by the equation litres of flow/min (up to 15L) multiplied by 0.03 plus 0.21.²⁵

Blinding

Although the allocation group will not be blinded to anaesthesiologists because they have an ethical responsibility to ensure patient safety during surgery, much attention will be given to ensuring strict blinding during the follow-up period and during data collection. At each participating centre, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal, blinded to the allocation group, under the supervision of the local principal investigator or design who will also be unaware of the trial group

allocation. Outcome assessors will be blinded to patient anaesthesia records throughout the study. The allocation group will be blinded to the patient, the clinical staff caring for the patient after surgery, the outcome assessors, the data manager and the statistician conducting the analyses until the data will be locked.

Study interventions

Patients eligible for inclusion will be allocated to one of the following two study groups:

- ▶ Driving-pressure-guided PEEP group (increased alveolar recruitment strategy): external PEEP will be individually set at the highest possible value (up to 15 cm H_2O), providing a driving pressure (airway P_{plat} minus PEEP) lower than 13 cm H_2O ,^{22 26} in addition to lung RM. The recruitment procedure will consist in applying a positive airway pressure of at least 30 cm H_2O for 20–30s¹⁴ after tracheal intubation and repeated every hour and/or in case of disconnection

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
▶ Adult (18 years or older)	▶ Patients already receiving mechanical ventilation for more than 12 hours before enrolment
▶ Emergency (defined by the need to proceed to surgery within a few hours after diagnosis) surgery	
▶ Laparoscopic or non-laparoscopic abdominal surgery under general anaesthesia	▶ Chronic respiratory disease requiring oxygen therapy or mechanical ventilation at home
▶ Expected duration of 2 hours or more	▶ Undrained pneumothorax or subcutaneous emphysema
	▶ Patients for which death is deemed imminent and inevitable or patients with an underlying disease process with a life expectancy of less than 3 months
	▶ Intracranial hypertension
	▶ Body mass index >40 kg/m ²
	▶ Pregnant or breastfeeding women
	▶ Patients already enrolled in the Intraoperative Lung Protective Ventilation (IMPROVE-2) trial
	▶ Participation in a confounding trial with mortality or postoperative respiratory failure as the main endpoint
	▶ Patient's or relative's refusal to participate
	▶ Guardianship or trusteeship patient
	▶ No affiliation to the social security system

from the ventilator or in case of an increase in driving pressure >13 cm H₂O during surgery.

- ▶ Low PEEP group (minimal distension strategy): external PEEP will be set at 5 cm H₂O or lower without RM.^{27–29}

In each group, patients will receive volume-controlled low VT ventilation, with a VT of 6–8 mL/kg predicted body weight, calculated according to a predefined formula: 50+0.91 x (centimetres of height – 152.4) for males and 45.5+0.91 x (centimetres of height – 152.4) for females. The respiratory rate will be adjusted to maintain end-tidal partial pressure of CO₂ between 35 and 45 mm Hg, with an inspiratory-to-expiratory time ratio of 1:2, an end-inspiratory pause of 30%, and an FiO₂ adjusted to maintain SpO₂ ≥94%. The maximum limit for respiratory rate is defined by the recognition of auto-positive end expiratory pressure, defined as an expiratory flow that does not return to zero before the next inspiration on the expiratory portion of the flow waveform. In addition, a Pplat of no more than 28 cm H₂O will be targeted. If the Pplat reaches or exceeds 28 cm H₂O, VT will be decreased by 1 mL/kg followed, in case of insufficiency, by a 1 cm H₂O decrease of PEEP, and so on, until Pplat drops below 28 cm H₂O. If the end-tidal partial pressure of CO₂ target is not achieved, and the maximum limit for respiratory rate is reached, VT will be increased up to 8 mL/kg predicted body weight unless Pplat is 28 cm H₂O. If patients meet criteria for denoting refractory acidosis (pH ≤7.10), anaesthesiologists caring for the patient will, at their discretion, deviate from the assigned ventilation strategy and stop the intervention.

In each group, in case of oxyhaemoglobin desaturation, defined as SpO₂ ≤92% for more than 5 min, a rescue strategy is provided (table 2).

In each group, the allocated mechanical ventilation strategy will be maintained until the end of surgery. Immediate interruption of sedation will be encouraged after the end of surgery and weaning from the ventilator will be initiated as soon as possible, using previously defined criteria.³⁰ The decision to stop sedation and to initiate weaning from the ventilator will be made by the clinical staff caring for the patient after surgery.

Decisions about all other aspects of patient care during the intraoperative and postoperative periods, including the requirement of invasive mechanical ventilation for reoperation or other procedures under general anaesthesia, will be decided following usual practice and the expertise of the staff of the involved centres to minimise interference with the trial intervention. Trial investigators will be strongly encouraged to manage postoperative analgesia using a multimodal approach targeting numeric rating scale pain scores <3 (or Behavioural Pain Scale score <5).³⁰

Outcome measures

Details on trial endpoints definitions are given in online supplemental file 1.

Primary outcome measure

The primary outcome is a composite of PRF, as defined previously as failure to wean from the ventilator after surgery or requiring unplanned reintubation or curative

Table 2 Rescue strategy in the study groups

Minimal distension strategy			Increased recruitment strategy		
Stage	FiO ₂	PEEP level	Stage	FiO ₂	PEEP level
1	Increase FiO ₂ up to 100%	6 cm H ₂ O	1	Do not change FiO ₂	16 cm H ₂ O+repeat recruitment manoeuvre
2	Increase FiO ₂ up to 100%	7 cm H ₂ O	2	Do not change FiO ₂	17 cm H ₂ O+repeat recruitment manoeuvre
3	Increase FiO ₂ up to 100%	8 cm H ₂ O	3	Do not change FiO ₂	18 cm H ₂ O+repeat recruitment manoeuvre
4	Increase FiO ₂ up to 100%	9 cm H ₂ O	4	Do not change FiO ₂	19 cm H ₂ O+repeat recruitment manoeuvre
5	Increase FiO ₂ up to 100%	10 cm H ₂ O (consider applying recruitment manoeuvre)	5	Increase FiO ₂ up to 100%	20 cm H ₂ O+repeat recruitment manoeuvre (consider increasing FiO ₂)

FiO₂, fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure.

non-invasive ventilation once extubated postoperatively,^{7,8} and all-cause mortality by day 30 or hospital discharge.

Secondary outcome measures

- ▶ Key secondary endpoints
 - PRF within 30 days following randomisation.
 - All-cause mortality within 30 days following randomisation.
- ▶ Secondary efficacy endpoints
 - Severity of postoperative pulmonary complications within 30 days following surgery. Pulmonary complications will be scored on a grade scale ranging from 0 to 4, with grade 0 representing the absence of any pulmonary complication and grades 1–4 representing successively the worse forms of pulmonary complications, as defined previously.³¹
 - Sepsis and septic shock within 30 days following surgery.
 - Renal dysfunction (defined as Kidney Disease: Improving Global Outcomes (KDIGO) stage 1 or higher within 30 days following surgery).
 - Sequential (sepsis-related) Organ Failure Assessment (SOFA, modified from³² score from postoperative day 1 to day 7).
 - Ventilator-free days (VFDs) to 30 days. A VFD is defined as the receipt as <2 hours of invasive mechanical ventilation or non-invasive mechanical ventilation (as curative therapy) within a 24-hour period.
 - Duration of mechanical ventilation from randomisation to first tracheal extubation.
 - Total duration of mechanical ventilation (additive, for all episodes up to 30 days after surgery).
 - Time to successful tracheal extubation (defined as absence of ventilatory support during the first 48 hours after extubation.³³
 - ICU-free days (censored at 30 days following surgery).

- Duration of ICU and hospital stay (patients who will be outside the hospital but in other types of healthcare facilities at day 30 will be considered to have been discharged home).
- Time to death (or censoring).

Tertiary outcome measures

- ▶ Postoperative hypoxaemia, as defined previously.³⁴
- ▶ Postoperative pneumonia, defined according to consensus guidelines.^{8,35}
- ▶ Acute respiratory distress syndrome (ARDS), defined according to the Berlin criteria.³⁶
- ▶ Amount of intravenous fluids (crystalloids and colloids) during surgery.
- ▶ Amount of vasopressor (norepinephrine, phenylephrine, ephedrine) during surgery.
- ▶ Mechanical power calculated as proposed previously.^{37,38}
- ▶ Ventilatory-related adverse events: haemodynamic instability (defined as a drop of arterial systolic pressure below 80 mm Hg for more than 5 min not responding to intravenous fluids and/or vasopressors), pneumothorax.
- ▶ Rescue therapy for hypoxaemia.
- ▶ All-cause mortality to day 90.

Statistics

Sample size estimation

Assuming a 10% mortality rate⁶ and a 15% rate of PRF 30 days after surgery^{7,9} (thus 25% for the composite endpoint), 2×340 patients will be needed to have 90% power to show an absolute between-group difference of 10% in the primary outcome measure at a two-sided alpha level of 0.05.

Statistical analysis

All analyses will be performed with the use of Stata software (V.15, StataCorp) before the breaking of the

randomisation code, in line with the International Conference on Harmonisation Good Clinical Practice guidelines. Analyses are detailed in a separate statistical analysis plan (see online supplemental file 2).

Data registration

Data are collected and entered into a web-based eCRF (CSOnline, Clinsight) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF, the trial database will be established. Paper case report form will be used in case of technical difficulties with the eCRF. Data collection will be monitored by trained research coordinators.

The following data will be registered:

Prerandomisation and baseline characteristics

Date and time of hospital admission, and source of admission (emergency department, surgical ward, ICU); demographic data (age, sex, weight, height, body mass index); American Society of Anesthesiologist physical status; comorbidities (arterial hypertension: Y/N, diabetes: Y/N, active smoking: Y/N, alcohol abuse: Y/N, chronic pulmonary disease: Y/N, cancer: Y/N); reoperation procedure: Y/N (if Y, date and time of previous surgical intervention); results of blood samples (standard lab. values for white cell count, haemoglobin, platelets, lactate, C reactive protein, bilirubin, creatinine); values for SOFA scoring, date and time of preoperative initiation of mechanical ventilation, if any; indication for emergency

At randomisation (± 1 hour)

Vasopressor use: Y/N (stratification variable); hypoxaemia ($\text{PaO}_2/\text{FiO}_2 < 300$): Y/N (stratification variable); haemodynamic variables: heart rate (beats/min), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), mean arterial pressure (mm Hg); oxyhaemoglobin percent saturation (SpO_2) and FiO_2 (or litres of oxygen flow/min and estimated FiO_2).

Intraoperative data

Date and time of admission in the operating room; type of surgery; type of surgical procedure (laparoscopic: Y/N, non-laparoscopic: Y/N); type of anaesthesia (epidural analgesia: Y/N, inhaled anaesthetic: Y/N, intravenous anaesthetic: Y/N, nitrous oxide: Y/N); type (sufentanil: Y/N, remifentanil: Y/N, other) and total dose of opioids; duration of anaesthesia (minutes) from the start of anaesthesia until discharge from the operating room; duration of surgery (minutes) from the start of skin incision until the end of skin closure; type (crystalloids and colloids) and volume (millilitres) of intraoperative fluids; vasopressor use: Y/N (receipt of norepinephrine, epinephrine, phenylephrine, ephedrine) and dose; inotrope use: Y/N (receipt of dobutamine, dopamine); haemodynamic (stroke volume and/or cardiac output) monitoring: Y/N; blood losses (millilitre) and volume of transfused blood (number of unit); ventilator settings after tracheal intubation and, then, hourly until after abdominal closure, and adjustments if any: VT (ml/kg PBW), PEEP (cm H_2O),

FiO_2 , peak pressure (cm H_2O), Pplat (cm H_2O), RM: Y/N (and number of manoeuvres); ventilator-related adverse events: Y/N (including haemodynamic instability, defined as a drop in systolic arterial pressure below 80 mm Hg for more than 5 min not responding to fluids and/or vaso-pressors, pneumothorax and any other life-threatening reason for which the clinician would decide to stop the intervention)

On postoperative day 1 (12 hours after surgery)

Patient location (ICU: Y/N, HDU: Y/N, surgical ward: Y/N); presence of invasive mechanical ventilation: Y/N (if yes, ventilation mode, VT, PEEP, FiO_2 , peak pressure, Pplat); sedation interruption: Y/N (if yes, date and time of sedation interruption); successful weaning test: Y/N (if yes, date and time of the first weaning test); failure to wean from the ventilator: Y/N; tracheal extubation: Y/N (if yes, date and time of tracheal extubation); oxygen therapy: Y/N (if yes, litres of oxygen flow/min); ventilatory support after extubation: Y/N (if yes, high-flow nasal cannula: Y/N, preventive NIV: Y/N); results of arterial blood gases (standard lab. values, when available, for PaO_2 , PaCO_2 , pH); values for Simplified Acute Physiology Score II and SOFA scoring; reintubation: Y/N (if yes, date, time and reason of reintubation); curative NIV: Y/N (if yes, date and time of initiation); survival status (date and time of death is any).

Daily (08:00 hour) from postoperative day 2 until ICU/High-Dependency Unit (HDU) discharge

Patient location (ICU: Y/N, HDU: Y/N); presence of invasive mechanical ventilation: Y/N (if yes, ventilation mode, VT, PEEP, FiO_2 , peak pressure, Pplat); sedation interruption (if still mechanically ventilated the day before): Y/N (if yes, date and time of sedation interruption); successful weaning test (if still mechanically ventilated the day before: Y/N (if yes, date and time of the weaning test); tracheal extubation (if still mechanically ventilated the day before): Y/N (if yes, date and time of tracheal extubation); oxygen therapy: Y/N (if yes, litres of oxygen flow/min); ventilatory support: Y/N; (if yes, high-flow nasal cannula: Y/N, preventive NIV: Y/N); reintubation: Y/N; (if yes, date, time and reason of reintubation); curative NIV: Y/N (if yes, date and time of initiation); values for SOFA scoring (until day 7 following surgery); postoperative pulmonary complications: Y/N (if yes, postoperative pulmonary complication grade (from 1 to 4), hypoxaemia: Y/N, pneumonia: Y/N, ARDS: Y/N); postoperative non-pulmonary complications: Y/N (if yes, sepsis/septic shock: Y/N, renal dysfunction (KDIGO score): Y/N, other: Y/N); discharge from ICU/HDU: Y/N (if yes, date and time of discharge); discharge from hospital: Y/N (if yes, date and time of discharge); survival status (date and time of death is any)

Thirty days after randomisation (or hospital discharge)

Discharge from hospital: Y/N (if yes, date and time of discharge); discharge from ICU/HDU: Y/N (if yes, date

and time of discharge); New ICU/HDU admission (in case of discharge from ICU/HDU before day 30): Y/N (if yes, date and time of admission); presence of invasive mechanical ventilation: Y/N; duration (days) of invasive mechanical ventilation from randomisation to first tracheal extubation following surgery; duration (days) of invasive mechanical ventilation from randomisation (additive, for all episodes up to 30 days after surgery); duration of NIV (additive, up to 30 days after surgery); VFDs to day 30; postoperative pulmonary complications: Y/N (if yes, hypoxaemia: Y/N, pneumonia: Y/N, ARDS: Y/N); postoperative non-pulmonary complications: Y/N (if yes, sepsis/septic shock: Y/N, renal dysfunction (KDIGO score): Y/N); length of stay (and date of discharge) in ICU/HDU/surgical ward; survival status (and date of death).

Ninety days after randomisation

Survival status (and date of death).

Study discontinuation and patient withdrawal

A participant or a patient's relative who no longer agrees to participate in the clinical trial may withdraw its consent at any time without need of further explanation. In order to conduct intention-to-treat analyses with as little missing data as possible, it is in the interest of the trial to collect as much data from each participant as possible. In accordance with the French law, data already collected prior and up to the date of consent withdrawal will be retained and analysed. If data for the primary endpoint are not yet available, the investigator may ask the participant and/or relatives, whenever possible, for permission to obtain data for the primary outcome measure. If this person declines, all data from that patient will be destroyed and a new patient will be randomised to obtain the full sample size. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Ethics and dissemination

The IMPROVE-2 trial is an investigator-initiated trial funded by the French Ministry of Health obtained in 2016 from a national hospital clinical research programme (Programme Hospitalier de Recherche Clinique National 2016).

The study protocol and statistical analysis plan have approved for all centres from a central ethics committee (Comité de Protection des Personnes Sud-Est III, Bron, France; Registration No. 2019-009B). The trial is registered in the European Clinical Trials Database (EudraCT No. 2019-A00265-52).

A scientific committee, including EF, SJ and TG conceived, drafted and wrote the project.

A data monitoring and safety committee (DMSC) will review unblinded data and serious adverse events at n=170 and n=340 to advise on any recruitment and safety issues

they identify and to investigate whether the conduct of the trial may compromise patient safety (a between-group difference in mortality). Recommendations for pausing or stopping the study will be made by the DMSC if the p value is less than 0.00001 (first interim analysis) or less than 0.003 (second interim analysis) for the between-group difference in the incidence of mortality (O'Brien-Fleming spending function).

Trial results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines. Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians, commissioners and service users.

Data handling and retention

Data will be entered into a web-based eCRF by trial personnel. Each site will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data. Data will be handled according to the French law. All original records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final data set.

Trial status

The current protocol is version 5.0. The trial began on the 18 February 2021. At the time of manuscript submission, 170 patients had been recruited, with a 2-year recruitment period per study site planned.

Data statement

The data generated and/or analysed during the trial are not yet publicly available as the trial is ongoing. When the trial is complete, data sets will be available from the principal investigator (EF) on reasonable request and after agreement by ethics (see online supplemental file 3).

Patient and public involvement

There is no patient and public involvement in the design and execution of this study.

DISCUSSION

The IMPROVE-2 trial is to allow us to evaluate whether a ventilation strategy of increased alveolar recruitment delivered to patients undergoing emergency abdominal surgery is associated with a significantly lower incidence of PRF and death. Postoperative pulmonary complications, and even more PRF, are a particularly significant problem following emergency surgery and affect several thousands of patients worldwide each year. The prevention of postoperative pulmonary complications has been identified one of the top ten current priorities in perioperative intensive care medicine.³⁹ Mechanical

ventilation is among the modifiable risk factors associated with the development of postoperative pulmonary complications. However, although some guidelines have been issued, providing evidence-based recommendations for the settings of mechanical ventilation during elective surgery,¹¹ there remains significant controversy about the effects of PEEP and RM and a gap in knowledge in the context of emergency surgery.

Among the strengths of the trial are the multicentre design and the use of a robust primary endpoint that is pertinent to this high-risk patient population. The composite primary endpoint in the IMPROVE-2 trial consists in two components (PRF and all-cause mortality by day 30 or hospital discharge). Combined, these components may provide a clinically meaningful measure of efficacy in improving outcome after mechanical ventilation. Additionally, the patient group is easily identified in daily clinical practice combined with limited exclusion criteria lessening the chance of selection bias.

One limitation of the study is that anaesthesiologists are aware of the inclusion group and the patient anaesthesia record may be accessible to the clinical staff caring for the patient after surgery. However, given the characteristics of the two ventilation strategies under evaluation, a double-blind trial is not possible. The IMPROVE-2 trial, however, aims at minimising detection bias by blinding of the outcome assessor. Additionally, adjustments will be made after multivariate logistic regression by including variables independently associated with the primary outcome, and anticipated relationship with PRF. Finally, the study is not aimed at collecting data on all potential covariates (including blood products other than red blood cells) that may influence the association between the intervention and postoperative outcome measures. However, stratified random allocation of patients to study groups will help minimise potential confounding.

In conclusion, the IMPROVE-2 trial is an investigator-initiated pragmatic randomised clinical trial empowered to test the hypothesis that a lung-protective ventilation strategy aimed at increasing alveolar recruitment, using RM and driving pressure-guided individualised high PEEP levels, in comparison to a lung-protective ventilation strategy aimed at limiting alveolar distension, would help at reducing PRF and death after emergency surgery. Emergency abdominal surgery is common and optimisation of the mechanical ventilation strategy holds a markedly clinical potential to improve outcome.

Author affiliations

¹Département Anesthésie Réanimation, Centre Hospitalier Universitaire (CHU) Clermont-Ferrand, Clermont-Ferrand, France

²Département Anesthésie Réanimation B (DAR B), Centre Hospitalier Universitaire (CHU) Montpellier, Montpellier, France

³Département Anesthésie Réanimation, Centre Hospitalier Universitaire (CHU) Nantes, Nantes, France

⁴Direction de la Recherche Clinique & Innovation (DRCI), CHU Clermont-Ferrand, Clermont-Ferrand, France

⁵Inserm U-1103, Université Clermont Auvergne (UCA), Clermont-Ferrand, France

Contributors EF, TG, KA, GC and SJ are members of IMPROVE-2 trial scientific committee, and contributed to the conception and design of the research protocol. EF and BP designed the statistical analysis plan. LK, EF, TG, LA, JB and SJ contributed for drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. EF, TG, SJ and BP critically revised the protocol for intellectual content and approved the final version to be published.

Funding The study is supported by funding from French Ministry of Health (Programme Hospitalier de Recherche Clinique National 2014). The study promoter is the University Hospital of Clermont-Ferrand, Clermont-Ferrand, France.

Disclaimer The funding sources had no role in the trial design, trial conduct, data handling, data analysis or writing and publication of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Saunders DI, Murray D, Pichel AC, *et al.* Variations in mortality after emergency laparotomy: the first report of the UK emergency laparotomy network. *Br J Anaesth* 2012;109:368–75.
- 2 Clarke A, Murdoch H, Thomas MJ, *et al.* Mortality and postoperative care after emergency laparotomy. *Eur J Anaesthesiol* 2011;28:16–19.
- 3 Sørensen LT, Malaki A, Wille-Jørgensen P, *et al.* Risk factors for mortality and postoperative complications after gastrointestinal surgery. *J Gastrointest Surg* 2007;11:903–10.
- 4 Vester-Andersen M, Lundstrøm LH, Møller MH, *et al.* Mortality and postoperative care pathways after emergency gastrointestinal surgery in 2904 patients: a population-based cohort study. *Br J Anaesth* 2014;112:860–70.
- 5 Al-Temimi MH, Griffee M, Ennis TM, *et al.* When is death inevitable after emergency laparotomy? analysis of the American College of surgeons national surgical quality improvement program database. *J Am Coll Surg* 2012;215:503–11.
- 6 Neto AS, Hemmes SNT, Barbas CSV, *et al.* Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. *Lancet Respir Med* 2014;2:1007–15.
- 7 Gupta H, Gupta PK, Fang X, *et al.* Development and validation of a risk calculator predicting postoperative respiratory failure. *Chest* 2011;140:1207–15.
- 8 Abbott TEF, Fowler AJ, Pelosi P, *et al.* A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *Br J Anaesth* 2018;120:1066–79.
- 9 Johnson RG, Arozullah AM, Neumayer L, *et al.* Multivariable predictors of postoperative respiratory failure after general and vascular surgery: results from the patient safety in surgery study. *J Am Coll Surg* 2007;204:1188–98.

- 10 Futier E, Marret E, Jaber S. Perioperative positive pressure ventilation: an integrated approach to improve pulmonary care. *Anesthesiology* 2014;121:400–8.
- 11 Young CC, Harris EM, Vacchiano C, *et al.* Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. *Br J Anaesth* 2019;123:898–913.
- 12 Guay J, Ochroch EA, Cochrane Anaesthesia, Critical and Emergency Care Group. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. *Cochrane Database Syst Rev* 2015;14. CD011151.
- 13 Futier E. Positive end-expiratory pressure in surgery: good or bad? *Lancet* 2014;384:472–4.
- 14 Futier E, Constantin J-M, Paugam-Burtz C, *et al.* A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369:428–37.
- 15 Severgnini P, Selmo G, Lanza C, *et al.* Protective mechanical ventilation during general anaesthesia for open abdominal surgery improves postoperative pulmonary function. *Anesthesiology* 2013;118:1307–21.
- 16 Hemmes SNT, Gama de Abreu M, *et al.*, PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014;384:495–503.
- 17 Bluth T, Serpa Neto A, *et al.*, Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVENet) for the Clinical Trial Network of the European Society of Anaesthesiology. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on postoperative pulmonary complications in obese patients: a randomized clinical trial. *JAMA* 2019;321:2292–305.
- 18 Richard JC, Maggiore SM, Jonson B, *et al.* Influence of tidal volume on alveolar recruitment: respective role of PEEP and a recruitment maneuver. *Am J Respir Crit Care Med* 2001;163:1609–13.
- 19 Slutsky AS, Ranieri VM. Ventilator-Induced lung injury. *N Engl J Med* 2013;369:2126–36.
- 20 Fanelli V, Mascia L, Puntorieri V, *et al.* Pulmonary atelectasis during low stretch ventilation: "open lung" versus "lung rest" strategy. *Crit Care Med* 2009;37:1046–53.
- 21 Maia LdeA, Samary CS, Oliveira MV, *et al.* Impact of different ventilation strategies on driving pressure, mechanical power, and biological markers during open abdominal surgery in rats. *Anesth Analg* 2017;125:1364–74.
- 22 Neto AS, Hemmes SNT, Barbas CSV, *et al.* Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data. *Lancet Respir Med* 2016;4:272–80.
- 23 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- 24 Brown SM, Duggal A, Hou PC, *et al.* Nonlinear imputation of PaO₂/FIO₂ from SpO₂/FIO₂ among mechanically ventilated patients in the ICU: a prospective, observational study. *Crit Care Med* 2017;45:1317–24.
- 25 Brown SM, Jones BE, Jephson AR, *et al.* Validation of the infectious disease Society of America/American thoracic Society 2007 guidelines for severe community-acquired pneumonia. *Crit Care Med* 2009;37:3010–6.
- 26 Amato MBP, Meade MO, Slutsky AS, *et al.* Driving pressure and survival in the acute respiratory distress syndrome. *N Engl J Med* 2015;372:747–55.
- 27 Güldner A, Kiss T, Serpa Neto A, *et al.* Intraoperative protective mechanical ventilation for prevention of postoperative pulmonary complications: a comprehensive review of the role of tidal volume, positive end-expiratory pressure, and lung recruitment maneuvers. *Anesthesiology* 2015;123:692–713.
- 28 PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SNT, Gama de Abreu M, *et al.* High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014;384:495–503.
- 29 Serpa Neto A, Hemmes SNT, Barbas CSV, *et al.* Protective versus conventional ventilation for surgery: a systematic review and individual patient data meta-analysis. *Anesthesiology* 2015;123:66–78.
- 30 Chanques G, Conseil M, Roger C, *et al.* Immediate interruption of sedation compared with usual sedation care in critically ill postoperative patients (SOS-Ventilation): a randomised, parallel-group clinical trial. *Lancet Respir Med* 2017;5:795–805.
- 31 Hulzebos EHJ, Helders PJM, Favié NJ, *et al.* Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. *JAMA* 2006;296:1851–7.
- 32 Vincent JL, Moreno R, Takala J, *et al.* The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. on behalf of the Working group on sepsis-related problems of the European Society of intensive care medicine. *Intensive Care Med* 1996;22:707–10.
- 33 Boles J-M, Bion J, Connors A, *et al.* Weaning from mechanical ventilation. *Eur Respir J* 2007;29:1033–56.
- 34 Jaber S, Lescot T, Futier E, *et al.* Effect of noninvasive ventilation on tracheal Reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. *JAMA* 2016;315:1345–53.
- 35 Jammer I, Wickboldt N, Sander M, *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European perioperative clinical outcome (EPCO) definitions: a statement from the ESA-ESICM joint Taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88–105.
- 36 Ards Definition Task Force, Ranieri VM, Rubenfeld GD, *et al.* Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33.
- 37 Gattinoni L, Tonetti T, Cressoni M, *et al.* Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567–75.
- 38 Urner M, Jüni P, Hansen B, *et al.* Time-Varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. *Lancet Respir Med* 2020;8:905–13.
- 39 Gillies MA, Sander M, Shaw A, *et al.* Current research priorities in perioperative intensive care medicine. *Intensive Care Med* 2017;43:1173–86.

Supplemental file 1. IMPROVE-2 trial endpoints definition

All definitions are assessed according to previously defined criteria and consensus guidelines.¹⁻⁶

Weaning failure after surgery: Unsuccessful liberation from mechanical ventilation within the first 12 hours after the end of surgery.

Criteria for reintubation:

Immediate reintubation will be performed in case of any of the following criteria:

- 1) Respiratory or cardiac arrest,
- 2) Respiratory pauses with loss of consciousness or gasping for air,
- 3) Massive aspiration,
- 4) Persistent inability to remove respiratory secretions,
- 5) Heart rate of less than 50/min with loss of alertness,
- 6) Severe hemodynamic instability without response to fluid and vasoactive drugs.

If the patient is to return to the operating room for diagnostic procedure and is intubated as part of the anesthesia/procedure, this will not be counted as a reintubation. If a patient self-extubated and has to be reintubated, then it will also not be counted as a reintubation.

Criteria for postoperative curative NIV:

Postoperative NIV will be considered in case of presence and persistence for more than 30 minutes of hypoxemia and at least one of the following:

- 1) A respiratory rate higher than 30/min
- 2) Clinical signs suggestive of intense respiratory muscle work and/or labored breathing, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retraction

Hypoxemia is defined as $\text{PaO}_2 < 8 \text{ kPa}$ (60 mmHg) when breathing room air or $< 80 \text{ mm Hg}$ when breathing 15 L/min of oxygen, or a $\text{PaO}_2/\text{FIO}_2$ ratio $< 40 \text{ kPa}$ (300 mmHg) or arterial oxyhemoglobin saturation measured with pulse oximetry $< 90\%$ when breathing room air

Ventilator-free days:

Ventilator-free days to day 30 (VFDs) is defined as the number of days from the time of initiating unassisted breathing (breathing without support of the mechanical ventilator - including invasive or non-invasive ventilation) until day 30 after enrollment. Patients who will die prior to day 30 after enrollment will receive a value of 0 for VFDs. Patients who will never achieve unassisted breathing prior to day 30 after enrollment will receive a value of 0 for VFDs. Patients who will achieve unassisted breathing, will return to assisted breathing (either invasive or non-invasive ventilation), and will not again achieve unassisted breathing before day 30 after enrollment will receive a value of 0 for VFDs. For patients who will achieve unassisted breathing, will return to assisted breathing (either invasive or non-invasive ventilation), and will subsequently achieve unassisted breathing again prior to day 30 after enrollment, VFDs will be awarded based on the time of the final initiation of unassisted breathing prior to day 30 after enrollment. Survivors who will never experience assisted breathing will received 30 VFDs.

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.

Organ dysfunction can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection.

Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressor to maintain MAP ≥ 65 mmHg and having a serum lactate level > 2 mmol/l despite adequate volume resuscitation.

Pneumonia: The CDC defines pneumonia as follows:

Two or more serial chest radiographs with the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

- 1) New or progressive and persistent infiltrates
- 2) Consolidation
- 3) Cavitation;

AND at least one of the following:

- 1) Fever ($> 38^{\circ}\text{C}$) with no other recognized cause
- 2) Leucopenia (white cell count $< 4 \times 10^9 \text{ l}^{-1}$) or leukocytosis (white cell count $> 12 \times 10^9 \text{ l}^{-1}$)
- 3) for adults > 70 years old, altered mental status with no other recognized cause;

AND at least two of the following:

- 1) New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
- 2) New onset or worsening cough, or dyspnea, or tachypnea
- 3) Rales or bronchial breath sounds
- 4) Worsening gas exchange (hypoxemia, increased oxygen requirement, increased ventilator demand).

Mechanical power:

Mechanical power (MP) will be calculated as proposed previously^{7 8}:

MP (expressed in J/min) = $0.098 \times \text{VT} \times \text{RR} \times (\text{P}_{\text{peak}} - 1/2 \times \Delta\text{P})$, using tidal volume (VT), peak pressure (P_{peak}), respiratory rate (RR), and driving pressure (ΔP) data.

MP will be computed from data at the beginning (surgical incision) and at the end of surgery (skin closure), and daily (08.00 am) in patients receiving invasive controlled mechanical ventilation.

KDIGO criteria for acute kidney injury:

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline or ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) increase	< 0.5 ml/kg/h for 6-12 h
2	2.0-2.9 times baseline or ≥ 4.0 mg/dl (≥ 353.6 $\mu\text{mol/l}$) increase	< 0.5 ml/kg/h for ≥ 12 h
3	3 times baseline or ≥ 4.0 mg/dl (≥ 353.6 $\mu\text{mol/l}$) increase or initiation of RRT	< 0.3 ml/kg/h ≥ 24 h or anuria ≥ 12 h

Sequential-related organ failure assessment (SOFA) scoring (excluding Glasgow Coma Score):

Organ system	0	1	2	3	4
Respiration PaO ₂ /FiO ₂ (mmHg)	≥ 400	< 400	$< 300^*$	$< 200^\dagger$	$\leq 100^\dagger$
Coagulation Platelets ($\times 10^3/\text{mm}^3$)	≥ 150	101–150	51–100	21–50	≤ 20
Liver Bilirubin ($\mu\text{mol/l}$)	< 20	20–32	33–101	102–204	> 204
Cardiovascular Hypotension	MAP ≥ 70 mmHg	MAP < 70 mmHg	dopamine ≤ 5.0 ($\mu\text{g/kg/min}$) or any dose dobutamine	dopamine > 5.0 ($\mu\text{g/kg/min}$) or noradrenalin ≤ 0.1 or adrenalin ≤ 0.1	dopamine > 15.0 ($\mu\text{g/kg/min}$) or adrenalin > 0.1 or noradrenalin > 0.1
Renal Creatinine ($\mu\text{mol/l}$)	< 110	110–170	171–299	300–440	> 440
OR urine output				or < 500 ml/day	or < 200 ml/day

*without respiratory support, \dagger with respiratory support

The most deranged value recorded in the previous 24 h is to be used. If a value has not been measured, the score 0 should be given.

Respiratory support is defined as any form of invasive or non-invasive ventilation including continuous positive airway pressure delivered through mask or tracheotomy

ICU-free days (censored at 30 days after enrollment surgery):

Intensive care unit-free days (ICU-free days) to day 30 is defined as the number of days from the time of the patient's physical transfer out of the ICU until day 30 after enrollment. Patients who will die prior to day 30 after enrollment will receive a value of 0 for ICU-free days. Patients who will never be transferred out of the ICU prior to day 30 after enrollment will receive a value of 0 for ICU-free days. Patients who will be transferred out of the ICU, will return to the ICU, and will not subsequently be transferred out of the ICU again before day 30 after enrollment will receive a value of 0 for ICU-free days. For patients who will be transferred out of the ICU, will be readmitted to the ICU, and will subsequently be transferred out of the ICU again prior to day 30 after enrollment, ICU-free days will be awarded based on the time of the final transfer out of the ICU prior to day 30 after enrollment.

References

1. Jammer I, Wickboldt N, Sander M, *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015;32:88-105.
2. Vincent JL, Moreno R, Takala J, *et al.* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-10.
3. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.
4. Singer M, Deutschman CS, Seymour CW, *et al.* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
5. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179-84.
6. Jaber S, Lescot T, Futier E, *et al.* Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. *JAMA* 2016;315:1345-53.
7. Gattinoni L, Tonetti T, Cressoni M, *et al.* Ventilator-related causes of lung injury: the mechanical power. *Intensive Care Med* 2016;42:1567-75.
8. Urner M, Juni P, Hansen B, *et al.* Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. *Lancet Respir Med* 2020;8:905-13.

Supplemental file 2. IMPROVE-2 trial statistical analysis plan

Populations

Intention-to treat (ITT) population: All randomised patients except those who withdrew their consent for the use of data.

Per-protocol populations:

- **Per-protocol #1:** All randomised patients except patients having one or more major protocol violations defined as:
 1. High PEEP level and/or recruitment manoeuvres not given in patients randomly allocated to the increased alveolar recruitment strategyOR
 2. High PEEP level and/or recruitment manoeuvres were applied in patients randomly allocated to the minimal alveolar distension strategyOR
 3. Monitoring revealed that a tidal volume higher than 8 ml/kg PBW was appliedOR
 4. Monitoring revealed that one or more inclusion or exclusion criteria were violatedOR
 5. Patients withdrawn from the protocol because the patient (or the patient's next of kin or his/her legally authorized surrogate) would have withdrawn consent
- **Per-protocol #2:** All randomised patients except patients having one or more major protocol violations defined as:
 1. High PEEP level and/or recruitment manoeuvres not given in patients randomly allocated to the increased alveolar recruitment strategyOR
 2. High PEEP level and/or recruitment manoeuvres were applied in patients randomly allocated to the minimal alveolar distension strategy

Analyses

All analyses will be performed with the use of Stata software (version 13, StataCorp, College Station, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines.

The primary analysis will be by intention-to-treat (ITT) on the primary composite endpoint (postoperative respiratory failure and all-cause mortality by day 30 or hospital discharge). In addition, each component of the composite primary outcome will be analysed separately. With the exception of components of the composite primary outcome, no adjustment will be made for multiple comparisons. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary and tertiary endpoints will be interpreted as exploratory.

We will perform per-protocol and subgroup analyses on the primary endpoint and the most important secondary outcomes. The criteria for including patients in the ITT and in the per-protocol populations, respectively, are provided below.

Primary analysis:

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome. Result will be expressed as absolute difference, relative risk and 95% confidence intervals.

Secondary analyses:

Adjusted analyses for the primary outcome will be performed with the use of random-effects (to take into account within and between centre variability, with centre as random-effect) robust Poisson generalized linear model:

- Model #1: using stratification variables (shock at randomisation, hypoxaemia at randomisation) as covariates in addition to centre as random-effect;
- Model#2: using the same covariates in addition to variables with anticipated relationship with outcome. Multiple logistic mixed regression will be conducted with the following covariates (criterion for entering variables tested in the model will be selected if $P < 0.10$ and according to clinically relevant covariates with anticipated relationship with outcome):
 - Categorical variable
 - Trial centre (stratification variable, treated as random-effect)
 - Binary covariates
 - Shock (vasopressor use) at randomisation (stratification variable) Y/N
 - Hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 300$) at randomisation (stratification variable) Y/N
 - Presence of mechanical ventilation at randomisation Y/N
 - Sepsis at randomisation Y/N
 - Active smoking Y/N
 - $\text{BMI} > 35 \text{ kg/m}^2$ Y/N
 - Cancer Y/N
 - ASA class ≥ 3 Y/N
 - Surgical technique (laparotomy Y/N)
 - Reoperation procedure (previous elective surgery during current hospital stay, but prior to randomization) Y/N
 - Ordinal covariates
 - SOFA score at randomisation

- Continuous covariates (treated first step as continuous, and then if appropriate, as categorical data)
 - Age
 - Duration of surgery
 - Volume of intraoperative fluids

Multicollinearity between variables will be assessed by computing the variance inflation factor and using the Farrar-Glauber test. The Akaike information criterion and Bayesian information criterion will be calculated and used as model diagnostics to determine how well the model fit improved following addition of covariates. Results will be presented as relative risks and 95% confidence intervals.

Each component of the composite primary outcome measure (key secondary endpoints) will be analysed separately using similar methods as described for the primary analysis. A chi-square test (or Fisher's test, as appropriate) will be used for secondary binary outcomes. Results will be expressed as absolute differences, relative risks and 95% confidence intervals. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome. Adjusted analyses will be performed using the same models described above.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test when appropriate. The Shapiro-Wilk test will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Results will be expressed as effect-sizes and 95% confidence intervals. For non-Gaussian data, results will be presented using median difference and 95% confidence intervals estimated using quantile regression model. For secondary efficacy endpoints and tertiary endpoints, adjusted analyses will be conducted using variables described in model #1. According to the statistical nature of dependant variable (continuous), linear mixed models will be performed including centre as random-effect. For ventilator-free days to day 30, generalized linear models will initially use Poisson distribution or alternatively negative binomial distribution. If assumptions for these distributions are not met, we will analyse the data using the nonparametric Van Elteren test adjusted for center, only.

Time-to-event curves will be calculated with the use of the Kaplan-Meier method and will be compared using log-rank test in univariate context and marginal Cox proportional hazards model in multivariate analysis. Centre will be considered as random-effect. The proportional-hazard hypothesis will be verified using Schoenfeld's test and plotting residuals. Results will be expressed as hazard ratios and 95% confidence interval. Adjusted analyses will be conducted using variables described in model #1.

Level of statistical significance for all analyses: $P = 0.05$.

Pre-planned subgroup analyses:

Planned subgroup analyses will assess heterogeneity of treatment effects of the primary endpoint across BMI categories (defined as underweight <18.5, normal 18.5-25, overweight 25-30, obese 30-35), ASA physical status (1 or 2, 3, 4), hypoxemia at

randomisation (Y/N), shock (vasopressor use) at randomisation (Y/N), sepsis at randomisation (Y/N), surgical procedure (laparoscopy or laparotomy), duration of surgery (approximate quartiles), volume of intraoperative fluids (approximate quartiles), preventive NIV after extubation (Y/N).

According to usual recommendations, the interactions between group randomization and subgroups will be evaluated in regression models (i.e., random-effects models, linear or generalized linear).

The primary outcome will be evaluated in the subgroup analyses without adjustments for multiplicity.

Interim analysis:

The DSMC will conduct two interim analyses, after data from 170 patients (25%) and 340 patients (50%) have been obtained, to evaluate whether the conduct of the trial may compromise patient safety (a between-group difference in mortality). Both interim analyses will use the same stopping criteria. Recommendations for pausing or stopping the study will be made by the DMSC if the P value is less than 0.00001 (first interim analysis) or less than 0.003 (second interim analysis) for the between-group difference in the incidence of mortality (O'Brien-Fleming spending function). The steering committee will be responsible to continue, hold or stop the study based on the DMSC recommendations. As even small between-groups differences would be clinically meaningful, and given the importance of determining with as much certainty as possible whether a ventilation strategy is superior to the other one, a futility stopping boundary will not be employed. Use of the conservative O'Brien-Fleming boundaries ($P < 0.00001$ and $P < 0.003$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$).

Endpoints

Primary endpoint:

A composite of postoperative respiratory failure (defined as failure to wean from the ventilator after surgery or requiring unplanned reintubation or curative non-invasive ventilation once extubated postoperatively) and all-cause mortality by day 30 or hospital discharge

Secondary Endpoints:

- Key secondary endpoints:
 - o Postoperative respiratory failure within 30 days
 - o All-cause mortality within 30 days
- Secondary efficacy endpoints
 - o Severity of postoperative pulmonary complications within 30 days following surgery. Pulmonary complications will be scored on a grade scale ranging from 0 to 4, with grade 0 representing the absence of any pulmonary complication and grades 1 through 4 representing successively the worse forms of pulmonary complications
 - o Renal dysfunction (defined as KDIGO stage 1 or higher) within 30 days following surgery
 - o Sepsis and septic shock within 30 days following surgery
 - o Sepsis-related Organ Failure Assessment score (excluding Glasgow Coma Score) from postoperative Day 1 to Day 7
 - o Ventilator-free days (VFDs) to Day 30. A ventilator-free day is defined as the receipt as <2 hours of invasive mechanical ventilation or non-invasive mechanical ventilation (as curative therapy) within a 24-hour period
 - o Duration of invasive mechanical ventilation from randomization to first tracheal extubation
 - o Total duration of mechanical ventilation (additive, for all episodes up to 30 days after surgery)
 - o Time to successful tracheal extubation
 - o Intensive care unit (ICU)-free days (censored at 30 days following surgery)
 - o Duration of ICU and hospital stay (patients who will be outside the hospital but in other types of health care facilities at day 30 will be considered to have been discharged home)
 - o Time to death (or censoring)

Tertiary Endpoints:

- Postoperative hypoxemia
- Postoperative pneumonia
- Acute respiratory distress syndrome (ARDS)
- Amount of intravenous fluids (crystalloids and colloids) during surgery
- Amount of vasopressor (norepinephrine, phenylephrine, ephedrine) during surgery
- Mechanical power
- Ventilatory-related adverse events: hemodynamic instability (defined as a drop of arterial systolic pressure below 80 mmHg for more than 5 minutes not responding to intravenous fluids and/or vasopressors), pneumothorax.
- Rescue therapy for intraoperative hypoxemia
- All-cause mortality to day 90

Missing data

Initially, a complete case-analysis will be performed. Supplementary analyses using imputed data will be also performed as described below:

Missing baseline data:

The SOFA score does not depend on when the patient is admitted to the hospital but we register SOFA at baseline including values from the first hours prior to randomisation. Patients randomised in a few hours after hospital admission may thus have missing values. If the frequency of missing data is >5%, an additional analysis will be performed using the multiple imputation method (STATA command mi).

Missing primary outcome data:

We do not expect missing data on the primary outcome measure and only complete case-analysis will be performed.

Missing secondary outcomes data:

Only complete case analysis will be made.

To put significant results into perspective the following sensitivity analysis will be conducted: We define a worst-case scenario as one where patients with missing data do not react on the treatment (whatever it may be). Missing data will be imputed according to this scenario. Let P be the estimate of the parameter reflecting the effect of the intervention calculated from the complete case analysis and $P\text{-imp}$ be the corresponding estimate calculated from the analysis of the imputed data.

$[(P\text{-imp} - P)/P\text{-imp}] * 100\%$ then a ball park figure of the bias is to be expected were the worst-case scenario true. $P\text{-imp} / (\text{standard error of } P\text{-imp})$ is calculated and the corresponding p value found to assess the potential impact of this bias on the significance level.

Supplemental File 3. Data Sharing Statement

Intraoperative Protective Mechanical Ventilation in Patients Requiring Emergency Abdominal Surgery: The multicenter prospective randomized IMPROVE-2 study protocol

Question	Response
Will the data collected for your study be made available to others?	Yes
What data will be shared?	The French National Data Safety Authority (CNIL) forbids making data freely available without prior agreement. Thus, the data underlying study findings cannot be made freely available because of ethical and legal restrictions. However, individual participant data underlying the results reported in the manuscript (text, tables, figures, and appendices) can be obtained after deidentification. Data can be obtained upon request from the IMPROVE-2 steering committee. Readers may contact: efutier@chu-clermontferrand.fr to request the data.
Additional information about data	—
How or where can the data be obtained?	The data cannot be freely available for the reasons mentioned above. Data access can be only possible after scientific assessment and data sharing agreement, detailing the type of data requested. This data sharing agreement has to be signed between applicants and the sponsor, Clermont-Ferrand University Hospital.
When will data be available (start and end dates)?	Beginning 6 months following article publication. No end date.
Will any supporting documents be available?	Yes

Which supporting documents?	Data dictionary
Additional information about supporting documents	—
How or where can supporting documents be obtained?	The data cannot be freely available for the reasons mentioned above. Data access can be only possible after scientific assessment and data sharing agreement, detailing the type of data requested. This data sharing agreement has to be signed between applicants and the sponsor, Clermont-Ferrand University Hospital.
When will supporting documents be available (start and end dates)?	Beginning 6 months following article publication. No end date.
To whom will data be available?	Any researcher whose proposed use of the data has been approved
For what type of analysis or purpose?	Any purpose. Applications will be assessed for their scientific relevance.
By what mechanism will data be available?	To gain access, data requestors will need to sign a data access agreement
Any other restrictions?	—
Additional information	—