RESEARCH PROTOCOL

Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery (GENERATOR) – a Randomized Clinical Trial

The GENERATOR–investigators
for the PROtective VEntilation (PROVE) Network

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	adverse event
AKIN	acute kidney injury network
ARDS	acute respiratory distress syndrome
ARISCAT risk score	Assess Respiratory Risk in Surgical Patients in Catalonia risk score
AVG	[Algemene Verordening Gegevensbescherming]
BIA	budget impact analysis
BMI	body mass index
CI	confidence interval
CO_2	carbon dioxide
COPD	chronic obstructive pulmonary disease
(e)CRF	(electronic) case record form
DESIGNATION	Driving Pressure During General Anesthesia for Open Abdominal Surgery – a randomized clinical trial
DSMB	data safety monitoring board
EIT	electric impedance tomography
ERAS	enhanced recovery after surgery
$etCO_2$	end–tidal carbon dioxide
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	generalized estimating equations
ICU	intensive care unit
IQR	interquartile range
ITT	intention–to–treat
H_2O	water
Hb	hemoglobin
LAS VEGAS	Local ASsessment of VEntilator management during General AneSthesia for surgery – a prospective observational study
MAP	mean arterial pressure
METC	[Medisch Ethische Toetsings Commissie]
NFU	[Nederlandse Federatie of UMCs]
OR	odds ratio
ΔP	driving pressure
PaO_2	partial pressure of oxygen in the arterial blood
PEEP	positive end–expiratory pressure
PBW	predicted body weight
PROBESE	PRotective intraoperative ventilation with higher versus lower levels of positive end-expiratory pressure in OBESE patients – a randomized clinical trial
PROVHILO	PROtective Ventilation HIgh versus LOw PEEP – a randomized clinical trial
PPC	postoperative pulmonary complication

RM	recruitment maneuver
SAE	serious adverse event
SD	standard deviation
SOFA score	Sequential Organ Failure Assessment score
SpO_2	oxygen saturation
TOF	train–of–four
UMC	University Medical Center
VAS	visual analogue scale
V_T	tidal volume
WBC	white blood cell
WMO	[Wet Medisch–wetenschappelijk Onderzoek met Mensen]

SUMMARY

Rationale

The intraoperative driving pressure (ΔP) has an independent association with the development of postoperative pulmonary complications (PPCs) in patients receiving ventilation during general anesthesia for major surgery. Ventilation with high intraoperative positive end–expiratory pressure (PEEP) with recruitment maneuvers (RMs) that results in a low ΔP has the potential to prevent PPCs.

Objective

To determine if an individualized high PEEP strategy with RMs, targeting a low ΔP, prevents PPCs in patients undergoing intraoperative ventilation during general anesthesia for major minimally invasive abdominal (i.e., laparoscopic, or robotic) surgery.

Hypothesis

Compared to standard low PEEP without RMs, an individualized high PEEP strategy with RMs prevents PPCs in patients receiving intraoperative protective ventilation during anesthesia for major minimally invasive abdominal surgery.

Trial design

Investigator–initiated international multicenter randomized clinical trial.

Trial population

Patients scheduled for major minimally invasive abdominal surgery and with an increased risk of PPCs based on: (i.) the ARISCAT risk score for PPCs (≥ 26 points), or (ii.): a combination of age > 40 years, scheduled surgery lasting > 2 hours and planned to receive an intra–arterial catheter for blood pressure monitoring during surgery.

Intervention

Individualized high PEEP titrated to the lowest ΔP with RMs *versus* standard low PEEP of 5 cm H_2O without RMs.

Main trial parameters/endpoints

The primary outcome is a collapsed composite endpoint of PPCs until postoperative day five. Secondary outcomes are intraoperative complications, extrapulmonary postoperative complications, length of hospital stay and related healthcare costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Patient burden and risks are low, the collection of general data from hospital charts and (electronic) medical records systems causes no harm to the patients; as the patient is already scheduled to receive general anesthesia during the intervention. PEEP titrations and RMs are standard care and will be protocolized in this trial.

1. INTRODUCTION AND RATIONALE

1.1 Postoperative pulmonary complications

Postoperative complication incidence rates of up to 40% have been reported in patients receiving ventilation during general anesthesia for major surgery (1-4). Postoperative complications that involve the lungs, so–called postoperative pulmonary complications (PPCs), greatly increase hospital death and hospital length of stay (3). Considering an estimated 55 million abdominal surgery procedures are performed each year worldwide, even a small reduction in PPCs would have an enormous impact on healthcare costs (4, 5).

1.2 Intraoperative driving pressure is associated with development of PPCs

Intraoperative lung–protective ventilation may prevent PPCs (6, 7). The intraoperative driving pressure (ΔP) has an independent association with PPCs (8). The ΔP is dependent on the diverse effects of positive end–expiratory pressure (PEEP) and applied recruitment maneuvers (RMs): when PEEP with RMs increase the amount of aerated lung tissue, ΔP will remain low or can even decrease. However, when PEEP with RMs does not increase the amount of aerated lung tissue and instead causes overdistention of nondependent lung tissue, ΔP will increase. Accordingly, ΔP has been proposed as a digital biomarker for guiding intraoperative PEEP settings (8). Currently, a trial named ‘Driving Pressure During General Anesthesia for Open Abdominal Surgery’ (DESIGNATION) tests whether individualized high PEEP with RMs targeting a low ΔP compared to standard low PEEP without RMs reduces the incidence of PPCs in patients planned for *open* abdominal surgery (9).

1.3 Trend towards minimally invasive surgery

Over the past decade, minimally invasive abdominal surgery has become more popular than open abdominal surgery. The rapidly expanding group of patients undergoing minimally invasive abdominal surgery represents a challenging cohort, as both the Trendelenburg positioning and the pneumoperitoneum cause a cephalad shift of the diaphragm, potentially changing the effects of PEEP with RMs on the amount of aerated lung tissue (10, 11) and consequently the effect on PPCs.

1.4 Need for a new trial

A recent worldwide prospective observational study showed that 65% of patients undergoing minimally invasive abdominal surgery are at increased risk for developing PPCs, and the association between intraoperative ΔP and PPCs has been found to be much stronger in patients undergoing minimally invasive abdominal surgery than in patients undergoing open abdominal surgery (12, 13). ΔP can be reliably and reproducibly determined during pneumoperitoneum (13). It remains uncertain whether the ventilatory approach tested in DESIGNATION could also prevent PPCs in patients undergoing minimally invasive abdominal surgery.

1.5 A trial in patients undergoing minimally invasive abdominal surgery

This proposed randomized clinical trial, named the ‘Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery’ (GENERATOR) investigates whether individualized high PEEP with RMs reduces the development of PPCs in patients planned for major minimally invasive abdominal surgery.

2. OBJECTIVES

The 'Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery' (GENERATOR) trial compares an intraoperative ventilation strategy with individualized high positive end–expiratory pressure (PEEP) with recruitment maneuvers (RMs) with standard low PEEP without RMs in patients undergoing major minimally invasive abdominal surgery.

2.1 Primary objective

The primary objective is to compare the two ventilation strategies with respect to the development of postoperative pulmonary complications (PPCs).

2.2 Secondary objectives

The secondary objective is to compare the two ventilation strategies with respect to intraoperative complications, extrapulmonary postoperative complications, duration of stay in the hospital and the associated related healthcare costs.

2.3 Hypotheses

We hypothesize that an intraoperative ventilation strategy that uses individualized high PEEP with RMs, targeting a low driving pressure (ΔP), may prevents PPCs when compared to a ventilation strategy that uses standard low PEEP without RMs. We further hypothesize that the individualized high PEEP strategy with RMs could shorten duration of hospital stay and reduces the associated healthcare costs.

3. TRIAL DESIGN

The ‘Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery’ (GENERATOR) trial is an investigator–initiated international, multicenter, parallel, randomized clinical superiority trial in patients scheduled for major minimally invasive abdominal surgery with an increased risk for postoperative pulmonary complications. The trial will be conducted according to the principles of the Declaration of Helsinki and comply with Good Clinical Practice-guidelines, international, national and local regulatory requirements and general data protection regulations. The trial will be registered in a public registry and the trial protocol with its statistical analysis plan will be prepublished.

4. TRIAL POPULATION

4.1 Population (base)

Patients scheduled for major minimally invasive abdominal surgery and at increased risk of developing postoperative pulmonary complications (PPCs) will be enrolled. Patients will be assessed for the risk of PPCs by using the 'Assess Respiratory Risk in Surgical Patients in Catalonia' (ARISCAT) risk score for postoperative pulmonary complications (3, 4), or a combination of inclusion criteria as recently used in a recent randomized clinical trial of ventilation in patients undergoing major surgery (14). Patients will be included in selected centers in The Netherlands and also in selected centers in other European countries.

4.2 Inclusion criteria

In order to be eligible to participate in this trial, a patient must meet the following criteria:

1. age > 18 years;
2. scheduled for minimally invasive abdominal surgery; **AND**
3. increased (i.e., intermediate or high) risk of PPCs according to the ARISCAT risk score (≥ 26 points, see Appendix I); **OR**
4. the combination of age > 40 years, scheduled surgery lasting > 2 hours and planned to receive an intra–arterial catheter for blood pressure monitoring during the surgery;
5. signed written informed consent

4.3 Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this trial:

1. planned for open abdominal surgery;
2. planned for surgery in lateral or prone position;
3. planned for combined abdominal and intra-thoracic surgery
4. confirmed pregnancy;
5. consent for another interventional trial during anesthesia;
6. having received invasive ventilation > 30 minutes within the last five days;
7. any previous lung surgery;
8. history of previous severe chronic obstructive pulmonary disease (COPD) with (noninvasive) ventilation or oxygen therapy at home or repeated systemic corticosteroid therapy for acute exacerbations of COPD;
9. history of acute respiratory distress syndrome (ARDS);
10. expected to require postoperative ventilation;
11. expected hemodynamic instability or intractable shock;
12. severe cardiac disease (New York Heart Association class III or IV, acute coronary syndrome or persistent ventricular tachyarrhythmia's).

4.4 Sample size calculation

The required sample size is calculated based on an estimated effect size derived from individual patient data from previous studies (6, 15, 16). Based on a recently published randomized clinical trial (14), we conservatively estimate an incidence of PPCs of 30% in the standard low positive end–expiratory pressure (PEEP) group. To have a power of 80% to detect a relative risk reduction in the incidence of PPC of 20% (24 vs 30%), under an alpha of 0.05, 860 patients in each group is needed. To allow for a dropout rate of 5% and accounting for conversion to open surgery, 903 patients per group are needed. The total sample size is therefore 1806 patients.

4.5 Safety analysis

Safety analyses will be performed at 25%, 50% and 75% of patients included. Results of the safety analysis will be presented to the members of the Data Safety Monitoring Board (DSMB) and will be discussed at planned meetings.

5. TREATMENT OF PATIENTS

5.1 The intervention to be investigated

The intervention to be investigated is an intraoperative ventilation strategy with individualized high positive end–expiratory pressure (PEEP) with recruitment maneuvers (RMs), aimed at maximum recruitment of lung tissue without causing overdistention, targeting a low driving pressure (ΔP) (hereafter named the 'individualized PEEP strategy'). The intervention is compared to an intraoperative ventilation strategy with standard low PEEP without RMs (hereafter named the 'standard PEEP strategy'). Detailed information on the two ventilation strategies is provided thereafter.

5.2 Standard of care – perioperative clinical management

Postoperative pain management, physiotherapeutic procedures and fluid management will be performed in the postoperative period according to the specific expertise and routine clinical use of each center. The investigators suggest adherence to the Enhanced Recovery After Surgery (ERAS) guidelines (http://erassociety.org/guidelines/list-of-guidelines/):

- to perform postoperative pain management in order to achieve a VAS pain score below 4, regional or neuraxial analgesia can be used whenever indicated;
- to use physiotherapy by early mobilization, deep breathing exercises with and without incentive spirometry, and stimulation of cough in the postoperative period;
- to avoid fluid overload (according to the discretion of the attending anesthesiologist);
- to use appropriate prophylactic antibiotics when indicated

Furthermore, regarding surgical perioperative procedures, the investigators suggest adhering to the Safe Surgery Checklist from the World Health Organization (Safe surgery [www.who.int]).

5.3 Standard of care – general aspects of anesthesia

General anesthesia is performed according to the specific expertise and routine clinical practice of each center. General anesthesia achieved by using both volatile anesthetics and/or intravenous anesthetics is allowed. Quantitative neuromuscular monitoring (e.g., train–of–four (TOF) monitoring) is required. Before extubation, residual curarization should be addressed (e.g., TOF > 0.9).

5.4 Standard of care – general aspects of abdominal insufflation

Abdominal insufflation, as part of minimally invasive abdominal surgery, is performed by the attending surgeon or anesthesiologist. The level of applied intra–abdominal pressure is suggested to be between 8 – 12 cm H_2O, but can be changed for clinical reasons as judged by the attending surgeon or anesthesiologist.

5.5 Standard of care – general aspects of ventilation

In both groups, intraoperative ventilation will be provided by a standard anesthesia ventilator in use in the respective participating centers. Patients will be ventilated in volume–controlled

mode, at the lowest inspired oxygen fraction (FiO_2), but at least 0.4, to maintain oxygen saturation (SpO_2) > 90%. A pause time (between inspiration and exhalation) of 15% for each breath will be used. It is left to the discretion of the attending anesthesiologist to use a higher fraction of FiO_2. Inspiratory to expiratory ratio is set at 1:2, respiratory rate will be adjusted to target normocapnia (end–tidal carbon dioxide partial pressure between 35–45 mm Hg or 4.6–5.9 kPa). Tidal volume (V_T) will be set at 8 ml/kg predicted body weight (PBW). The PBW is calculated according to a predefined formula: 50 + 0.91 x (centimeters of height – 152.4) for males and 45.5 + 0.91 x (centimeters of height – 152.4) for females. V_T throughout this protocol refers to the actual V_T measured constantly in the ventilator circuit. In both groups, ventilation starts with 5 cm H_2O PEEP.

5.6 The intervention – individualized high PEEP

The intervention is ventilation with individualized high PEEP titrated to the lowest ΔP with RMs. After abdominal insufflation, patients randomized to the individualized high PEEP group will receive a RM followed by a 'decremental PEEP trial'. This is followed by a second RM after which PEEP is set at the level indicated by the decremental PEEP trial. This is illustrated in figure 1 and each step is described in detail below. The abdominal insufflation pressure needs to be stable during the intervention (RM's + decremental PEEP trial). The peak pressure alarm needs to be raised to 50 cm H_2O.

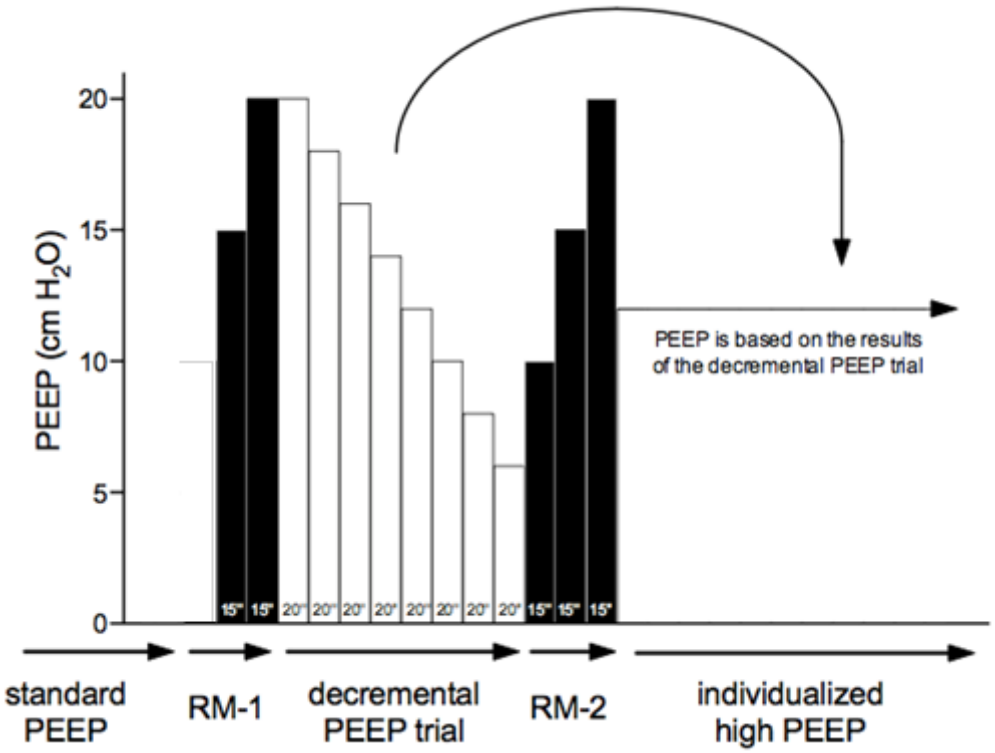

Figure 1 The RMs and decremental PEEP trial. See text for a detailed description of the RMs and the decremental PEEP trial. The numbers projected in each bar represent the duration of each step (in seconds).

RMs

The RM, as part of the individualized high PEEP strategy, will be performed after induction of anesthesia and after any disconnection from the mechanical ventilator. RMs are only to be performed in a hemodynamically stable situation, as judged by the attending anesthesiologist. For this, the ventilator remains in a volume–controlled mode, with the respiratory rate set at 15 breaths per minute and PEEP at 10 cm H_2O. Every 15 seconds, PEEP is increased in steps of 5 cm H_2O up to a PEEP level of 20 cm H_2O.

First RM

The first RM will be performed after abdominal insufflation and placement of all surgical instruments, i.e., in a steady state with sufficient working space for the surgeon. The surgeon is allowed to start surgery if no significant external pressure is applied on the abdomen and the abdominal insufflation pressure is stable.

The decremental PEEP trial

The decremental PEEP trial, as part of the individualized high PEEP strategy, is performed directly following the first RM. During the decremental PEEP trial, which is expected to last approximately 4 minutes, intra–abdominal surgical procedures are allowed. External pressure on the thorax and abdomen, however, must be avoided and no new instruments should be inserted. If the decremental PEEP trial is disturbed by this, the procedure is stopped and restarted. The decremental PEEP trial starts in a volume–controlled mode with PEEP at 20 cm H_2O and a respiratory rate of 15 breaths per minute. Every 20 seconds, PEEP is decreased in steps of 2 cm H_2O until the level of PEEP reaches 6 cm H_2O. Next, a PEEP–ΔP plot is drawn as has been done before in other trials (9, 17). Examples are shown in Appendix IV. A PEEP–ΔP chart will be used to draw this plot (see Appendix IV). From this plot, the highest PEEP at the lowest ΔP is determined. If no nadir in the PEEP–ΔP plot is present, PEEP of 12 cm H_2O will be selected.

Second RM

After the individualized PEEP level has been determined, a second RM from PEEP 6 cm H_2O to 20 cm H_2O will be performed passing the PEEP levels of 10 cm H_2O and 15 cm H_2O. After completion of the second RM, the individualized PEEP will be set and maintained until the end of ventilation.

Additional RM and decremental PEEP trials

The decremental PEEP trial is repeated after: (i.) a radical change in patient position, or (ii.) a radical change in intra–abdominal pressure (e.g. conversion to laparotomy, raising or lowering of intra-abdominal insufflation pressure, continuation of surgery without pneumoperitoneum), as judged by the attending anesthesiologist. Accordingly, if the additional decremental PEEP trial results in a different optimal PEEP level, this PEEP will be used until the end of surgery or until another radical change in patient position or intra–abdominal pressure. Of note, the

impact of these additional decremental PEEP trials on the optimal individualized PEEP level is evaluated after the first 100 patients and its necessity will be reconsidered.

Conversion to laparotomy

In case of conversion to laparotomy, the PEEP will be set to 10 cm H_2O during the conversion. After opening of the abdomen, the decremental PEEP trial will be repeated and the correct PEEP will be set until the end of surgery or until another radical change in patient position or intra–abdominal pressure.

Rescue therapies

Desaturation (defined as $SpO_2 \leq 90\%$; or if preoperative $SpO_2 < 90\%$ an absolute decrease in $SpO_2 > 5\%$) in patients receiving the individualized high PEEP strategy could reflect the presence of overdistention of aerated lung tissue, despite a low ΔP. If desaturations occur, in absence of airway problems, severe hemodynamic impairment or ventilator malfunction, a rescue strategy is allowed in which PEEP is stepwise *decreased* and eventually the fraction of inspired oxygen (FiO_2) is increased, as shown in Table 1.

Table 1. Rescue for desaturation

Step	PEEP	FiO_2
1	20	0.4
2	18	0.4
3	16	0.4
4	14	0.4
5	12	0.4
6	12	0.5
7	12	0.6
8	10	0.6
9	8	0.6
10	6	0.6
11	6	0.7
12	6	0.8

Table 1: Down–titration of PEEP as rescue of desaturation. Starts at the level of PEEP set after the decremental PEEP trial

5.7 The comparison – standard low PEEP

Patients randomized to the standard low PEEP group will receive 5 cm H_2O PEEP for the complete duration of general anesthesia. They will neither receive one of the planned RMs nor a decremental PEEP trial.

Rescue therapies

Desaturation (defined as $SpO_2 \leq 90\%$; or if preoperative $SpO_2 < 90\%$ an absolute decrease in $SpO_2 > 5\%$) in patients receiving the standard low PEEP strategy could reflect the presence of atelectasis. If desaturations occur, in absence of airway problems, severe hemodynamic impairment or ventilator malfunction, a rescue strategy is allowed in which FiO_2 is increased first, eventually followed by increasing PEEP and a RM, as shown in Table 2.

Table 2. Rescue for desaturation		
Step	PEEP	FiO_2
1	5	0.4
2	5	0.5
3	5	0.6
4	5	0.7
5	5	0.8
6	6	0.8
7	RM	

Table 2: Up titration of FiO_2, PEEP and RMs as rescue of desaturation.

5.8 Preapproved protocol deviations

In both groups, the attending anesthesiologist is allowed to change ventilator settings at any time point upon the surgeons' request or if there is any concern about patient's safety. If one of the following complications occurs and does not respond to conventional therapy, PEEP can be changed, according to the judgement of the anesthesiologist in charge:

- after PEEP titration, a mean arterial pressure < 65 mm Hg, lasting > 1 minute, not responding to fluids and/or vasoactive drugs (18);
- new arrhythmias not responding to the treatment suggested by the Advanced Cardiac Vascular Life Support Guidelines (19);
- need for a dosage of vasoactive drugs at the highest level tolerated, according to the decision of the anesthesiologist in charge;
- need of massive transfusion, more than 5 units of blood to maintain hematocrit > 21% and hemoglobin > 7 mg/dl; and
- surgical complication resulting in life–threatening situations.

6. METHODS

6.1 Trial period

Patients will be assessed before and during surgery, on postoperative days 1 to 5, the day before discharge and around day 90. Clinical data, occurrence and timing of intraoperative and postoperative complications will be captured. Intra– and postoperative complications will be scored as pulmonary– or extrapulmonary complication. Patients' health status (location i.e., in hospital or at home – alive or deceased, in case of the latter the day of dying) will be scored around postoperative day 90.

6.2 Primary endpoint

The primary outcome is a collapsed composite endpoint of postoperative mild and severe pulmonary complications (PPCs), as used before in preceding studies of intraoperative ventilation by our group (9, 15). PPCs will be scored on the first 5 postoperative days, but only on the days the patient is still admitted to the hospital, using a daily checklist in the eCRF. If the patient is discharged before postoperative day 5, we assume no PPCs occur, and therefore no PPCs will be scored on the days after discharge. If the patient is admitted for more than 5 days, there will be a day of discharge form and a checklist for the occurrence of PPCs between day 5 and the day of discharge. PPCs, as described below, occurring up to postoperative day 5, are all added together and weighed equally. The selected PPCs can be added together as they share common pathophysiological mechanisms, while it is plausible the intervention we investigate has a beneficial impact on these shared pathophysiological mechanisms. Patients who develop at least one PPC are scored as having met the primary endpoint. One local investigator, who will remain blinded for the allocated trial arm treatment, will score the occurrence of PPCs. The collapsed composite endpoint of PPCs includes:

- mild respiratory failure, defined as the occurrence of one or multiple of the following conditions:
  1. the occurrence of oxygen saturation (SpO_2) < 90% or partial pressure of oxygen in the arterial blood (PaO_2) < 7.9 kPa (or < 50 mm Hg) in room air, but responding to supplemental oxygen;
  2. a sudden increase in supplemental oxygen requirement to maintain adequate saturation (SpO_2 > 90%) in patients receiving routine postoperative oxygen therapy;
  3. any level of supplemental oxygen after more than two days postoperatively
- severe respiratory failure, defined as need for noninvasive or invasive mechanical ventilation, or a PaO_2 < 60 mm Hg (or < 7.9 kPa) or SpO_2 < 90% despite supplemental oxygen in spontaneously breathing patients;
- bronchospasm, defined as newly detected expiratory wheezing treated with bronchodilators;

- suspected pulmonary infection, defined as receiving antibiotics and meeting at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest radiograph when clinically indicated, tympanic temperature > 38.3°C, white blood cell (WBC) count > 12,000/µL;
- pulmonary infiltrate, defined as any unilateral or bilateral infiltrates on chest radiography;
- aspiration pneumonitis, defined as respiratory failure after the inhalation of regurgitated gastric contents;
- atelectasis, defined as lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non–atelectatic lung on chest radiography;
- acute respiratory distress syndrome (ARDS), according to the 'Berlin definition of ARDS' (20);
- pleural effusion, defined as blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows on chest radiography;
- cardiopulmonary edema, defined as clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest radiograph demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates; and
- pneumothorax, defined as air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiography.

6.3 Secondary endpoints

The secondary endpoints include intraoperative complications and fluid strategy, extrapulmonary postoperative complications, duration of hospital stay and related healthcare cost. Accordingly, the following variables are captured:

- intraoperative complications, that are not related to induction or change of the depth of anesthesia, are scored during steady state. Furthermore, of all intraoperative complications the relatedness to the ventilation strategy used must be reported (related, possibly related, not related). Intraoperative complications include:
  - any episode of desaturation, defined as oxygen saturation (SpO_2) ≤ 90% or if preoperative SpO_2 < 90% an absolute decrease in SpO_2 > 5%, and lasting > 1 minute;
  - any episode of hypotension, defined as a mean arterial pressure (MAP) below 65 mm Hg, lasting > 1 minute (18);

  - any need for vasoactive agents, either as bolus or continuous administration, defined as more than needed to compensate for vasodilating effects of anesthesia as judged by the attending anesthesiologist; and
  - any new arrhythmias needing intervention as suggested by the Advanced Cardiac Life Support Guidelines (19);
- intraoperative fluid strategy, including the total amount of fluids administered during anesthesia, including the amounts of colloids, crystalloids, and blood products;
- impaired wound healing, as judged and mentioned in the medical record by the attending ward physician;
- postoperative extrapulmonary complications (see Appendix III for definitions);
- all–cause mortality at day 5, day 30 and 90, and in–hospital mortality; and
- cost–effectiveness parameters:
  - presence, duration and levels of postoperative supplemental oxygen;
  - use of antibiotics for pneumonia;
  - occurrence of imaging (chest X–ray; computed tomography scan);
  - length of stay in hospital; and
  - unplanned admission to an intensive care unit (and if applicable, length of stay in the intensive care unit).

6.4 Trial procedures

6.4.1 Screening for eligibility

Patients scheduled for major minimally invasive abdominal surgery will be identified by the attending anesthesiologist at the preoperative assessment and ask their consent to be approached by the research team. Patient characteristics of screened patients meeting the inclusion criteria will be recorded, including age category of the patient, date of screening and if volunteered reason for not enrolling.

6.4.2 Patient consent

. Upon obtaining consent, the patient will be approached by members of the research team to obtain informed consent. The eligible patient will be informed either by phone or in person after the preoperative screening. The informed consent process will adhere to the applicable CCMO guidelines, and will be conducted as soon as possible after identifying a suitable patient but never later than one day before the surgery, with a minimum reflection period of 24 hours. No trial –related actions will be performed before written informed consent is obtained. Informed consent will be documented on a paper form and signed by the patient and attending researcher. One signed informed consent form remains with the patient, the other will be stored in a designated secure folder in the respective participating center.

6.4.3 Patient demographics and baseline data collection

Preoperative variables will be collected at pre–anesthetic visit or before induction of general anesthesia. The following variables are recorded:

- sex;
- age;
- height;
- weight;
- functional status (independent, partially dependent or totally dependent);
- physical status (according to the American Society of Anesthesiologists score);
- cardiac status (heart failure, according to the New York Heart Association score, acute coronary syndrome, or persistent ventricular tachyarrhythmia's);
- chronic obstructive pulmonary disease (if inhalation therapy and/or systemic steroids are used);
- respiratory infection in the last month;
- smoking status;
- history of active cancer;
- weight loss >10% in the last 6 months;
- history of diabetes mellitus, use of insulin or oral antidiabetics;
- type of scheduled surgery (emergency or non–emergency and surgical procedure);
- transfusion of blood products in the preceding 6 hours;
- vital parameters (tympanic temperature, respiratory rate, oxygen saturation (SpO_2), blood pressure, heart rate);
- visual analog scale (VAS) scores for pain;
- blood tests (glucose, hemoglobin A1c, urea, creatinine, hemoglobin, white blood cell count, (*only* if deemed necessary for clinical care for the patient); and
- chest imaging (assessed for mono– and bilateral infiltrate, pleural effusion, atelectasis, pneumothorax, cardiopulmonary edema; *only* if it was deemed necessary for clinical care for the patient).

6.4.4 Randomization, blinding and treatment allocation

Randomization

In order to prevent dropouts, randomization is performed shortly before the start of surgery as soon as it is certain the surgery will proceed and the surgical approach remains minimally invasive. Randomization will then be performed by local investigators using the randomization tool in Castor Electronic Data Capture (EDC). Included patients will be randomly allocated in a 1:1 ratio to the individualized, targeting a low driving pressure (ΔP), high positive end–expiratory pressure (PEEP) with recruitment maneuvers (RMs) group or standard low PEEP

group without RMs. The allocation sequence is generated by Castor EDC, using per-muted blocks with a maximum block size of 8 and stratified per center and by body mass index (≤ 30 vs. > 30 kg/m2).

Blinding

In our study, both the patient and the researcher assessing the primary endpoint are blinded. The patient will not be informed about the outcome of the randomization process. Throughout the intervention, the patient will be under general anesthesia, guaranteeing their blinding. Furthermore, each participating center will work with a team of at least two researchers. The researcher responsible for collecting outcome data will not have been involved in the randomization or the intervention in the operating room. This blinding is safeguarded in the electronic Case Report Form (eCRF) through a function that conceals the randomization arm from the researcher entering outcome data. Additionally, the eCRF will utilize the same function to also ensure blinding of the trial coordinators to the randomization arm. Inherently to the type of intervention, the attending anesthesiologist is not blinded. Other caregivers, including the surgeon, research staff and ward nurses will be blinded to treatment allocation.

6.4.5 Intraoperative data collection

The local investigator who performed randomization will record intraoperative variables. After induction of anesthesia, the following variables are captured every hour:

- ventilation variables including PEEP, driving pressure, tidal volume, respiratory rate, plateau pressure, peak pressure, inspiratory to expiratory ratio, fraction of inspired oxygen ($FiO_{2)}$ and end–tidal carbon dioxide pressure;
- patient positioning variables including angulation of operation table
- abdominal insufflation pressure; and
- vital parameters including oxygen saturation (SpO_2), systolic arterial blood pressure, diastolic arterial blood pressure and mean arterial blood pressure.

After completion of surgery, the following intraoperative variables are recorded:

- duration and type of both anesthesia and surgical procedures; (volatile versus totally intravenous anesthesia or combined);
- need of rescue therapy for hypoxemia and intraoperative complications possibly related to PEEP titrations;
- number of RMs, as stipulated by protocol and if performed as rescue strategy;
- time of start and end of anesthesia (i.e. time of tracheal intubation and extubation);
- time of start and end of surgery;
- presence of neuraxial pain management (lumbar or thoracic epidural catheter);
- neuromuscular monitoring and residual curarization (train–of–four < 0.9);
- temperature at end of surgery;

- arterial blood gas variables including PaO_2, pH, $PaCO_2$, HCO_3^- (only if available, i.e., if deemed necessary for clinical care)
- administration of vasopressors;
- administration of fluids including colloids, crystalloids and blood products; and
- total amount of fluid loss including urine production and blood loss.

6.4.6 Postoperative data collection

The patients will be assessed daily in the first five days after surgery, as well as on the last day before hospital discharge. The postoperative investigator, blinded to the randomized intervention, will collect postoperative variables. Clinical data and the presence of pulmonary and extrapulmonary postoperative complications are scored according to strict criteria and international guidelines; the day of development of any complication will be indicated (for definitions, see Appendix II). Blood tests and chest imaging can only be collected if available, i.e., obtained as part of the clinical care for the patient. The following variables are recorded on the first five days after surgery and the day before discharge:

- patient status (location, i.e., in hospital or at home – alive or deceased, and in case of the latter the day of dying);
- occurrence of postoperative pulmonary complications as defined in our primary endpoint;
- occurrence of extrapulmonary complications as defined in our secondary endpoints;
- requirement and duration of postoperative mechanical ventilation;
- admission to intensive care unit (ICU);
- unplanned admission to another monitored ward;
- physiotherapy (e.g. for early mobilization, deep breathing exercise or stimulation of cough);
- urine output if collected;
- need for renal replacement therapy;
- vital parameters including heart rate, tympanic temperature, oxygen saturation, respiratory rate, visual analogue scale pain score and blood pressure if collected;
- surgical wound infection; and
- blood tests including glucose, urea, creatinine, hemoglobin and white blood cell count if performed.

The following variables are collected around day 90 after surgery:

- health status (location i.e., in hospital or at home – alive or deceased, in case of the latter the day of dying); and
- total length of hospital and (if applicable) ICU or other monitored wards stay
- QoL-5D-5L survey

6.5 Withdrawal of individual patients

Patients can leave the trial at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a patient from the trial for urgent medical reasons.

6.6 Protocol violation

Any deviation from the protocol, other than those mentioned in section 5.8 preapproved protocol deviations, are considered protocol violations. Protocol violations are to be reported and will be discussed with the Data Safety Monitoring Board (DSMB).

6.7 Drop outs

Patient will be classified as drop out if the patient has been randomized, but did not undergo minimally invasive abdominal surgery. Drop outs will not be replaced. A dropout rate of 5% has been accounted for in the sample size.

6.8 Replacement of individual patients after withdrawal

In case of withdrawal after randomization, the patient will not be replaced. Captured data until the moment of withdrawal will be stored and used for analysis. If the patient has not been randomized yet, the patient will be replaced to reach the intended sample size of 1806 patients.

6.9 Premature termination of the trial

The trial will be terminated if, as a result of our intervention, a disproportional amount of (serious) adverse events occur and causality between the intervention and adverse events is assumed. Interim analysis on safety will be performed and the results will be communicated, blinded for randomization, to the data safety monitoring board (DSMB).

7. SAFETY REPORTING

7.1 Temporary halt for reasons of patient safety

In accordance to section 10, subsection 4, of the Dutch Medical Research Involving Human Subjects Act (WMO), the sponsor will suspend the trial if there are sufficient grounds that continuation of the trial will jeopardize patient health or safety. The sponsor will notify the accredited Medical Ethical Committee (METC) without undue delay of a temporary halt including the reason for such an action. The trial will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all patients are kept informed.

7.2 Adverse events and serious adverse events

7.2.1 Adverse events

Adverse events (AEs) are defined as any undesirable experience occurring to a patient during the trial, whether or not considered related to the intervention. All procedure related or possibly procedure related adverse events reported spontaneously by the patient or observed by the investigator or his staff will be recorded and may be entered in the (e)CRF directly.

7.2.2 Serious adverse events

A serious adverse event (SAE) is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a SAE. For this trial, pulmonary SAEs which are related to the trial intervention according to the principal investigators (PIs), will be directly reported to the accredited METC. Whereas pulmonary SAEs which are deemed to be unrelated to the trial intervention as judged by the PIs will be recorded and reported to the METC once a year in a line–listing. The sponsor will report the SAEs related to the intervention through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum 8 days to complete the initial preliminary report. SAEs not related to the intervention (but for example related to minimally invasive abdominal surgery) will be reported to the METC in a line–listing as part of the annual report.

7.3 Follow–up of adverse events

All (S)AEs will be followed until they have abated or until a stable situation has been reached and may be entered in the (e)CRF directly. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till the end of trial within the Netherlands, as defined in the protocol.

7.4 Trial organization

7.4.1 Steering committee

The steering committee is composed of the principal investigator, the coordinating investigator, the local Amsterdam UMC, location AMC investigators, and five international experts of ventilation who contribute to the design and revisions of the trial protocol.

7.4.2 Data Safety Monitoring Board

An independent data safety monitoring board (DSMB), consisting of renowned, independent anesthesiologists, watches over the ethics of conducting the trial in accordance with the Declaration of Helsinki, monitors safety parameters and the overall conduct of the trial. The DSMB is composed of four independent experts. The following experts will be invited:

- Arthur Bouwman, Catharina Ziekenhuis, Eindhoven, The Netherlands
- Francesca Rubulotta , McGill University Health Centre, Montreal, Canada
- John Laffey, Galway University Hospitals, Galway, Ireland, and
- Idit Matot, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

The DSMB will meet after 25%, 50% and 75% of patients are included or at least within nine months after the first patient is enrolled. All unexpected non–trial related (S)AEs will be reported to the DSMB twice a year. Trial–related SAEs will be sent to the DSMB, as soon as possible but at latest within 7 days after being received by the coordinating center. The advice of the DSMB will only be sent to the sponsor of the trial, the Amsterdam UMC, location AMC. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing medical ethical committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

8. STATISTICAL ANALYSIS

A full statistical analysis plan will be published online before the end of recruitment. All statistical analyses will be conducted according to the modified intention–to–treat (ITT) principle considering all patients in the treatment groups to which they were randomly assigned, excluding cases lost to follow–up due to withdrawal of consent or cancellation of surgery. For both arms, the baseline characteristics will be expressed as counts and percentages, means and standard deviations (SD) or medians and interquartile ranges (IQR), depending on normality of data distribution. Hypothesis tests will be two–sided with a statistical significance level of 5% (i.e., $p < 0.05$) for all outcomes. We will not adjust the *p*–value for multiple comparisons. Statistical analysis will be performed using the free software program 'R' (R Core Team, 2020, Vienna, Austria).

8.1 Primary trial parameter(s)

The effects of the intervention (individualized high positive end–expiratory pressure with recruitment maneuvers ventilation strategy, targeting a low driving pressure (ΔP), on the incidence of postoperative pulmonary complications (PPCs) will be reported as a number and percentages. The effect of the intervention will be estimated by calculating risk ratios and 95% confidence intervals using the Wald's likelihood ratio approximation test and with χ2 tests for hypothesis testing.

8.2 Secondary trial parameters

The effect of the intervention on other binary outcomes will be assessed with risk ratio and 95% confidence intervals calculated with Wald's likelihood ratio approximation test and with χ2 tests for hypothesis testing. Time–to–event data will be assessed using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with Cox proportional hazard models. The effects of the intervention on length of hospitalization and ICU stay will be estimated using an appropriate model. In all analyses statistical uncertainties will be quantified with two–sided 95% confidence intervals. A two–sided *p*–value < 0.05 will be considered statistically significant. Data analysis will be performed blinded for the allocated trial intervention.

8.3 Subgroup analyses

Treatment effects on incidence of PPCs will be analyzed according to the following subgroups: 1) age < 65 years versus ≥ 65 years; 2) body mass index (BMI) < 30 kg/m2 versus BMI ≥ 30 kg/m2; 3) baseline oxygen saturation (SpO_2) < 96% versus SpO2 ≥ 96%; 4) moderate versus high risk for developing PPCs; 5) duration of surgery < 3 hours versus ≥ 3 hours; and 6) planned postoperative destination, intensive care unit or high dependency unit versus ward. Analyses of heterogeneity of effects across subgroups will performed with the use of treatment–by–covariate terms added to a generalized linear model and will be presented in a forest plot.

8.4 Other exploratory analyses

N.A.

8.5 Cost–effectiveness analysis/budget impact analysis

A cost–effectiveness and cost–utility analysis of the intervention will be performed from a health care perspective for the Dutch patient population. The cost per prevented pulmonary complication and cost per quality–adjusted–life–year, as measured by the EuroQol–5D-5L utility score around day 90 is the main outcome measure Based on a reduction in PPCs, thereby reducing length of stay in hospital, a conservative estimation suggests a potential annual efficiency gain of €11.1 million in the Netherlands. To determine the financial impact on national healthcare costs in the future a budget impact analysis (BIA) will be performed.

8.6 Trial profile

Patient flows will be presented in a consolidated standard of reporting trials (CONSORT) flowchart.

8.7 Baseline comparisons

Patient's baseline characteristics will be presented by trial arm. The proportion of patients who were treated according to their treatment assignment will be reported by treatment group.

8.8 Adherence to trial interventions and ventilatory variables

Comparisons of the collected variables will be performed using $\chi 2$ tests for equal proportion, Student's t–test for normally distributed data or a non-parametric Wilcoxon rank sum (otherwise known as Mann Whitney U). Plots comparing ventilatory variables and vital signs among the groups during the first three hours of surgery and in the last hour will be constructed (presenting the data as mean and 95% confidence interval in each time point). Comparisons of these longitudinal data will be performed using mixed–effect linear modelling, fitting main effects for treatment and time and an interaction between the two to determine if treatments differed over time, and with patients and centers as random–effects.

8.9 Cleaning and locking of the database

The database will be locked as soon as all data is entered and all discrepant or missing data are resolved – or if all efforts are employed and we consider that the remaining issues cannot be fixed. At this step, the data will be reviewed before database locking. After that, the trial database will be locked and exported for statistical analysis. At this stage, permission for access to the database will be removed for all investigators, and the database will be archived.

8.10 Missing data

No or minimally losses to follow–up for the primary and secondary outcomes are anticipated. Complete–case analysis will be carried out for all the outcomes, that is, excluding patients with missing data in the outcome of interest. However, if any missing data is found for the primary

outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be performed.

9. CONSIDERATIONS

9.1 Regulation statement

The trial will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil 2013, comply with Good Clinical Practice (GCP). Guidelines and all applicable international, national (for example WMO for the Netherlands) and local regulatory requirements, as well as general data protection regulations (GDPR).

9.2 Recruitment and consent

Patients will be recruited at the anesthesiology or surgical out–patient clinic, or at the surgical ward. Patients will be informed verbally by local researchers and will be provided a patient information letter. The patient will be given sufficient time (minimum 12 hours) to consider their decision and to discuss the decision with their relatives or the independent expert.

9.3 Benefits and risks assessment, group relatedness

Patient burden is considered minimal. A small reduction in postoperative pulmonary complications achieved by our investigated intervention could lead to improved patient outcomes and major healthcare cost saving on a national and international scale.

9.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research patients through injury or death caused by the trial. The insurance applies to the damage that becomes apparent during the trial or within 4 years after the end of the trial.

9.5 Incentives

There is no financial incentive for patients to participate in this trial.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All of the patients directly identifying personal data (e.g., name, address, email, etc.) will be separated from the research data (e.g., measurement data, etc.) and replaced by an assigned code. The directly identifying data will only be used to contact the patients and is only available to the local investigators. The handling of personal data complies with the general data protection regulations (GDPR). To perform data collection and validation an electronic case report form (eCRF), including validation checks and appropriate user access rights, will be set up in Castor EDC This application has been deployed for several trials by the Protective Ventilation Network (www.provenet.eu) and is a GCP compliant application that meets the standard for information security management. With the consent of the patient, all data will be stored in a secure place for 15 years after termination of the trial and used for future research in the field of lung-protective ventilation. Electronic files will be archived on a trial–designated folder on the cloud server of the respective participating center in a secure and controlled environment to maintain confidentiality. Electronic files will be controlled with password protection according to best practices. Paper data will be stored in a locked cabinet. Access to the folder and storage will be limited to researchers who are involved in the study and documented on the delegation log. At Amsterdam UMC, location AMC all study-related documents will be stored in a password protected folder on the G drive of the Department of Anesthesiology (G:\divh\Onderzoek\GENERATOR). Agreements regarding data exchange with hospitals in the Netherlands and other countries will be established in a clinical trial agreement and data transfer agreement in accordance with applicable law. No patient data will be shared from the coordinating center to the participating centers, this applies to national− (Dutch) and international centers. A GCP–certified monitor will monitor the trial according to ICH–GCP guidelines throughout its duration. Any data leaks that might occur regardless of these safety precautions will be reported to all parties within 1 working day after discovery of the leak. A detailed data mangement plan will be made detailing where an under which restrictions data will be made available. The results of this study will be published in a peer-reviewed medical journal. After publication of the primary results, access to source data will be made available by providing de-identified datasets on request and after agreement of the steering committee of GENERATOR.

10.2 Monitoring and Quality Assurance

The objective of the clinical data management plan is to provide high–quality data by adopting standardized procedures to minimize the number of errors and missing data, and consequently, to generate an accurate database for analysis. Accuracy and consistency checks will be carried out by way of automatic validation, pre–specified and ad hoc checking by personnel at the coordinating centers. A qualified monitor will be installed to perform trial

monitoring according to the monitoring plan. Remote monitoring will be performed to signal early aberrant patterns, issues with consistency, credibility, and other anomalies. On–site monitoring will comprise controlling presence and completeness of the research dossier and the informed consent forms, and source data checks will be performed as described in the monitoring plan.

10.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited MTC once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of trial report

The investigator/sponsor will notify the accredited METC of the end of the trial within a period of 8 weeks. The end of the trial is defined as the last included patient's last follow up moment. The sponsor will notify the METC immediately of a temporary halt of the trial, including the reason of such an action. In case the trial is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the trial, the investigator/sponsor will submit a final trial report with the results of the trial, including any publications/abstracts of the trial, to the accredited METC.

10.6 Public disclosure and publication policy

The trial protocol will be registered before inclusion of the first patient on Clinicaltrials.gov. The results of the trial will be published in (inter–) national scientific journals and guidelines. We will submit a summary of results to scientific journals in the field of anesthesiology. Data will be made accessible according to the FAIR guidelines.

11. STRUCTURED RISK ANALYSIS

This trial has a negligible risk according to a tool developed by the clinical research unit of the Amsterdam University Medical Center (UMC). This tool aims to provide a regulatory framework for clinical research projects with assurance that the rights, safety and well–being of research patients are protected and that the results of clinical research projects are credible. This tool is in line with the international and national recommendations (Netherlands Federations of University Medical Centers (NFU). There are three possible risks which may occur in this trial: (i.) desaturation due to possible atelectasis in the standard positive end–expiratory pressure (PEEP) – or individualized PEEP group, (ii.) barotrauma due to possible overdistention in the individualized PEEP group, and (iii.) hypotension.

11.1 Desaturations

In one of the randomized clinical trials by the PROVE network investigators, named 'High versus low positive end–expiratory pressure during general anesthesia for open abdominal surgery' (PROVHILO) (15) (METC AMC registration number: 10/251), rescue for desaturation was needed in 2% of the high PEEP group (12 cm H_2O) and in 8% of the low PEEP group (2 cm H_2O). Since we will provide the patients with a PEEP level of at least 5 cm H_2O, we expect the incidence of desaturation to be less than 8% in the current trial. However, if desaturation occurs, we have a clear rescue strategy (see paragraph 5.6 and 5.7, sections on rescue strategies).

11.2 Barotrauma

In the same trial, pneumothorax was reported in 3% of the patients in the high PEEP group, and in 3% of the patients in the low PEEP group. Hence, we also expect a low incidence of pneumothorax in this trial.

11.3 Hypotension

We do expect hypotension to occur. First, hypotension during anesthesia is a common phenomenon. In the Amsterdam UMC, the incidence of hypotension during anesthesia, defined as a mean arterial blood pressure < 65 mm Hg and lasting > 1 minute, is 60% for an average of 10% of surgery time in non–cardiac surgical patients (21, 22). Second, hypotension occurs often during pneumoperitoneum. Third, we expect higher incidences of hypotension in this trial because of higher PEEP in the individualized high PEEP group. In the trial mentioned above, PROVHILO (15), 46% of the patients in the high PEEP group experienced hypotension compared to 36% of the patients in the standard low PEEP group. This was also found in another randomized clinical trial by our group, named 'Protective intraoperative ventilation with higher versus lower levels of positive end–expiratory pressure in obese patients (PROBESE) (23) (METC AMC, registration number: 2014_261). In this trial, 32% of the patients in the high PEEP group experienced hypotension compared to 17% in the standard low PEEP group. We recently analyzed the occurrence of hypotension in an ongoing randomized clinical trial, named

‘Driving pressure during general anesthesia for open abdominal surgery’ (DESIGNATION, METC AMC registration number: 2018_319). In this trial, the incidence of hypotension was also higher in the high PEEP group compared to the standard low PEEP group (55 versus 44%) (unpublished data). Anesthesiologists are well trained in the treatment and prevention of hypotension. Anesthesiologists are also familiar with performing RMs and experienced with preventing hypotension during this maneuver. They are prepared for a possible hypotensive episode during the RM, resulting in a proactive approach in anticipating hypotension. Since prevention and treatment of hypotension is common practice for anesthesiologists, we do not consider hypotension to be a high risk, despite the high prevalence. Of note, when clinically necessary, the anesthesiologist in charge is always free to deviate from the protocol if hypotension occurs.

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13. APPENDICES

13.1 APPENDIX I Table for ARISCAT Risk Score (3)

Risk for PPC of Variables Selected for the Logistic Regression Model			
	Multivariate Analysis	**β Coefficients**	**Risk Score[§]**
	OR (95% CI) N = 1624		
Age, year			
≤ 50	1		
51 – 80	1.4 (0.6–3.3)	0.331	3
> 80	5.1 (1.9–13.3)	1.619	16
Preoperative SpO_2, %			
≥ 96	1		
91 – 95	2.2 (1.2–4.2)	0.802	8
≤ 90	10.7 (4.1–28.1)	2.375	24
Respiratory infection in the last month	5.5 (2. –11.5)	1.698	17
Preoperative anemia (≤ 10 g/dL or < 6.2 mmol/L)	3.0 (1.4–6.5)	1.105	11
Surgical incision			
Peripheral	1		
Upper abdominal	4.4 (2.3–8.5)	1.480	15
Intrathoracic	11.4 (4.9–26.0)	2.431	24
Duration of surgery, hours			
≤ 2	1		
> 2 to 3	4.9 (2.4–10.1)	1.593	16
> 3	9.7 (4.7–19.9)	2.268	23
Emergency procedure	2.2 (1.04–4.5)	0.768	8

Abbreviations: CI, confidence interval; OR, odds ratio; SpO_2, oxyhemoglobin saturation by pulse oximetry breathing air in supine position

[§]The simplified risk score was the sum of each logistic regression coefficient multiplied by 10, after rounding off its value.

High or intermediate risk for postoperative pulmonary complications following abdominal surgery: ARISCAT risk score ≥ 26.

13.2 APPENDIX II DEFINITIONS for PPCs

Severe respiratory failure:

Need for non–invasive or invasive mechanical ventilation *or* a PaO_2 < 60 mm Hg or SpO_2 < 90% *despite* supplemental oxygen (excluding hypoventilation).

ARDS:

According to the Berlin definition of ARDS (20).

Suspected pulmonary infection:

In case patient receives antibiotics and meets at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest X–ray when clinically indicated, tympanic temperature > 38.3^0C, white blood cell count > 12,000/mm^3.

Pulmonary infiltrate:

Chest X–ray demonstrating unilateral or bilateral infiltrate.

Pleural effusion:

Chest X–ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemi–thorax with preserved vascular shadows.

Atelectasis:

Suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent non–atelectatic lung.

Pneumothorax:

Defined as air in the pleural space with no vascular bed surrounding the visceral pleura.

Bronchospasm:

Defined as newly detected expiratory wheezing treated with bronchodilators.

Aspiration pneumonitis:

Defined as respiratory failure after the inhalation of regurgitated gastric contents.

Cardiopulmonary edema:

Defined as clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest X–ray demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates.

13.3 APPENDIX III DEFINITIONS of extra–pulmonary post–operative complications

Sepsis

According to the SEPSIS–3 definition (24).

Septic shock

According to the SEPSIS–3 definition (24).

Extra–pulmonary infection

Any wound infection + any other infection.

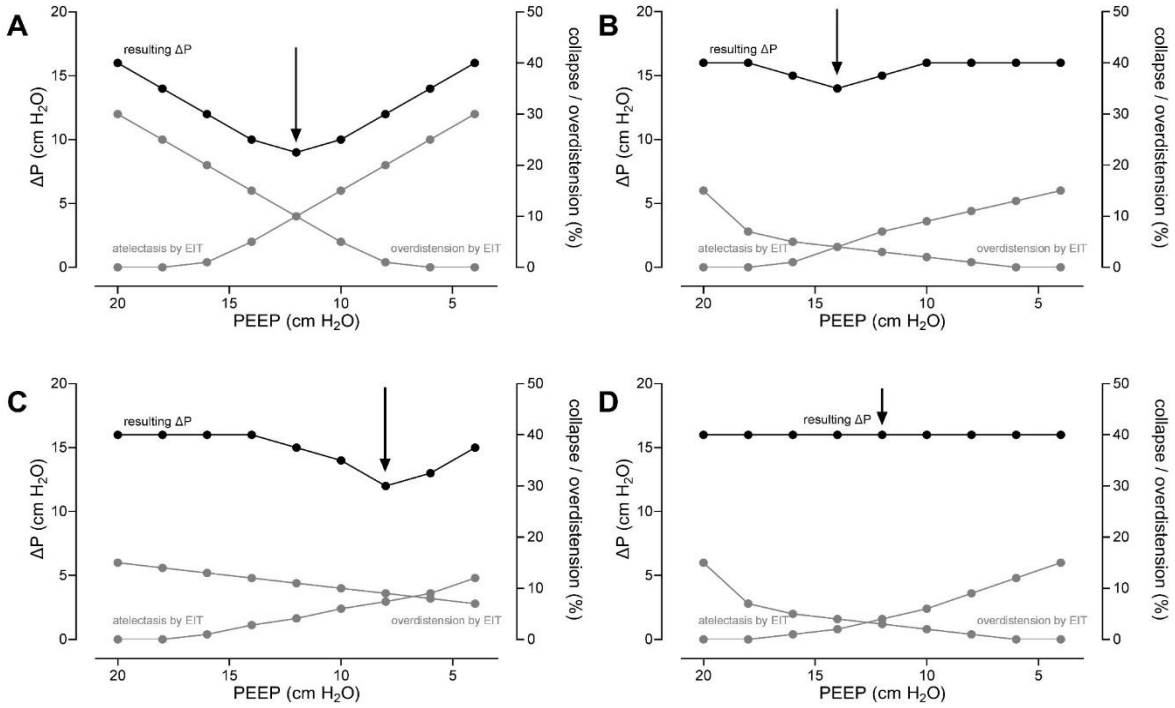
Anastomotic leak

The situation of (perceived) failure of an anastomosis leading to leakage of intraluminal substances to the exterior.

Acute renal failure

According to the AKIN definition (25).

13.4 APPENDIX IV Examples of ΔP–PEEP plots



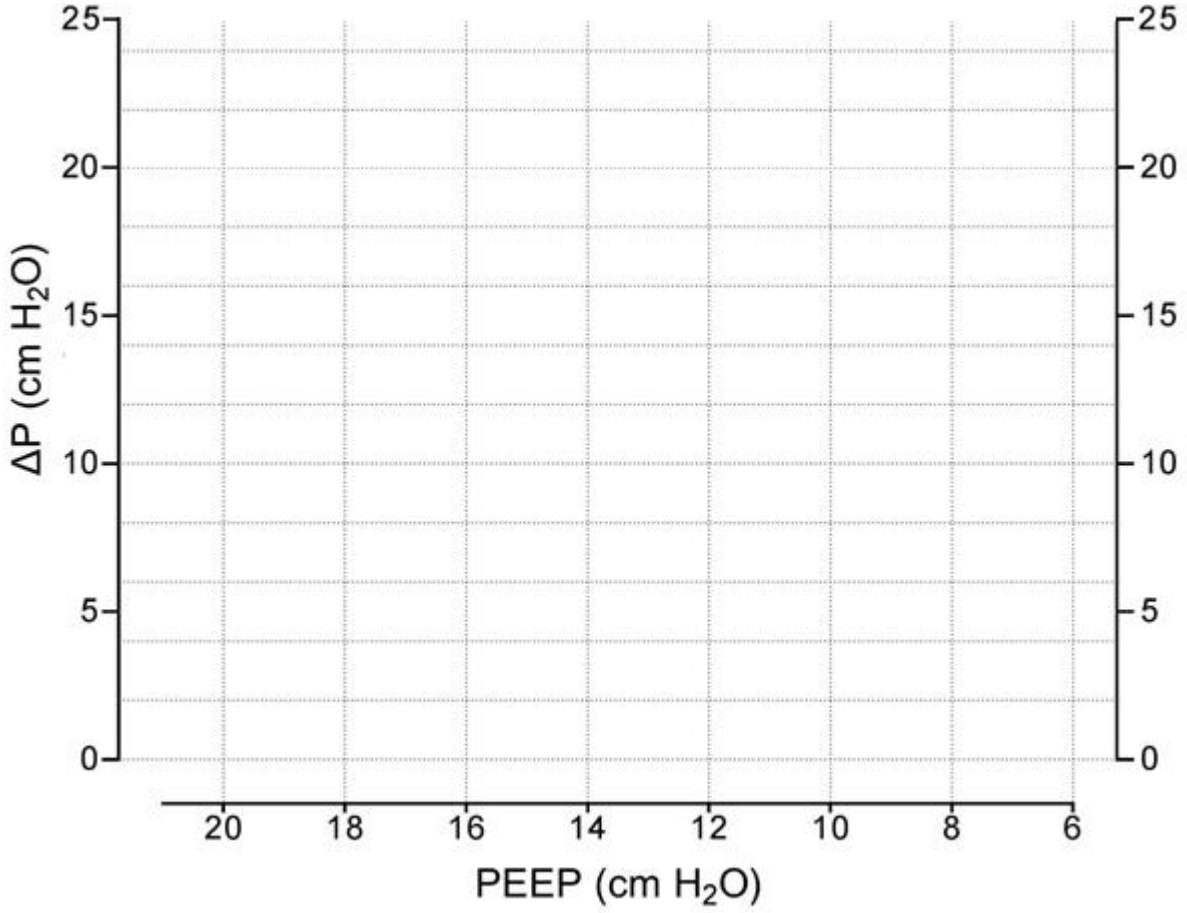
Four hypothetical scenarios, based on findings from a recent trial (17) using a comparable decremental positive end–expiratory pressure (PEEP trial) in combination with electric impedance tomography (EIT) to determine the amount of collapsed and overdistended lung tissue.

Scenario A shows a clear nadir of the driving pressure (ΔP). The arrow indicates the level of PEEP to be used after the second recruitment maneuver (RM) in the current trial. Note that adding extra PEEP immediately results in more overdistention.

Scenarios B and C also show a nadir of ΔP, though at a higher and lower PEEP level, respectively. Again, the arrow indicates what level of PEEP should be used after the second RM.

Scenario D is a scenario when no nadir for ΔP is found. In this case PEEP should be set at 12 cm H_2O after the second RM.

13.5 APPENDIX V: The ΔP–PEEP chart



This chart MUST be completed during the decremental PEEP trial.

With every step, calculate the resulting driving pressure (ΔP) by subtracting PEEP from the plateau pressure after 20 seconds. Draw a smooth line using the eight PEEP–ΔP points. Determine the nadir of the ΔP and use this level of PEEP until the end of anesthesia. This chart MUST be filed; either by importing it into the electronic patient file, or by filing it in the local investigator site file.

13.6 APPENDIX VI: Participating centers

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