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Original Contribution

Safety and feasibility of intraoperative high PEEP titrated to the lowest driving pressure during anesthesia for minimally invasive abdominal surgery – Interim analysis of GENERATOR

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HIGHLIGHTS

- Individualized high PEEP ventilation is feasible in minimally invasive abdominal surgery.
- Intraoperative hypotension is similar between individualized high PEEP and standard low PEEP.
- Vasopressors were used in higher doses with individualized high PEEP compared to standard low PEEP.
- Driving pressure was lower with individualized high PEEP compared to standard low PEEP.

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[1] GENERATOR, 'Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery' study;
[2] PROVE Network, 'Protective Ventilation Network'

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ABSTRACT

Background: The optimal level of positive end–expiratory pressure (PEEP) during minimally invasive abdominal surgery is uncertain. Intraoperative ventilation with individualized high PEEP and recruitment maneuvers can be used to keep the driving pressure (ΔP) low, but can also lead to hypotension. In addition, the resulting ΔP and feasibility of individualized high PEEP in minimally invasive abdominal surgery is unclear.

Methods: Planned interim analysis on safety and feasibility of 'Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery' (GENERATOR), an ongoing randomized clinical trial that compares individualized high PEEP, titrated to the lowest ΔP, with a standard low PEEP ventilation strategy with respect to postoperative pulmonary complications. The primary endpoint for this analysis was the proportion of patients with intraoperative hypotension. Secondary endpoints were other intraoperative complications, ventilation variables and feasibility parameters.

Results: From December 2023 to July 2024, 181 patients were enrolled. Data for analysis were available for 177 patients, of which 87 patients were randomized to individualized high PEEP and 90 to standard low PEEP. Intraoperative hypotension was similar between the individualized high PEEP vs standard low PEEP group (11.5 vs 11.1 %, relative risk ratio 1.0 [95 % CI 0.5–2.4], $p = 1.00$), while vasopressor use was higher in the intervention group. The median difference in ΔP between both groups was 6 cm H_2O. Protocol compliance was 81.6 % in the individualized high PEEP group vs 97.8 % in the standard low PEEP group; most instances of non–compliance in the individualized high PEEP group concerned a level of PEEP that was too high.

Discussion: In minimally invasive abdominal surgery, a ventilation strategy using individualized high PEEP was not associated with a higher incidence of hypotension, but did show an increased use of vasopressors. The intervention was highly feasible, and led to a lower ΔP. These interim findings warrant confirmation in the main analysis of GENERATOR.

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1. Introduction

Intraoperative ventilation during general anesthesia for minimally invasive abdominal surgery can be challenging. The application of pneumoperitoneum leads to altered respiratory mechanics [1], often requiring recruitment maneuvers (RMs) and higher levels of positive end–expiratory pressure (PEEP) to prevent atelectasis and ensure adequate oxygenation. Intraoperative high PEEP with RMs, due to increased intrathoracic pressures, is known to increase the risk of hypotension by leading to impaired cardiac filling and output [2–5]. Pneumoperitoneum might exacerbate hypotension by further decreasing stroke volume and venous return [6]. Previous reports of high PEEP in this population however provide little information on hypotension [7,8].

Use of lung–protective settings during intraoperative ventilation has the potential to reduce postoperative pulmonary complications (PPCs) [9,10]. Intraoperative driving pressure (ΔP) has an independent association with PPCs and has been proposed as a digital biomarker to guide the titration of PEEP levels during intraoperative ventilation [11]. The ongoing 'Driving Pressure During General Anesthesia for Minimally Invasive Abdominal Surgery' (GENERATOR) trial is investigating whether ventilation with individualized high PEEP, titrated to the lowest ΔP, can reduce PPCs [12]. The intervention is based on a RM, a decremental PEEP trial and a second RM, followed by an individualized high PEEP for the duration of anesthesia. Although tested before in *open* abdominal surgery [2,13], it is unclear if this strategy is safe in *minimally invasive* abdominal surgery.

This analysis assesses the safety, feasibility, and practical implementation of individualized high PEEP in minimally invasive abdominal surgery. We hypothesized that this intervention is safe and viable, and that the study protocol can be effectively applied throughout the remainder of the trial.

2. Methods

2.1. Study design

Planned interim analysis at 10 % recruitment of GENERATOR, an investigator–initiated international, multicenter, parallel, randomized clinical superiority trial in patients scheduled for minimally invasive abdominal surgery with an increased risk for PPCs. Written informed consent was obtained from all participating patients. The study protocol and its amendments have been approved by the institutional review board of the Amsterdam University Medical Center (ID 2023.0439). GENERATOR is registered at clinicaltrials.gov (study identifier NCT06101511; October 24, 2023) and the study protocol has been published [12]. A data safety monitoring board (DSMB) oversees the conduct of the study and performs safety analyses at 25 %, 50 % and 75 % of recruitment. The current analysis was performed outside the scope of regular DSMB meetings, hence stopping criteria were not defined. Of note, the members of the DSMB did assist with the interpretation of this analysis.

2.2. Inclusion and exclusion criteria

GENERATOR includes patients that fulfill all of the following criteria 1) age > 18 years; 2) scheduled for minimally invasive abdominal surgery; 3) increased risk of PPCs according to the 'Assess Respiratory Risk in Surgical Patients in Catalonia' (ARISCAT) risk score (≥ 26 points) [14], *or* increased risk for PPCs based on the combination of age > 40 years; scheduled surgery length > 2 h and planned to receive an intra–arterial catheter for blood pressure monitoring during the surgery; and 4) written informed consent.

A potential patient who met any of the following exclusion criteria could not participate: 1) planned for open abdominal surgery; 2) surgery in lateral or prone position; 3) 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; and 12) presence of severe cardiac disease (New York Heart Association class III or IV, acute coronary syndrome or persistent ventricular tachyarrhythmias).

2.3. Data collected

Data collected in the GENERATOR study included patient demographics and comorbidities; surgical characteristics; anesthesia characteristics; the incidence of intraoperative complications; intraoperative vital and ventilation variables—including but not limited to ΔP, plateau pressure (Pplat), PEEP, peak pressure (Ppeak), tidal volume (V_T), respiratory rate (RR), fraction of inspired oxygen (FiO_2), intra–abdominal pressure (IAP), mean arterial pressure (MAP), oxygen saturation (SpO_2); details about the decremental PEEP trial; and protocol compliance.

Patient demographics and comorbidities were captured before anesthesia. In both groups, vitals, ventilation variables and intraoperative complications were collected after induction of anesthesia and hourly thereafter. In the intervention group, these variables were also collected before the first RM and after the second RM. Surgical and anesthesia characteristics and the number of protocol violations were captured at the end of anesthesia.

2.4. Standard of care

For both groups, induction of general anesthesia was performed according to the routines and expertise of the participating center and attending anesthesiologist. Ventilation was in volume–controlled modus, with a V_T of 8 mL/kg predicted bodyweight (PBW). Inspiration to expiration ratio was set at 1:2, FiO_2 at 0.4. An inspiratory pause of 15 % was applied, RR was adjustable to maintain normocapnia (pCO_2 4.5–5.5 kPa). PEEP was set according to the randomization arm and is defined below in section 2.5 and 2.6.

2.5. Intervention group

Patients allocated to the individualized PEEP group received an intraoperative ventilation strategy with individualized high PEEP, set according to a decremental PEEP trial with RMs (**Supplementary fig. 1**).

After intubation, the PEEP was originally set at 5 cm H_2O. However, after 8 weeks and 20 enrolled patients a protocol adjustment was made and approved by the institutional review board to set the PEEP at 10 cm H_2O after intubation in the intervention group. This was due to an unforeseen long waiting time between intubation and a steady state of pneumoperitoneum, which is the protocolized moment to start the intervention. In order to create a difference in PEEP settings between the groups, it was decided to create this difference from the start of ventilation. Hence, from February 6, 2024 onwards, PEEP was set at 10 cm H_2O directly after intubation.

Next, when a steady state of pneumoperitoneum was achieved and the patient was in the starting position of the procedure, the intervention started. First, a RM with 20 cm H_2O was performed. To reach 20 cm H_2O, PEEP was increased from 10 cm H_2O in steps of 5 cm H_2O every 15 s. After 15 s at PEEP 20, the decremental PEEP trial commenced. Every 20 s PEEP was lowered in steps of 2 cm H_2O. At each step ΔP was calculated. This was repeated until PEEP reached 6 cm H_2O (**Supplementary fig. 1 A**). A ΔP–PEEP graph was drawn and the *highest* PEEP corresponding to the *lowest* ΔP was identified (**Supplementary fig. 1B and 1C**). Next, from PEEP 6 cm H_2O a second RM was performed in the same manner as the first, after which the individualized PEEP found in the decremental PEEP trial was set for the remaining duration of anesthesia.

If all ΔPs in the decremental PEEP trial did not differ more than 2 cm H_2O, a clear nadir in ΔP was considered absent (**Supplementary fig. 1C**). In this case, after the second RM, PEEP 12 cm H_2O was chosen for the remaining duration of anesthesia, equal to a previous study of ΔP guided individualized high PEEP [15].

The decremental PEEP trial and RMs were repeated in case of 1) conversion to laparotomy; 2) a radical change in surgical position as judged by the attending anesthesiologist or 3) a radical change in intrabdominal pressure as judged by the attending anesthesiologist. In case of any disconnection from the ventilator–patient circuit, RMs were repeated. Of note, RMs and decremental PEEP trials were only performed in hemodynamically stable patients, as judged by the attending anesthesiologist.

2.6. Control group

Patients allocated to the 'standard low PEEP' group received intraoperative ventilation with PEEP fixed at 5 cm H_2O. No decremental PEEP trials nor RMs were performed in these patients.

2.7. Rescue therapies

If desaturation occurred, in the absence of airway issues, severe hemodynamic instability, or ventilator malfunction, a predefined rescue strategy was implemented. For patients in the individualized high PEEP group, desaturation could still indicate overdistention, so PEEP was reduced in steps, with a possible subsequent increase in FiO_2 (**Supplementary table 1 A**). In the standard low PEEP group, FiO_2 was increased initially, followed by a stepwise increase in PEEP if necessary, and ultimately a recruitment maneuver if required (**Supplementary table 1 A**).

2.8. Pre–approved protocol deviations

Ventilator settings, including PEEP, could be adjusted at any time if there were safety concerns or in the rare case that PEEP interfered with the surgical procedure. (**Supplementary table 1B**).

2.9. Definitions and calculations

Intraoperative complications included:

- any episode of hypotension, defined as a mean arterial pressure (MAP) below 65 mmHg, lasting >1 min [16];
- increased use of vasopressors, defined as 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;
- any episode of desaturation, defined as oxygen saturation (SpO_2) ≤ 90 % or if preoperative SpO_2 was <90 %, an absolute decrease in SpO_2 > 5 %, and lasting >1 min; and
- any new heart arrhythmias needing intervention as suggested by the Advanced Cardiac Life Support Guidelines [17].

A nadir in ΔP during the decremental PEEP trial was defined as a drop of more than 2 cm H_2O from the highest ΔP. We used the following equations to calculate ΔP, respiratory compliance (C_{RS}) and V_T corrected for predicted bodyweight (PBW):

$$\Delta P = \text{Pplat–PEEP} \tag{1}$$

$$V_T = \text{absolute } V_T/\text{PBW [kg]} \tag{2}$$

$$\text{PBW} = 50.0 + 0.91 \times (\text{height [cm]–152.4}) \text{ (in males) or } 45.5 + 0.91 \times (\text{height [cm]–152.4}) \text{ (in females)} \tag{3}$$

$$C_{RS} = \text{absolute } V_T/\Delta P \tag{4}$$

2.10. Endpoints

The primary endpoint was the proportion of patients developing intraoperative hypotension. Secondary endpoints included the

incidence of other intraoperative complications (increased use of vasopressors, desaturation, heart arrhythmia) ventilator variables (PEEP; Pplat; Ppeak; RR) and feasibility variables (ΔP, presence of a nadir in the decremental PEEP trial and overall protocol compliance).

To measure protocol compliance, a patient was classified as overall study compliant if all of the following criteria were met: (i) correct PEEP selection after intubation according to the study arm; (ii) correct PEEP settings over the first four hours of general anesthesia; and (iii.) correct PEEP selection according to the decremental PEEP trial (only in the individualized high PEEP group). Deviations that were allowed due to safety concerns did not count as protocol violation.

2.11. Sample size

A sample size calculation was not performed. The main goal of this analysis was to detect major safety and feasibility issues at an early stage of the trial, allowing for timely adjustments to the study if needed. An interim analysis at 10 % of total recruitment (181 patients) was considered to provide enough information to identify concerning trends, while still allowing for early adaptations of the study design.

2.12. Statistical analysis

The analysis was conducted according to a modified intention–to–treat principle. Patients who withdrew consent after randomization and patients where the surgical approach—after randomization but prior to the start of surgery—changed to open abdominal, were excluded. Continuous variables were presented as medians with interquartile range and categorical variables as numbers and percentages. Proportions were compared between groups using a Fisher's exact test for hypothesis testing including computation of risk ratios and absolute risk differences with 95 % confidence intervals. Continuous variables were compared using a Student's t or Mann–Whitney *U* tests where appropriate. Ventilation variables were plotted over time, *p* values were computed for differences between groups, and for differences with an interaction between group and time by using a generalized linear mixed effect model with patients as random effect. Cumulative distribution plots were constructed to visualize the distributions of PEEP and ΔP after induction and hourly thereafter. We reported the difference in PEEP settings, i.e., between set PEEP and the PEEP that should have been used according to study protocol.

A p value <0.05 was considered statistically significant and 95 % confidence intervals were shown to express statistical uncertainty. All analyses were performed using R version 4.3.2 (Vienna, Austria). Missing data per variable can be found in **Supplementary table 2.**

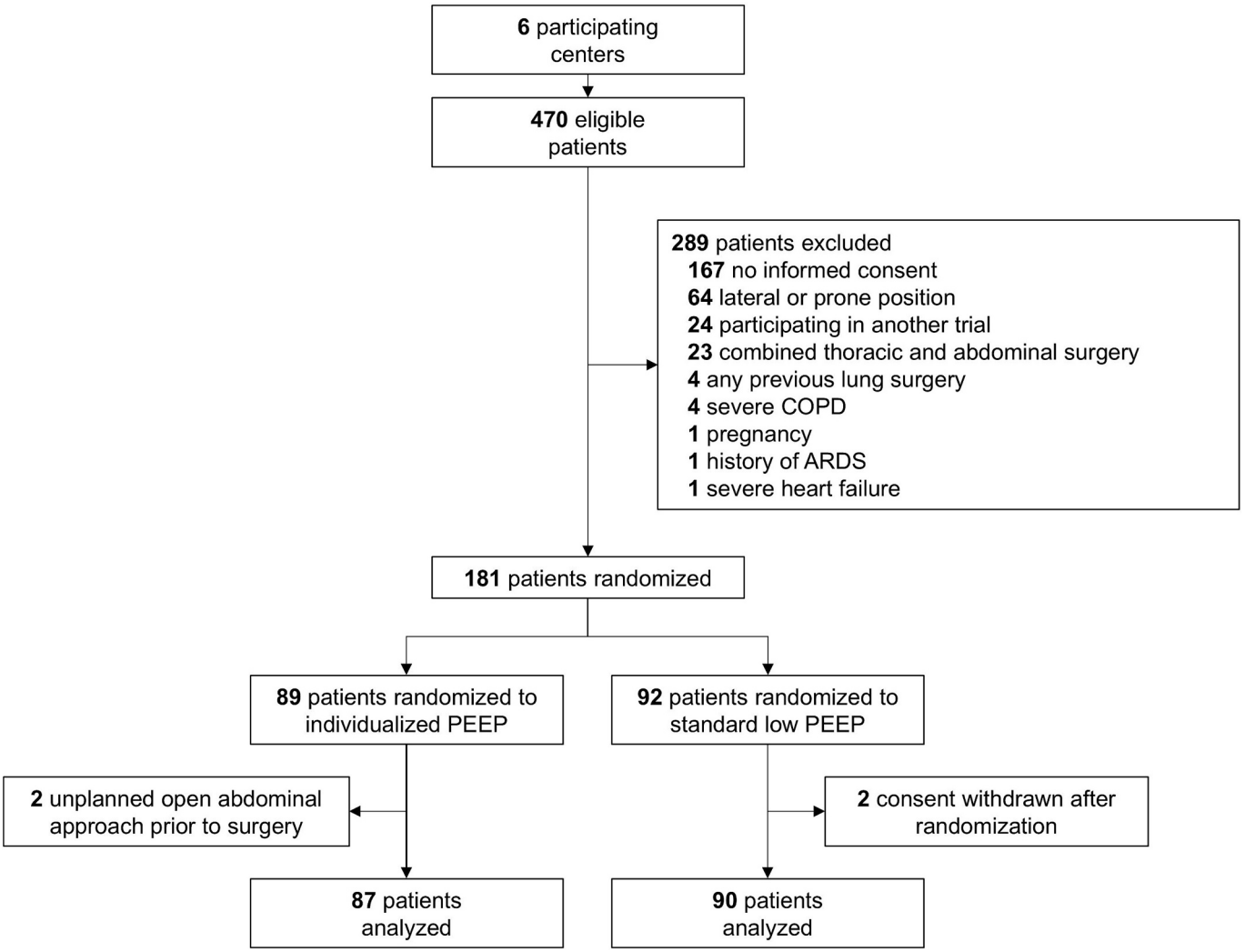

Fig. 1. CONSORT flow diagram. COPD = chronic obstructive pulmonary disease; ARDS = acute respiratory distress syndrome; PEEP = positive end–expiratory pressure.

3. Results

3.1. Patients

Between 11 December 2023 and 09 July 2024, 470 patients were eligible for participation (Fig. 1). Main reasons for exclusion were no consent, lateral or prone position, combined thoracic–abdominal surgery, and participation in another trial. A total of 181 patients were randomized. After excluding two patients due to withdrawn consent and two to unexpected open abdominal surgery, 87 patients remained in the individualized high PEEP group and 90 patients in the standard low PEEP group.

Patient characteristics are shown in Table 1. The median age was 68 years and approximately three–quarters of patients had male sex. Almost all patients had an intermediate risk for PPCs according to the ARISCAT score. Diabetes was more present in the individualized high PEEP group, while COPD was more present in the standard low PEEP group. Prostate surgery was the most common type of surgery, followed by bowel– and gynecological procedures. Most procedures were performed or assisted by robot. Trendelenburg was the most frequent surgical position. Conversion to open abdominal surgery, after starting minimally invasive, occurred in two individualized high PEEP patients and four standard low PEEP patients.

3.2. Safety

Intraoperative hypotension was similar between the individualized high PEEP group compared to standard low PEEP (11.5 and 11.1 %, relative risk ratio 1.0 [95 % CI 0.5–2.4], $p = 1.00$) (Table 2). Increased use of vasopressors was more present in the individualized high PEEP group ($p = 0.03$) (Table 2). Norepinephrine and ephedrine were used more frequently and with higher dosages during individualized high PEEP, while administered fluids were similar between groups (**Supplementary table 3**). The incidence of desaturation and arrhythmias was comparable between groups ($p = 0.37$ and $p = 0.49$). Recruitment maneuvers were not associated with an increased incidence of hypotension or any other intraoperative complication (**Supplementary table 4**).

3.3. Ventilation variables

Individualized high PEEP led to a higher Pplat, Ppeak and C_{RS} (Table 3, **Supplementary table 5, Supplementary fig. 2**). These differences remained until the end of anesthesia. Respiratory rate and all other ventilation variables—except ΔP— were similar between groups (Table 3, **Supplementary fig. 2**).

3.4. Feasibility

Compared to the standard low PEEP group, median intraoperative ΔP was 6 cm H_2O lower in the individualized high PEEP group, while PEEP was higher (Table 3, Fig. 2, **Supplementary table 5, Supplementary fig. 2–4)**. A nadir was present in 77.9 % of decremental PEEP trials. At the nadir, the median ΔP was 14 cm H_2O [12–16] and the median PEEP 20 cm H_2O [18–20] (Table 4).

Overall protocol compliance was achieved in 71 of 87 patients (81.6 %) in the individualized high PEEP group, compared with 88 of 90 patients (97.8 %) in the standard low PEEP group (Table 4). PEEP levels were set according to the protocol in 86.2 % of patients in the individualized high PEEP group vs 97.8 % in the standard low PEEP group. Most deviations in the individualized high group involved selecting higher PEEP levels than recommended. This typically occurred in patients without a clear nadir during PEEP titration, where the highest PEEP was chosen, instead of the protocolized PEEP 12 cm H_2O, as dictated by the study protocol.

Table 1
Patient and surgical characteristics.

	Individualized high PEEP $N = 87$	Standard low PEEP $N = 90$
Demographics		
Age, years, median [IQR]	69 [64–74]	68 [64–72]
Male sex, n (%)	63 (72.4)	70 (77.8)
Female sex, n (%)	24 (27.6)	20 (22.2)
BMI, kg/m^2, median [IQR]	26 [24–30]	26 [24–29]
ARISCAT risk score, median [IQR]	26 [26–26]	26 [26–26]
ARISCAT risk score group, n (%)		
low, < 26	1 (1.1)	1 (1.1)
intermediate, 26–45	85 (97.7)	89 (98.9)
high, ≥ 45	1 (1.1)	0 (0.0)
Combination of age > 40 & surgery >2 h & scheduled arterial catheter, yes, n (%)	18 (20.7)	18 (20.0)
ASA group, n (%)		
ASA 1	9 (10.3)	10 (11.1)
ASA 2	57 (65.5)	57 (63.3)
ASA 3	19 (21.8)	20 (22.2)
ASA 4	2 (2.3)	3 (3.3)
Functional status, n (%)		
Independent	87 (100.0)	89 (98.9)
Partially dependent	0 (0.0)	1 (1.1)
Totally dependent	0 (0.0)	0 (0.0)
Preoperative testing		
Preoperative vitals, median [IQR]		
Mean arterial pressure (MAP), mmHg	103 [92–110]	102 [95–110]
spO_2, %	98 [97–98]	98 [96–98]
Blood test, median [IQR]		
Hemoglobine, mmol/L	9 [8–10]	9 [8–10]
Creatinine, μmol/L	89 [78–97]	81 [71–87]
White blood cell count, $\times 10^9$ cells/L	7 [5–10]	9 [6–11]
Preoperative transfusion, yes, n (%)	0 (0.0)	1 (1.1)
Abnormalities on chest imaging, yes, n (%)	1 (1.1)	1 (1.1)
Comorbidities, yes, n (%)		
History of persistent ventricular Tachyarrhythmias	0 (0.0)	0 (0.0)
History of coronary disease	7 (8.0)	4 (4.4)
Heart failure	1 (1.1)	2 (2.2)
NYHA 1	0 (0.0)	2 (2.2)
NYHA 2	1 (1.1)	0 (0.0)
COPD	1 (1.1)	6 (6.7)
Inhalation therapy	0 (0.0)	3 (3.3)
Systemic corticosteroid use	0 (0.0)	0 (0.0)
Smoking status		
Never	52 (59.8)	40 (44.4)
Former	31 (35.6)	37 (41.1)
Current	4 (4.6)	12 (13.3)
Unknown	0 (0.0)	1 (1.1)
Diabetes mellitus	11 (12.6)	5 (5.6)
Diet	0 (0.0)	0 (0.0)
Oral medication	9 (10.3)	4 (4.4)
Insulin	2 (2.3)	1 (1.1)
Active cancer	75 (86.2)	71 (78.9)
Surgical characteristics, yes, n (%)		
Specialty of surgery		
Gynaecologic	9 (10.3)	9 (10.0)
Urologic	5 (5.7)	5 (5.6)
Vascular	0 (0.0)	0 (0.0)
Pancreatic	4 (4.6)	7 (7.8)
Bowel	12 (13.8)	12 (13.3)
Liver	0 (0.0)	0 (0.0)
Gastric	4 (4.6)	2 (2.2)
Biliary tract	0 (0.0)	1 (1.1)
Prostate	53 (60.9)	53 (58.9)
Spleen	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (1.1)
Primary surgical approach		
Laparoscopic	16 (18.4)	19 (21.1)
Robotic	71 (81.6)	71 (78.9)
Surgical position*		
Supine	24 (27.6)	22 (24.4)
Anti trendelenburg	7 (8.0)	5 (5.6)
Trendelenburg	38 (43.7)	36 (40.0)
Extreme trendelenburg	18 (20.7)	27 (30.0)
Conversion to laparotomy	2 (2.3)	4 (4.4)

Data is presented as median with IQR for continuous variables and as numbers and proportions for categorical variables.
Abbreviations, PEEP = Positive End–Expiratory Pressure; IQR = Inter Quartile Range; BMI = Body Mass Index; ARISCAT = Assess Respiratory Risk in Surgical Patients in Catalonia; ASA = American Society of Anaesthesiology physical status score; MAP = mean arterial pressure; spO_2 = oxygen saturation measured by pulse oximetry; NYHA = New York Heart Association; COPD = chronic obstructive pulmonary disease.
* most frequent surgical position during surgery.

4. Discussion

The GENERATOR trial is an ongoing randomized clinical trial, comparing an individualized high PEEP ventilation strategy to a standard low PEEP strategy in patients undergoing minimally invasive abdominal surgery under general anesthesia. The main findings of this analysis can be summarized as follows: (1) the incidence of intraoperative hypotension was similar between groups; (2) individualized high PEEP led to an increased use of vasopressors, while the occurrence of desaturation and arrhythmia was comparable; (3) individualized high PEEP successfully reduced intraoperative ΔP for the duration of general anesthesia and led to a clear contrast in set PEEP levels; and (4) protocol compliance was good in both groups.

This analysis has several strengths. We adhered strictly to a predefined analysis plan which enabled a structured assessment of safety and feasibility. We performed the analysis in an early stage of the trial, allowing study adjustment if necessary. Clear and commonly used definitions were applied for the collection and measurement of all endpoints, ensuring the validity and reliability of the analysis. The data was derived from multiple centers, including academic and non–academic hospitals, strengthening the generalizability of the results.

Intraoperative hypotension has been linked to many adverse outcomes [18–24]. Although ventilation with high PEEP and RMs is known to induce hypotension [2–5], the incidence in our analysis was low. In line with two previous studies in laparoscopic procedures with individualized high PEEP ventilation [7,8], we did not observe more hypotension compared to standard low PEEP. Despite pneumoperitoneum induced reduction in stroke volume and cardiac output [6], the combination with high PEEP ventilation does not seem to increase the incidence of hypotension. Two things need to be considered here. First, pneumoperitoneum generally tends to increase blood pressure through various mechanisms [25–29], especially in the Trendelenburg position [30]. Of note, more than 60 % of procedures in our study were in Trendelenburg or extreme Trendelenburg position. Second, our study observed a median titrated PEEP of 20 cm H_2O and showed an increased use of vasopressors with individualized high PEEP ventilation, aligning with previous reports in both open abdominal and laparoscopic procedures [2–4,8]. Anesthesiologists likely anticipated hypotension from high PEEP levels and administered vasopressors at higher doses, preventing blood pressure reductions from reaching the hypotension threshold.

In contrast to open abdominal surgery with high PEEP ventilation [2–4], a striking finding was the low *overall* incidence of hypotension and increased use of vasopressors. Besides the blood pressure increasing effects of pneumoperitoneum, several things need to be considered here; 1) epidural anesthesia is commonly used in open abdominal surgery, causing hypotension by inducing peripheral blood pooling and vasodilation [31]. In contrast, it is rarely used in laparoscopic procedures, avoiding hemodynamic instability; 2) pneumoperitoneum leads to a reduction in cardiac output which can lead to hypotension in severe cases, especially in patients with cardiopulmonary comorbidities. However, patients with severe cardiopulmonary comorbidities could not participate in our study. As such, the reduction in cardiac output due to pneumoperitoneum was likely mild, contributing to a low incidence of hypotension; 3) our study applied a more recent and strict definition of hypotension [16], which likely classified fewer patients as hypotensive compared to other studies.

Desaturation can occur more quickly in laparoscopic procedures. Pneumoperitoneum causes a cephalad shift of the diaphragm that can induce severe atelectasis, leading to desaturation [8,32,33]. While desaturation occurred more frequently in the standard low PEEP group, this was not statistically significant. As low PEEP has been associated with more desaturations in previous investigations [3,4], this should be evaluated again in future safety analyses by the DSMB. Pneumoperitoneum raises blood levels of CO_2 and can increase the heart's sensitivity to arrhythmias [28]. We observed no differences in heart arrhythmias and found that respiratory rates were adjusted effectively to maintain normocapnia.

Our analysis showed that individualized high PEEP, compared to standard low PEEP, leads to a substantial reduction in intraoperative ΔP. Previous studies in laparoscopic procedures, depending on the surgical positions investigated, have reported varying ΔP reductions but all were lower than in our analysis [7,8,34,35]. Lower abdominal procedures, often performed in (extreme) Trendelenburg position, exacerbate atelectasis from pneumoperitoneum, increasing ΔP. In our study, lower abdominal procedures in Trendelenburg were the most frequent, explaining the high median titrated PEEP and large ΔP reduction. ΔP guided PEEP in *open* abdominal surgery showed a smaller ΔP reduction than we observed in this study [2,13,36]. This is likely caused by the absence of pneumoperitoneum, leading to fewer atelectasis which high PEEP can mitigate to reduce ΔP. Of note, a recent investigation into individualized high PEEP as part of a wider perioperative open lung approach has not shown a reduction in PPCs in open abdominal surgery [13]. This finding needs to be evaluated by the DESIGNATION trial in open abdominal surgery [15], and by GENERATOR in minimally

Table 2
Intraoperative complications.

	Individualized high PEEP *N* = 87	Standard low PEEP N = 90	Absolute risk difference (95 % CI)	Relative risk ratio* (95 % CI)	*P**
Hypotension, n (%)	10 (11.5)	10 (11.1)	0.4 [−8.9–9.7]	1.0 [0.5–2.4]	1.00
Increased use of vasopressors, n (%)	9 (10.3)	2 (2.2)	8.1 [1.0–15.2]	4.7 [1.0–20.9]	0.03
Heart arrhythmias, n (%)	1 (1.1)	0 (0.0)	1.1 [−1.1–3.4]	1.0 [0.0–inf]	0.49
Desaturation, n (%)	1 (1.1)	4 (4.4)	−3.3 [−8.1–1.5]	0.2 [0.0–1.8]	0.37

Data is presented as numbers and proportions (percentages), all calculated values are rounded to one decimal.
Definitions:
hypotension: any episode of hypotension, defined as a mean arterial pressure (MAP) below 65 mmHg, lasting >1 min.
increased use of vasopressors: 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.
heart arrhythmias: any new arrhythmias needing intervention as suggested by the Advanced Cardiac Life Support Guidelines.
desaturation: oxygen saturation (SpO_2) ≤ 90 % or if preoperative SpO_2 was <90 %, an absolute decrease in SpO_2 > 5 %, and lasting >1 min.
Abbreviations: PEEP = Positive End–Expiratory Pressure; CI = confidence interval; inf = infinity.
* The relative risk ratio and 95 % confidence intervals were computed using the Wald likelihood ratio approximation test with adjustment for small samples where appropriate. *P* values were calculated using a Fisher exact test for hypothesis testing.

Table 3
intraoperative characteristics.

	Individualized high PEEP N = 87	Standard low PEEP N = 90
Length, minutes, median [IQR]		
duration of anesthesia	212 [175–266]	209 [176–264]
duration of surgery	184 [152–236]	182 [149–236]
Anesthesia characteristics, yes, n (%)		
epidural	0 (0.0)	0 (0.0)
maintenance of anesthesia		
totally intravenous	85 (97.7)	89 (98.9)
volatile	0 (0.0)	0 (0.0)
mixed	2 (2.3)	1 (1.1)
type of neuromuscular blocking agent		
depolarizing	0 (0.0)	0 (0.0)
non–depolarizing	87 (100.0)	90 (100.0)
neuromuscular function monitored	84 (96.6)	89 (98.9)
residual curarization at end anesthesia	37 (42.5)	31 (34.4)
antagonized, yes, n/N (%)	36/37 (97.3)	29/31 (93.5)
intrabdominal pressure*, mmHg, median [IQR]	10 [8–12]	10 [7–12]
Ventilation characteristics*, median [IQR]		
PEEP, cm H_2O	20 [12−20]	5 [5–5]
ΔP, cm H_2O	12 [11–14]	18 [15–20]
V_T, mL	575 [525–625]	575 [525–625]
V_T, mL/PBW	8 [8–8]	8 [8–8]
Ppeak, cm H_2O	34 [29–37]	27 [24–30]
Pplat, cm H_2O	31 [26–33]	23 [20–26]
Respiratory rate, n/min	12 [12–14]	12 [11–14]
FiO_2	0.4 [0.4–0.4]	0.4 [0.4–0.4]
$EtCO_2$, kPa	4.7 [4.5–4.9]	4.7 [4.6–4.9]
Crs, mL/cm H_2O	43 [36–50]	33 [28–39]
Vital parameters, median [IQR]		
SpO_2, %	99 [98–99]	98 [97–99]
Mean arterial pressure, mmHg	83 [79–87]	85 [79–90]

Data is presented as median with IQR for continuous variables and as numbers and proportions for categorical variables.
Abbreviations, PEEP = Positive End–Expiratory Pressure; IQR = Inter Quartile Range; $etCO_2$ = end–tidal CO_2; mmHg = millimetres of mercury pressure; ΔP = driving pressure; FiO_2 = fraction of inspired oxygen; $etCO_2$ = end–tidal CO_2; SpO_2 = oxygen saturation measured by pulse oximetry.
* Median from all available measurements per patient over all timepoints.

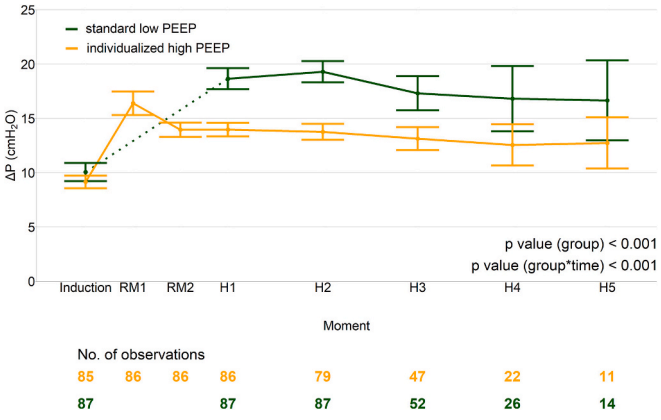

Fig. 2. ΔP over time according to groups. PEEP = positive end–expiratory pressure; ΔP = driving pressure; H_2O = water; RM1 = recruitment maneuver 1; RM2 = recruitment maneuver 2; H = hour.

invasive abdominal surgery [12].

The results of this interim analysis are encouraging with respect to safety, as the incidence of intraoperative hypotension and other complications was low.

Table 4
feasibility and protocol compliance.

	Individualized high PEEP N = 87	Standard low PEEP N = 90
Overall compliance†, patients, n/N (%)		
protocol compliant	71/87 (81.6)	88/90 (97.8)
protocol non–compliant	16/87 (18.4)	2/90 (2.2)
PEEP settings, patients, yes, n/N (%)		
PEEP set correctly	75/87 (86.2)	88/90 (97.8)
PEEP, cm H_2O, median [IQR]	20 [14–20]	5 [5–5]
PEEP set too high,	8/87 (9.2)	1/90 (1.1)
0–2 cm H_2O	0 (0.0)	0 (0.0)
3–4 cm H_2O	0 (0.0)	1/90 (1.1)
5–6 cm H_2O	2/87 (2.3)‡	0 (0.0)
> 6 cm H_2O	6/87 (6.9) ‡	0 (0.0)
PEEP set too low	4/87 (4.6)	0 (0.0)
0–2 cm H_2O	0 (0.0)	–
3–4 cm H_2O	2/87 (2.3)	–
5–6 cm H_2O	0 (0.0)	–
> 6 cm H_2O	2/87 (2.3)	–
Intervention feasibility		
Time to intervention, minutes, median [IQR]	32 [28–41]	Not applicable
RM and PEEP titration, patients, n/N (%)		Not applicable
first RM	86/87 (98.9)	
PEEP titration	86/87 (98.9)	
second RM	86/87 (98.9)	
Presence of nadir (ΔP difference > 2 cm H_2O), yes, n (%)	67/86 (77.9)	Not applicable
ΔP at nadir, cm H_2O, median [IQR]	14 [12–16]	
PEEP at nadir, cm H_2O, median [IQR]	20 [18–20]	
Intervention repeated, patients, n/N (%)		Not applicable
once	4/86 (4.7)	
twice	2/86 (2.3)	

Abbreviations, PEEP = Positive End–expiratory Pressure; IQR = interquartile range; RM = recruitment maneuver; ΔP = driving pressure.
Data is presented as median with IQR for continuous variables and as numbers and proportions for categorical variables.
† overall compliance is defined if a patient complied with all of the following: (i) correct PEEP selection after intubation; (ii) correct PEEP settings over the first 4 h of general anesthesia; and—only for patients in the individualized high PEEP group— (iii) correct PEEP selection after titration. If any of the previous criteria was not fulfilled due to predefined protocol deviations, this patient was classified as protocol compliant;
‡ occurred in patients without a nadir during PEEP titration; in these patients the highest PEEP was chosen, instead of the protocolized PEEP 12 cm H_2O, as dictated by the study protocol.

Overall protocol compliance was high for both groups. A nadir in ΔP during PEEP titration was present in most patients, consistent with previous findings in open abdominal surgery [2]. The main cause of non–compliance was failure to recognize the absence of a nadir leading to incorrect PEEP selection early in the study. This issue was quickly identified and promptly communicated to participating centers, after which this no longer occurred. While patients with incorrect PEEP settings will remain in the intention–to–treat analysis, they will be excluded from the per protocol analysis.

This analysis has limitations. First, the method used to capture hypotension in GENERATOR was limited. Further research is needed to fully assess the intervention's impact on the frequency, duration and severity of hypotension, including precise blood pressure levels and the length of hypotensive episodes. Second, local investigators and anesthesia staff were not blinded to the allocated ventilation strategy, which may have introduced observer bias. Third, we did not account for a possible center effect on our outcomes. Fourth, there is a risk of underreporting of safety endpoints. Hypotension may have been prevented or managed with vasoactive drugs. Whether this use exceeded 'normal' levels—defined as amounts beyond those required to

counteract the vasodilatory effects of anesthetics—was left to the judgment of the attending anesthesiologist. Finally, the median PEEP in our study was 20 cm H_2O, corresponding to the highest level used in the decremental PEEP trial. It is plausible that, for some patients, the PEEP level associated with the lowest ΔP exceeded 20 cm H_2O, suggesting they may not have received truly optimal PEEP. However, we were concerned that PEEP levels above 20 cm H_2O could be perceived as too excessive by anesthesia staff, might significantly reduce cardiac output, and compromise the safety and feasibility of the intervention. Nevertheless, the intervention group still achieved a substantial lower ΔP. Future studies should explore whether higher PEEP levels could further optimize ΔP, while maintaining safety and feasibility.

5. Conclusion

During general anesthesia for minimally invasive abdominal surgery, ventilation with individualized high PEEP did not lead to more hypotension compared to standard low PEEP ventilation, but did show an increased use of vasopressors. The study protocol for selecting the correct PEEP was feasible, and led to a lower ΔP. GENERATOR will continue without adjustments and is scheduled to finish enrollment in late 2026.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2025.112014.

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