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# **Personalized driving pressure-guided positive end-expiratory pressure in patients at risk of postoperative respiratory failure (IMPROVE-2): a multicenter, pragmatic, randomized clinical trial**

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**Keywords:**

Clinical trial; Emergency surgery; Mechanical ventilation; Postoperative respiratory failure.

# Abstract

## **Purpose:**

Airway driving pressure has garnered considerable attention for lung-protective ventilation. We evaluated the clinical effectiveness of airway driving pressure as a target to individualize positive-end-expiratory pressure (PEEP) setting in mechanically ventilated patients at risk for postoperative respiratory failure.

## **Methods:**

We conducted a multicenter, pragmatic, assessor-masked, randomized trial among adult patients undergoing emergency abdominal surgery in 22 hospitals in France. Patients were assigned 1:1 to receive individually adjusted highest PEEP targeting a driving pressure < 13 cmH<sub>2</sub>O after an initial recruitment maneuver (intervention group) or to a fixed PEEP level of 5 cmH<sub>2</sub>O (control group). The primary outcome was a composite of postoperative respiratory failure (failure to wean from the ventilator or the composite of reintubation or curative non-invasive ventilation) or all-cause mortality at 30 days. Secondary outcomes included components of the composite primary outcome.

## **Results:**

The primary outcome occurred in 87 out of 338 (25.7%) intervention patients and in 69 out of 341 (20.2%) control patients (difference, 5.5%; 95% confidence interval [CI] - 0.8 to 11.8; relative risk, 1.27; 95%CI 0.96-1.68; p = 0.08). The difference was primarily due to an increased incidence of reintubation or need for curative non-invasive ventilation among intervention patients (difference, 7.1%; 95% CI 2.5-11.9; relative risk, 1.97; 95% CI 1.24-3.11; p = 0.004). Other secondary outcomes did not differ.

## **Conclusion:**

Among patients at risk for postoperative respiratory failure after emergency abdominal surgery, a strategy of individually adjusted highest PEEP in targeting driving pressure lower than 13 cmH<sub>2</sub>O did not reduce postoperative respiratory failure or death.

## **Trial registration:**

ClinicalTrials.gov Identifier: NCT03987789.

### Take-home message

Airway driving pressure could be a potential target for lung-protective ventilation. In patients at risk for postoperative respiratory failure after emergency abdominal surgery, a strategy of individually adjusted highest PEEP in targeting driving pressure did not reduce postoperative respiratory failure or death.

## Introduction

Postoperative respiratory failure is a potentially life threatening complication and is a significant source of hospital and post-discharge morbidity and mortality [1–3]. Overall risk of postoperative respiratory failure is approximately 0.5–4% in general surgery but may exceed 20% in high-risk populations, especially after emergency surgery [4].

Mechanical ventilation that uses lower tidal volume (VT), positive end-expiratory pressure (PEEP) and recruitment maneuvers – termed lung-protective ventilation strategy – has the potential to improve outcomes in patients receiving mechanical ventilation for surgery [5], and a recent consensus statement recommends its use [6]. Tidal overinflation and tidal recruitment may both contribute to ventilator-induced lung injury, even in patients without acute respiratory distress syndrome. Patient positioning and increased intra-abdominal and pleural pressures (e.g., in obese patients or during Trendelenburg position with pneumoperitoneum) may also predispose to lung derecruitment of dependent lung regions with alveolar collapse and small airways closure during general anesthesia. Clinical trials, however, have reported conflicting findings in response to the manipulation of individual components of lung protection [7–10], especially PEEP setting, with ensuing uncertainty among clinicians on how best to set the ventilator. The airway driving pressure, which is defined as the distending pressure above the applied PEEP required to generate VT, could be a potential target for lung-protective strategies [11]. Driving pressure is affected by the respiratory system's elastance and varies according to the proportion of lung available for ventilation. The level of applied PEEP has an important influence on the respiratory-system elastance and, consequently, on the driving pressure for a given VT. Several observational studies and a meta-analysis of individual patient data have suggested an association between high driving pressure and poor outcome in patients mechanically ventilated for surgery [11, 12].

A recent consensus statement recommends targeting driving pressure to individualize PEEP setting [6]. However, robust evidence supporting this recommendation is limited and the few available clinical trials in this setting reveal conflicting findings [13, 14]. Recent meta-analyses suggested that individualized PEEP may contribute to decreased risk of postoperative pulmonary complications; however, these studies did not solely assess driving pressure-guided ventilation or included trials conducted in a single center with small sample

sizes, compromising the generalization of the findings [15, 16]. Therefore, to date, the benefit of a personalized approach targeting driving pressure to adjust PEEP is uncertain.

We conducted the Intraoperative Protective Mechanical Ventilation-2 (IMPROVE-2) trial to investigate the effect of using airway driving pressure to individualize PEEP setting among patients at risk for postoperative respiratory failure. Our hypothesis was that a strategy of targeting airway driving pressure would result in a lower rate of postoperative respiratory failure or death than usual care.

## Methods

### Trial design

The trial was an investigator-initiated, multicenter, randomized, assessor-blinded, pragmatic clinical trial conducted at 22 French centers. The trial protocol and statistical analysis plan were published elsewhere [17] and are available in the electronic supplementary material (ESM). The trial was approved for all centers by the Sud-Est III Committee for the Protection of Research Subjects (2019-009B) prior to enrolment and is registered with ClinicalTrials.gov (NCT03987789). Patients or their legally authorized representative provided written informed consent. An independent data-monitoring committee reviewed safety data at pre-specified intervals.

The study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines for parallel group randomized trials [18].

### Participants

Eligible patients were individuals aged  $\geq 18$  years who had an increased risk of postoperative respiratory failure while requiring emergency open or laparoscopic abdominal surgery with an expected duration of at least 2 h. Patients who received invasive mechanical ventilation for more than 12 h prior to surgery, patients with chronic respiratory disease requiring oxygen therapy or home mechanical ventilation, patients with expected death deemed to be imminent and inevitable, body mass index  $> 40$  kg/m<sup>2</sup>, undrained pneumothorax or subcutaneous emphysema, and those previously randomized into the trial were excluded. Detailed descriptions of all exclusion criteria are presented in ESM 3.

### Randomization and masking

Participants were randomized in a 1:1 ratio by local investigators to receive either a strategy of personalized driving pressure-guided PEEP (intervention group) or to receive usual care using a fixed PEEP strategy (control group) using an encrypted web-based system.

Participants were randomized by the attending anesthetist upon arrival in the operating room. Randomization was stratified according to site, the presence or absence of shock (defined by continuous intravenous infusion of vasoactive drugs) and hypoxemia (partial pressure of arterial oxygen tension/fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) ratio  $\leq 300$ ) at

randomization. Patients, trial personnel, research staff collecting and assessing clinical outcomes, and statisticians were unaware of study group allocation.

## Procedures

Participants in the intervention group received PEEP individually titrated in volume-controlled ventilation, by a 1-cmH<sub>2</sub>O stepwise decremental PEEP trial from 15 cmH<sub>2</sub>O, at the highest possible value (up to 15 cmH<sub>2</sub>O) providing driving pressure was lower than 13 cmH<sub>2</sub>O [11, 19], after an initial recruitment maneuver consisting in a 20–30-s breath-hold at 30 cmH<sub>2</sub>O airway pressure [5]. The trial was stopped when the driving pressure was lower than 13 cmH<sub>2</sub>O. A decrease in PEEP was suggested by 1-cmH<sub>2</sub>O decrements thereafter in the event driving pressure exceeded 13 cmH<sub>2</sub>O during the surgery.

Recruitment maneuvers were repeated hourly and in case of disconnection from the ventilator or in case of changes in respiratory-system compliance (indicated by an increase of driving pressure above 13 cmH<sub>2</sub>O). Participants in the control group received a fixed PEEP of 5 cmH<sub>2</sub>O without recruitment maneuvers [6]. All participants received volume-controlled ventilation using a strategy of low (6–8 mL/kg predicted body weight) tidal volume ventilation, with the respiratory rate adjusted to maintain end-tidal partial pressure of CO<sub>2</sub> between 35 and 45 mmHg, an inspiratory-to-expiratory time ratio of 1:2, an end-inspiratory pause of 30%, and FiO<sub>2</sub> adjusted to maintain SpO<sub>2</sub> ≥ 94%. Rescue procedures were allowed in case of arterial oxygen desaturation (ESM 3). In both groups, immediate interruption of sedation coupled with a spontaneous-breathing trial was recommended after the end of surgery [20] if patients met prespecified criteria (ESM 3). The use of light-to-moderate sedation targeting a Richmond Agitation-Sedation Scale of +1 to -2 was recommended in patients who failed the test [21]. Decisions regarding other aspects of patient care were at the discretion of the treating teams.

## Outcomes

The primary outcome measure was a composite of postoperative respiratory failure (defined as failure to wean from the ventilator within 12 h after surgery or the composite of reintubation or curative non-invasive ventilation for acute respiratory failure within 30 days after surgery) [4, 22, 23] or all-cause in-hospital death at 30 days. Prespecified criteria for reintubation and curative non-invasive ventilation are provided in ESM 3.

Secondary outcomes were the individual components of the primary composite outcome; postoperative pulmonary complications grade (grades range from 1 to 4) [24]; duration of mechanical ventilation to first tracheal extubation; total time to successful tracheal extubation; days alive and free of mechanical ventilation at day 30; cumulative total duration of mechanical ventilation at day 30; organ failure to day 7, measured by means of the score on the Sequential Organ Failure Assessment (SOFA), modified by excluding the Glasgow Coma Scale [25]; acute kidney injury at day 30, defined by the Kidney Disease: Improving Global Outcome (KDIGO) criteria [26]; sepsis or septic shock at day 30; days alive not in the ICU at day 30; and duration of ICU and hospital stay.

Tertiary outcomes included the number of patients with hypoxemia, pneumonia, and acute respiratory distress syndrome [27] at day 30, use of rescue procedures, ventilator-associated adverse events, mechanical power, and in-hospital death to day 90.

## Statistical analysis

We determined that a sample size of 680 participants (340 in each group) would provide the trial with 90% power to show an absolute between-group difference of 10% in the primary outcome measure at a two-sided alpha level of 0.05, assuming a 10% mortality rate and a 15% rate of postoperative respiratory failure at 30 days (25% for the primary composite endpoint) [2, 4, 28]. The data and safety monitoring board reviewed the results of interim analyses and recommended continuation of the trial. Recommendations for pausing or stopping the study were made according to O'Brien-Fleming spending function.

All the analyses were performed by the trial statistician according to a predefined statistical analysis plan on an intention-to-treat principle. Patients who withdrew consent or those for whom their legal surrogate withdrew consent to continue and to use data were excluded from the analysis.

The primary analysis was an unadjusted comparison of the primary outcome in the two groups with the use of a chi-square test, and results were presented as absolute differences with 95% confidence intervals. We also analyzed two per-protocol populations, which included participants from the intention-to-treat except those with one or more major protocol deviations. Multiple logistic mixed regression was used to identify prespecified covariates associated with the primary outcome in addition to the stratification variables. Adjusted analyses were performed with the use of a robust random-effect Poisson generalized linear mixed model regression with robust variance and study site as a random effect. Time-to-event data were estimated with the use of the Kaplan–Meier method and were compared between groups using a marginal Cox proportional hazard models to estimate hazard ratios and 95% confidence intervals. Between-group differences in secondary and tertiary categorical outcomes were analyzed with unadjusted chi-square test. For safety outcomes, we reported the number of patients with prespecified adverse events during surgery in each group.

Treatment effects were analyzed across prespecified subgroups: (1) body-mass index (calculated as weight in kilograms divided by height in meters squared) (< 18.5 vs 18.5–25 vs 25–30 vs > 30); (2) ASA physical status (1 or 2 vs 3 vs 4); (3) hypoxemia at randomization; (4) shock (vasopressor use) at randomization; (5) sepsis at randomization; (6) open vs laparoscopy surgery; (7) duration of surgery; (8) volume of fluid infused; and (9) use of prophylactic noninvasive ventilation. Interaction terms in the regression model were used to test for heterogeneity of effect between subgroups.

Post-hoc exploratory analyses were performed to assess the effect of driving pressure on the results (1) to evaluate between-group differences in driving pressure ( $\leq 7$ , 8–9, 10–12,  $\geq 13$ ) and the primary outcome, (2) to compare the evolution of driving pressure between groups, (3) to repeat the main analysis for the primary outcome after excluding patients documented as having driving pressure values greater than 13 in the intervention group.

The widths of confidence intervals were not adjusted for multiplicity and may not be used in place of hypothesis testing, except for the primary outcome analysis. A two-sided  $p$  value  $< 0.05$  was considered to indicate statistical significance. All analyses were generated with the use of Stata software, version 15.0 (StataCorp) after the database had been locked.

## Results

Between 22 March 2021 to 22 July 2022 (last follow-up 27 October 2022), a total of 845 patients were assessed for eligibility, of whom 707 were enrolled in the trial. Twenty-eight patients were excluded after randomization from subsequent data collection and analysis (15 in the intervention group and 13 in the control group).

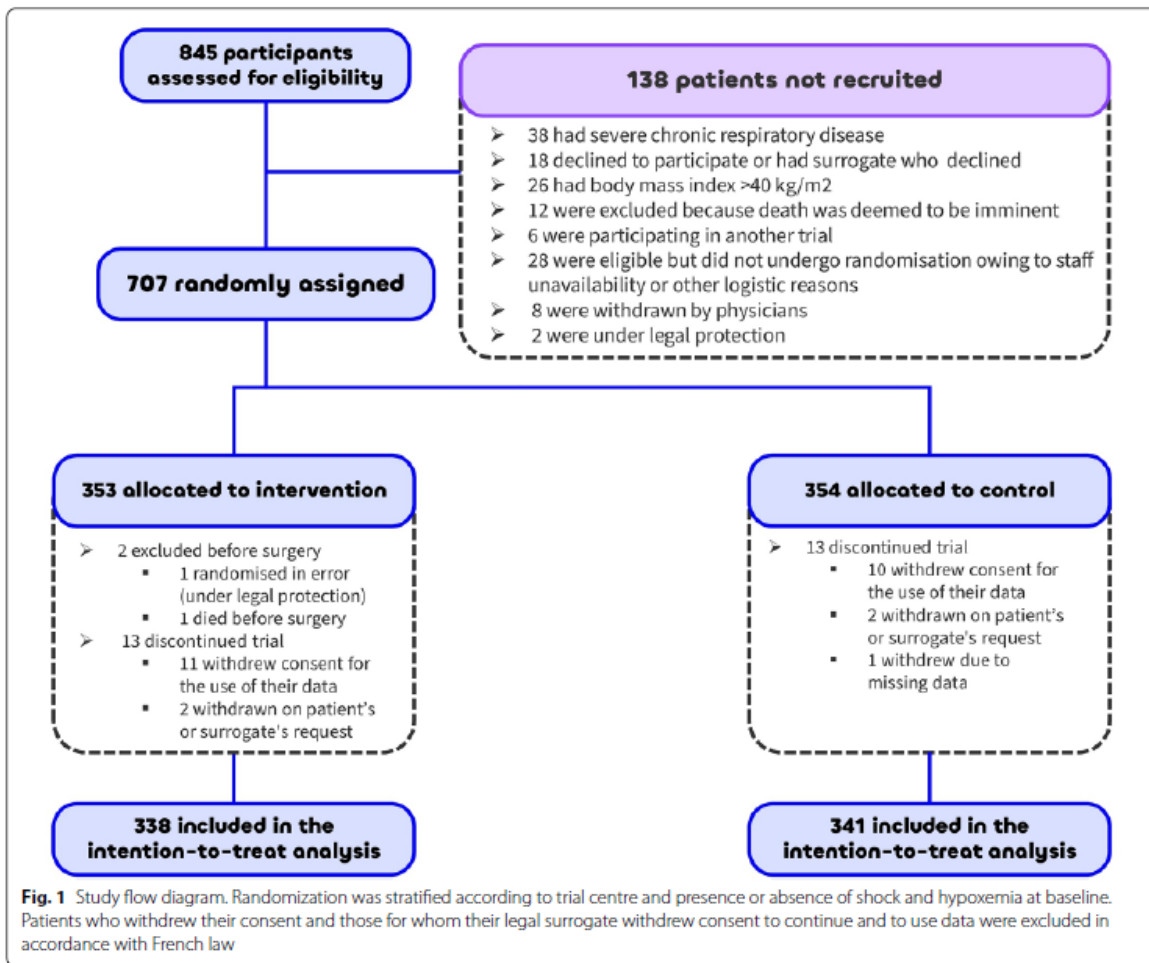
The remaining 679 patients were included in the primary analysis (Fig. 1). The characteristics of the patients at baseline and surgical procedures were well balanced between the trial groups (Table 1; electronic supplementary table 1). Especially, open surgery accounted for 74.6% in the intervention group and 77.4% in the control group.

### Ventilator Settings and Other Care Processes

Details regarding the ventilator settings and other aspects of patient care are provided in Table 2 and electronic supplementary table 1. After initial ventilator setting, the median driving pressure (interquartile range) was 8 cmH<sub>2</sub>O (7 to 11) in the intervention guided group and 10 cmH<sub>2</sub>O (8 to 13) in the control group (between group difference,  $-2$  cmH<sub>2</sub>O; 95% CI  $-3$  to  $-1$ ). Overall, during surgery, patients in the intervention group had lower driving pressure values and higher plateau pressure than patients in the control group (Table 2; electronic supplementary table 2 and electronic supplementary figure 2). In the intervention group, 94 patients (27.9%) had driving pressure values that exceeded the target value of 13 cmH<sub>2</sub>O (electronic supplementary figure 3). A rescue therapy for persistent hypoxemia was used in 3.9% of the patients in the intervention group, as compared with 8.8% of the patients in the control group (electronic supplementary table 2). There were no between-group differences in the median volume of intravenous fluids or in the hemodynamic variables (electronic supplementary table 1).

### Primary and secondary outcomes

A primary outcome event occurred in 87 (25.7%) intervention patients and in 69 (20.2%) control patients to 11.8; relative risk, 1.27; 95% CI 0.96–1.68;  $p = 0.08$ ) (Table 3). A time-to-event analysis also did not show a significant difference between the two groups with respect to the primary composite outcome (Fig. 2). The composite of reintubation or curative noninvasive ventilation for acute respiratory failure occurred in 49 (14.5%) intervention patients and 25 (7.4%) control patients (absolute between-group difference, 7.1%; 95% CI 2.5–11.9;  $p = 0.004$ ) (Table 3; electronic supplementary figures 4 and 5). The difference was primarily due to a greater number of participants requiring curative non-invasive ventilation (absolute difference, 5.9%, 95% CI 2.2–9.8;  $p = 0.002$ ). Reintubation occurred in 28 (8.4%) intervention patients and 16 (4.7%) control patients (absolute difference, 3.6%, 95% CI  $-0.1$  to 7.3;  $p = 0.06$ ). Supplementary Figures S1 and S2 show the time-to-event analyses in individual components of the primary outcomes. There was no evidence of heterogeneity of the treatment effect across the prespecified subgroups (electronic supplementary figure 6).



The results were also consistent in the per-protocol populations (electronic supplementary tables 4 and 5). Electronic supplementary table 3 shows the results of associated univariable and multivariable analyses. After adjustment for stratification variables and covariates, the relative risk for the primary outcome was 1.31 (95% CI 1.06–1.63;  $p = 0.012$ ). Data regarding other secondary outcomes are provided in Table 3.

### Tertiary outcomes

Ventilator-associated adverse events, oxygen desaturation, pneumonia, ARDS, pneumothorax during surgery, and all-cause mortality to day 90 did not differ significantly between the two groups (Table 3). Mechanical power was significantly higher in the intervention group than the control group (Table 2; electronic supplementary table 2).

### Post hoc analyses

A post hoc analysis excluding 94 intervention patients having driving pressure values that exceeded the target value of 13 cmH<sub>2</sub>O showed that the effect of the intervention did not differ (absolute between-group difference, 1.1%; 95% CI –5.6 to 7.8; relative risk, 1.05; 95% CI 0.76–1.45;  $p = 0.751$ ). The post hoc analysis exploring whether intervention effect size varied with driving pressure groups showed significant differences in the primary outcome (electronic supplementary figure 7).

**Table 1 Demographic and characteristics of participants at baseline\***

	Intervention (n = 338)	Control (n = 341)
Age (years), mean (SD)	60 (16)	59 (17)
Male gender, no. (%)	214 (63.3)	194 (56.9)
Body-mass index, mean (SD) <sup>a</sup>	25.0 (4.9)	25.3 (5.0)
Height (cm), mean (SD)	170 (9)	169 (10)
Weight (kg), mean (SD)	73 (16)	73 (16)
Ideal body weight (kg/m <sup>2</sup> ), mean (SD)	65 (10)	63 (11)
<i>ASA physical status classification<sup>b</sup></i>		
1	25/334 (7.5)	19/334 (5.7)
2	122/334 (36.5)	111/334 (33.2)
3	169/334 (50.6)	181/334 (54.2)
4	18/334 (5.4)	23/334 (6.9)
<i>Coexisting conditions, no. (%)</i>		
Hypertension	152 (45.0)	156 (45.7)
Diabetes mellitus	53 (15.7)	56 (16.4)
Chronic respiratory failure	45 (13.3)	35 (10.3)
Cancer	85 (25.1)	76 (22.3)
Active smoking	69 (20.4)	67 (19.6)
COVID-19 at admission	10 (3.0)	8 (2.3)
<i>Location before surgery, no. (%)</i>		
Surgical ward	155 (45.9)	153 (44.9)
Emergency department	40 (11.8)	40 (11.7)
Intensive care unit	92 (27.2)	101 (29.6)
Other	51 (15.1)	47 (13.8)
Sepsis at time of surgery, no. (%) <sup>c</sup>	109 (32.2)	109 (32.0)
SOFA score, median (IQR) <sup>d</sup>	2 (0–4)	2 (0–4)
Mechanical ventilation before randomisation, no. (%)	9 (2.7)	10 (2.9)
Time (hours) with ventilation, median (IQR)	2.0 (0.5–5.0)	4.4 (1.5–7.2)
Ratio of PaO <sub>2</sub> to FiO <sub>2</sub> (mm Hg), mean (SD) <sup>e</sup>	458 ± 171	456 ± 154
Value of ≤ 300 mm Hg, No. (%)	42 (12.4)	33 (9.7)
Vasopressor infusion, no. (%)	20 (5.9)	24 (7.0)
<i>Main reason for surgery, no. (%)</i>		
Intraabdominal infection	110 (32.5)	106 (31.1)
Bowel occlusion	73 (21.6)	79 (23.2)
Intraabdominal haemorrhage	16 (4.7)	14 (4.1)
Acute mesenteric ischemia	25 (7.4)	19 (5.6)
Organ transplant	108 (32.0)	120 (35.2)
Unplanned reoperation after initial surgery	65 (19.2)	67 (19.6)
Other	24 (7.1)	24 (7.0)
<i>Values for laboratory variables, median (IQR)</i>		
Lactate (mmol/L)	1.4 (1–2.3)	1.6 (1–2.3)
Serum creatinine (µmol/L)	78 (58–168)	83 (62–191)
C reactive protein (mg/L)	22 (5–116)	19 (5–101)
Haemoglobin (g/dL)	12 (10–13)	12 (10–13)

\*Percentages may not total 100 because of rounding. Regarding the overall representativeness of the trial, the ethics committee does not allow the collection of information regarding characteristics of patients who are not included in a trial (i.e., patients who have not given consent); in addition, French law prohibits the collection of information regarding race or ethnic group

Data are presented as means ± standard deviation or numbers (%)

Abbreviations: COVID-19 coronavirus disease 2019, IQR interquartile range, PEEP positive end-expiratory pressure

<sup>a</sup> The body-mass index is the weight in kilograms divided by the square of the height in meters

<sup>b</sup> ASA physical status classes: (1) normal health, (2) mild systemic disease, (3) severe systemic disease, and (4) severe systemic disease that is a constant threat to life

<sup>c</sup> Sepsis at admission was defined according to the Sepsis-3 criteria

<sup>d</sup> The Sequential Organ Failure Assessment (SOFA) score was calculated from the worst values corresponding to six organ systems prior to surgery. Scores range from 0 to 24, with higher scores indicating more severe organ failure. Data on SOFA score at baseline were available for 303 patients in the driving-pressure guided group and 305 in the control group

<sup>e</sup> The FiO<sub>2</sub> value reflects the value that was recorded closest to the time of randomisation within the 24 h before randomisation. If an arterial blood gas analysis was not available at randomization, the PaO<sub>2</sub>/FiO<sub>2</sub> ratio could be inferred from the oxygen saturation as measured by pulse oximetry. The imputed PaO<sub>2</sub>/FiO<sub>2</sub> ratio was calculated in 318 patients in the intervention group and 307 in the control group

**Table 2 Ventilator settings and respiratory variables in participants during the intervention period**

	Intervention (n = 338)	Control (n = 341)	Difference (95% CI)	p value
<i>Tidal volume (ml/kg PBW), mean (SD)<sup>a</sup></i>				
Mean lowest	6.3 (0.9)	6.5 (0.9)	-0.2 (-0.4 to -0.1)	<0.001
Mean highest	7.2 (1.2)	7.3 (1.1)	-0.1 (-0.3 to 0.1)	0.169
<i>Plateau pressure (cmH<sub>2</sub>O), median (IQR)</i>				
Median lowest	21 (18–23)	14 (12–16)	7 (6–8)	<0.001
Median highest	25 (24–27)	18 (15–22)	7 (6–8)	<0.001
<i>PEEP, median (IQR), cmH<sub>2</sub>O</i>				
Median lowest	15 (10–15)	5 (5–5)	9 (8–10)	<0.001
Median highest	15 (15–15)	5 (5–5)	10 (10–10)	<0.001
<i>Driving pressure (cmH<sub>2</sub>O), median (IQR)<sup>b</sup></i>				
Median lowest	7 (6–9)	9 (7–11)	-2 (-3 to -1)	<0.001
Median highest	11 (9–13)	13 (10–16)	-2 (-3 to -1)	<0.001
<i>Peak inspiratory pressure (cmH<sub>2</sub>O), median (IQR)</i>				
Median lowest	26 (23–28)	18 (16–21)	8 (7–9)	<0.001
Median highest	30 (28–33)	23 (20–27)	7 (6–8)	<0.001
<i>FiO<sub>2</sub> (%), median (IQR)</i>				
Median lowest	35 (30–40)	35 (30–41)	-1 (-3 to -1)	0.038
Median highest	47 (40–55)	47 (40–60)	-2 (-5 to 1)	0.319
<i>Respiratory rate (b/min), mean (SD)</i>				
Median lowest	14.8 (2.9)	14.4 (3.0)	0.3 (-0.1 to 0.8)	0.133
Median highest	18.4 (4.0)	17.7 (4.0)	0.6 (0.1 to 1.2)	0.045
Receipt of rescue therapy, no. (%) <sup>c</sup>	13 (3.9)	30 (8.8)	-5.0 (-8.6 to -1.3)	0.008
Increase in PEEP	13 (3.9)	7 (2.1)	1.8 (-0.1 to 4.3)	0.167
Recruitment manoeuvre	NA	28 (8.2)	NA	NA
<i>Mechanical power (Joules/min), median (IQR)<sup>d</sup></i>				
Lowest value	13 (10–15)	8 (6–10)	5 (4–5)	<0.001
Highest value	19 (15–24)	12 (9–16)	7 (6–8)	<0.001

Abbreviations: CI confidence interval, FiO<sub>2</sub> fraction of inspired oxygen, IQR interquartile range, PEEP positive end-expiratory pressure, PBW predicted body weight

<sup>a</sup> Predicted body weight was calculated as 50 kg + 0.91 kg/cm × (height - 152.4 cm) for men and 45.5 kg + 0.91 kg/cm × (height - 152.4 cm) for women

<sup>b</sup> The driving pressure was calculated as plateau pressure minus positive end-expiratory pressure

<sup>c</sup> Rescue therapy was for oxygen desaturation, defined as oxygen-saturation level on pulse oximetry of less than 92% for more than 5 min

<sup>d</sup> The mechanical power was calculated as 0.098 × respiratory rate × tidal volume × (peak inspiratory pressure - (0.5 × driving pressure))

## Discussion

Among patients at risk of postoperative respiratory failure after emergency abdominal surgery, in contrast with our hypothesis, a strategy of individually titrated highest PEEP in targeting driving pressure did not reduce postoperative respiratory failure or death. However, the intervention led to a higher incidence of reintubation or need for curative non-invasive ventilation for acute respiratory failure within 30 days.

Several observational studies have assessed the association of driving pressure with outcomes after surgery [11, 12, 19]. However, these investigations were limited by biases inherent to the observational designs used. The effect of a driving pressure-guided PEEP strategy as compared with a fixed PEEP strategy has been evaluated previously in small and moderate-sized single-center trials involving patients mechanically ventilated for planned abdominal surgery, which limits the generalizability of the findings [13, 14]. Our findings seem to contrast with those of the iPROVE-OLV randomized controlled trial, which showed a 56% decrease in severe postoperative pulmonary complications after thoracic surgery with a driving pressure-guided PEEP strategy [29]. A notable difference with this trial was the use of the highest dynamic compliance (or lowest driving pressure) for individual PEEP selection in the iPROVE-OLV trial. However, a particular feature in the iPROVE-OLV trial was the use

of postoperative high-flow oxygen therapy in 40% of patients; this may have confounded the effects of the driving pressure-guided PEEP strategy. In a multicenter trial involving 1170 patients undergoing thoracic surgery, an individualized PEEP strategy titrated to the lowest driving pressure did not decrease postoperative pulmonary complications compared with conventional lung-protective ventilation [30]. Additionally, it is not clear that driving pressure is an appropriate surrogate for lung strain under conditions of one-lung ventilation or when the chest wall is open. Finally, transpulmonary driving pressure through esophageal pressure measurement could help better define targets for mechanical ventilation than airway driving pressure, to determine separate contributions of lung and chest wall in determining respiratory system mechanics [31], especially in situations of increased pleural or abdominal pressure such as in patients with obesity and/ or during laparoscopic surgery [32].

**Table 3 Primary, secondary and tertiary outcomes**

	Intervention (n = 338)	Control (n = 341)	Absolute or median difference (95% CI) <sup>a</sup>	p value
<i>Primary outcome</i>				
Postoperative respiratory failure or in-hospital death by day 30 of randomisation, no. (%)	87 (25.7)	69 (20.2)	5.5 (−0.8 to 11.8) <sup>b</sup>	0.088
<i>Secondary outcomes</i>				
Postoperative respiratory failure, no. (%)	79 (23.4)	63 (18.5)	4.8 (−1.3 to 10.9)	0.256
Failure to wean	44 (13.0)	48 (14.1)	−1.1 (−6.3 to 4.0)	0.665
Reintubation or noninvasive ventilation	49 (14.5)	25 (7.3)	7.1 (2.5–11.9)	0.004
Death, no. (%)	22 (6.5)	19 (5.6)	0.9 (−2.3 to 4.5)	0.608
<i>Postoperative pulmonary complications by day 30, no. (%)<sup>c</sup></i>				
Grade 1 or 2	46 (13.6)	44 (12.9)	0.7 (−4.4 to 5.8)	0.512
Grade ≥ 3	80 (23.7)	61 (17.9)	5.8 (−0.3 to 11.9)	0.052
Acute kidney injury by day 30, no. (%) <sup>d</sup>	88 (26.0)	95 (27.9)	−1.8 (−8.5 to 4.8)	0.592
Stage ≥ 2 acute kidney injury	63/88 (71.6)	69/95 (72.6)	−1.0 (−5.2 to 3.0)	0.875
Renal replacement therapy, no. (%)	25 (7.4)	29 (8.5)	−1.1 (−5.2 to 3.0)	0.594
<i>SOFA score, median (IQR)</i>				
Day 1 (n = 289/278)	3 (1–6)	3 (1–6)	0.0 (−0.7 to 0.7)	0.717
Day 2 (n = 252/245)	2 (0–6)	3 (0–5)	0.0 (−1.0 to 1.0)	0.860
Day 3 (n = 240/233)	2 (0–5)	2 (1–5)	0.0 (−0.9 to 0.9)	0.359
Day 4 (n = 218/212)	2 (0–5)	3 (1–5)	−1.0 (−1.9 to 0.8)	0.438
Day 5 (n = 211/192)	2 (0–4)	2 (1–5)	0.0 (−0.9 to 0.9)	0.322
Day 6 (n = 204/182)	2 (0–4)	2 (1–4)	0.0 (−0.8 to 0.8)	0.714
Day 7 (n = 169/159)	3 (0–4)	2 (1–4)	1.0 (−1.2 to 1.8)	0.873
Sepsis or septic shock by day 30, no. (%)	64 (18.9)	61 (17.9)	1.0 (−4.8 to 6.9)	0.725
Time to successful tracheal extubation (hours), median (IQR) <sup>e</sup>	5 (4 to 11)	5 (3 to 10)	0.4 (−0.3 to 1.1)	0.207
Total time alive and without exposure to invasive or noninvasive ventilation by day 30 (days), mean (SD)	26.8 (8.4)	27.1 (8.2)	−0.3 (−1.5 to 1.0)	0.156
Cumulative total duration of mechanical ventilation by day 30 (days), mean (SD)	5.4 (7.2)	5.8 (7.9)	−0.5 (−3.2 to 2.3)	0.407
Days alive not in the ICU by day 30(days), median (IQR)	24 (17 to 30)	25 (17 to 30)	−1.0 (−2.9 to 0.9)	0.718
Total duration of stay in ICU (days), median (IQR)	8 (5 to 14)	8 (5 to 14)	0.0 (−1.3 to 1.3)	0.864
Total duration of hospital stay (days), median (IQR)	14 (7 to 24)	14 (7 to 25)	0.0 (−2.7 to 2.7)	0.977
<i>Tertiary outcomes</i>				
Use of prophylactic noninvasive ventilation, no. (%)	42 (12.4)	39 (11.4)	0.9 (−4.0 to 5.8)	0.691
Postoperative hypoxaemia by day 30, no. (%) <sup>f</sup>	108 (32.0)	96 (28.2)	3.8 (−3.0 to 10.7)	0.280
Pneumonia by day 30, no. (%)	21 (6.2)	21 (6.1)	0.0 (−3.6 to 3.6)	0.976
ARDS by day 30, no. (%)	4 (1.2)	6 (1.8)	−0.6 (−2.4 to 1.2)	0.752
Death by day 90, no. (%)	34 (10.1)	31 (9.1)	1.0 (−3.5 to 5.4)	0.668
<i>Ventilator-related adverse events<sup>g</sup></i>				
Arterial hypotension, no. (%)	101 (29.9)	85 (24.9)	5.0 (−1.7 to 11.7)	0.148
Pneumothorax, no. (%)	2 (0.6)	1 (0.3)	0.3 (−0.7 to 1.3)	0.623

Abbreviations: ARDS acute respiratory distress syndrome, ICU intensive care unit, IQR interquartile range

<sup>a</sup> The widths of the confidence intervals for the secondary and tertiary outcomes were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between trial groups

<sup>b</sup> Unadjusted relative risk 1.27, (95% CI 0.96–1.68); *P* = 0.088. Adjusted relative risk 1.31, (95% CI 1.06–1.63); *p* = 0.012

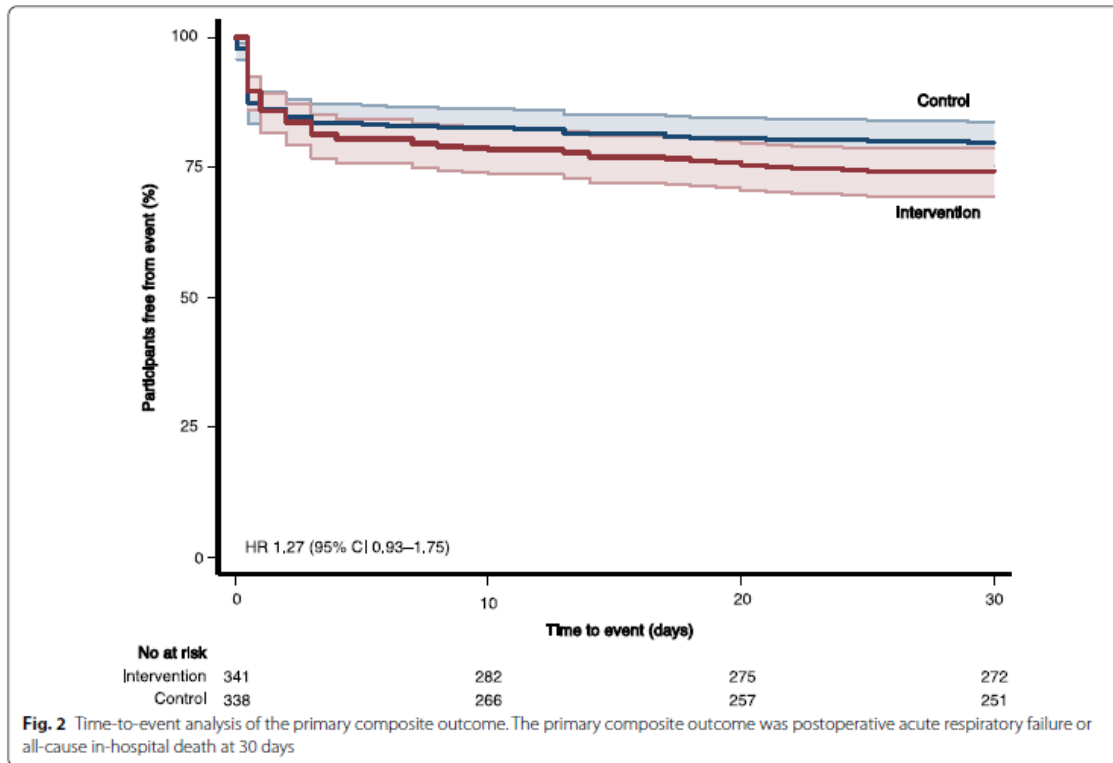
<sup>c</sup> Postoperative pulmonary complications are scored with the use of a grade scale ranging from 0 to 4, with grade zero representing absence of complications, and grades 1 to 4 representing increasing (worsening) levels of complications (ESM 2) [24]

<sup>d</sup> Acute kidney injury is defined according to Kidney Disease Improving Global Outcomes criteria

<sup>e</sup> Successful tracheal extubation is defined as extubation without reintubation within 48 h

<sup>f</sup> Hypoxemia is defined as arterial partial pressure of oxygen (PaO<sub>2</sub>) < 8 kPa (60 mmHg) or peripheral oxygen saturation as measured with pulse oximetry < 90% while breathing room air or PaO<sub>2</sub> < 80 mmHg while breathing 15 L/min of oxygen, or a PaO<sub>2</sub>/FIO<sub>2</sub> ratio < 40 kPa (300 mmHg)

<sup>g</sup> Arterial hypotension is defined as systolic blood pressure less than 80 mm Hg for more than 5 min



Previous clinical trials comparing higher versus lower PEEP did not target a limited driving pressure strategy. Our findings are at variance with those of previous studies, suggesting that PEEP increments might be protective when associated with a change in lung mechanics and lower driving pressure [33]. A particular feature of the ventilation strategy in this trial was the use of recruitment maneuvers (to promote the re-aeration of non- or poorly aerated lung regions) and PEEP titration aimed at minimizing derecruitment by selecting the highest permissible PEEP level based on a predefined driving pressure target. The synergistic role of recruitment maneuvers and driving pressure-guided ventilation in reducing postoperative pulmonary complications through a lung-protective strategy was suggested in a recent meta-analysis with trial sequential analysis [34, 35]. Unlike previous studies in which the PEEP titration trial was performed using stepwise PEEP decrements to identify the lung closing pressure (i.e., the PEEP level at which alveolar units begin to collapse)—a method that often includes a second recruitment maneuver after the optimal PEEP has been determined [8, 29], the PEEP trial in this study was stopped as soon as the target driving pressure was reached. One plausible explanation for the divergent findings is that the approach of selecting the highest PEEP level in targeting a fixed driving pressure value in our trial may have contributed to the use of excessive levels of PEEP and injurious overdistension of aerated lung regions in some patients, especially those with lower potential for lung recruitability. Higher levels of PEEP may benefit only those patients with higher potential for alveolar recruitment (i.e., the re-aeration of non-aerated and poorly aerated lung regions), but excessive PEEP may cause harm by increasing strain. This is consistent with the between group difference in mechanical power, a finding that is in line with previous data that suggest greater risks of postoperative respiratory failure and mortality in patients receiving higher intensity of mechanical ventilation [36, 37]. The driving-pressure target in this trial was extrapolated from that arising from a mediation analysis and large cohort studies [11, 12,

9], with suggested cutoffs of less than or equal to 10–13 cmH<sub>2</sub>O. Nevertheless, this trial does not inform whether outcomes would have differed with a lower driving pressure target. It is also possible that a patient-centered rather than a fixed driving pressure target may be more appropriate, consistent with findings of prior studies that individualized PEEP based on the highest compliance of the respiratory system [38, 39]. Moreover, because different effects of ventilator settings could arise among patients with different functional lung sizes, and females on average have smaller lungs, whether different driving pressure threshold targets should be considered depending on the functional lung size remains to be evaluated.

Despite being relevant to this patient population, the observed between-group treatment effect size (5.5%) was lower than the clinically important difference in the composite primary outcome (10%) defined in the protocol. Although more patients in the intervention group than in the control group (8.4% vs 4.8%) underwent reintubation, the percentages of reintubation were lower than rates reported in previous studies [4, 40]. One explanation is the use of noninvasive ventilation to treat patients with acute respiratory failure, which has been suggested to help prevent reintubation [41, 42].

The present trial has several limitations. The trial was not double-blinded. Masking of the operating-room team to group assignment was not feasible, and physicians deciding to wean patients from the ventilator were not masked to the intervention group. However, the use of predefined criteria for interruption of sedation and durations of ventilation in the two groups suggests that a significant imbalance between the two groups was unlikely. This trial was intended to be pragmatic and did not include standardized criteria for prophylactic postoperative respiratory support, including the use of high-flow oxygen therapy after extubation. Nonetheless, the percentages of patients who received prophylactic noninvasive ventilation were similar between trial groups. There was also no evidence of heterogeneity according to the use or non-use of prophylactic noninvasive ventilation. The adherence rate to the intervention was lower than expected, with approximately 30% of patients who had driving pressure higher than the target value. Nonadherence is important in this setting and may have substantially altered our findings owing to the observed effect sizes in post hoc analyses. The effect of higher PEEP on hemodynamics was not extensively evaluated in this trial. This limitation should be acknowledged, as higher PEEP levels and recruitment maneuvers may contribute to hemodynamic instability. We did not collect data on body positioning, which might have affected lung volume and respiratory mechanics, and consequently PEEP setting.

Lastly, the findings may not be generalizable to another patient population. Thus, further research is warranted to determine whether potentially important subgroups that we did not assess could benefit from the intervention.

## Conclusion

A strategy of individually adjusted highest PEEP in targeting driving pressure among patients at risk of postoperative respiratory failure did not reduce the incidence of postoperative respiratory failure or death. However, the intervention was associated with more reintubation or need for non-invasive ventilation.

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## **Author contributions**

EF obtained funding from the French Ministry of Health to undertake the study. EF and SJ conceived the study, participated in protocol development, study design, and data interpretation, and shared first authorship. TG, ADJ, MJ, JMC, GL, NG, PB, LH, DM, CC and MG assisted in setup, recruitment, and local execution of the study, and contributed to data analysis. BP and CL handled the statistical analysis. EF, SJ and BP had full access to all the verified and raw data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors provided revisions on the manuscript and approved the final version. EF and SJ had the final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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## **Data availability**

Deidentified data will be shared with other authenticated researchers for further research and research publications on this topic, but only if they guarantee to preserve the confidentiality of the information requested. Requests for data sharing will be considered by the data sharing committee of the Clermont-Ferrand University Hospital in accordance with its data sharing policy.

## **Declarations**

## **Conflicts of interest**

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Ethics approval The trial was approved for all centers by the French Committee for the Protection of Research Subjects (CPP Sud-Est III, number 2019-009B) prior to enrolment.

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