Journal of Clinical Anesthesia 95 (2024) 111465

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

One-lung ventilation with fixed and variable tidal volumes on oxygenation and pulmonary outcomes: A randomized trial

Katalin Szamos, MD [a,1], Boglárka Balla, MD [a], Balázs Pálóczi, MD [a], Attila Enyedi, MD, PhD [b], Daniel I. Sessler, MD [c,d], Béla Fülesdi, MD, PhD, DSc [a,c], Tamás Végh, MD, PhD [a,c,*]

[a] University of Debrecen, Department of Anesthesiology and Intensive Care, Debrecen, Hungary
[b] University of Debrecen, Institute of Surgery, Department of Thoracic Surgery, Debrecen, Hungary
[c] Outcomes Research Consortium, Cleveland, OH, USA
[d] Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

HIGHLIGHTS

- Variable tidal volume ventilation improves oxygenation in animals and humans with acute respiratory distress syndrome.
- We compared oxygenation and pulmonary complications in patients randomized to one-lung ventilation with variable or fixed tidal volumes
- Ventilation with variable tidal volume did not improve oxygenation or reduce postoperative pulmonary complications.

ARTICLE INFO

Keywords:
Thoracic anesthesia
One-lung ventilation
Tidal volume
Postoperative pulmonary complications
Intraoperative oxygenation
Variable ventilation

ABSTRACT

Objective: Test the hypothesis that one-lung ventilation with variable tidal volume improves intraoperative oxygenation and reduces postoperative pulmonary complications after lung resection.
Background: Constant tidal volume and respiratory rate ventilation can lead to atelectasis. Animal and human ARDS studies indicate that oxygenation improves with variable tidal volumes. Since one-lung ventilation shares characteristics with ARDS, we tested the hypothesis that one-lung ventilation with variable tidal volume improves intraoperative oxygenation and reduces postoperative pulmonary complications after lung resection.
Design: Randomized trial.
Setting: Operating rooms and a post-anesthesia care unit.
Patients: Adults having elective open or video-assisted thoracoscopic lung resection surgery with general anesthesia were randomly assigned to intraoperative ventilation with fixed ($n = 70$) or with variable (n = 70) tidal volumes.
Interventions: Patients assigned to fixed ventilation had a tidal volume of 6 ml/kgPBW, whereas those assigned to variable ventilation had tidal volumes ranging from 6 ml/kg PBW ± 33% which varied randomly at 5-min intervals.
Measurements: The primary outcome was intraoperative oxygenation; secondary outcomes were postoperative pulmonary complications, mortality within 90 days of surgery, heart rate, and SpO_2/FiO_2 ratio.
Results: Data from 128 patients were analyzed with 65 assigned to fixed-tidal volume ventilation and 63 to variable-tidal volume ventilation. The time-weighted average PaO_2 during one-lung ventilation was 176 (86) mmHg in patients ventilated with fixed-tidal volume and 147 (72) mmHg in the patients ventilated with variable-tidal volume, a difference that was statistically significant ($p < 0.01$) but less than our pre-defined clinically meaningful threshold of 50 mmHg. At least one composite complication occurred in 11 (17%) of patients ventilated with variable-tidal volume and in 17 (26%) of patients assigned to fixed-tidal volume ventilation, with a relative risk of 0.67 (95% CI 0.34–1.31, $p = 0.24$). Atelectasis in the ventilated lung was less common with variable-tidal volumes (4.7%) than fixed-tidal volumes (20%) in the initial three postoperative days, with a relative risk of 0.24 (95% CI 0.01–0.8, $p = 0.02$), but there were no significant late postoperative differences. No other secondary outcomes were both statistically significant and clinically meaningful.

* Corresponding author at: University of Debrecen, Department of Anesthesiology and Intensive Care, Debrecen, Nagyerdei krt 98, Hungary.
E-mail address: veghdr@med.unideb.hu (T. Végh).
[1] Dr. Szamos and Dr. Balla contributed equally.

https://doi.org/10.1016/j.jclinane.2024.111465
Received 29 October 2023; Received in revised form 22 March 2024; Accepted 1 April 2024

Conclusion: One-lung ventilation with variable tidal volume does not meaningfully improve intraoperative oxygenation, and does not reduce postoperative pulmonary complications.

1. Introduction

Conventionally, tidal volumes are kept nearly constant during surgery [1–3]. However, the human respiratory system is not designed for monotony [4–6] and there is increasing evidence that constant-volume ventilation promotes atelectasis [2,7,8]. Perhaps consequently, tidal volume variability during spontaneous breathing at rest — which can be quantified with the coefficient of variation — is approximately 33 ± 15% of the tidal volume in healthy subjects [9,10], 22 ± 5% in patients with restrictive lung disease [11,12] and 25 ± 16% in patients with chronic obstructive pulmonary disease [12,13].

Mimicking physiological variability in tidal volume during mechanical ventilation may improve oxygenation and reduce the risk of ventilator-induced lung injury. Studies in animals [14–19] and in humans [20] with acute respiratory distress syndrome (ARDS), for example, report that ventilation with variable tidal volumes improves oxygenation, although benefit is not apparent in patients with healthy lungs during routine anesthesia [8,21,22]. Patients having thoracic surgery often have pre-existing lung injury, and one-lung ventilation further stresses the ventilated lung [23]. One-lung ventilation (OLV) shares characteristics of ARDS because the lung volume is smaller than usual in both conditions [24,25]. Patients having one-lung ventilation for thoracic surgery may thus benefit from variable-tidal volume ventilation [26].

We therefore tested the primary hypothesis that oxygenation during one-lung ventilation is improved by variable-tidal volume ventilation in patients having thoracic surgery. We a priori defined differences of 50 mmHg in PaO_2 to be clinically meaningful [27–29]. Secondarily, we tested the hypotheses that variable-tidal volume ventilation reduces complications and mortality on post-operative days (POD) 1–3 and 1–3 months later [30–32].

2. Methods

Our randomized clinical trial was approved by the Ethics Committee (DEOEC RKEB/IKEB 4737–2017) of the University of Debrecen and the Ethics Board of the Hungarian National Institute of Pharmacy and Nutrition (OGYÉI/24107/2017) and was registered at ClinicalTrials.gov before the first patient was enrolled (NCT03364465). Written informed consent was obtained from participating patients. The study was conducted in accordance with the declaration of Helsinki and the principles of Good Clinical Practice guidelines.

2.1. Study design and population

We considered consenting adults >18 years who had a body mass index (BMI) < 35 kg/m^2 and were scheduled for elective open or video-assisted thoracoscopic surgery with general anesthesia in whom we anticipated >60 min of one-lung ventilation.

We excluded patients who had severe pulmonary disease (chronic obstructive pulmonary disease, lung fibrosis, documented bullae, severe emphysema, pneumothorax, uncontrolled asthma), heart failure and/or coronary heart disease, previous thoracic surgery, pulmonary arterial, neuromuscular disease, planned postoperative mechanical ventilation, bilateral procedures, lung separation with bronchial blocker, intracranial injury or tumor, previous neurosurgical procedures, enrollment in another interventional study, or were pregnant (**Supplementary Material** Table 1).

2.2. Randomization

Patients were randomly assigned to variable-tidal volume and or fixed-tidal volume ventilation. Randomization, without blocking or stratification, was based on computer-generated codes that were maintained in sequentially numbered sealed opaque envelopes.

The treatment groups were: (1) routine lung-protective one-lung ventilation with fixed-tidal volume; and (2) lung-protective one-lung ventilation with variable-tidal volume.

2.3. Interventions and intraoperative management

Patients were premedicated with 5 mg of midazolam and 0.5 mg of atropine given intramuscularly 30 min before entering the operating room. An epidural catheter was inserted at the mid-thoracic level (T5–8) before anesthetic induction. An infusion of 0.125% bupivacaine was initiated at a rate of 0.1 mg/kg/h and maintained throughout the surgery.

Table 1
Baseline characteristics.

	Fixed-tidal volume ventilation (n = 65)	Variable-tidal volume ventilation (n = 63)	Absolute standardized difference*
Age (years)	61 (11)	62 (10)	0.13
ARISCAT score	44 (5)	43 (5)	0.25
Male	36 (55%)	34 (54%)	0.03
Height (cm)	166 (8)	166 (10)	0.00
Actual bodyweight (kg)	72 (16)	75 (16)	0.22
Predicted bodyweight (kg)	61 (9)	61 (11)	0.04
FVC (% predicted)	99 (18)	97 (18)	0.16
FEV1 (% predicted)	94 (21)	88 (19)	0.24
FEV1/FVC (% predicted)	97 (13)	97 (11)	0.07
PaO_2 (mmHg)	87 (16)	86 (14)	0.07
$PaCO_2$ (mmHg)	36 (4)	37 (3)	0.26
Heart rate (min^{-1})	81 (15)	81 (14)	0.04
SpO_2 (%)	97 (2)	97 (2)	0.01
Duration of anesthesia (min)	154 (51)	156 (50)	0.03
Duration of TLV (min)	50 (33)	51 (31)	0.01
Duration of OLV (min)	98 (41)	98 (39)	0.01
Duration of surgery (min)	115 (45)	104 (43)	0.27
Blood loss (ml)	117 (104)	113 (40)	0.04
Crystalloids (ml)	1188 (457)	1338 (443)	0.33
Left-sided OLV	30 (46%)	37 (59%)	0.25
VATS	34 (52%)	42 (67%)	0.3
Segmentectomy	14 (22%)	13 (21%)	0.02
Lobectomy	45 (69%)	48 (76%)	0.16
Pneumonectomy	6 (9%)	2 (3%)	0.25

ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in one second; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; SpO_2, oxygen saturation measured by pulse oximetry; OLV, one-lung ventilation; VATS, Video-assisted thoracoscopic surgery.
Summary statistics are presented as n (%) for categorical variables and means (SD) for continuous variables.
* Presented for all baseline characteristics. Standardized differences >0.35 were considered imbalanced.

Routine intraoperative monitoring included electrocardiography, continuous arterial pressure monitoring via a catheter inserted into a radial artery, pulse oximetry, and acceleromyography to assess neuromuscular block.

Anesthesia was induced using 80% inspired oxygen, along with a combination of 2–3 mg/kg of propofol and 2–3 μg/kg of fentanyl. Intubation was facilitated by 0.2 mg/kg of cis-atracurium.

Sevoflurane, in combination with an air/oxygen mixture (40% oxygen during two-lung ventilation and 80% oxygen during one-lung ventilation), was used to maintain anesthesia. The concentration of sevoflurane was adjusted to achieve a target Bispectral Index (BIS) between 40 and 60.

Normothermia was targeted with forced-air warming. Intravascular volume was maintained by infusion of balanced crystalloid solutions, with blood transfusions as necessary.

Patients were intubated with double-lumen endotracheal tubes. During two-lung ventilation, patients were ventilated with a volume-controlled square-wave flow pattern at a tidal volume of 8 mL/kg predicted body weight (PBW) and positive end-expiratory pressure (PEEP) of 5 cmH_2O. An initial respiratory rate of 10–14/min was adjusted to a target minute ventilation of 100 ml/kg PBW, with an inspiratory-to-expiratory (I:E) ratio of 1:2. After induction of general anesthesia and intubation, a recruitment maneuver was performed [33,34], followed by ventilation of both lungs in the supine position for 10 min. For lung recruitment, we used the automated multi-step recruitment function of Draeger Perseus anesthesia machine which applies a sequence of pressure-controlled breaths at variable pressures. During the maneuver, inspiratory pressure is automatically increased in steps to a maximum of 35 cmH_2O and the expiratory pressure is increased to a maximum of 15 cmH_2O. Both pressures are sustained for several breaths and then reduced again in steps to the starting levels. For parameters such as respiratory rate and tidal volume, the values from the previous ventilation mode were used. The time intervals for each step, the pressure rise or decrease depends on the selected patient category and is automated.

Patients were then turned laterally, and position of the double-lumen tube confirmed. One-lung ventilation was initiated once the thoracic cavity was opened. In patients randomized to fixed-tidal volume ventilation, tidal volume was kept constant at 6 ml/kgPBW throughout one-lung ventilation. In patients assigned to variable-tidal volume ventilation, tidal volumes were varied within a 33% range of 6 ml/kgPBW using a random integer generator (**Supplementary Material** Fig. 1).

Previous studies report that changes in the alveolar-arterial oxygen gradient ($AaDO_2$) are apparent within two minutes of discontinuing positive end-expiratory pressure (PEEP), and that changes in PaO_2 can be detected within five minutes of altering PEEP or tidal volume [35–38]. We therefore selected five-minute equilibration periods. For example, a tidal volume of 6-ml/kg is 420 ml in a 70 kgPBW patient. Using a coefficient of variation of 33%, tidal volumes would thus range from 280 to 560 ml. Volumes were randomly changed at 5-min intervals, with the respiratory rate being adjusted as necessary to maintain 100 ml/kg/PBW minute ventilation (**Supplementary Material** Table 2).

Rescue maneuvers were implemented as necessary during one-lung ventilation. For hypoxemia (SpO_2 < 90% for >1 min), treatments included increasing FiO_2, performing a recruitment maneuver for the ventilated lung, increasing PEEP, increasing inspired oxygen and/or providing continuous positive airway pressure (CPAP) to the non-ventilated lung, considering surgical interventions such as clamping the pulmonary artery, inhalation of nitric oxide or prostacyclin, and switching from one-lung to two-lung ventilation. For hypercapnic acidosis ($PaCO_2$ > 60 mmHg and pH <7.20), the following rescue maneuvers were sequentially implemented as necessary: 1) the respiratory rate was increased to a maximum of 30/min; 2) tidal volume was increased up to 7 ml/kgPBW; and 3) ventilation was switched from one-lung to two-lungs [39–41].

Following closure of the thoracic cavity, a recruitment maneuver was performed for the ventilated lung, and two-lung ventilation was resumed with 40% inspired oxygen. Patients were extubated in the operating room and monitored in the postanesthesia care unit for at least 12 h. Nasal oxygen was given as needed, and epidural analgesia was continued.

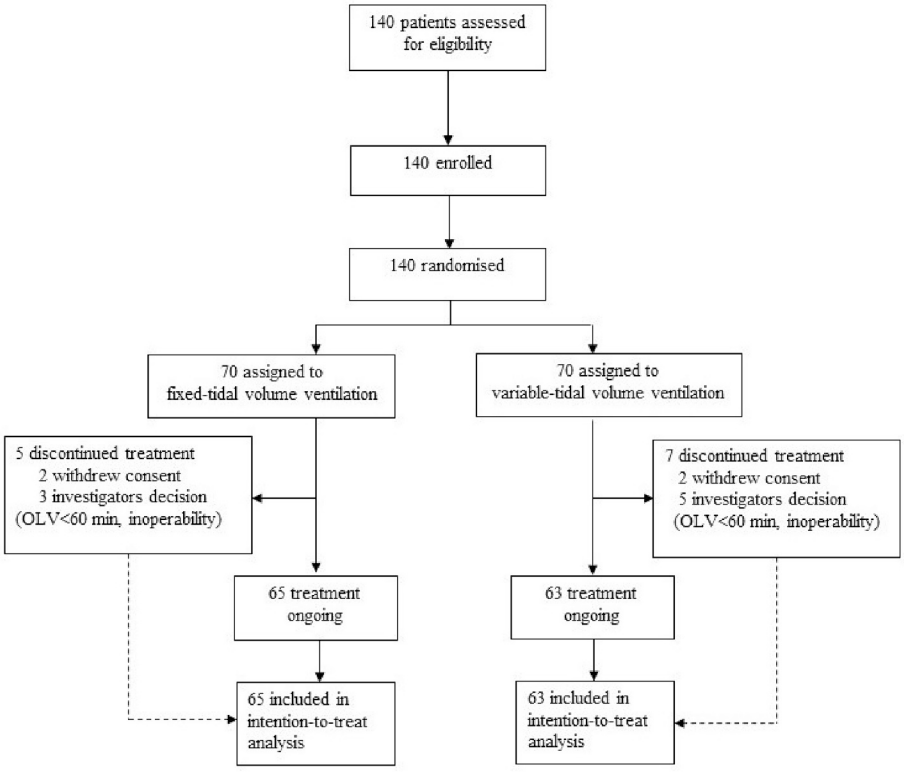

Fig. 1. Trial profile.

Table 2
Secondary outcome variables in the postoperative period.

	Fixed-tidal volume (n = 65)	Variable-tidal volume (n = 63)	Treatment effect	p
Composite pulmonary complications (atelectasis and infiltrations)	17 [26.2]	11 [17.5]	0.67 (0.34–1.31)	0.24
Atelectasis				
POD1–3	13 [20]	3[4.7]	0.24 (0.01–0.8)	0.02
POD30	1 [1.7][6]	1 [1.8][8]	1.03 (0.07–16.1)	0.98
POD90	2 [4][15]	0 [0][9]	0.2 (0.01–4.2)	0.31
Infiltration				
POD1–3	3 (4.6)	7 (11.1)	2.33 (0.63–8.63)	0.2
POD30	3 (5.1)[6]	1 (1.8)[8]	0.36 (0.04–3.33)	0.37
POD90	3 (6)[15]	0 (0)[9]	0.13 (0.01–2.5)	0.18
HR (min^{-1})				
Time-weighted average	86 (15)	84 (14)	2 (−0.6–4)	0.15
HR (min^{-1})				
POD1–3	86 (14)	87 (15)	-1 (−4–2)	0.4
POD30	86 (18)[6]	79 (10)[8]	7 (1−12)	0.02
POD90	85 (16)[15]	80 (12)[8]	6 (1–12)	0.02
SpO_2/FiO_2				
Time-weighted average	444 (47)	447 (37)	-3 (−10–4)	0.41
SpO_2/FiO_2				
POD1–3	435 (54)	440 (39)	-5 (−15–5)	0.32
POD30	464 (7)[6]	462 (8)[8]	2 (−1–4)	0.26
POD90	464 (6)[15]	462 (11)[8]	2 (−1–6)	0.16
Median length of hospital stay (days)	6 [4]	6 [3]	0.76 (0.53–1.08)	0.12
Median length of ICU stay (days)	0 [1]	0 [3]	1.32 (0.71–2.46)	0.38
Median length of chest drainage (days)	4 [3]	4 [2]	0.98 (0.69–1.4)	0.92

Data are presented as n [%], means (SD), and medians [IQR].
The relative risk (95%CI) as treatment effect was estimated for occurrence of atelectasis and infiltration for varieble-tidal volume ventilation.
For continuous variables (such as heart rate and SpO_2/FiO_2 ratio) the treatment effect presented as mean difference (95%CI).
Superscripts represent the number of patients with missing data.
POD: Post-operative day; HR: Heart rate; SpO_2: peripheral oxygen saturation measured by pulse oximetry; FiO_2: fraction of inspired oxygen; POD1–3: average of postoperative first three days while patients were hospitalized.
There were no deaths and adverse events (atrial fibrillations, myocardial infarct, wound infection, sepsis, renal failure, etc.) within 90 postoperative days.

2.4. Data collection

Only four anesthesiologists participated, and the corresponding author personally supervised patient selection, randomization, each anesthesia procedure, and a postoperative visit to maximize protocol adherence. All postoperative measurements were made by the same team of clinicians and investigators; the trial was thus unblinded. Baseline demographic and morphometric characteristics were recorded, as were co-existing diseases, medications, lung-function tests with whole-body plethysmography, arterial blood gas analysis while breathing room air, electrocardiography, echocardiography, computerized tomographic lung scan, and bronchoscopy.

Blood gas results, ventilation, and hemodynamic variables were recorded 10 min after anesthesia induction during supine two-lung ventilation, 10 min after changing to the lateral decubitus position, at 5-min intervals during one-lung ventilation, and at the end of surgery during two-lung ventilation with patients positioned supine. Arterial blood samples were analyzed with calibrated in-room blood gas analyzers.

During the initial three days after surgery, we daily recorded heart rate, SpO_2 measured by pulse oximetry, spirometry measurements using bedside spirometer, chest X-ray radiographs, and body temperature. The same tests were repeated 30 and 90 days after surgery. Postoperative outcomes and complications were defined based on the European Perioperative Clinical Outcome (EPCO) definitions [42]. Vital status was assessed at 90 days using electronic medical record-based registries of University of Debrecen.

2.5. Outcomes

Our primary outcome was time-weighted average arterial partial pressure of oxygen during one-lung ventilation. Based on previous work, we a priori defined a 50-mmHg difference in time-weighted average PaO_2 as a clinically meaningful [27–29].

Secondary outcomes were variously evaluated during the early (POD 1–3) and late (1 and 3 month) postoperative periods [30,31].

1) **Composite of pulmonary complications**. During the initial three days after surgery, we took chest X-ray radiographs daily, and subsequently repeated the tests at 30 and 90 days after surgery. Our collapsed (one or more) composite included respiratory complications, respiratory failure and distress, reintubations, pulmonary edema, and infiltration or atelectasis in the ventilated lung as defined by the European Perioperative Clinical Outcome (EPCO) criteria [42]**.** Chest x-rays were assessed by faculty in the Department of Radiology of the University of Debrecen who were blinded to patient grouping and outcomes. Atelectasis was suggested by lung opacification with or without shift of the mediastinum, hilum, or hemidiaphragm shift towards the affected area, and compensatory overinflation in the adjacent non-atelectatic lung. Our analysis was based on electronic records which reported atelectasis dichotomously.

2) **Mortality**. All-cause mortality was evaluated 3 months after surgery.

3) **Heart rate**. During the initial three days after surgery, heart rates were recorded daily and subsequently at 30 and 90 postoperative days. Changes in heart rate of 10 beats per minute were deemed clinically meaningful based on previous evidence linking high resting heart rate to adverse outcomes in surgical patients [43–45].

4) **Postoperative oxygenation**; the SpO_2/FiO_2 ratio was recorded daily during the initial three days after surgery and subsequently at 30 and 90 days after surgery; We used SpO_2/FiO_2 ratio as a measure of postoperative oxygenation because it provides good sensitivity and specificity compared to invasive PaO_2/FiO_2 ratios in diagnosing lung injury [46–50]. We considered differences of 15% in SpO_2/FiO_2 ratio between groups clinically meaningful [51].

5) **Durations of hospitalization, intensive care unit (ICU) stay, and chest tube drainage**.

Adverse events such as atrial fibrillation, myocardial infarction, wound infection, sepsis, renal failure, and others were recorded and categorized by severity, with events classified as serious if they prolonged hospitalization or posed a life-threatening risk.

2.6. Data analysis

140 patients provided 80% power to detect a two-tailed difference of 50 mmHg in PaO_2 during OLV with an α error of 5% based on an expected standard deviation of 100 mmHg with a repeated-measures analysis [27–29,52]. Thus, we enrolled 70 patients per group to

account for an anticipated dropout of 5% due to declining participation, interruption of intervention, and unplanned complications.

Groups were considered well balanced when absolute standardized differences (difference in means divided by the pooled SD) was <1.96 x $\sqrt{(n1+n2)/(n1\,x\,n2)}$ = 0.35, where n1 = 65 patients and n2 = 63 patients are the number of patients in each group [53].

Linear mixed models with restricted maximum likelihood were used to model PaO_2 during one-lung ventilation, our primary outcome. Time was included after an expansion with 3 degrees-of-freedom natural splines to allow for a potentially non-linear effect of elapsed intraoperative time on PaO_2. We also evaluated the interaction between spline-expanded time and randomization group to determine whether the pattern differed over time rather than just being shifted.

Interaction *P*-values were calculated using Kenward-Roger's approximation of the denominator degrees of freedom. If the interaction effect was not significant ($P > 0.05$), treatment effect estimates would be summarized using the mean difference comparing ventilation with variable-tidal volume versus fixed-tidal volume. If the interaction was significant, the effects of each intervention would be assessed within levels of the other intervention. Missing data were not imputed. Blood gas, ventilatory, and hemodynamic responses during one-lung ventilation were modeled and evaluated in the same framework.

For secondary outcomes, a log-binomial GLM model was used to estimate treatment effect for binary outcomes. For pulmonary complications, we made a simple collapsed composite of atelectasis and/or infiltration anytime on the first three PODs while patients were hospitalized, and again at 30 and 90 days. We used the log-binomial model to estimate relative risk (RR) instead of odds ratio.

For continuous variables such as heart rate and SpO_2/FiO_2 ratio, we used a repeated-measures mixed model. We averaged values over the initial three PODs, and then separately evaluated 30 and 90 days. If the interaction effect was not significant ($P > 0.05$), treatment effect estimates would be summarized using the mean difference comparing ventilation with variable-tidal volume versus fixed-tidal volume. If the interaction was significant, the effects of each intervention would be assessed within levels of the other intervention.

Time-to-event outcomes including hospitalization, ICU stay, and duration of chest drainage were evaluated with Cox proportional hazards regression model.

The relationship between SpO_2/FiO_2 and occurrence of postoperative pulmonary complications during the first three postoperative days was evaluated with point-biserial correlation.

The effect of extent of lung resection (segmentectomy, lobectomy, pneumonectomy) and the type of the surgery (thoracoscopic or thoracotomy) on postoperative pulmonary complications was evaluated with binary generalized linear models with extension to the binomial family with log link/risk ratios were used with restricted maximum likelihood. The extent of resction and the type of surgery was a confounder.

P values <0.05 were considered significant. All the analyses were conducted in Stata Statistical Software (Release 17. College Station, TX: StataCorp LLC, USA) and NCSS 2023 Statistical Software 2023 (NCSS, LLC. Kaysville, Utah, USA).

3. Results

3.1. Population

Between February 1, 2017, and April 1, 2018, 140 participants were enrolled and randomly allocated to treatment; 128 patients were analyzed: 65 patients assigned to fixed-tidal volume ventilation and 63 patients assigned to variable-tidal volume ventilation, and the primary outcome was available for each (Fig. 1). All baseline characteristics were well balanced with an absolute standardized difference of 0.35 or less, and therefore none was adjusted for in our analyses (Table 1 **and Supplementary Material Table 3)**. There were no intraoperative adverse events (hypoxemia, hypercapnia, arrhythmia, myocardial infarct, etc.); consequently, no patients required rescue therapy or pulmonary interventions.

3.2. Primary outcome

PaO_2 over time is shown in Fig. 2**.** Patients assigned to fixed-tidal volume ventilation had a time-weighted group average PaO_2 during OLV of 176 (86) mmHg whereas the variable-tidal volume ventilation group averaged 147 (72) mmHg, corresponding to a difference of 28 mmHg (95% CI 20–36). Oxygenation was thus significantly worse with variable tidal volume ($p < 0.01$), but not by a clinically meaningful amount which we defined as ≥50 mmHg. There was no significant interaction across time ($p = 0.091$). Furthermore, there were no significant interactions of the primary outcome for time-weighted averages of hemodynamic values, ventilation setting, blood gas values during one-lung ventilation (**Supplementary Material Table 4, 5)**. The type of the surgery (thoracocopic or thoracotomy) had no significant influence on PaO_2 during OLV ($p = 0.24$).

3.3. Secondary outcomes

Our composite of complications included composite included respiratory complications, respiratory failure and distress, reintubations, pulmonary edema, and infiltration or atelectasis in the ventilated lung. However, atelectasis and infiltration were the only component complications that were observed. Composite postoperative pulmonary complications were observed in 11 (17.5%) patients assigned to ventilation with variable tidal volume, and 17 (26.2%) patients assigned to ventilation with a fixed-tidal volume within the 90-day postoperative period (RR = 0.67, 95% CI 0.34–1.31, p = 0.24). Atelectasis in the ventilated lung was less common with variable-tidal volumes (4.7%) than fixed-tidal volumes (20%) during the initial three postoperative days, with a relative risk of 0.24 (95% CI: 0.01–0.8), $p = 0.02$. There were no significant differences in atelectasis on postoperative days 30 (RR = 1.03, 95% CI 0.07–16.1, $p = 0.98$) or 90 (RR = 0.2, 95% CI 0.01–4.2, $p = 0.31$). There were no significant differences in the proportion of infiltrates formed in the ventilated lungs during the detailed analysis in any of the postoperative periods between patients assigned to variable-tidal volume ventilation and fixed-tidal volume ventilation **(**Table 2**)**.

There were no deaths or serious adverse events (atrial fibrillations, myocardial infarct, wound infection, sepsis, renal failure, etc.) within 90 postoperative days. There were no significant differences in time-weighted heart rate within 90 postoperative days **(**Table 2**)**. However, there were significant differences in heart rate values measured at POD30: 86 (18) beats/min in patients assigned to fixed-tidal volume ventilation and 79 (10) beats/min in patients assigned to variable-tidal volume ventilation, $p = 0.02$. There were also differences at POD90: 85 (16) beats/min in patients assigned to fixed-tidal volume ventilation and 80 (12) beats/min in patients assigned to variable-tidal volume ventilation, p = 0.02. Difference in the means of heart rates at both times were < 10 beats per minute which we a priori defined not to be clinically meaningful **(**Table 2**)**.

There were no significant or clinically meaningful differences in SpO_2/FiO_2 ratios as time-weighted averages over the first three postoperative days or on the 30th and 90th postoperative days **(**Table 2**)**. There were also no significant differences in the median length of hospital stay, intensive care unit stay, chest drainage **(**Table 2**)**. And finally, there were no significant correlations between the SpO_2/FiO_2 values and occurrence of atelectasis (point biserial correlation: 0.02, CI 0.14–0.1, $p = 0.74$) or infiltration (point biserial correlation: 0.002, CI 0.12–0.12, $p = 0.98$) during the first three postoperative days. The effect of variable-tidal volume ventilation on postoperative pulmonary complications did not differ by surgery type ($p = 0.89$; Fig. 3, **Supplementary Material Table 6, 7**), or by extent of lung resection ($p = 0.57$; **Supplementary Fig. 2**, **Supplementary Material Table 8**).

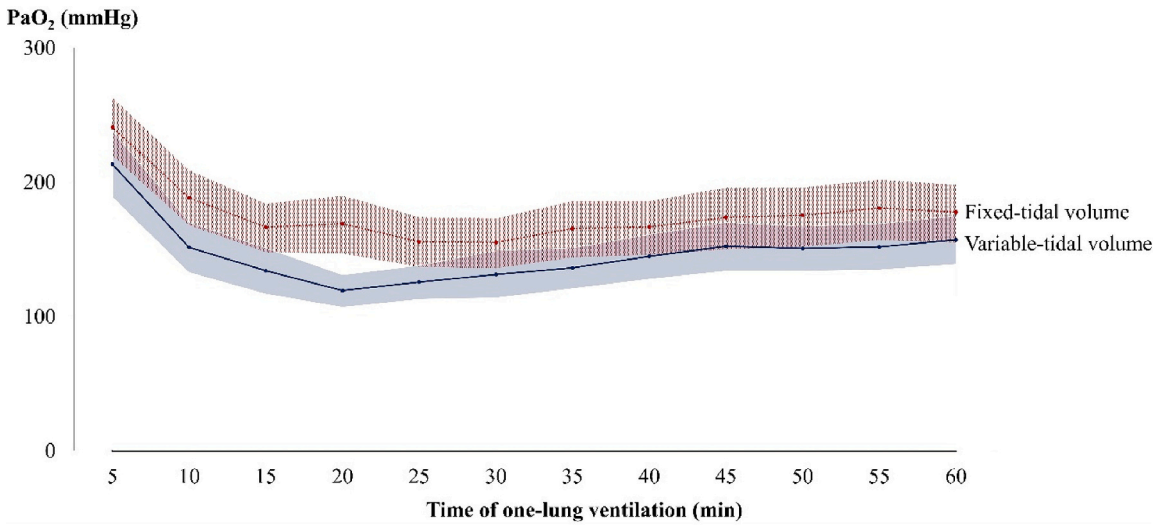

Fig. 2. PaO_2 values measured during one-lung ventilation (OLV) at an FiO_2 of 0.8.
Data are presented as means and 95% confidence intervals (CI).

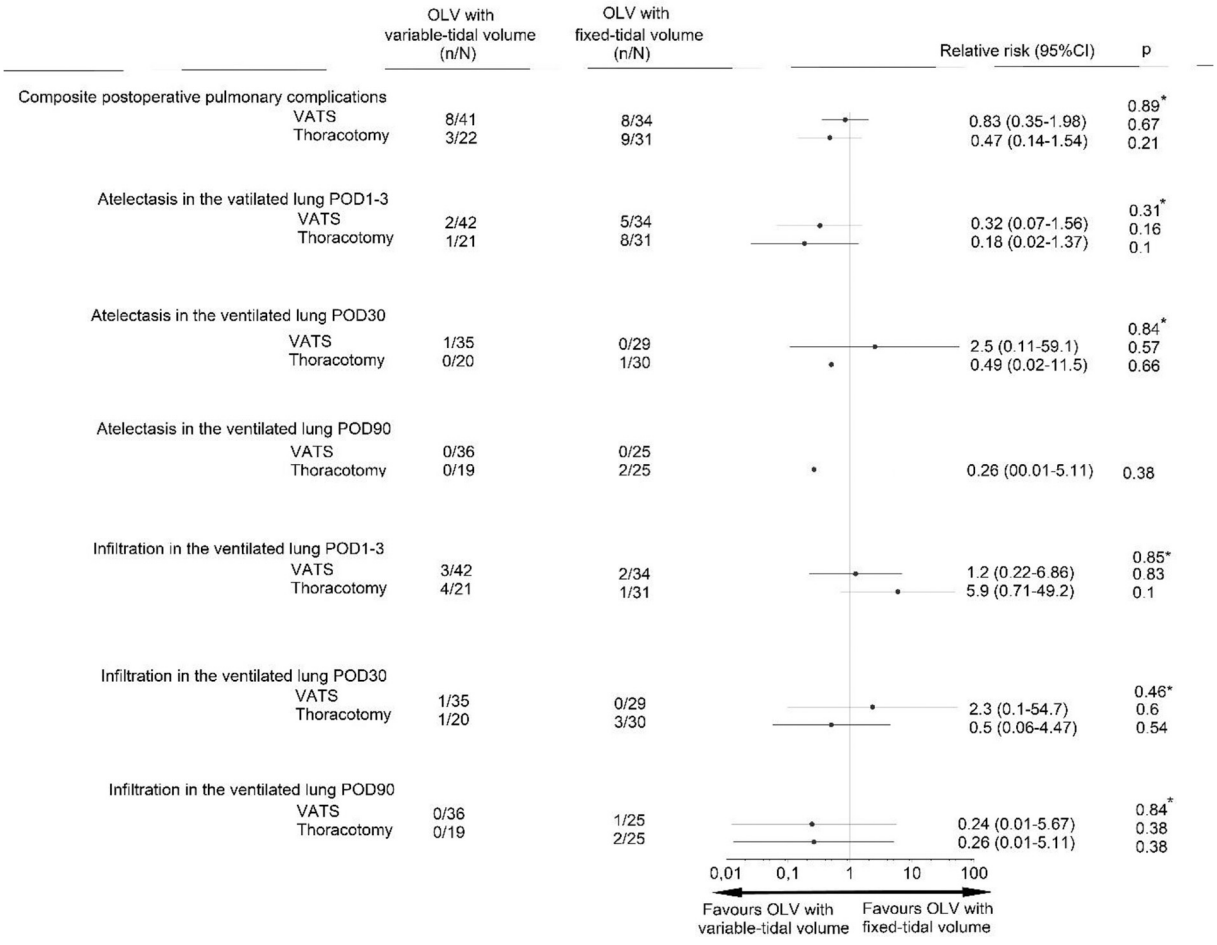

Fig. 3. Subgroup analysis of the components of postoperative pulmonary complications.
The circles represent the relative risk of variable-tidal volume ventilation. Error bars show 95% CIs.
*: $p_{interaction}$: effect of type of surgery on components postoperative pulmonary complications.
POD, post-operative day; POD1–3: summary of postoperative first three days while patients were hospitalized.

4. Discussion

Mechanical ventilation with variable tidal volumes improves oxygenation in patients with lung injury (ARDS) [22] and during prolonged ventilation [8,23]. However, benefit takes several hours to become apparent in ARDS patients, and 5 or more hours in patients with

healthy lungs [8,23]. In contrast, we did not observe an oxygenation benefit from variable tidal volumes during one-lung ventilation — possibly because the duration of one-lung ventilation was short, averaging only 1.5 h.

PaO_2 decreased in the first 20 min but remained relatively stable afterward, possibly because accommodation for hypoxic pulmonary vasoconstriction in humans has three phases: an acute phase within 5 min, a sustained or plateau phase starting after a latency period of 20–30 min and lasting for 2 h, followed by a chronic phase lasting upward of 8 h [54–59]. Our patients thus spent nearly all their OLV time during the second accommodation phase.

The reported incidence of PPCs following lung resection varies from 10% to 49%, probably reflecting widely differing definitions [31,32,60–63]. We considered a composite which encompassed respiratory complications, respiratory failure and distress, reintubations, pulmonary edema, and infiltration or atelectasis in the ventilated lung. The incidence was 17% with variable ventilation versus 26% with fixed ventilation, a difference that might be clinically meaningful but did not differ significantly in our relatively small trial.

In contrast, atelectasis differed significantly, but was not associated with complications or clinically meaningful outcomes including prolonged duration of hospital or ICU stays or the duration of chest drainage. Ventilation with a variable tidal volume possibly reduced the incidence of atelectasis because variable pulmonary stretch stimulates surfactant production in type II pneumocytes [64–67]. More surfactant presumably enhances benefit from the recruitment maneuvers that all patients had at the end of surgery.

Moderate-to-severe hypoxia during the initial three postoperative days is associated with one-year mortality [51,68,69]. We used SpO_2/FiO_2 ratio as a measure of postoperative oxygenation because it provides sensitivity and specificity comparable to PaO_2/FiO_2 ratios in diagnosing lung injury [48–53]. We did not observe a correlation between radiological findings and oxygenation during the first three postoperative days, but note that chest X-rays are an insensitive measure of atelectasis [70].

High mechanical power may promote ventilator-induced lung injury which can manifest as lung infiltration. The severity of this injury is influenced by tidal volume, driving pressure, flow, respiratory rate, and positive end-expiratory pressure [71–73]. Our patients assigned to variable-tidal volume ventilation generally had slightly higher respiratory rates, and some required atypically high rates. Nonetheless, average mechanical power did not exceed the generally accepted harmful limit of 12 J/min [74], and lung infiltration was similar in each group.

Tidal volumes in the variable-tidal group varied between 4 ml/kgPBW and 8 ml/kgPBW, neither of which is harmful during one-lung ventilation [75].

Although there were no significant differences in the type of surgery (VATS vs thoracotomy) between the two groups, type of surgery may influence the development of postoperative respiratory complications. Therefore, following the analysis of the secondary outcomes, we performed a subgroup analysis considering the types of surgery which showed that VATS versus thoracotomy had no effect development of postoperative respiratory complications **(**Fig. 3**).** The extent of lung resection also had no significant influence on results of postoperative pulmonary complications.

A major limitation of our trial is that we were unable to blind our small research team. However, most of our outcomes are objective and unlikely to be influenced by investigator bias.

Previous trials of variable ventilation changed volume on a breath-by-breath basis within a similar range [8,23]. In contrast, we varied volume at 5-min intervals. It thus remains possible, although unlikely, that results would differ substantively had we instead varied volume breath-by-breath. An additional difference is that previous studies used intensive care ventilators with intravenous anesthesia whereas we used anesthesia ventilators and volatile anesthetics. While the population and duration of ventilation are clearly critical, it seems unlikely that type of ventilator or anesthesia matters much in this context. We restricted inclusion to patients with BMI <35 kg/m^2 who did not have severe coexisting pulmonary disease such as chronic obstructive pulmonary disease. Results may have differed in heavier patients, or those with pre-existing pulmonary disease.

We did not collect data on preoperative pulmonary rehabilitation, neoadjuvant chemo- and radiotherapy, blood transfusion, postoperative fluid balance as factors that may have influence on postoperative pulmonary complications.

In summary, one-lung ventilation with variable tidal volume does not meaningfully improve intraoperative oxygenation, and does not reduce postoperative pulmonary complications or hospital and intensive care unit stay. Results may differ with longer periods of variable-tidal volume ventilation, or in patients with pre-existing lung disease.

Financial support

Support was provided solely from institutional and departmental sources.

CRediT authorship contribution statement

Katalin Szamos: Investigation, Data curation, Writing – original draft. **Boglárka Balla:** Data curation, Investigation, Writing – original draft. **Balázs Pálóczi:** Data curation, Investigation. **Attila Enyedi:** Data curation, Investigation. **Daniel I. Sessler:** Visualization, Writing – review & editing. **Béla Fülesdi:** Methodology, Writing – review & editing. **Tamás Végh:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization, Data curation, Formal analysis, Investigation, Methodology.

Declaration of competing interest

The authors declare that they have no conflicts of interest. None of the authors received compensation to perform this study.

Data availability

Complete deidentified individual-patient data, including a data dictionary and supporting documentation, will be available for collaborative analyses 1 year after publication. Interested investigators should submit proposed protocols to the corresponding author at veghdr@med.unideb.hu. Approval by the authors and a data use agreement will be required.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2024.111465.

References

[1] Naik BI, LCr, Durbin CG Jr.. Variability in mechanical ventilation: What's all the noise about? Respir Care 2015;60:1203–10.
[2] Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controled ventilation. A concept of atelectasis. N Engl J Med 1963;269:991–6.
[3] Gattinoni L, Carlesso E, Cressoni M. Recruitability, recruitment, and tidal volume interactions: is biologically variable ventilation a possible answer? Crit Care Med 2011;39:1839–40.
[4] Shimabukuro DW, Gropper MA. Noisy mechanical ventilation: listen to the melody. Anesthesiology 2009;110:214–5.
[5] West B. Fractal physiology and the fractional calculus: a perspective. Front Physiol 2010;1.
[6] West JB. How well designed is the human lung? Am J Respir Crit Care Med 2006;173:583–4.
[7] Hedenstierna G, Tokics L, Strandberg A, Lundquist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. Acta Anaesthesiol Scand 1986;30:183–91.

[8] Mutch WA, Eschun GM, Kowalski SE, Graham MR, Girling LG, Lefevre GR. Biologically variable ventilation prevents deterioration of gas exchange during prolonged anaesthesia. Br J Anaesth 2000;84:197–203.
[9] Tobin MJ, Mador MJ, Guenther SM, Lodato RF, Sackner MA. Variability of resting respiratory drive and timing in healthy subjects. J Appl Physiol 1985;1988(65):309–17.
[10] Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA. Breathing patterns. 1. Normal subjects. Chest 1983;84:202–5.
[11] Brack T, Jubran A, Tobin MJ. Dyspnea and decreased variability of breathing in patients with restrictive lung disease. Am J Respir Crit Care Med 2002;165:1260–4.
[12] Tobin MJ, Chadha TS, Jenouri G, Birch SJ, Gazeroglu HB, Sackner MA. Breathing patterns. 2. Diseased subjects. Chest 1983;84:286–94.
[13] Loveridge B, West P, Anthonisen NR, Kryger MH. Breathing patterns in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1984;130:730–3.
[14] Berry CA, Suki B, Polglase GR, Pillow JJ. Variable ventilation enhances ventilation without exacerbating injury in preterm lambs with respiratory distress syndrome. Pediatr Res 2012;72:384–92.
[15] Bellardine CL, Hoffman AM, Tsai L, Ingenito EP, Arold SP, Lutchen KR, et al. Comparison of variable and conventional ventilation in a sheep saline lavage lung injury model. Crit Care Med 2006;34:439–45.
[16] Mutch WA, Harms S, Lefevre GR, Graham MR, Girling LG, Kowalski SE. Biologically variable ventilation increases arterial oxygenation over that seen with positive end-expiratory pressure alone in a porcine model of acute respiratory distress syndrome. Crit Care Med 2000;28:2457–64.
[17] Spieth PM, Carvalho AR, Pelosi P, Hoehn C, Meissner C, Kasper M, et al. Variable tidal volumes improve lung protective ventilation strategies in experimental lung injury. Am J Respir Crit Care Med 2009;179:684–93.
[18] Graham MR, Gulati H, Kha L, Girling LG, Goertzen A, Mutch WA. Resolution of pulmonary edema with variable mechanical ventilation in a porcine model of acute lung injury. Can J Anaesth 2011;58:740–50.
[19] Güldner A, Huhle R, Beda A, Kiss T, Bluth T, Rentzsch I, et al. Periodic fluctuation of tidal volumes further improves variable ventilation in experimental acute respiratory distress syndrome. Front Physiol 2018;9:905.
[20] Kowalski S, McMullen MC, Girling LG, McCarthy BG. Biologically variable ventilation in patients with acute lung injury: a pilot study. Can J Anaesth 2013;60:502–3.
[21] Spieth PM, Güldner A, Uhlig C, Bluth T, Kiss T, Conrad C, et al. Variable versus conventional lung protective mechanical ventilation during open abdominal surgery (PROVAR): a randomised controlled trial. Br J Anaesth 2018;120:581–91.
[22] Boker A, Haberman CJ, Girling L, Guzman RP, Louridas G, Tanner JR, et al. Variable ventilation improves perioperative lung function in patients undergoing abdominal aortic aneurysmectomy. Anesthesiology 2004;100:608–16.
[23] Lohser J, Slinger P. Lung injury after one-lung ventilation: a review of the pathophysiologic mechanisms affecting the ventilated and the collapsed lung. Anesth Analg 2015;121:302–18.
[24] Bussières JS, Marques E. Atelectasis in one lung ventilation: the good, the bad, and the ugly: a narrative review. Current challenges in thoracic. Surgery 2022:5.38.
[25] Şentürk M. New concepts of the management of one-lung ventilation. Curr Opin Anaesthesiol 2006;19:1–4.
[26] McMullen MC, Girling LG, Graham MR, Mutch WA. Biologically variable ventilation improves oxygenation and respiratory mechanics during one-lung ventilation. Anesthesiology 2006;105:91–7.
[27] Reid CW, Slinger PD, Lenis S. A comparison of the effects of propofol-alfentanil versus isoflurane anesthesia on arterial oxygenation during one-lung ventilation. J Cardiothorac Vasc Anesth 1996;10:860–3.
[28] Unzueta MC, Casas JI, Moral MV. Pressure-controlled versus volume-controlled ventilation during one-lung ventilation for thoracic surgery. Anesth Analg 2007;104. 1029–33, [tables of contents].
[29] Végh T, Juhász M, Szatmári S, Enyedi A, Sessler DI, Szegedi LL, et al. Effects of different tidal volumes for one-lung ventilation on oxygenation with open chest condition and surgical manipulation: a randomised cross-over trial. Minerva Anestesiol 2013;79:24–32.
[30] Las Vegas investigators. Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - an observational study in 29 countries. Eur J Anaesthesiol 2017;34:492–507.
[31] Licker M, de Perrot M, Spiliopoulos A, Robert J, Diaper J, Chevalley C, et al. Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 2003;97:1558–65.
[32] Piccioni F, Langiano N, Bignami E, Guarnieri M, Proto P, D'Andrea R, et al. One-lung ventilation and postoperative pulmonary complications after major lung resection surgery. A multicenter randomized controlled trial. J Cardiothorac Vasc Anesth 2023;37(12):2561–71.
[33] Kiss T, Wittenstein J, Becker C, Birr K, Cinnella G, Cohen E, et al. Protective ventilation with high versus low positive end-expiratory pressure during one-lung ventilation for thoracic surgery (PROTHOR): study protocol for a randomized controlled trial. Trials 2019;20:213.
[34] Hess DR. Recruitment maneuvers and PEEP titration. Respir Care 2015;60:1688–704.
[35] Salem MR, Dalal FY, Zygmunt MP, Mathrubhutham M, Jacobs HK. Does PEEP improve intraoperative arterial oxygenation in grossly obese patients? Anesthesiology 1978;48:280–1.
[36] Burns D, West TA, Hawkins K, O'Keefe GE. Immediate effects of positive end-expiratory pressure and low and high tidal volume ventilation upon gas exchange and compliance in patients with acute lung injury. J Trauma 2001;51:1177–81.
[37] Aschkenasy SV, Hofer CK, Zalunardo MP, Zaugg M, Weder W, Seifert B, et al. Patterns of changes in arterial PO2 during one-lung ventilation: a comparison between patients with severe pulmonary emphysema and patients with preserved lung function. J Cardiothorac Vasc Anesth 2005;19:479–84.
[38] Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. Jama 1993;269:2122–7.
[39] Campos JH, Feider A. Hypoxia during one-lung ventilation-a review and update. J Cardiothorac Vasc Anesth 2018;32:2330–8.
[40] Karzai W, Schwarzkopf K. Hypoxemia during one-lung ventilation: prediction, prevention, and treatment. Anesthesiology 2009;110:1402–11.
[41] Lohser J. Evidence-based management of one-lung ventilation. Anesthesiol Clin 2008;26(241–72):v.
[42] Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European perioperative clinical outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015;32:88–105.
[43] Bui AL, Grau-Sepulveda MV, Hernandez AF, Peterson ED, Yancy CW, Bhatt DL, et al. Admission heart rate and in-hospital outcomes in patients hospitalized for heart failure in sinus rhythm and in atrial fibrillation. Am Heart J 2013;165.567–74.e6.
[44] Laskey WK, Alomari I, Cox M, Schulte PJ, Zhao X, Hernandez AF, et al. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. J Am Heart Assoc 2015;4.
[45] Fu D, Wu C, Li X, Chen J. Elevated preoperative heart rate associated with increased risk of cardiopulmonary complications after resection for lung cancer. BMC Anesthesiol 2018;18:94.
[46] Carvalho EB, Leite TRS, Sacramento RFM, Nascimento P, Samary CDS, Rocco PRM, et al. Rationale and limitations of the SpO2/FiO2 as a possible substitute for PaO2/FiO2 in different preclinical and clinical scenarios. Rev Bras Ter Intensiva 2022;34:185–96.
[47] Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007;132:410–7.
[48] Ray S, Rogers L, Pagel C, Raman S, Peters MJ, Ramnarayan P. PaO2/FIO2 ratio derived from the SpO2/FIO2 ratio to improve mortality prediction using the pediatric index of mortality-3 score in transported intensive care admissions. Pediatr Crit Care Med 2017;18. e131-e6.
[49] Khemani RG, Patel NR, Bart 3rd RD, Newth CJL. Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the PaO2/fraction of inspired oxygen ratio in children. Chest 2009;135:662–8.
[50] Festic E, Bansal V, Kor DJ, Gajic O. SpO2/FiO2 ratio on hospital admission is an indicator of early acute respiratory distress syndrome development among patients at risk. J Intensive Care Med 2015;30:209–16.
[51] Turan A, Esa WAS, Rivas E, Wang J, Bakal O, Stamper S, et al. Tidal volume and positive end-expiratory pressure and postoperative hypoxemia during general anesthesia: a single-center multiple crossover factorial cluster trial. Anesthesiology 2022;137:406–17.
[52] Guo Y, Pandis N. Sample-size calculation for repeated-measures and longitudinal studies. Am J Orthod Dentofacial Orthop 2015;147:146–9.
[53] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107.
[54] Szegedi LL. Pathophysiology of one-lung ventilation. Anesthesiol Clin North America 2001;19(435–53):v.
[55] Ariyaratnam P, Loubani M, Morice AH. Hypoxic pulmonary vasoconstriction in humans. Biomed Res Int 2013;2013:623684.
[56] Hughes JM. Hypoxic pulmonary vasoconstriction: clinical implications. Eur Respir J 2016;47:31–4.
[57] Dunham-Snary KJ, Wu D, Sykes EA, Thakrar A, Parlow LRG, Mewburn JD, et al. Hypoxic pulmonary vasoconstriction: from molecular mechanisms to medicine. Chest 2017;151:181–92.
[58] Lumb AB, Slinger P. Hypoxic pulmonary vasoconstriction: physiology and anesthetic implications. Anesthesiology 2015;122:932–46.
[59] Benumof JL. One-lung ventilation and hypoxic pulmonary vasoconstriction: implications for anesthetic management. Anesth Analg 1985;64:821–33.
[60] Licker M, Fauconnet P, Villiger Y, Tschopp JM. Acute lung injury and outcomes after thoracic surgery. Curr Opin Anaesthesiol 2009;22:61–7.
[61] Uhlig C, Neto AS, van der Woude M, Kiss T, Wittenstein J, Shelley B, et al. Intraoperative mechanical ventilation practice in thoracic surgery patients and its association with postoperative pulmonary complications: results of a multicenter prospective observational study. BMC Anesthesiol 2020;20:179.
[62] Della Rocca G, Coccia C. Acute lung injury in thoracic surgery. Curr Opin Anaesthesiol 2013;26:40–6.
[63] Agostini P, Cieslik H, Rathinam S, Bishay E, Kalkat MS, Rajesh PB, et al. Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? Thorax 2010;65:815–8.
[64] Arold SP, Suki B, Alencar AM, Lutchen KR, Ingenito EP. Variable ventilation induces endogenous surfactant release in normal guinea pigs. Am J Physiol Lung Cell Mol Physiol 2003;285:L370–5.
[65] Rentzsch I, Santos CL, Huhle R, Ferreira JMC, Koch T, Schnabel C, et al. Variable stretch reduces the pro-inflammatory response of alveolar epithelial cells. PloS One 2017;12:e0182369.
[66] Wirtz HR, Dobbs LG. Calcium mobilization and exocytosis after one mechanical stretch of lung epithelial cells. Science 1990;250:1266–9.

[67] Bartolák-Suki E, Noble PB, Bou Jawde S, Pillow JJ, Suki B. Optimization of variable ventilation for physiology, immune response and surfactant enhancement in preterm lambs. Front Physiol 2017;8:425.
[68] Bartels K, Kaizer A, Jameson L, Bullard K, Dingmann C, Fernandez-Bustamante A. Hypoxemia within the first 3 postoperative days is associated with increased 1-year postoperative mortality after adjusting for perioperative opioids and other confounders. Anesth Analg 2020;131:555–63.
[69] Liu K, Scott JB, Jing G, Li J. Management of postoperative hypoxemia. Respir Care 2021;66:1136–49.
[70] Touw HR, Parlevliet KL, Beerepoot M, Schober P, Vonk A, Twisk JW, et al. Lung ultrasound compared with chest X-ray in diagnosing postoperative pulmonary complications following cardiothoracic surgery: a prospective observational study. Anaesthesia 2018;73:946–54.
[71] Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016;42:1567–75.
[72] Paudel R, Trinkle CA, Waters CM, Robinson LE, Cassity E, Sturgill JL, et al. Mechanical power: a new concept in mechanical ventilation. Am J Med Sci 2021; 362:537–45.
[73] Dianti J, Matelski J, Tisminetzky M, Walkey AJ, Munshi L, Del Sorbo L, et al. Comparing the effects of tidal volume, driving pressure, and mechanical power on mortality in trials of lung-protective mechanical ventilation. Respir Care 2021;66: 221–7.
[74] Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, et al. Mechanical power and development of ventilator-induced lung injury. Anesthesiology 2016; 124:1100–8.
[75] Blank RS, Colquhoun DA, Durieux ME, Kozower BD, McMurry TL, Bender SP, et al. Management of one-lung ventilation: impact of tidal volume on complications after thoracic surgery. Anesthesiology 2016;124(6):1286–95. Jun.