BJA

British Journal of Anaesthesia, 130 (1): e106–e118 (2023)

doi: 10.1016/j.bja.2022.06.037
Advance Access Publication Date: 20 August 2022
Thoracic Anaesthesia and Respiration

Driving pressure-guided ventilation and postoperative pulmonary complications in thoracic surgery: a multicentre randomised clinical trial

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This article is accompanied by an editorial: Do we have the 'power' to 'drive' down the incidence of pulmonary complications after thoracic surgery by Shelley & Marczin, *Br J Anaesth* 2023:130:e37–e40, doi: 10.1016/j.bja.2022.07.017

Abstract

Background: Airway driving pressure, easily measured as plateau pressure minus PEEP, is a surrogate for alveolar stress and strain. However, the effect of its targeted reduction remains unclear.

Methods: In this multicentre trial, patients undergoing lung resection surgery were randomised to either a driving pressure group (n=650) receiving an alveolar recruitment/individualised PEEP to deliver the lowest driving pressure or to a conventional protective ventilation group (n=650) with fixed PEEP of 5 cm H_2O. The primary outcome was a composite of pulmonary complications within 7 days postoperatively.

Results: The modified intention-to-treat analysis included 1170 patients (mean [standard deviation, SD]; age, 63 [10] yr; 47% female). The mean driving pressure was 7.1 cm H_2O in the driving pressure group *vs* 9.2 cm H_2O in the protective ventilation group (mean difference [95% confidence interval, CI]; −2.1 [−2.4 to −1.9] cm H_2O; P<0.001). The incidence of pulmonary complications was not different between the two groups: driving pressure group (233/576, 40.5%) *vs* protective ventilation group (254/594, 42.8%) (risk difference −2.3%; 95% CI, −8.0% to 3.3%; P=0.42). Intraoperatively, lung compliance (mean [SD], 42.7 [12.4] *vs* 33.5 [11.1] ml cm H_2O^{-1}; P<0.001) and Pa_{o2} (median [inter-quartile range], 21.5 [14.5 to 30.4] *vs*

Received: 1 March 2022; **Accepted:** 16 June 2022

19.5 [13.5 to 29.1] kPa; P=0.03) were higher and the need for rescue ventilation was less frequent (6.8% *vs* 10.8%; P=0.02) in the driving pressure group.

Conclusions: In lung resection surgery, a driving pressure-guided ventilation improved pulmonary mechanics intraoperatively, but did not reduce the incidence of postoperative pulmonary complications compared with a conventional protective ventilation.

Clinical trial registration: NCT04260451.

Keywords: airway driving pressure; lung protective ventilation; positive end-expiratory pressure; postoperative pulmonary complications; thoracic surgery

Editor's key points

- Alveolar stress during mechanical ventilation in the form of airway driving pressure can cause barotrauma leading to postoperative pulmonary complications.
- This large multicentre randomised trial was designed to determine whether reduction in driving pressure during one-lung ventilation in thoracic surgery can reduce postoperative pulmonary complications in this high-risk group.
- Compared with a conventional protective ventilation strategy, reduction in driving pressure did not reduce pulmonary complications in the first postoperative week, although it did increase oxygenation.
- Whether other modes of ventilation, or reduced driving pressure ventilation in other populations, might reduce complications requires further study.

Mechanical ventilation is essential for critically ill patients and those undergoing major surgeries but it imposes a number of potential risks including lung volutrauma, barotrauma, and shear stress injury by repeated alveolar collapse and reopening. Protective ventilation is an important approach to minimising these injurious effects. Although a variety of putative protective techniques have been described, this term generally refers to the use of lower tidal volumes combined with a moderate amount of PEEP with or without alveolar recruitment manoeuvre.[1–5]

Patients undergoing lung resection surgery are at significantly elevated risk of pulmonary complications because of pre-existing lung disease, the large degree of surgical trespass, loss of lung parenchyma and injurious factors related to one-lung ventilation.[6–9] Despite increasing adoption of 'lung protective' measures, the overall incidence of pulmonary complications remains high.[6,10,11] Furthermore, in a recent multicentre cohort study, adherence to a standard protective ventilation strategy was not associated with a decreased incidence of pulmonary complications in lung resection surgery.[12]

Airway driving pressure, easily measured as plateau pressure minus PEEP, is a surrogate for alveolar stress and strain[13,14] and has an inverse relationship with static lung compliance. Airway driving pressure has emerged as the only ventilation parameter that is independently associated with adverse outcomes in ventilated patients; tidal volume, plateau pressure, and PEEP were not associated with pulmonary complications or mortality when they do not influence driving pressure in patients with acute respiratory distress syndrome (ARDS)[14–16] or in patients undergoing major surgery.[17,18] In addition to these retrospective studies, recent single-centre trials provide preliminary evidence that driving pressure can be actively lowered in thoracic and open abdominal surgeries, thereby reducing pulmonary complications.[19,20] However, definitive conclusions regarding the efficacy of driving pressure reduction for outcome improvement are limited by the size and scope of available studies and the lack of standardised techniques to produce driving pressure reduction.

We conducted a large multicentre, randomised trial (Driving Pressure [DP] trial) to determine whether a strategy utilising a systematic alveolar recruitment and individualised PEEP titration to minimise airway driving pressure (driving pressure-guided ventilation) would reduce the occurrence of pulmonary complications within the first 7 postoperative days compared with a conventional protective ventilation regimen with fixed PEEP (5 cm H_2O) in lung resection surgery.

Methods

The DP trial was an investigator-initiated, multicentre, randomised controlled, patient- and evaluator-blinded trial with a two-arm parallel design to assess the superiority of driving pressure-guided ventilation compared with a conventional ventilation regimen. The trial was conducted at six hospitals in South Korea between March 2020 to April 2021. The ethics committee at each participating centre approved the trial protocol and all participants provided written informed consent before enrolment. We registered the study protocol at clinicaltrials.gov (study identifier: NCT04260451). This study adhered to the applicable Consolidated Standards Of Reporting Trials (CONSORT) guidelines. Details of the trial are presented in the Supplementary material and study protocol. The data are available upon reasonable request from the corresponding author (hyunjooahn@skku.edu).

Eligibility and randomisation

Adult patients scheduled for elective lung resection surgery (segmentectomy, lobectomy, bilobectomy, sleeve lobectomy, pneumonectomy) were screened for eligibility. Inclusion criteria were age 19 yr or older, ASA physical status 1–3, and expected one-lung ventilation duration of >60 min. We excluded patients with heart failure symptoms, large bullae/blebs, pneumothorax, pregnancy, those receiving supplemental oxygen or ventilation care, extra-pulmonary surgical

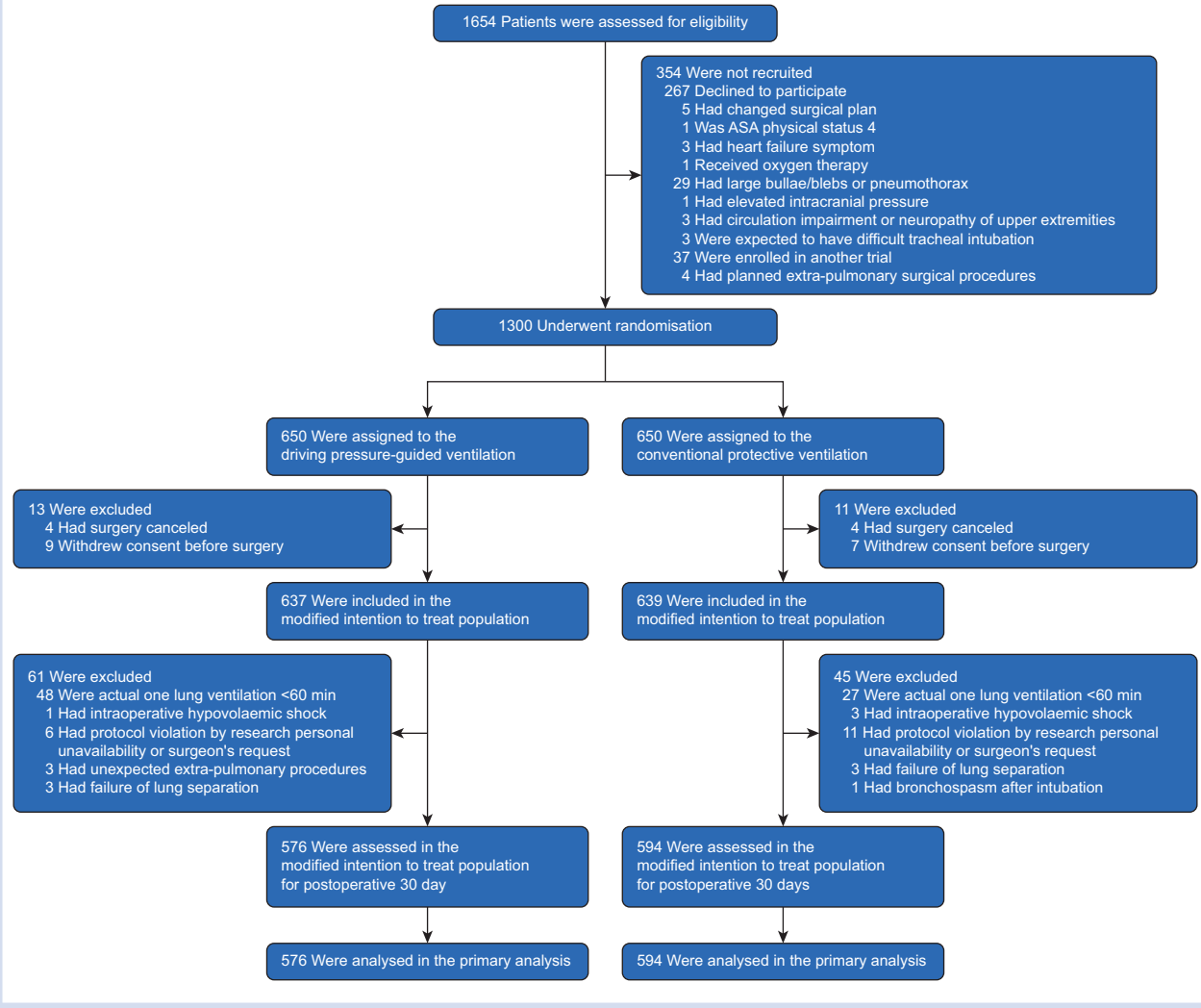

Fig 1. Study flow diagram.

procedures, and those who refused to participate in the trial. Drop-out criteria were withdrawal of consent, actual one-lung ventilation <60 min, surgery cancellation, unexpected extrapulmonary surgical procedures, hypovolaemic shock, or severe hypotension during surgery.

After written informed consent was obtained, eligible patients were randomly assigned in a 1:1 ratio to undergo either the driving pressure-guided ventilation strategy (the driving pressure group) or conventional protective ventilation strategy (the protective ventilation group). Central randomisation was performed using an interactive, web-based response system (www.thoracickorea.org) with stratification according to preoperative pulmonary function test (category A: diffusing capacity for carbon monoxide [DLCO] <60%; B: DLCO ≥60% and forced expiratory volume in 1 s [FEV_1] <60%; C: DLCO ≥60% and FEV_1 ≥60%). This trial was partially blinded; attending anaesthetists were aware of the assigned group, but subjects, treating surgeons, outcome assessors, and statisticians were unaware of trial treatment. Details on patient selection, and the blinding and randomisation process are provided in Supplement 2.

Procedures

In the driving pressure group, manoeuvres for lowering driving pressure were performed three times during the operation (at the start of mechanical ventilation, at the start of one-lung ventilation, and at re-initiation of two-lung ventilation). Driving pressure lowering manoeuvres consisted of an alveolar recruitment manoeuvre to open collapsed alveoli and an individualised PEEP titration to achieve the lowest driving pressure. Recruitment was performed by increasing PEEP from 5 up to 15 cm H_2O by 5 cm H_2O intervals. Each PEEP level was maintained for four to five respiratory cycles (volume-controlled mode, ventilatory frequency=10 min^{-1}, inspiratory:expiratory [I:E] ratio=1:1). Subsequently, PEEP was titrated in

Table 1 Baseline and intraoperative characteristics. *Charlson comorbidity index is a method to estimate 10-yr survival in patients with multiple comorbidities. Estimated 10-yr survival is calculated as 10-yr survival=$0.983^{\text{eCCI}\times 0.9}$. †ARISCAT score predicts postoperative pulmonary complications. Patients with ARISCAT score <26 have a low risk of pulmonary complications, whereas those with 45 or higher have a high risk of pulmonary complications. ‡American Society of Anesthesiologists (ASA) physical status is a simple classification system to assess comorbidities. Higher class indicating more severe systemic diseases. ¶Chronic kidney disease is defined as preoperative estimated glomerular filtration rate less than 60 ml min^{-1} 1.73 m^{-2}. §Continuous variables with missing values: FEV_1 (5/594 in protective ventilation group; 3/576 in driving pressure group), DLCO (14/594 in protective ventilation group; 7/576 in driving pressure group), FEV_1/FVC (4/594 in protective ventilation group; 2/576 in driving pressure group), left ventricular ejection fraction (132/594 in protective ventilation group; 129/576 in driving pressure group. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiration volume in 1 s; FVC, forced vital capacity; IQR, inter-quartile range.

Characteristic	Driving pressure (*n*=576)	Protective ventilation (*n*=594)
Age (yr), mean (range)	63.1 (20, 84)	63.0 (21, 86)
Female sex, *n* (%)	265 (46.0)	283 (47.6)
Body mass index (kg m^{-2}), mean (SD)	24.2 (3.0)	24.3 (3.1)
Current smoker, *n* (%)	78 (13.5)	63 (10.6)
Heavy alcohol drinker, *n* (%)	52 (9.0)	82 (13.8)
Tumour pathology, *n* (%)		
Squamous cell carcinoma	69 (12.0)	77 (13.0)
Adenocarcinoma	368 (63.9)	399 (67.2)
Other type cancer	115 (20.0)	85 (14.3)
Non-cancer	24 (4.2)	33 (5.6)
Cancer clinical stage, *n*/total (%)		
I	355/523 (67.9)	346/540 (64.1)
II	127/523 (24.3)	133/540 (24.6)
III	28/523 (5.4)	48/540 (8.9)
IV	13/523 (2.5)	13/540 (2.4)
Neoadjuvant therapy, *n* (%)	38 (6.6)	35 (5.9)
Charlson Comorbidity Index, mean (SD)*	4.4 (1.5)	4.3 (1.4)
ARISCAT score, mean (SD)†	39.1 (10.3)	39.0 (9.6)
ASA physical status, *n* (%)‡		
1	77 (13.4)	76 (12.8)
2	411 (71.4)	448 (75.4)
3	88 (15.3)	70 (11.8)
Hypertension, *n* (%)	217 (37.7)	235 (39.6)
Diabetes mellitus, *n* (%)	100 (17.4)	115 (19.4)
Dyslipidaemia, *n* (%)	185 (32.1)	179 (30.1)
Atrial fibrillation, *n* (%)	21 (3.6)	9 (1.5)
Other arrhythmias, *n* (%)	8 (1.4)	6 (1.0)
Angina, *n* (%)	21 (3.6)	21 (3.5)
Myocardial infarction, *n* (%)	9 (1.6)	8 (1.3)
Percutaneous coronary intervention, *n* (%)	16 (2.8)	13 (2.2)
Coronary artery bypass graft, *n* (%)	1 (0.2)	1 (0.2)
Chronic obstructive pulmonary disease, *n* (%)	47 (8.2)	36 (6.1)
Asthma, *n* (%)	6 (1.0)	9 (1.5)
Interstitial lung disease, *n* (%)	7 (1.2)	10 (1.7)
Bronchiectasis, *n* (%)	17 (3.0)	22 (3.7)
Respiratory infection within 1 month, *n* (%)	5 (0.9)	7 (1.2)
Previous lung operation, *n* (%)	18 (3.1)	22 (3.7)
Obstructive sleep apnoea, *n* (%)	1 (0.2)	1 (0.2)
Stroke, *n* (%)	32 (5.6)	33 (5.6)
Chronic kidney disease,¶ *n*/total (%)	32/574 (5.6)	18/592 (3.0)
Haemoglobin (g dl^{-1}), mean (SD)	13.2 (1.5)	13.3 (1.4)
Albumin (g dl^{-1}), mean (SD)	4.3 (0.4)	4.3 (0.4)
FEV_1 (%), mean (SD)§	92.7 (14.8)	92.8 (15.9)
DLCO (%), mean (SD)§	89.0 (17.3)	89.4 (16.9)
FEV_1/FVC (%), mean (SD)§	73.8 (8.5)	74.5 (8.1)
Pulmonary function test (Category A/B/C)	21(4)/1(0)/554(96)	21(4)/6(1)/567(95)
Left ventricular ejection fraction (%), mean (SD)§	64.6 (5.1)	64.3 (5.1)
Surgical procedure, *n* (%)		
Segmentectomy	104 (18.1)	107 (18.0)
Lobectomy	441 (76.6)	453 (76.3)
Bilobectomy	15 (2.6)	17 (2.8)
Sleeve lobectomy	10 (1.7)	10 (1.7)
Pneumonectomy	6 (1.0)	7 (1.2)
Minimally invasive surgery, *n* (%)		
Video-assisted thoracic surgery	501 (87.0)	495 (83.3)
Robot-assisted thoracic surgery	5 (0.9)	10 (1.7)
Open thoracotomy	55 (9.5)	65 (10.9)
Conversion to open thoracotomy	15 (2.6)	24 (4.0)

Continued

Table 1 Continued

Characteristic	Driving pressure (n=576)	Protective ventilation (n=594)
Intraoperative characteristics		
Anaesthesia duration (min), median (IQR)	173 (148–206)	176 (150–209)
Operation duration (min), median (IQR)	122 (99–153)	125 (101–155)
One-lung ventilation duration (min), median (IQR)	107 (86–135)	110 (89–138)
Crystalloid infused (ml), mean (SD)	738 (339)	757 (313)
Colloid infused (ml), median (IQR)	0 (0–0)	0 (0–0)
Transfusion, *n* (%)	2 (0.3)	4 (0.7)
Estimated blood loss (ml), median (IQR)	100 (50–150)	100 (50–100)
Urine output (ml), median (IQR)	170 (100–263)	178 (100–300)
Inotrope/vasopressor *n* (%)	44 (7.6)	40 (6.7)

decremental fashion, starting at 10 cm H_2O and then decreased to 0 cm H_2O in 1 cm H_2O intervals. PEEP titration was performed with five respiratory cycles at each PEEP level (volume controlled mode, ventilatory frequency=12 min^{-1}, I:E ratio=1:2). The PEEP level resulting in the lowest driving pressure was applied during surgery.

In the protective ventilation group, patients received an identical recruitment manoeuvre at the start of mechanical ventilation to treat atelectasis generated during mask ventilation and tracheal intubation; subsequently, a fixed PEEP of 5 cm H_2O was applied. Tidal volumes (8 or 5 ml kg^{-1} predicted body weight for two- or one-lung ventilation, respectively) and I:E ratio were identical in both study groups.

In both groups, alveolar recruitment was stopped if plateau pressure reached 30 cm H_2O to avoid barotrauma. During surgery, both groups received inspired oxygen fraction (FiO_2) 0.5 and 0.8 for two- and one-lung ventilation, respectively. The ventilation frequency was adjusted in the range of 10–18 min^{-1} to maintain end-tidal carbon dioxide between 4.5 and 6.0 kPa. When SpO_2 fell below 90%, rescue ventilation including re-institution of two-lung ventilation or administration of CPAP to the operative lung was performed. Details of the ventilation strategy are shown in eFig. 1 and Supplement 2.

Outcomes and follow-up

The primary outcome was occurrence of pulmonary complications within the first 7 postoperative days. The following pulmonary complications were recorded: hypoxaemia (SpO_2 <90%), oxygen therapy on postoperative Day 2 or later, initial ventilator support longer than 24 h, re-intubation and mechanical ventilation, tracheostomy, pneumonia, empyema, atelectasis requiring bronchoscopy, ARDS, postoperative acute lung injury,[21] indwelling chest tube for 5 days or more owing to persistent air leak or pleural effusion, bronchopleural fistula, contralateral pneumothorax, and pulmonary embolism. Definitions were based on the Society of Thoracic Surgeons (STS) general thoracic surgery databases (https://www.sts.org/registries/sts-national-database/general-thoracic-surgery-database; STS General Thoracic Surgery Database Data Specifications Version 2.41).[22] Exceptions included the following: (1) definition of ARDS was based on the Berlin definition which requires PEEP or CPAP application[23]; (2) hypoxaemia (SpO_2 <90%) and oxygen therapy on postoperative day 2 or later were included; (3) duration of ventilatory care was >24 h rather than 48 h[10,24–27]; and (4) postoperative acute lung injury was added because some patients met ARDS criteria but were managed by O_2 mask or nasal prong and thus did not receive PEEP or CPAP.[21]

Secondary outcomes included Pa_{o2}, Pa_{o2}:FiO_2 ratio, static lung compliance 15 min after initiation of one-lung ventilation, C-reactive protein on postoperative Day 1, postoperative transfusion within the first 3 postoperative days, extrapulmonary complications within the first 7 postoperative days, length of stay in the ICU and hospital, readmission, and mortality within the first 30 postoperative days.

We also obtained data on intervention-related adverse events (safety outcomes) including dynamic hyperinflation during recruitment, recruitment interruption because of haemodynamic instability, and need for rescue ventilation. Definitions of the primary, secondary, and safety outcomes are provided in Supplements 1 and 2.

Statistical analysis

This study was designed to detect a 30% relative reduction in pulmonary complications in the driving pressure group compared with the protective ventilation group. The choice of a 30% relative reduction was based on what we believed *a priori* to be of clinical significance and is consistent with that of other major trials in mechanical ventilation.[24,28] Assuming that the incidence of pulmonary complications is 19% in the protective ventilation group,[8,10,26,29] 1170 participants were needed for 80% power with a significance level of 0.05. We anticipated a 10% drop-out rate; the final sample size was determined to be 1300.

All analyses were performed according to a modified intention-to-treat principle – that is including patients who underwent randomisation and only excluding prespecified drop-out cases. Sensitivity analyses of the primary endpoint were performed in the intention-to-treat population, using multiple imputation to account for missing data over a wide range of possible scenarios, from worst to best.[30] Detailed statistical analysis methods are shown in the Statistical Analysis Plan in Supplements 1 and 2. Descriptive statistics are presented with (standard deviation [SD]), median (interquartile range [IQR]), or frequencies (percentages), as appropriate. In the analyses of the primary outcome and dichotomous secondary outcomes, incidence risk difference and risk ratio are presented and 95% Wald confidence intervals are provided to each point estimate. For other discrete variables, proportions of subjects between groups were compared with χ^2 test or Fisher's exact test. For continuous variables, between-group differences were assessed with Student *t*-test or Mann–Whitney *U*-test according to the normality of the data. Prespecified subgroup analyses were performed with logistic regression, including treatment arm, subgroup variable, and interaction term.

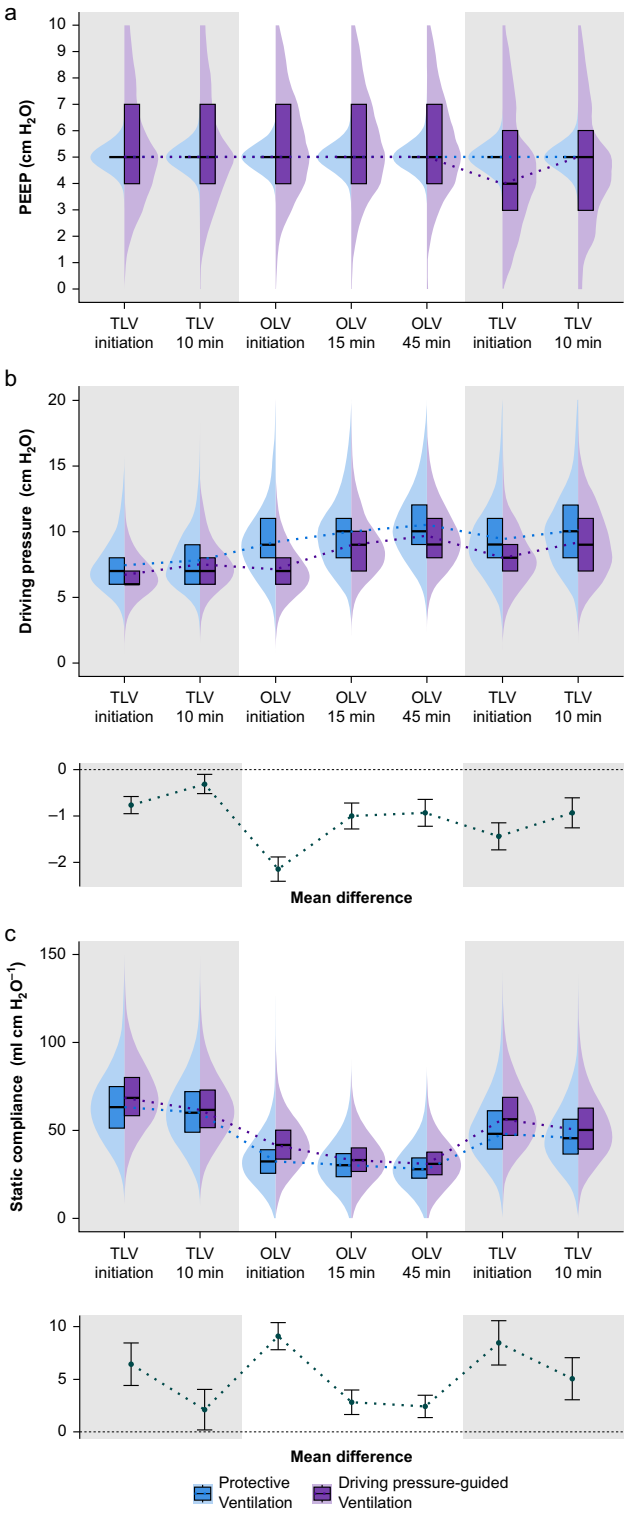

Fig 2. Intraoperative positive end-expiratory pressure, driving pressure, and static lung compliance. (a) PEEP, (b) driving pressure, and (c) static lung compliance at seven measurement points during the study. Median and inter-quartile range of each parameter are presented as a boxplot and entire distributions of the measurements are shown with rotated kernel density plot on each side. Mean differences in driving pressure and static lung compliance between treatment groups at each time point are presented in the lower panels (points indicate mean differences and error bars indicate 95% confidence intervals). The driving pressure and static lung compliance between conventional protective and driving pressure groups were different throughout the seven measurement points (all P values $\leq$0.003). OLV, one-lung ventilation; TLV, two-lung ventilation.

All statistical analyses were two-tailed with a significance level of 0.05. For secondary endpoints, no multiple comparison adjustment was applied. Thus, all analyses except that of the primary outcome were exploratory. Statistical analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Trial population

From March, 2020 to April, 2021, a total of 1654 patients were assessed for eligibility and 1300 patients were enrolled. Of the 1300 patients who underwent randomisation, 130 patients were excluded after randomisation. A total of 1170 subjects (576 and 594 subjects in each driving pressure and protective ventilation group, respectively) were included in the final modified intention-to-treat population (Fig. 1).

Baseline and intraoperative characteristics of the study population are shown in Table 1. The mean (SD) Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score[35] was 39 (10), indicating that most of the study subjects had intermediate to high risk of pulmonary complications. Most of the baseline and operative characteristics of the study population were well-balanced between groups; the proportion of atrial fibrillation was higher in the driving pressure group (3.7% *vs* 1.5%; P=0.02), and the proportion of heavy drinkers was higher in the protective ventilation group (9.0% *vs* 13.8%; P=0.01).

Effect on driving pressure and static lung compliance

Significantly lower driving pressure values were seen in the driving pressure group compared with values in the protective ventilation group throughout the operation (Fig. 2 and eTables 1 and 2 in Supplement 2). The mean difference in driving pressure was 2.1 cm H_2O (95% CI, −2.4 to −1.9) immediately after PEEP titration during one-lung ventilation (driving pressure group *vs* protective ventilation group; mean [SD], 7.1 [1.8] *vs* 9.2 [2.6] cm H_2O; P<0.001). However, driving pressure increased over time in both driving pressure and protective ventilation groups, and the difference in driving pressure between groups decreased over time. Driving pressure-guided ventilation increased static lung compliance compared with conventional protective ventilation throughout the operation (mean [SD], 42.7 [12.4] *vs* 33.5 [11.1] ml cm H_2O^{-1}; P<0.001, maximum difference immediately after PEEP titration during one-lung ventilation).

Primary and secondary outcomes

Data regarding the primary outcome were available for all subjects. The targeted intervention to reduce driving pressure did not result in a decreased incidence of pulmonary complications; at postoperative Day 7, the primary composite of pulmonary complications had occurred in 233 subjects (40.5%) in the driving pressure group compared with 254 subjects (42.8%) in the protective ventilation group (risk difference, −2.3%; 95% confidence interval [CI], −8.0% to 3.3%; relative risk, 0.95; 95% CI, 0.83 to 1.08; P=0.42; Table 2 and Fig. 3). There were no differences between groups with respect to any component of the primary composite outcome. Among pulmonary complications, ARDS occurred in 0 (0%) and 3 (0.5%) subjects in the driving pressure and protective ventilation groups (P=0.25), respectively, and postoperative acute lung injury occurred 7 (1.2%) and 14 (2.4%) subjects in the driving pressure and protective ventilation groups, respectively (P=0.14). Within the first 30 postoperative days, no subject (0%) in the driving pressure group and one subject (0.17%) in the protective ventilation group died. These results were also consistent with those of a sensitivity analysis with multiple imputation to account for the original intention-to-treat population (eFig. 3 in Supplement 2).

The effect of driving pressure-guided ventilation on pulmonary complications did not differ across pre-specified subgroups (Fig. 4). Risk factors for pulmonary complications such as age, obesity, high ARISCAT score, underlying pulmonary disease, poor pulmonary function test results, and longer duration of one-lung ventilation did not modify the treatment effect.

There were no differences in other secondary outcomes except Pa_{o2} and Pa_{o2}:FiO_2 ratio during one-lung ventilation (Table 2). The median Pa_{o2} (IQR) was higher in the driving pressure group than in the protective ventilation group (15 min after the initiation of one-lung ventilation, 21.5 [14.5−30.4] *vs* 19.5 [13.5−29.1] kPa; P=0.03). Accordingly, the Pa_{o2}:FiO_2 ratio was higher in the driving pressure group than in the protective ventilation group (15 min after the initiation of one-lung ventilation; median [IQR], 27.7 [18.5−38.5] *vs* 24.4 [16.8−37.5] kPa; P=0.03).

In a *post-hoc* analysis, pulmonary complications increased as a function of driving pressure (odds ratio=1.07 for each quantile of driving pressure, in total of eight quantiles, 95% CI 1.016−1.118; P=0.008). However, the association was non-linear. Pulmonary complications reached a plateau at a driving pressure 9 cm H_2O and above (P for non-linearity=0.02; eFig. 2 in Supplement 2).

Safety outcome

The need for intraoperative rescue ventilation was lower in the driving pressure group than in the protective ventilation group (39 of 576 [6.8%] *vs* 64 of 594 [10.8%]; P=0.02). The incidence of dynamic hyperinflation and recruitment interruption were not significantly different in two groups (5 of 576 [0.87%] *vs* 2 of 594 [0.34%]; P=0.28 and 5 of 576 [0.87%] *vs* 2 of 594 [0.34%]; P=0.28, in the driving pressure and protective ventilation groups, respectively).

Discussion

In this multicentre randomised trial of patients undergoing lung resection surgery, a driving pressure-guided ventilation strategy did not reduce the rate of pulmonary complications within the first 7 postoperative days compared with a conventional ventilation strategy. This outcome was unchanged across high-risk subpopulations including those with obesity and underlying pulmonary disease. Although intraoperative lung compliance and Pa_{o2} were substantially higher, and the need for rescue ventilation to treat hypoxaemia was lower, in the driving pressure group, this benefit did not translate into a clinically significant reduction in the incidence of pulmonary complications or extrapulmonary complications, hospital stay, or all-cause mortality.

Although many retrospective and observational studies have shown a close relationship between high driving pressure and morbidity/mortality rates which suggested driving pressure as a new ventilation target,[14–18] the feasibility of a

Table 2 Primary and secondary outcomes. *The 95% CIs were not adjusted for multiple comparisons. †Oxygen was supplied via face mask, nasal prong, continuous positive airway pressure, noninvasive positive pressure breathing or high flow nasal cannula in patients who showed SpO_2 <90% between postoperative Day 2 and 7. ‡For continuous outcomes, *P*-values are from Mann–Whitney *U*-test. ¶Pa_{o2} and Pa_{o2}:FiO_2 ratio 15 min after the initiation of one-lung ventilation. §Acute kidney injury network criteria stage ≥1. CI, confidence interval; FiO_2, inspired oxygen fraction; IQR, inter-quartile range; Pa_{o2}, arterial oxygen partial pressure; SpO_2, arterial oxygen saturation measured by pulse oximetry.

	Driving pressure (*n*=576)	Protective ventilation (*n*=594)	Risk difference (95% CI)*	Risk ratio (95% CI)*	*P*-value
Primary outcome					
Pulmonary complications, *n* (%)	233 (40.5)	254 (42.8)	−2.31 (−7.96 to 3.34)	0.95 (0.83 to 1.08)	0.42
Components of the primary outcomes					
SpO_2 <90%, *n* (%)	113 (19.6)	122 (20.5)	−0.92 (−5.51 to 3.67)	0.96 (0.76 to 1.20)	0.69
Oxygen supply between postoperative Days 2 and 7, *n* (%)†	103 (17.9)	108 (18.2)	−0.30 (−4.71 to 4.11)	0.98 (0.77 to 1.26)	0.89
Initial ventilator supports >24 h, *n* (%)	0 (0)	0 (0)			
Reintubation and mechanical ventilation, *n* (%)	1 (0.2)	3 (0.5)	−0.33 (−1.00 to 0.33)	0.34 (0.04 to 3.30)	0.63
Tracheostomy, *n* (%)	0 (0)	0 (0)			
Pneumonia, *n* (%)	53 (9.2)	48 (8.1)	1.12 (−2.10 to 4.34)	1.14 (0.78 to 1.65)	0.50
Empyema, *n* (%)	2 (0.4)	1 (0.2)	0.18 (−0.40 to 0.76)	2.06 (0.19 to 22.68)	0.62
Atelectasis requiring bronchoscopy, *n* (%)	6 (1.0)	5 (0.8)	0.20 (−0.91 to 1.31)	1.24 (0.38 to 4.03)	0.72
Acute respiratory distress syndrome, *n* (%)	0 (0)	3 (0.5)			0.25
Postoperative acute lung injury, *n* (%)	7 (1.2)	14 (2.4)	−1.14 (−2.65 to 0.37)	0.52 (0.21 to 1.27)	0.14
Air leakage requiring chest tube for 5 days or more, *n* (%)	61 (10.6)	64 (10.8)	−0.18 (−3.72 to 3.36)	0.98 (0.71 to 1.37)	0.92
Pleural effusion requiring chest tube for 5 days or more, *n* (%)	48 (8.3)	55 (9.3)	−0.93 (−4.17 to 2.32)	0.90 (0.62 to 1.30)	0.58
Bronchopleural fistula, *n* (%)	1 (0.2)	0 (0)			0.49
Contralateral pneumothorax, *n* (%)	0 (0)	0 (0)			
Pulmonary embolism, *n* (%)	1 (0.2)	2 (0.4)	−0.16 (−0.74 to 0.41)	0.52 (0.05 to 5.67)	>0.99
Secondary outcomes					
Pa_{o2} (kPa), median (IQR)‡,¶	21.5 [14.5 to 30.4]	19.5 [13.5 to 29.1]			0.03
Pa_{o2}:FiO_2, median (IQR)‡,¶	27.7 [18.5 to 38.5]	24.4 [16.8 to 37.5]			0.03
Acute kidney injury, *n* (%)§	23 (4.0)	30 (5.1)	−1.06 (−3.44 to 1.32)	0.79 (0.47 to 1.35)	0.39
Acute myocardial infarction, *n* (%)	9 (1.6)	8 (1.4)	0.22 (−1.16 to 1.59)	1.16 (0.45 to 2.99)	0.76
Percutaneous coronary intervention or coronary artery surgery, *n* (%)	3 (0.5)	2 (0.3)	0.18 (−0.57 to 0.93)	1.55 (0.26 to 9.22)	0.68
New onset arrhythmia, *n* (%)	43 (7.5)	31 (5.2)	2.25 (−0.55 to 5.04)	1.43 (0.92 to 2.24)	0.12
Cerebral infarction, *n* (%)	1 (0.2)	1 (0.2)	0.01 (−0.47 to 0.48)	1.03 (0.07 to 16.45)	>0.99
Delirium, *n* (%)	15 (2.6)	9 (1.5)	1.09 (−0.54 to 2.72)	1.72 (0.76 to 3.90)	0.19
Septic shock, *n* (%)	1 (0.2)	2 (0.3)	−0.16 (−0.74 to 0.41)	0.52 (0.05 to 5.67)	>0.99
Surgical site infection, *n* (%)	3 (0.5)	4 (0.7)	−0.15 (−1.03 to 0.73)	0.77 (0.17 to 3.44)	>0.99
Transfusion, *n* (%)	19 (3.3)	21 (3.5)	−0.24 (−2.32 to 1.84)	0.93 (0.51 to 1.72)	0.82
C-reactive protein at postoperative day 1 (mg dl^{-1}), median (IQR)‡	2.8 (1.6–4.6)	2.7 (1.5–4.5)			0.70
Hospital length of stay (day), median (IQR)‡	5 (4–7)	5 (4–7)			0.12
Intensive care unit length of stay (day), median (IQR)‡	1 (0–1)	1 (0–1)			0.22
Readmission within postoperative 30 days, *n* (%)	31 (5.4)	18 (3.1)	2.35 (0.05–4.65)	1.78 (1.01 to 3.14)	0.41
Mortality within postoperative 30 days, *n* (%)	0 (0)	1 (0.2)			>0.99

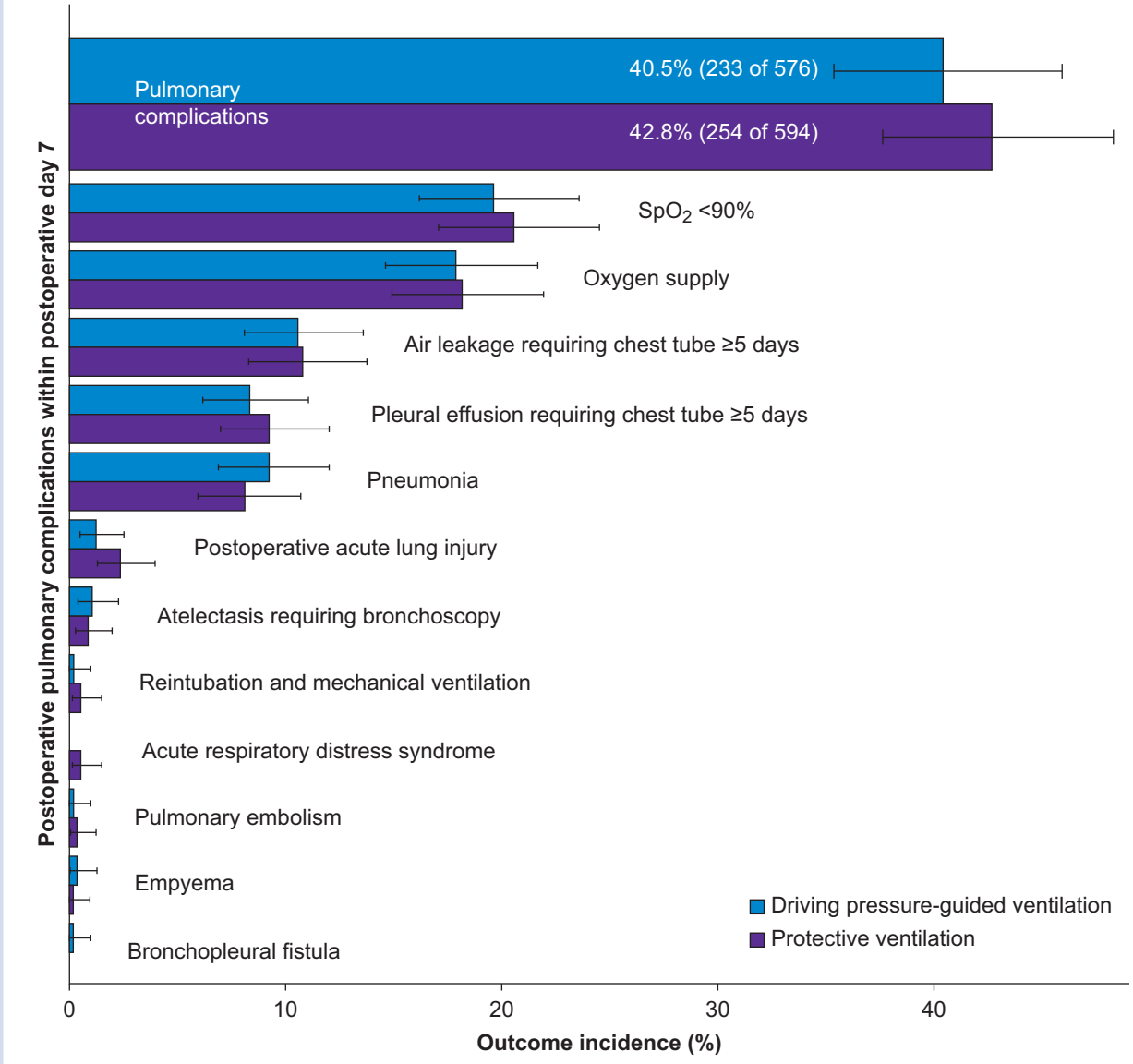

Fig 3. Incidence of pulmonary complications in the driving pressure group and protective ventilation group.

driving pressure-guided ventilation strategy and its impact on clinical outcomes have been evaluated only in small single-centre randomised trials.[19,20] In a previous thoracic surgery study (n=292), driving pressure-guided ventilation reduced the occurrence of the primary outcome, pulmonary complications until postoperative Day 3.[19] Direct comparison of results to our study are limited by several important methodological differences.[19] For example the earlier trial used a single incremental PEEP titration method (*vs* several decremental PEEP titrations), examined a more limited composite outcome based on the Melbourne Group Scale,[19] and studied a smaller and more heterogeneous surgical population limited to a single centre. Moreover, the reported outcome improvement disappeared when the observation period was extended to postoperative Day 7.[19] In light of these limitations and results of the present study, the clinical significance of this earlier trial remains unclear. In open abdominal surgery (n=134), driving pressure-guided ventilation reduced postoperative pulmonary complication score 2 and higher (score 2 is met when two or more items exist from productive cough, bronchospasm, hypoxaemia, atelectasis, and hypercarbia) within postoperative 7 days.[20] The authors performed one manual recruitment manoeuvre and incremental PEEP titration, which was conducted over a prolonged period (64 min) during the surgical procedure, potentially limiting practicality and precision of driving pressure measurement.[20]

Compared with that used in these previous studies, decremental PEEP titration after systematic alveolar recruitment is a more commonly used technique,[31,32] and known to keep alveoli open at lower driving pressures because of lung hysteresis.[33,34] This method might have also contributed to a more effective reduction in driving pressure (2.1 cm H_2O in the present study *vs* 1 cm H_2O and 1.8 cm H_2O in the previous thoracic[19] and abdominal surgery trials,[20] respectively). Neither of these

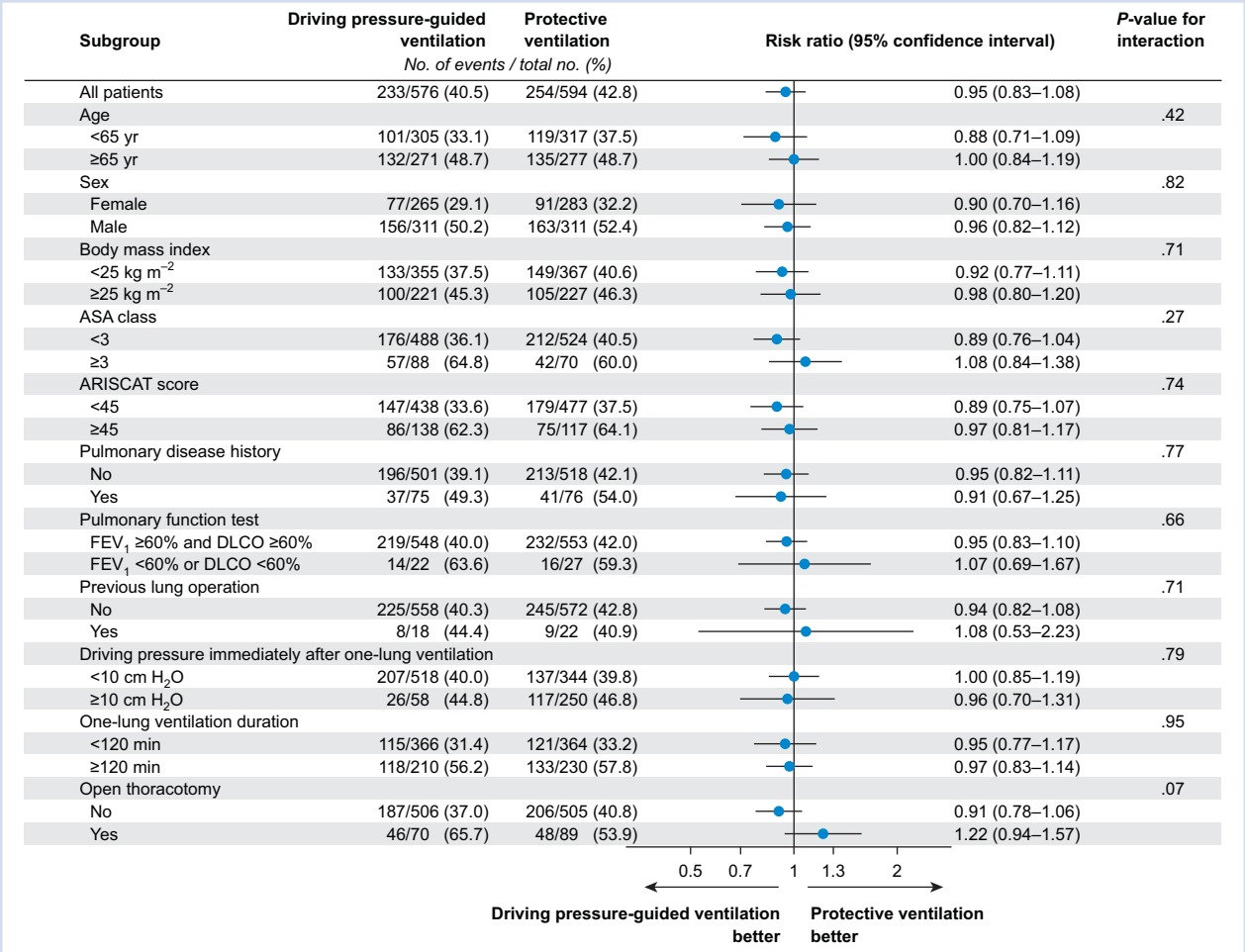

Fig 4. Risk ratio for postoperative pulmonary complications in pre-specified subgroups. Points indicate risk ratio in each stratum and horizontal bars indicate 95% confidence intervals. ASA physical status is a simple classification system to assess comorbidities. Higher class indicating more severe systemic diseases. Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score predicts postoperative pulmonary complications. Patients with ARISCAT score <26 have a low risk of pulmonary complications, whereas those with a score of 45 or more have a high risk of pulmonary complications. DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s.

studies showed a significant difference in the length of hospital stay or 30-day mortality as in our current study.

The individualized PeriopeRative Open lung Ventilatory StratEgy in Patients on One-lung Ventilation (iPROVE) trial[31] compared an open lung approach (alveolar recruitment at 40 cm H_2O and titrated PEEP based on maximal respiratory system compliance) with conventional protective ventilation (PEEP 5 cm H_2O) in abdominal surgery patients. Although driving pressure was not specifically targeted by the experimental regimen, this variable was diminished in magnitude by the intervention. The open lung approach group did not reduce the incidence of the primary outcome, a composite of pulmonary and systemic complications, but the incidence of pulmonary complications, a secondary outcome, was lower in the open lung approach group (39% *vs* 48%; P=0.047). This potential benefit, however, may not be attributable to either the intraoperative open lung approach or the resultant lowering of driving pressure as the use of postoperative CPAP may have impacted outcomes, and multiple comparison adjustment was not performed in the four group study design.[31] Although an open lung approach has the potential to decrease airway driving pressure, it has become clear that a significant potential for harm also exists. In a prominent ARDS trial, an aggressive open lung strategy resulted in increased 28-day all-cause mortality[32] compared with conventional protective ventilation because of increased barotrauma and haemodynamic instability.[31,32,35,36] In an effort to achieve an open lung condition while minimising pulmonary and haemodynamic risks, we conducted a limited alveolar recruitment (plateau pressure <30 cm H_2O) and PEEP was titrated to minimise driving pressure. The incidence of haemodynamic instability (0.34–0.87%) and use of inotropes/vasopressors (6.7%–7.6%) were very low in our study.

The lack of a significant effect of the experimental intervention on the primary outcome could be related to the relatively small differences in driving pressure between groups. Although reflective of improvements in alveolar mechanics and gas exchange, this difference might nonetheless be insufficient to elicit

a significant improvement in clinical outcomes.[31,32] In the previous and current studies, driving pressure decreased by ~2 cm H_2O or less by intervention,[19,20,31,32] and this difference in driving pressure between groups decreased over time. Mean driving pressures increased to 9.7 and 10.6 cm H_2O after 45 min of one-lung ventilation in the driving pressure and protective ventilation groups, respectively (eTable 1 in Supplement 2). Thus, alveolar recruitment and PEEP titration alone may be insufficient to maintain a reduction in driving pressure. It is not clear if other ventilatory strategies might be more effective in driving pressure reduction and maintenance.

The shape of the driving pressure/pulmonary complication relationship could have influenced our ability to elicit a discernible effect on the primary outcome. Whereas the association between driving pressure and mortality in ARDS appears linear,[14] this may not be the case for pulmonary complications in surgical patients. Previous retrospective studies have failed to identify a significant relationship between pulmonary complications and either driving pressure[10] or modified driving pressure (peak pressure minus PEEP)[12] after thoracic surgery. The relationship between pulmonary complications and driving pressure was non-linear in our study, and reached a plateau at a driving pressure of 9 cm H_2O. The proximity of the mean driving pressure values in both groups to the plateau portion of the curve might have further reduced our ability to identify a clinically significant reduction in pulmonary complications.

Among secondary outcomes, the driving pressure group exhibited improved oxygenation and reduced need for rescue ventilation. Prior studies have also shown improved oxygenation with the use of PEEP titration.[20,31,37] This oxygenation benefit is likely a direct result of recruitment of lung units and patient-specific selection of PEEP. Driving pressure-guided ventilation could represent a useful ventilation strategy for improving pulmonary mechanics and gas exchange in ventilated surgical patients, particularly during one-lung ventilation even though it did not lead to a clinically significant primary outcome difference.

This trial has several significant strengths. To our knowledge, it is the largest study to date and the only large multicentre trial to assess driving pressure-guided ventilation in a surgical population. As a study of lung resection surgery utilising one-lung ventilation, this trial examined effects of the experimental intervention on a population at high risk for pulmonary complications, potentially increasing the putative effect of the intervention. Bias was controlled by using concealed allocation, modified intention-to-treat analysis, that is only excluding predefined drop-out cases, and by no losses to follow-up. Protocol violations were uncommon, thus minimising performance bias.

This study had several limitations. First, we did not measure intrinsic (auto) PEEP. The presence of intrinsic PEEP overestimates the actual driving pressure.[38] However, operating room ventilators cannot measure intrinsic PEEP. Second, airway driving pressure might not accurately reflect transpulmonary driving pressure, with the latter being of greater physiologic significance with regard to alveolar mechanics and lung injury.[38,39] Oesophageal manometry is required to measure transpulmonary driving pressure. However, in most patients and surgeries, airway driving pressure is a reasonable surrogate for transpulmonary driving pressure. Third, reductions in driving pressure can also be achieved by reducing tidal volume, an approach not investigated in this trial. However, hypercarbia and respiratory acidosis, already common during one-lung ventilation, can be further exacerbated with the use of low tidal volumes. Hypercarbia can be attenuated by increased ventilatory frequencies, but high ventilatory frequencies would worsen intrinsic PEEP and might be as harmful as high tidal volume or high driving pressure.[40,41] Fourth, although the primary outcome, a composite of multiple pulmonary complications, has been widely used as a primary outcome in prior studies,[10,24–27] the plausibility of pathophysiologic linkage between components of the composite outcome to the ventilation exposures may vary. Outcome events related directly to volutrauma and lung injury such as ARDS, postoperative acute lung injury,[21] pneumonia, and contralateral pneumothorax might be more closely linked to the ventilation exposures than other outcome events included within the composite. The inclusion of other outcome event types, if not as plausibly linked to the ventilation exposures (e.g. prolonged ventilatory support, air leak), has the potential to affect study findings. Although the incidence of ARDS (0 [0%] and 3 [0.5%] in the driving pressure and protective ventilation groups, respectively) and postoperative acute lung injury (7 [1.2%] and 14 [2.4%] in the driving pressure and protective ventilation groups, respectively) were too low to permit meaningful comparison, they are consistent with those of a previous thoracic surgery trial,[19] suggesting that further studies limited to outcomes directly related to lung injury are warranted. Fifth, we chose lung resection surgery because (1) the incidence of postoperative pulmonary complications is high; (2) its occurrence greatly influences individual patient outcomes, economic costs, and hospital length of stay; and (3) the large body of evidence demonstrating the impact of protective ventilation strategies in this surgical population. However, injurious effects of surgical manipulation of the operative lung may also contribute significantly to pulmonary complications, potentially obscuring our ability to discern effects of the exposure variable. Sixth, we limited PEEP to 10 cm H_2O because (1) of a lack of evidence that higher PEEP levels are beneficial and (2) substantial evidence that higher PEEP levels cause harm. Specifically, previous major PEEP trials (PROtective Ventilation using HIgh versus LOw PEEP [PROVHILO],[35] PRotective Ventilation with Higher versus Lower PEEP during General Anesthesia for Surgery in OBESE Patients [PROBESE],[36] and Protective Ventilation in Cardiac Surgery [PROVECS][42] trials) and a prominent meta-analysis[43] have consistently failed to demonstrate clinical outcome improvements related to higher PEEP levels, but did demonstrate the potential for over-distension related lung injury[44] and haemodynamic derangements.[43] PEEP levels utilised in this study are consistent with current guidelines[45] and recommendations[7] for lung resection surgery. However, it is possible that some patients may have benefited from a higher PEEP level.

In conclusion, driving pressure-guided ventilation improved pulmonary mechanics and gas exchange but did not reduce the incidence of pulmonary complications in the first 7 postoperative days compared with a conventional protective ventilation strategy in thoracic surgery. Our finding does not support the routine use of driving pressure-guided ventilation in lung resection surgical patients for the purpose of reducing postoperative pulmonary complications. However, further studies of driving pressure guided-ventilation for high-risk patients and in other surgical populations is warranted.

Authors' contributions

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Supervision: HJA, HK, HJK, HC, JHB, ICC
Software: HJA, SCY
Validation: MHP, SY, SKN, HJA, HK, HJK, HC, HKK, RSB, SCY, DKL, JHB, JK, SL, YJO, WH, BGL, BYH
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Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: MHP, SY, SKN, HJA

Acknowledgements

We thank Yuri Lee for postoperative data collection.

Declarations of interest

The authors declare no conflict of interest.

Funding

Samsung Medical Centre grant (2020, # SMO1200261) and Korean Society of Cardiothoracic and Vascular Anaesthesiologists grant (2020, #PHO0204041). The funding sources had no role in the study design and performance; data collection, management, analysis, and interpretation; manuscript preparation, review, or approval; or decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.06.037.

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Handling editor: Hugh C Hemmings Jr