Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: a meta-analysis of individual patient data

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Summary

Background **Protective mechanical ventilation strategies using low tidal volume or high levels of positive end-expiratory pressure (PEEP) improve outcomes for patients who have had surgery. The role of the driving pressure, which is the difference between the plateau pressure and the level of positive end-expiratory pressure is not known. We investigated the association of tidal volume, the level of PEEP, and driving pressure during intraoperative ventilation with the development of postoperative pulmonary complications.**

Methods **We did a meta-analysis of individual patient data from randomised controlled trials of protective ventilation during general anesthaesia for surgery published up to July 30, 2015. The main outcome was development of postoperative pulmonary complications (postoperative lung injury, pulmonary infection, or barotrauma).**

Findings **We included data from 17 randomised controlled trials, including 2250 patients. Multivariate analysis suggested that driving pressure was associated with the development of postoperative pulmonary complications (odds ratio [OR] for one unit increase of driving pressure 1·16, 95% CI 1·13–1·19; p<0·0001), whereas we detected no association for tidal volume (1·05, 0·98–1·13; p=0·179). PEEP did not have a large enough effect in univariate analysis to warrant inclusion in the multivariate analysis. In a mediator analysis, driving pressure was the only significant mediator of the effects of protective ventilation on development of pulmonary complications (p=0·027). In two studies that compared low with high PEEP during low tidal volume ventilation, an increase in the level of PEEP that resulted in an increase in driving pressure was associated with more postoperative pulmonary complications (OR 3·11, 95% CI 1·39–6·96; p=0·006).**

Interpretation **In patients having surgery, intraoperative high driving pressure and changes in the level of PEEP that result in an increase of driving pressure are associated with more postoperative pulmonary complications. However, a randomised controlled trial comparing ventilation based on driving pressure with usual care is needed to confirm these findings.**

Funding **None.**

Introduction

More than 230 million surgical procedures are done worldwide each year.[1] Complications after surgery are associated with increased use of resources and are an important cause of death.[2] In particular, postoperative pulmonary complications have a strong effect on morbidity and mortality of patients who have had surgery.[2–4]

Three large randomised controlled trials[5–7] of intraoperative ventilation showed that reduced tidal volume combined with high levels of positive end-expiratory pressure (PEEP) during intraoperative ventilation prevents postoperative pulmonary complications. Slutsky and Ranieri[8] suggest that ventilation with a low tidal volume necessitates the use of moderate to high levels of PEEP to reduce the mechanical stress related to atelectasis. However, a randomised controlled trial[9] has shown no difference in the development of postoperative pulmonary complications after intraoperative ventilation with low tidal volumes with either high or low levels of PEEP.

Several investigations[10–12] suggest an association between high driving pressure (the difference between the plateau pressure and the level of PEEP) and outcome for patients with acute respiratory distress syndrome. It is uncertain whether a similar association exists for high driving pressure during surgery and the occurrence of postoperative pulmonary complications. Indeed, in

Research in context

Evidence before this study

Postoperative complications can cause death of patients after surgery. Several randomised controlled trials of intraoperative ventilation have shown that the combination of low tidal volume and high positive end-expiratory pressure (PEEP) during surgery reduces the occurrence of postoperative pulmonary complications. However, a recent trial and a meta-analysis of individual patient data showed no difference in development of postoperative pulmonary complications after intraoperative ventilation with high PEEP levels when patients were already ventilated with low tidal volume. Driving pressure could be the key ventilatory variable related to outcome in patients having surgery and, thus, the mediator of the effects of tidal volume and PEEP. In patients with acute respiratory distress syndrome, investigations suggest an association between high driving pressures and worse outcome, but it is not known whether this association also applies to patients with healthy lungs.

Added value of this study

This study is the first to assess the relation between driving pressure and postoperative pulmonary complications in patients undergoing mechanical ventilation for surgery. The findings that the driving pressure is independently associated with the development of postoperative pulmonary complications, and that patients in whom a change in ventilator settings increases driving pressure have a worse outcome, suggest that driving pressure is the key variable determining the effect of intraoperative mechanical ventilation, and explains the controversial effects found with the use of PEEP.

Implications of all the available evidence

Current evidence supports the use of low tidal volume ventilation in patients having surgery. However, the use of high levels of PEEP is still a matter of debate. Intraoperative high driving pressure and a change in PEEP level that results in an increase in driving pressure are associated with more postoperative pulmonary complications. Thus, driving pressure seems to be the unifying parameter to optimise mechanical ventilation in non-injured and injured lungs as well as during mechanical ventilation for surgery. This suggests that, differently from common practice, the plateau pressure and end-expiratory pressure (including auto-PEEP) should be routinely measured during surgery. However, trials comparing ventilation based on driving pressure versus usual care in patients with or without lung injury are warranted before any definitive conclusion is made.

patients having surgery, the clinical effects of ventilatory parameters and the relative importance of plateau pressure, tidal volume, and PEEP in the pathogenesis of ventilator-induced lung injury are not completely clear. Because respiratory-system compliance is strongly related to the end-expiratory lung volume, especially in normal lungs, we postulated that the driving pressure, which is the tidal volume normalised by respiratory-system compliance, would be a better predictor of postoperative pulmonary complications than tidal volume normalised by the predicted bodyweight.

To assess this association, we did a meta-analysis of individual patient data from randomised controlled trials comparing different intraoperative ventilation strategies in patients under general anaesthesia for surgery.[5,6,9,13–26]

Methods

Systematic review

The protocol of this study has been published previously.[27] We searched Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) up to July 30, 2015, with the following terms: (protective ventilation OR lower tidal volume OR low tidal volume OR positive end-expiratory pressure OR positive end expiratory pressure OR PEEP) AND (surgery OR surgical OR intraoperative OR anesthesia). There was no language restriction (appendix). We screened all articles after excluding duplicates and checked the reference lists of selected articles for other relevant studies. ASN and CSVB independently assessed eligibility based on the titles, abstracts, full-text reports, and further information from investigators as needed. We included randomised controlled trials comparing protective ventilation with conventional ventilation in adults having surgery under general anaesthetic.

Because of the high number of patients from randomised controlled trials, and to prevent bias from observational studies, we deviated from our original protocol and restricted the meta-analysis to individual patient data from randomised controlled trials of protective intraoperative ventilation in the primary analysis. The trials all compared protective with conventional ventilation in adult patients undergoing general anaesthesia for surgery.

Collection of data

We contacted the corresponding authors of eligible studies via email with a cover letter detailing the objectives of the study, background information, and a datasheet for input of individual patient results. The completed data templates were sent to the principal investigator and further communication was done mainly by email. Corresponding authors were also contacted about unpublished data to enlarge the data pool. The same two investigators who did the literature search also collected and assembled the individual patient data provided by the investigators. Data were accepted in any kind of electronic format and only the coordinators of the collaboration had direct access to it.

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Both investigators validated the data and checked the dataset for mistakes and inconsistency. Differences were discussed and settled by consensus, and by contact with the corresponding author. We excluded studies for which individual patient data were not available. The aggregate data were not extracted from these excluded studies because they did not report the driving pressure.

The corresponding author of each study was asked to provide demographic characteristics (age, gender, height, weight, American Society of Anesthesiologists physical status classification system, type of surgery, and presence of risk factors for postoperative pulmonary complications), mechanical ventilator parameters (plateau and peak pressure, PEEP level, respiratory rate, and inspired fraction of oxygen) obtained hourly during the procedure, oxygenation parameters (partial pressure of oxygen, partial pressure of carbon dioxide, and pH), and clinical outcomes (death, postoperative pulmonary complications, transfusion, length of stay in intensive care unit and in hospital).

ASN and CSVB independently assessed the studies for risk of bias using the Cochrane risk-of-bias tool. We assigned a value of low, unclear, or high risk of bias for the following domains: random sequence generation, allocation concealment, masking of participants and personnel, masking of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Outcomes

The predefined primary outcome was development of postoperative pulmonary complications during follow-up. Postoperative pulmonary complications were a composite of postoperative lung injury, pulmonary infection, or barotrauma, as defined by the authors in the original studies (appendix p 9).

Statistical analysis

To expand our results, increase the power, and assess the effect of the study design on the association between driving pressure and outcome, we did a secondary analysis using only individual patient data from observational studies. We did a one-stage analysis, in which the individual patient data from all studies were modelled simultaneously while accounting for the clustering of patients within studies. The one-stage analysis was a multilevel logistic regression model with random effects.

For all analyses, the driving pressure during intraoperative ventilation was averaged per patient and the resultant median driving pressure was treated as a continuous variable. We built a multivariable model to quantify the effect of driving pressure on the occurrence of postoperative pulmonary complications, while controlling for other preoperative and intraoperative risk factors.

We did multilevel analyses to adjust for clustering of data. We used generalised linear mixed models to determine predictors of postoperative pulmonary complications by modelling it as the dependent variable. Independent variables were selected according to biological plausibility, and when a p value less than 0·2 was found in the univariate analysis. Then, the generalised linear mixed model was built with these predictor variables as fixed effects, and the study (cluster) as a random effect. Effects were expressed as an average odds ratio (OR) with their respective 95% CIs. The OR represents how the predictor affects outcome for the combined population of all clusters instead of one specific cluster. In the multivariable model statistical significance was set at a p value less than 0·05.

To assess the effect of intraoperative changes in the level of PEEP on driving pressure and the associations with postoperative pulmonary complications, we studied patients included in two trials using different levels of PEEP at the same tidal volume.[9,23] Patients were stratified according to changes of driving pressure after the change in level of PEEP (ie, after randomisation to a higher level). We analysed four groups: patients who were assigned to a low level of PEEP (0–2 cm H_2O); patients in whom the driving pressure increased after raising the PEEP level to 6 cm H_2O or higher; patients in whom the driving pressure decreased after raising the PEEP level to 6 cm H_2O or higher; and patients in whom the driving pressure did not change after raising the PEEP level to 6 cm H_2O or higher. Because the extent of lung damage could theoretically depend on duration of mechanical ventilation, we did a post-hoc analysis of the effect of driving pressure on the development of postoperative pulmonary complications stratified by quartiles of duration of intraoperative ventilation.

Finally, to investigate whether driving pressure was related to outcome measures, we did a multilevel mediation analysis (appendix pp 4–6) using the whole cohort, searching for variables mediating positive outcomes after randomisation. We tested three mediators: tidal volume size (mL/kg predicted bodyweight), level of PEEP (cm H_2O), and driving pressure (cm H_2O). Following standard procedures for mediation analysis, we assessed each potential mediator through a sequence of four logical tests, ultimately checking whether variations in the mediator explained the average benefit of the assigned treatment, as well as assessing the dose–response effect on outcomes. To avoid possible bias resulting from baseline severity, we pre-adjusted all mediation models by the same set of covariates included in the multivariable model.

Our analyses were stratified for three different cohorts on the basis of the type of intervention studied: protective ventilation (low tidal volume plus high PEEP level) versus conventional ventilation (high tidal volume plus low PEEP level); low tidal volume versus high tidal volume (with same level of PEEP in each group); and

high versus low PEEP (with same tidal volume in each group). Finally, we did similar analyses in a cohort of patients from two observational studies.[28,29]

We did all analyses with SPSS (version 20.0), and R (version 2.12.0). We used the R package for Causal Mediation Analysis for the mediation analysis. For all analyses, two-sided p values less than 0·05 were considered significant.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search identified 28 investigations, of which 25 were randomised controlled trials of intraoperative ventilation. We excluded eight randomised controlled trials (appendix p 12). In one trial, the difference in mechanical ventilation between the two groups was restricted to use of recruitment manoeuvres,[23] in another trial to use of recruitment manoeuvres plus the level of PEEP,[9] and in four trials the only differences between the groups was in the tidal volume size.[16,20,21,26] In the remaining trials, tidal volume size and the level of PEEP differed between the strategies for which patients were randomly assigned. We were able to collect individual patient data for 19 investigations, including 17 randomised controlled trials.

We included 2250 patients from the 17 randomised controlled trials in this analysis (figure 1, table 1, appendix pp 10–11).[5,6,9,13–26] There were no important discrepancies or concerns regarding the integrity of the data. The appendix (p 16) details the risk-of-bias assessment. We analysed two cohorts from observational studies[28,29] in a similar way.

In univariate analysis, we detected several significant associations between independent predictor variables and postoperative pulmonary outcomes (appendix p 13). After the inclusion of variables with p less than 0·2 in the univariate analysis, one baseline variable (static compliance), and only one ventilatory parameter (driving pressure) were significantly associated with postoperative pulmonary complications (table 2). The effect of driving pressure remained significant in the cohort comparing protective versus conventional ventilation, but was not significant when comparing low versus high tidal volume (6·1 mL/kg predicted bodyweight, 95% CI 5·9–6·6, *vs* 10·6, 9·9–12·3) or when comparing low versus high PEEP (0·0 cm H_2O, 95% CI 0·0–2·0, *vs* 12·0, 5·0–12·0; table 2). Indeed, no ventilatory parameter was associated with postoperative pulmonary complications in these two cohorts (table 2). Higher driving pressure predicted the development of postoperative pulmonary complications in most trials (p for heterogeneity=0·113, appendix p 17). The effects of driving pressure according to the type of surgery (p=0·777), and the effects of driving pressure in one-lung ventilation during thoracic surgery were similar to those in two-lung ventilation during abdominal surgery (appendix p 18). Finally, driving pressure was consistently associated with postoperative pulmonary complications after multivariable adjustments using generalised linear mixed models in the cohort of patients from observational studies (appendix p 14) and including all the studies (appendix p 15). There was no interaction between duration of intraoperative ventilation and the effect of the driving pressure on outcome (p=0·669; appendix p 19).

In the two trials that compared low with high PEEP during low tidal volume ventilation,[9,23] the incidence of postoperative complications was not affected by the level of PEEP. However, an increase in the level of PEEP that

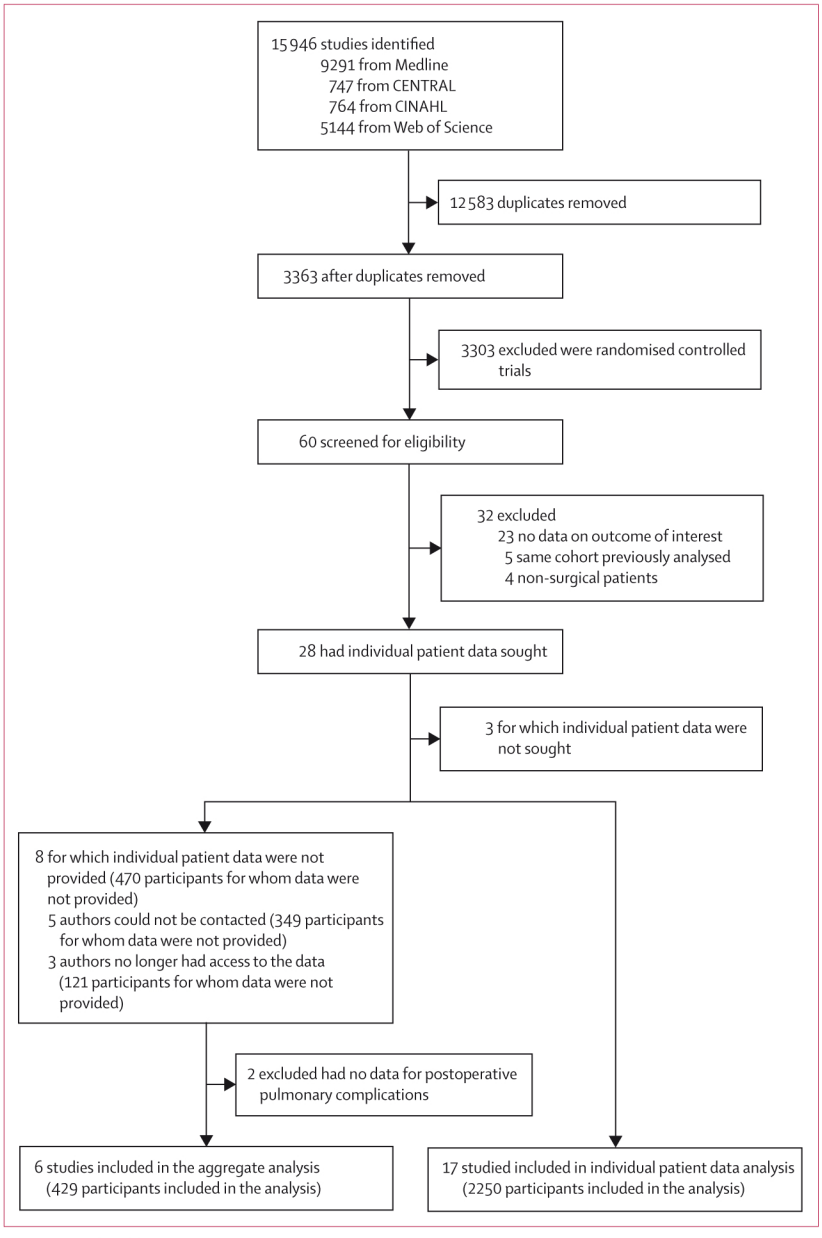

Figure 1: **Study selection**

	N	Protective						Conventional						Type of surgery	Jadad score
		V_T	PEEP	ΔP	Mean age (years)	Male	N	V_T	PEEP	ΔP	Mean age (years)	Male	N		
Wrigge et al (2004)	62	6	10	13·8	57·0	79·3%	29	12	0	12·2	60·5	69·7%	33	Abdominal or thoracic	3
Zupancich et al (2005)	33	8	10	8·3	66·5	60·0%	21	10	2–3	12·8	68·7	75·0%	12	Cardiac	3
Reis Miranda et al (2005)	44	6	10 plus RM	9·2	63·0	54·5%	23	8	5	18·8	65·0	59·1%	21	Cardiac	4
Schilling et al (2005)	110	5	0-2	14·0	60·0	87·5%	75	10	0–2	14·4	61·0	75·0%	35	Thoracic	3
Wolthuis et al (2008)	46	6	10	13·3	62·0	67·0%	24	12	0	24·9	61·0	74·0%	22	General	3
Lin et al (2008)	102	5	3-5	13·5	55·0	75·0%	50	9	0	20·0	58·4	80·0%	52	Thoracic	2
Weingarten et al (2010)	40	6	12 plus RM	9·6	73·8	75·0%	20	10	0	19·8	72·1	80·0%	20	Abdominal	3
Sundar et al (2011)	149	6	5	11·6	66·0	66·7%	75	10	5	14·8	66·5	75·7%	74	Cardiac	4
Treschan et al (2012)	101	6	5	5·8	68·0	72·0%	52	12	5	8·7	68·0	76·0%	49	Abdominal	4
Memtsoudis et al (2012)	24	6	8	5·3	60·0	46·1%	10	12	0	7·2	50·0	46·1%	14	Spine	4
Unzueta et al (2012)	40	6	8 plus RM	11·7	59·0	75·0%	40	..	..	..	..	..	..	Thoracic	3
Severgnini et al (2013)	55	7	10 plus RM	8·3	65·5	64·3%	28	9	0	9·7	67·0	59·2%	27	Abdominal	4
Futier et al (2013)	400	6	6–8 plus RM	8·4	61·6	58·0%	200	12	0	16·3	63·4	60·5%	200	Abdominal	4
Maslow et al (2013)	32	5	5	13·6	61·2	25·0%	16	10	0	22·9	69·6	50·0%	16	Thoracic	3
Hemmes et al (2014)	889	8	12 plus RM	15·0	65·0	58·0%	445	8	≤2	15·8	66·0	57·0%	449	Abdominal	4
Qutub et al (2014)	39	4–6	5 plus RM	..	41·8	80·8%	26	8	5 plus RM	..	38·2	76·9%	13	Thoracic	4
Kokulu et al (2015)	40	6	8	5·3	41·7	0·0%	20	12	0	10·0	39·5	0·0%	20	Abdominal	3

V_T=tidal volume (mL/kg predicted bodyweight). RM=recruitment manoeuvre. PEEP=positive end-expiratory pressure. ΔP=driving pressure

Table 1: **Characteristics of included studies**

	Overall (n=2250)		Protective *vs* conventional* (n=834)		Low *vs* high tidal volume† (n=443)		Low *vs* high PEEP‡ (n=973)	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age (years)	1·04 (0·99–1·08)	0·085	0·99 (0·94–1·04)	0·784	1·02 (0·98–1·06)	0·303	..	..
Male sex	0·63 (0·39–1·02)	0·060	..	..	..	..	1·16 (0·73–1·86)	0·530
ASA	1·82 (0·60–5·48)	0·289	0·97 (0·52–1·81)	0·929	2·62 (2·06–3·34)	<0·001	1·42 (1·00–2·00)	0·048
Presence of risk factor§	1·88 (0·18–20·09)	0·601	34·38 (15·83–74·66)	<0·001	0·32 (0·00–38·24)	0·641	1·52 (0·41–5·55)	0·529
Static compliance	1·01 (1·00–1·02)	0·017	0·85 (0·85–0·86)	<0·001	1·01 (1·00–1·02)	0·002	..	..
Transfusion of PRBC	2·58 (0·40–16·63)	0·318	2·11 (1·29–3·46)	0·003	10·54 (0·15–726·47)	0·276	2·03 (1·20–3·43)	0·009
Median $PaCO_2$	0·97 (0·89–1·05)	0·432	0·83 (0·66–1·03)	0·093	..	..	..	..
Median PaO_2/FiO_2	1·00 (0·99–1·00)	0·787	0·99 (0·99–1·01)	0·398	..	..	..	..
Ventilatory parameters								
Tidal volume (mL/kg PBW)	1·05 (0·98–1·13)	0·179	1·21 (1·06–1·38)	0·005	1·10 (0·99–1·21)	0·071	..	..
PEEP (cm H_2O)	..	..	0·78 (0·73–0·83)	<0·001	..	..	1·01 (0·96–1·06)	0·668
Respiratory rate (movements per min)	..	..	1·11 (0·75–1·65)	0·601	..	..	1·02 (0·90–1·15)	0·796
Driving pressure (cm H_2O)	1·16 (1·13–1·19)	<0·0001	1·31 (1·19–1·45)	<0·001	1·10 (0·99–1·22)	0·089	0·98 (0·93–1·03)	0·468
Plateau pressure (cm H_2O)	..	..	1·29 (1·19–1·40)	<0·001	..	..	..	..
FiO_2 (%)	13·17 (0·43–404·52)	0·140	..	..	17·14 (0·54–439·36)	0·106	1·50 (0·05–41·71)	0·810

ASA=American Society of Anesthesiologists physical status classification system. PEEP=positive end-expiratory pressure. PaO_2=arterial partial pressure of oxygen. $PaCO_2$=arterial partial pressure of carbon dioxide. PBW=predicted bodyweight. PRBC=packed red blood cells. FiO_2=fraction of inspired oxygen. *Trials comparing low tidal volume plus high PEEP versus high tidal volume plus low PEEP. †Trials comparing low tidal volume versus high tidal volume with the same PEEP in each group. ‡Trials comparing low versus high PEEP with the same tidal volume in each group. §Transfusion of blood products, sepsis, shock, or pneumonia.

Table 2: **Multivariable analyses of factors affecting postoperative pulmonary complications**

resulted in an increase in driving pressure was associated with a greater risk of postoperative pulmonary complications than in patients ventilated with low PEEP (adjusted OR 3·11, 95% CI 1·39–6·96; p=0·006). There was no association in patients for whom the change in PEEP level did not affect driving pressure (adjusted OR 0·77, 95% CI 0·22–2·74; p=0·791) or decreased driving pressure (0·19, 0·02–1·50; p=0·154; table 3, figure 2).

	Low PEEP group (n=432)	Decrease in driving pressure (n=185)		No change in driving pressure (n=150)		Increase in driving pressure (n=139)	
		Mean (SD)	p value vs low PEEP group	Mean (SD)	p value vs low PEEP group	Mean (SD)	p value vs low PEEP group
Age (years)	66·1 (12·9)	62·5 (13·6)	0·01	62·7 (15·1)	0·039	65·0 (12·9)	0·83
ASA	2·3 (0·7)	2·2 (0·6)	0·89	2·1 (0·6)	0·23	2·3 (0·7)	0·99
Ventilatory parameters							
Tidal volume (mL/kg PBW)	8·3 (0·7)	8·2 (0·7)	0·66	8·2 (0·5)	0·88	8·4 (1·3)	0·83
PEEP (cm H_2O)	1·1 (1·1)	11·4 (1·8)	<0·0001	11·0 (2·0)	<0·0001	11·4 (1·8)	<0·0001
Driving pressure (cm H_2O)	11·6 (4·3)	10·3 (3·3)	<0·0001	11·8 (3·5)	0·043	15·6 (4·4)	<0·0001
FiO_2 (%)	0·4 (0·1)	0·5 (0·2)	0·048	0·5 (0·2)	0·033	0·5 (0·1)	0·067
Plateau pressure (cm H_2O)	20·2 (4·9)	24·1 (3·5)	<0·0001	23·5 (3·9)	<0·0001	23·8 (4·8)	<0·0001
Change in driving pressure (cm H_2O)	0·5 (3·8)	−3·7 (3·0)	<0·0001	0·4 (0·5)	0·30	4·3 (3·4)	<0·0001
Static compliance (mL/cm H_2O)	34·7 (12·2)	46·1 (21·9)	<0·0001	48·1 (21·3)	<0·0001	43·0 (15·0)	<0·0001
Presence of risk factor*	9 (2·3)	2 (1·2)	0·58	3 (2·3)	0·74	2 (1·5)	0·83
Incidence of PPC (n, %)	47 (11%)	18 (10%)	0·76	17 (11%)	0·96	19 (14%)	0·40
Odds ratio for PPC (95% CI)†	1 (reference)	0·19 (0·02–1·50)	0·154	0·77 (0·22–2·74)	0·791	3·11 (1·39–6·96)	0·006

Data are mean (SD) unless stated otherwise. PEEP=positive end-expiratory pressure. ASA=American Society of Anesthesiologists physical status classification system. PBW=predicted bodyweight. FiO_2: fraction of inspired oxygen. PPC=postoperative pulmonary complications. *Transfusion of blood products, sepsis, shock, or pneumonia. †Adjusted by age, ASA, presence of risk factor, plateau pressure, and static compliance (low PEEP group as reference).

Table 3: **Characteristics of patients according to changes in driving pressure after increase of positive end-expiratory pressure**

Despite a higher plateau pressure in those with a decrease in driving pressure, no change, or an increase in driving pressure compared with the low PEEP group (p<0·001), there was no effect of the plateau pressure in the final model (OR 0·95, 95% CI 0·87–1·04; p=0·250; table 3).

Reductions in driving pressure according to randomisation were significantly associated with reduced incidence of postoperative pulmonary complications independent of baseline characteristics (p=0·009). Except for driving pressure, no other potential mediator consistently passed through the stepwise mediation tests. Tidal volume (p=0·577) and PEEP level (p=0·261) were not significant mediators. By contrast, a reduction in driving pressure mediated benefits (p=0·027), and this was enough to suppress the significance of the direct effect of randomisation (p=0·104), classically characterising complete mediation (table 4, appendix pp 20–21). Thus, although driving pressure was not an explicit target, benefits of protective ventilation were related to reductions in driving pressure caused by randomisation, rather than in proportion to changes in tidal volume or level of PEEP.

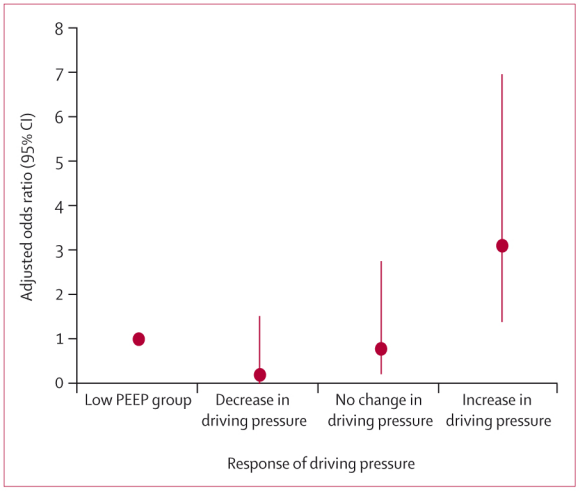

Figure 2: **Odds of postoperative pulmonary complications according to response of driving pressure after increase of PEEP**
PEEP=positive end-expiratory pressure.

Discussion

Our findings suggest that the driving pressure during intraoperative ventilation is independently associated with development of pulmonary complications after surgery. No other mechanical ventilation variable had such a mediating effect. These data provide new information about how to select tidal volume and PEEP level according to driving pressure during surgery.

We included a large cohort of patients having different types of surgery, pooling data from the most recent high

	Univariate logistic regression (OR, 95% CI)	Multivariable logistic regression* (OR, 95% CI)	Mediation analysis using bootstrap* (ACME, 95% CI)
Randomisation (protective)	0·56 (0·42–0·75)	0·85 (0·05–13·50)	0·42 (0·14–1·19)
Tidal volume (mL/kg PBW)	1·14 (1·07–1·22)	1·05 (0·98–1·13)	0·91 (0·62–1·26)
PEEP (cm H_2O)	0·99 (0·95–1·02)	0·83 (0·59–1·16)	1·46 (0·88–2·36)
Driving pressure (cm H_2O)	1·06 (1·02–1·11)	1·16 (1·13–1·19)	1·27 (1·07–1·48)

OR=odds ratio. ACME=average causal mediation effect. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. *Adjusted for variables described in table 2 and using generalised linear mixed model.

Table 4: **Effect of driving pressure on postoperative pulmonary complications according to three regression methods for the whole cohort of patients**

quality randomised controlled trials.[5,6,9] We used a primary outcome measured at an interval relevant to this study population. Also, we used a statistical tool able to identify the individual roles of potential mediators of an independent intervention.

The results of this analysis accord with laboratory studies showing that cell and tissue damage are more closely related to the amplitude of cyclic stretch than the maximal or sustained stretch,[30,31] as well as experiments demonstrating the deleterious effects of cyclic alveolar recruitment or high lung strain with high driving pressure.[32,33] Our findings also support results from investigations showing an association between high driving pressure and worse outcomes in patients with acute respiratory distress syndrome.[10–12] Indeed, a similar analysis of individual patient data from randomised controlled trials assessing the effects of protective ventilation in patients with acute respiratory distress syndrome also suggests that, among the respiratory variables monitored at the bedside, driving pressure was the strongest predictor of mortality.[34]

Even in non-injured lungs, closed but recruitable zones and overdistended areas can coexist during general anaesthesia. Such zones usually show inhomogeneous expansion behaviour, which works as a multiplier of mechanical stress,[35] and are thus vulnerable to injury from mechanical ventilation. Also, mechanical ventilation damages the fragile pulmonary intercellular matrix structure in the absence of previous lung injury.[36] Therefore, several mechanisms can underlie the development of different pulmonary adverse advents. Such mechanisms are similar to those present in injured lungs, and also modifiable by intraoperative mechanical ventilation. Surgical intervention, intraoperative blood loss, and general and local ischaemia-reperfusion due to hypotensive and low-perfusion periods, as well as tissue trauma itself, might cause the release of inflammatory mediators and spread of bacteria that can prime the lungs further to the stress of mechanical ventilation.[1,29] In turn, injured epithelial and endothelial layers might facilitate bacterial translocation, whereas the presence of postoperative atelectasis might create more favourable conditions for bacterial growth. Finally, it is important to emphasise that normal compliance does not enable inferences to be made about regional properties of mechanical ventilation, in which tidal recruitment and overdistension are easily overlooked.[37]

Despite similarities, our study is substantially different from a previous individual patient analysis of driving pressure[34] in several respects. Most importantly, the analysis by Amato and colleagues[34] included critically ill patients with acute respiratory distress syndrome undergoing long-term ventilation, whereas we focused exclusively on non-critically ill patients with uninjured lungs undergoing short-term ventilation for surgery. Thus, our results extend knowledge about protective ventilation and the potential role of the driving pressure. Indeed, the results of the two analyses are complementary, and not interchangeable. Atelectasis develops in a vast majority of patients undergoing general anaesthesia for surgery,[38] and can be as large as 25% of the normal lung, resulting in clinically relevant hypoxaemia.[38–40] Additionally, the development of atelectasis decreases the amount of aerated tissue, leading to a decrease in compliance. Since respiratory compliance is linearly related to the amount of aerated tissue, a low compliance is not due to a stiff lung, but rather loss of aerated lung tissue.[41] In the past, ventilation with tidal volumes of as much as 15 mL/kg predicted bodyweight were advocated to treat and prevent atelectasis, as such preventing hypoxaemia.[42] Although the size of tidal volumes with intraoperative mechanical ventilation has declined since 2000,[2,3] tidal volumes of 10 mL/kg predicted bodyweight are still used.[43,44] Thus, ventilation with such large tidal volumes in combination with a low compliance because of atelectasis could result in high driving pressure, which, according to our findings, is associated with increased risk for postoperative pulmonary complications. Indeed, the driving pressure can be considered as the tidal volume corrected for the static compliance of the respiratory system (or end-expiratory lung volume).

The protective role of intraoperative PEEP has been a matter of intense debate. Our group showed that the use of high levels of PEEP did not prevent pulmonary complications after surgery.[9] The present analysis suggests that the lack of benefit of high PEEP might best be explained by opposite effects of an increase in driving pressure. The effect of an increase in PEEP was diverse: it resulted in an increase, no change, or a decrease in the driving pressure. Theoretically, recruitment of lung tissue by the use of higher PEEP levels could lead to a decrease in the driving pressure, as an increase in aerated lung tissue results in a lower driving pressure when tidal volumes are not changed. If the driving pressure does not change, or when it increases, it could mean that the increase of the level of PEEP does not result in recruitment of lung tissue, or that lung tissue becomes overstretched. It is increasingly questioned whether protection of the lung against the harmful effects of positive pressure ventilation could be more important than optimising gas exchange. This possibility should be confirmed in future randomised controlled trials, in which the benefits of intraoperative ventilation strategies aiming at a low driving pressure are determined. Such trials should not only focus on intraoperative effects (ie, lung physiology), but also on the occurrence of postoperative pulmonary complications (ie, lung pathology). However, those hypotheses need to be confirmed in randomised controlled trials of intraoperative ventilation comparing ventilation guided by driving pressure to usual care.

Our meta-analysis had several limitations. First, the analysis was not pre-planned and deviated from the original protocol. Second, since the diagnosis of

postoperative pulmonary complications was based on clinical criteria, misclassification of patients might underestimate the effect, but this factor should have equally affected the different groups analysed. Third, our analysis does not explicitly account for chest wall elastance and pleural pressure. During ventilation, the cyclic gradient of pressures across the lung (transpulmonary driving pressure), potentially generating parenchymal injury, might be lower in patients with increased chest wall elastance, such as in people who are obese and those undergoing pneumoperitoneum for laparoscopic surgery.[45] Fourth, the original studies did not include predictive scores of postoperative pulmonary complications, limiting our ability to adjust for lung injury before surgery in the regression models. However, because all studies included patients undergoing elective surgery, one could consider that most if not all patients had uninjured lungs. Fifth, since none of the studies directly compared strategies of ventilation based on driving pressure or measured driving pressure (ie, driving pressure was calculated from other data collected and reported in the original studies), there is a small risk that unmeasured variables affecting the driving (eg, the mode of ventilation, differences in anaesthetic circuits, different ventilators) were not noticed. However, when driving pressure is calculated from inspiratory plateau pressure, these issues should have little or no effect.

Sixth, the analyses that focused on changes in the driving pressure in response to changes in PEEP level as dictated by the study protocols were mostly affected by the results of the largest study in this meta-analysis, the PROVHILO trial.[9] Seventh, data on oxygenation were incomplete, as blood gases are seldom analysed in patients receiving ventilation under general anaesthesia for surgery. Therefore, we chose not to analyse the effects of driving pressure on oxygenation. Eighth, the incidence and definition of the outcome are heterogeneous among the studies included. Ninth, the agreement of definitions of postoperative pulmonary complications and timeframe of diagnosis was heterogeneous among the included studies. Finally, the effect of driving pressure might be different in patients undergoing thoracic surgery than in those undergoing abdominal surgery. During one-lung ventilation in lateral decubitus, the compression atelectasis of dependent lung regions, the loss of elastic recoil after thoracotomy, and mediastinal surgical manipulations can greatly reduce the aerated lung capacity, impair ventilation distribution, and worsen ventilation–perfusion mismatch.[46] In this group of patients, the resultant driving pressure for the same tidal volume could be higher, requiring the use of lower tidal volumes, higher levels of PEEP, or even both.

In conclusion, in patients having surgery, high intraoperative driving pressure and a change in the level of PEEP that results in an increase in driving pressure are associated with more postoperative pulmonary complications. However, to confirm these findings, a randomised controlled trial comparing ventilation based on driving pressure versus usual care is necessary.

Contributors

ASN designed the study, collected, analysed, and interpreted data, and wrote the report. SNTH, CSVB, MBPA, ELVC, MGdA, and PP designed the study, interpreted data, and reviewed the report. MB, AF-B, EF, OG, MRE-T, AAAG, EG, SJ, SK, AK, ML, W-QL, ADM, SGM, DRM, PM, TN, DP, VMR, FS, TS, GS, PS, JS, SS, DT, TT, CU, TNW, EKW, and HW collected and interpreted data, and reviewed the report. MJS designed the study, analysed and interpreted data, and reviewed the report. All authors reviewed and revised the report.

Declaration of interests

We declare no competing interests.

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