Lung-protective perioperative mechanical ventilation

Hemmes, S.N.T.

Publication date
2015

Document Version
Final published version

Chapter 2

Intraoperative Ventilatory Strategies to Prevent Postoperative Pulmonary Complications – a Metaanalysis

Hemmes SNT, Serpa Neto A, Schultz MJ

Current Opinion in Anesthesiology 2013; 26(2):126-33

Abstract

Purpose. It is uncertain whether patients undergoing short–lasting mechanical ventilation for surgery benefit from lung–protective intraoperative ventilatory settings including the use of lower tidal volumes, higher levels of positive end–expiratory pressure (PEEP) and/or recruitment manoeuvres (RM). We meta–analysed trials testing the effect of lung–protective intraoperative ventilatory settings on the incidence of postoperative pulmonary complications.

Recent findings. Eight articles (1669 patients) were included. Metaanalysis showed a decrease in lung injury development (risk ratio [RR] 0.40; 95% CI 0.22–0.70; I^2 0%; number needed to treat [NNT] 37), pulmonary infection (RR 0.64; 95% CI 0.43–0.97; I^2 0%; NNT 27) and atelectasis (RR 0.67; 95% CI 0.47–0.96; I^2 48%; NNT 31) in patients receiving intraoperative MV with lower tidal volumes. Metaanalysis also showed a decrease in lung injury development (RR 0.29; 95% CI 0.14–0.60; I^2 0%; NNT 29), pulmonary infection (RR 0.62; 95% CI 0.40–0.96; I^2 15%; NNT 33) and atelectasis (RR 0.61; 95% CI 0.41–0.91; I^2 0%; NNT 29) in patients ventilated with higher levels of PEEP, with or without RM.

Summary. Lung–protective intraoperative ventilatory settings may have the potential to protect against postoperative pulmonary complications.

Keywords. Mechanical ventilation, Intraoperative, Postoperative complications, Tidal volume, Positive end-expiratory pressure

Introduction

Mechanical ventilation (MV) has the potential to cause so–called ventilator–associated lung injury (VALI). VALI results from overdistention of non–dependent lung tissue causing excessive cyclic strain of alveolar cells,[1] and repetitive opening and closing of dependent lung tissue resulting in cyclic cell stress due to the extreme forces exposed to lung cells at the interfaces between open and closed alveoli.[2,3] Lung–protective MV with use of lower tidal volumes, which is suggested to prevent alveolar overdistention, benefits critically ill patients suffering from acute respiratory distress syndrome (ARDS).[4] MV with higher levels of positive end–expiratory pressure (PEEP) with or without recruitment manoeuvres (RM), which is suggested to prevent repetitive opening and closing of alveoli, also seems beneficial at least in patients with severe ARDS.[4] Recent clinical studies suggest MV with lower tidal volumes even to benefit critically ill patients without ARDS.[5-7]

MV is an essential supportive strategy during general anaesthesia for surgery. It is uncertain whether short–lasting MV during surgery also has the potential to cause VALI.[8] However, both animal and human studies show VALI can develop shortly after initiation of MV.[7,9,10] In addition, general anaesthesia causes large atelectasis, especially when muscle relaxants are used.[11] As a consequence, there is an increased risk of overdistention of non–atelectatic lung tissue as well as repetitive opening and closing of partly atelectatic lung tissue. Thus, patients who need MV for surgery may also be vulnerable to the harmful effects of MV. Notably, surgical patients frequently suffer from postoperative pulmonary complications, with reported incidences of up to 5.0%.[12,13] It is tempting to speculate on a causal relation between these complications and intraoperative ventilatory settings.

We hypothesize use of intraoperative lung–protective ventilatory settings to lower the incidence of postoperative pulmonary complications, and consequently on the postoperative clinical course and length of hospital stay. To test this hypothesis, we meta–analysed clinical trials of MV for surgery, focusing on the use of lower tidal volumes and/or higher levels of PEEP and RM. This is a secondary metaanalysis of a previously published metaanalysis of clinical trials testing lung–protective MV in patients who received short–term MV (i.e., in the operation room for surgery) or long–term MV (i.e., in the intensive care unit because of critical illness).[14] The present metaanalysis is restricted to the clinical trials in the operation room.

Methods

We searched Medline (1966–2012), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). All reviewed articles and cross–referenced studies from retrieved articles were screened for pertinent information. Articles were selected for inclusion in the metaanalysis if they evaluated two types of MV in patients with uninjured lungs undergoing surgery. In one arm of the trial, MV should be protective (lower tidal volumes, and/or higher levels of PEEP with or without use of RMs). Then, this protective strategy should be compared with conventional methods (higher tidal volumes, and no or lower levels of PEEP and no use of RMs) in the other arm of the trial. We excluded trials of patients undergoing cardiac surgery. We also excluded revisions and trials that did not report the outcomes of interest (defined below). When we found duplicate articles of the same trial in preliminary abstracts and articles, we analysed data from the most complete data set.

Data were extracted from each article using a data recording form developed for the previously published metaanalysis.[14] After extraction, data were reviewed and compared by the second author. Whenever needed, we obtained additional information about a specific study by directly questioning the principal investigator of the specific trial.

The primary endpoint was the incidence of lung injury in each arm of the trial. Secondary endpoints included incidence of pulmonary infection (using the authors' definition) or atelectasis. Statistical analysis was performed as described in the original metaanalysis.[14]

Results

The initial search yielded 2.123 articles (459 from MEDLINE, 141 from CENTRAL, 885 from CINAHL, and 638 from Web of Science) (figure 1). After removing 711 duplicate articles, we evaluated the abstracts of 1.412 articles. After evaluating them, 1.364 articles were excluded because they did not meet inclusion criteria. Another five articles were excluded because MV was applied for other reasons than surgery, no data on outcome of interest was reported in 28, and same cohort previously analysed in seven. Finally, eight articles were included in the final analysis.[15-22]

Tidal volume reduction
Our search of the literature revealed eight articles (1669 patients) reporting on trials comparing lower with conventional tidal volumes during surgery (table 1 and table 2). Metaanalysis of these trials showed that 17 of 858 patients (2.0%) ventilated with lower tidal volumes and 36 of 755 patients (4.7%) ventilated with conventional tidal volumes developed lung injury during follow-up (risk ratio [RR] 0.40; 95% confidence interval [CI] 0.22–0.70; number needed to treat [NNT] 37) (figure 2). The analysis displayed no signs of heterogeneity (I^2 = 0%). Pulmonary infection and atelectasis showed lower incidence in patients receiving lower tidal volume ventilation (RR 0.64; 95% CI 0.43–0.97; NNT 27 and RR 0.67; 95% CI 0.47–0.96; NNT 31, respectively). The I^2 test indicated no heterogeneity in the analysis of pulmonary infection, but moderate heterogeneity in the analysis of atelectasis (0% and 48% respectively).

Higher levels of PEEP and RMs
Our search of the literature revealed five articles (1323 patients) reporting on trials comparing no or lower levels of PEEP (up to 3 cmH_2O) with higher levels of PEEP (from 3 to 12 cmH_2O) during surgery (table 1).

Metaanalysis of these trials shows that 9 of 654 patients (1.4%) ventilated with higher levels of PEEP developed postoperative lung injury compared to 31 of 629 patients (4.9%) receiving

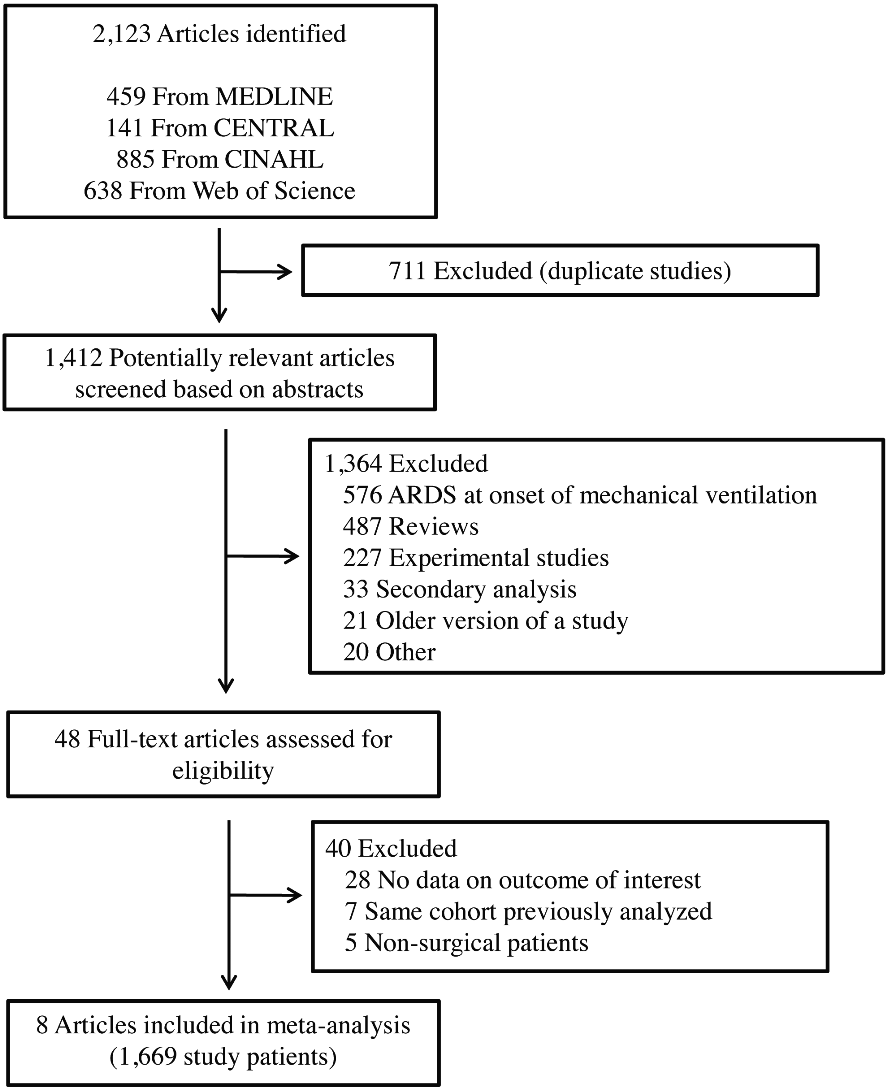


Figure 1. Literature search strategy; ARDS indicates acute respiratory distress syndrome

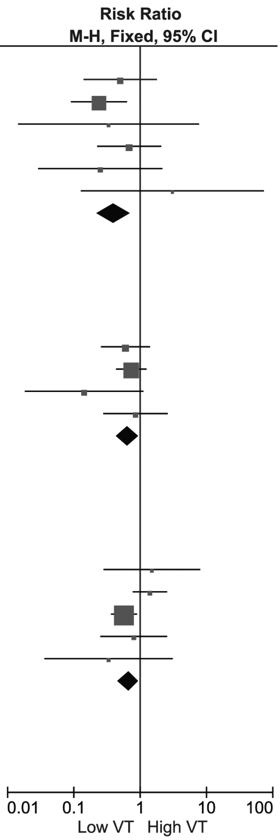
lower levels of PEEP (RR 0.29; 95% CI 0.14–0.60; NNT 29) (figure 3), without any signs for heterogeneity within the analysis ($I^2 = 0\%$). A beneficial effect of higher levels of intraoperative PEEP on postoperative pulmonary infection and atelectasis was also found (RR 0.62; 95% CI 0.40–0.96; NNT 33 and RR 0.61; 95% CI 0.41–0.91; NNT 29, respectively). The I^2 test indicated moderate heterogeneity in the analysis of pulmonary infection, but not in the analysis of atelectasis (15% and 0% respectively). We did not find trials specifically investigating exclusively the effects of intraoperative RM.

Table 1. Characteristics of the included studies and summary of continuous variables

	Protective				Conservative							Protective	Conservative	
Study	**N**	**VT**	**PEEP**	**RM**	**N**	**VT**	**PEEP**	**RM**	**N**	**Setting**	**Design**	**FU**	**Time of MV**		**Primary Outcome**
Michelet[15]	52	5	5	N	26	9	0	N	26	OS	RCT	18	7.06 ± 1.81	7.76 ± 1.85	Cytokines in blood
Cai[16]	16	6	0	N	8	10	0	N	8	Neuro	RCT	7.15	6.90 ± 2.20	7.4 ± 3.10	CT Atelectasis
Lin[7]	40	5	3-5	N	20	9	0	N	20	OS	RCT	24	4.33 ± 0.90	4.23 ± 0.71	Cytokines in blood
Licker[18]	1091	6	3	Y	558	9	3	N	533	OS	COH	---	2.93 ± 1.20	2.76 ± 1.0	LI
Weingarten[19]	40	6	12	Y	20	10	0	N	20	Surgical	RCT	Discharge	5.13 ± 1.86	5.73 ± 1.71	Oxygenation
Bustamante[20]	229	8	4	N	154	10	4	N	75	Surgical	CRO	---	NS	NS	TMV; ICULS; Mortality
Yang[21]	100	6	5	N	50	10	0	N	50	OS	RCT	168	2.00 ± 0.68	2.11 ± 0.80	LI
Treschan[22]	101	6	5	Y	50	12	5	Y	51	Surgical	RCT	120	8.70 ± 5.20	8.70 ± 5.90	Spirometry
Total	1,669	6.14 ± 0.86	4.50 (3.0 -5.0)	---	886	10.35 ± 1.15	0 (0 - 3.75)	---	783	---	---	6.57 (4.50 – 19.50)	6.90 (3.63 – 8.70)	7.40 (3.49 – 10.35)	---

Mean ± standard deviation; Median (interquartile range); VT: Tidal volume (in mL/kg); FU: Follow-up; OS: Oncology surgery; RCT: Randomized controlled trial; COH: Cohort; CRO: Cross-sectional; CT: Computed tomography; NS: Not specified; LI: Lung injury; TMV: Time of mechanical ventilation; ICULS: ICU length of stay

Study or Subgroup	Low VT Events	Low VT Total	High VT Events	High VT Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.2.1 Lung Injury							
Michelet 2006	3	26	6	26	15.3%	0.50 [0.14, 1.79]	2006
Licker 2009	5	558	20	533	52.2%	0.24 [0.09, 0.63]	2009
Weingarten 2010	0	20	1	20	3.8%	0.33 [0.01, 7.72]	2010
Bustamante 2011	7	154	5	75	17.2%	0.68 [0.22, 2.08]	2011
Yang 2011	1	50	4	50	10.2%	0.25 [0.03, 2.16]	2011
Treschan 2012	1	50	0	51	1.3%	3.06 [0.13, 73.35]	2012
Subtotal (95% CI)		**858**		**755**	**100.0%**	**0.40 [0.22, 0.70]**	
Total events	17		36				
Heterogeneity: Chi² = 3.86, df = 5 (P = 0.57); I² = 0%							
Test for overall effect: Z = 3.20 (P = 0.001)							
1.2.3 Pulmonary Infection							
Michelet 2006	6	26	10	26	18.6%	0.60 [0.26, 1.41]	2006
Licker 2009	23	558	30	533	57.2%	0.73 [0.43, 1.24]	2009
Yang 2011	1	50	7	50	13.1%	0.14 [0.02, 1.12]	2011
Treschan 2012	5	50	6	51	11.1%	0.85 [0.28, 2.61]	2012
Subtotal (95% CI)		**684**		**660**	**100.0%**	**0.64 [0.43, 0.97]**	
Total events	35		53				
Heterogeneity: Chi² = 2.54, df = 3 (P = 0.47); I² = 0%							
Test for overall effect: Z = 2.13 (P = 0.03)							
1.2.4 Atelectasis							
Lin 2008	3	20	2	20	3.2%	1.50 [0.28, 8.04]	2004
Cai 2007	7	8	5	8	7.9%	1.40 [0.77, 2.54]	2007
Licker 2009	28	558	47	533	76.2%	0.57 [0.36, 0.89]	2009
Weingarten 2010	4	20	5	20	7.9%	0.80 [0.25, 2.55]	2010
Yang 2011	1	50	3	50	4.8%	0.33 [0.04, 3.10]	2011
Subtotal (95% CI)		**656**		**631**	**100.0%**	**0.67 [0.47, 0.96]**	
Total events	43		62				
Heterogeneity: Chi² = 7.67, df = 4 (P = 0.10); I² = 48%							
Test for overall effect: Z = 2.19 (P = 0.03)							



Test for subgroup differences: Chi² = 2.57, df = 2 (P = 0.28), I² = 22.3%

Figure 2. Effect of intraoperative ventilation with lower tidal volumes

Table 2. Synthesis of demographic, ventilatory and laboratorial characteristics of the patients in the final follow-up

	Protective Ventilation (*n* = 886)	Conventional Ventilation (*n* = 73)	*p*-value
Age, years	60.27 ± 8.31	60.33 ± 8.06	0.910
Weight, kg	73.04 ± 13.04	73.01 ± 12.56	0.965
Tidal volume, ml/kg IBW[a]	6.14 ± 0.86	10.35 ± 1.15	< 0.0001
PEEP, cmH_2O[a]	6.62 ± 2.65	2.74 ± 2.82	0.001
Plateau pressure, cmH_2O[a]	16.62 ± 2.76	20.45 ± 2.54	0.021
Respiratory rate, beats per minute[a]	16.62 ± 2.72	10.78 ± 2.67	0.007
Minute-ventilation, litres/minute[a]	7.76 ± 2.61	8.56 ± 2.58	0.917
PaO_2 / FiO_2[a]	332.86 ± 61.48	339.68 ± 67.70	0.797
$PaCO_2$, mmHg[a]	41.86 ± 3.32	39.05 ± 3.42	0.052
pH[a]	7.35 ± 0.03	7.39 ± 0.03	0.073

Mean ± standard deviation; IBW: ideal body weight; PEEP: positive end expiratory pressure; [a]: in the final of the follow-up

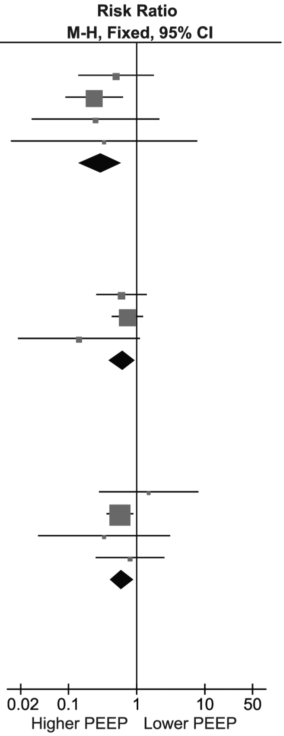
Discussion

This metaanalysis suggests that intraoperative MV with lower tidal volumes may protect surgical patients from development of postoperative lung injury, pulmonary infections and atelectasis. This metaanalysis also suggests that intraoperative use of higher levels of PEEP during MV attenuates development of lung injury, pulmonary infection and atelectasis.

Implementation of lung–protective MV for surgery has the potential to significantly reduce postoperative pulmonary complications. Considering the high number of surgical procedures performed worldwide daily,[23] reduction of postoperative pulmonary complications could be of great importance. Notably, a recent international prospective trial shows the incidence of postoperative mortality to be as high as 4%, much higher than previously assumed.[24] A large international observational study is underway to address the effect of intraoperative ventilatory settings on postoperative complications.[25]

Prescription of MV in critically ill patients has definitely changed over the last decades. There has been progressive reduction of tidal volume size, from > 12 ml/kg in the 1970s [26,27] to < 9 ml/kg in more recent epidemiologic studies of MV practice in Europe and the Americas.[28-31] This change was largely stimulated by results from animal studies, which clearly show injurious tidal volume settings to aggravate pre–existing pulmonary injury.[9] Several clinical trials confirm the existence of VALI by showing reduced morbidity and mortality in patients with ARDS ventilated with lower tidal volumes.[4] While initially intensive care unit physicians have been reluctant to use lower tidal volumes as part of their MV strategy, guidelines now strongly support the use

Study or Subgroup	Higher PEEP Events	Higher PEEP Total	Lower PEEP Events	Lower PEEP Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.9.1 Lung Injury							
Michelet 2006	3	26	6	26	18.8%	0.50 [0.14, 1.79]	2006
Licker 2009	5	558	20	533	64.0%	0.24 [0.09, 0.63]	2009
Yang 2011	1	50	4	50	12.5%	0.25 [0.03, 2.16]	2011
Weingarten 2010	0	20	1	20	4.7%	0.33 [0.01, 7.72]	2012
Subtotal (95% CI)		**654**		**629**	**100.0%**	**0.29 [0.14, 0.60]**	
Total events	9		31				
Heterogeneity: Chi^2 = 0.87, df = 3 (P = 0.83); I^2 = 0%							
Test for overall effect: Z = 3.40 (P = 0.0007)							
1.9.3 Pulmonary Infection							
Michelet 2006	6	26	10	26	21.0%	0.60 [0.26, 1.41]	2006
Licker 2009	23	558	30	533	64.4%	0.73 [0.43, 1.24]	2009
Yang 2011	1	50	7	50	14.7%	0.14 [0.02, 1.12]	2011
Subtotal (95% CI)		**634**		**609**	**100.0%**	**0.62 [0.40, 0.96]**	
Total events	30		47				
Heterogeneity: Chi^2 = 2.34, df = 2 (P = 0.31); I^2 = 15%							
Test for overall effect: Z = 2.16 (P = 0.03)							
1.9.4 Atelectasis							
Lin 2008	3	20	2	20	3.4%	1.50 [0.28, 8.04]	2004
Licker 2009	28	558	47	533	82.8%	0.57 [0.36, 0.89]	2009
Yang 2011	1	50	3	50	5.2%	0.33 [0.04, 3.10]	2011
Weingarten 2010	4	20	5	20	8.6%	0.80 [0.25, 2.55]	2012
Subtotal (95% CI)		**648**		**623**	**100.0%**	**0.61 [0.41, 0.91]**	
Total events	36		57				
Heterogeneity: Chi^2 = 1.69, df = 3 (P = 0.64); I^2 = 0%							
Test for overall effect: Z = 2.43 (P = 0.01)							



Test for subgroup differences: Chi^2 = 3.55, df = 2 (P = 0.17), I^2 = 43.7%

Figure 3. Effect of intraoperative ventilation with higher levels of PEEP

of lower tidal volumes in patients with ARDS, e.g., in patients with sepsis.[32] Critically ill patients without ARDS also seem to benefit from ventilation with lower tidal volumes.[5,6] One recent randomized controlled trial shows a lower tidal volume strategy to protect against lung injury in patients without ARDS at onset of MV in the intensive care unit.[7]

Notably, a recent observational study in patients undergoing short–term postoperative MV after cardiac surgery shows MV with tidal volumes > 10 ml/kg to be associated with prolonged MV, hemodynamic instability, multiple organ failure, and prolonged stay in the ICU, compared to MV with lower tidal volumes. In this study women and obese patients are found to be particularly at risk of receiving ventilation with too large tidal volumes.[33] These results confirm, at least in part findings from another recent study that identifies female gender, overweight and underweight as independent factors for MV with too large tidal volumes.[34]

MV with lower tidal volumes may not come without challenges. Use of lower tidal volumes could increase cyclic alveolar collapse of dependent lung regions, raising the risk of atelectrauma. Application of PEEP is an easy intervention that may counteract this side–effect of lower tidal volume ventilation. Lower tidal volume ventilation could also lead to hypercapnia and hypercapnic acidosis. Notably, so-called permissive hypercapnia is thought to have lung–protective qualities, even though the exact clinical implications are not entirely clear.[35]

Prescription of PEEP in critically ill patients has also changed over the last decades. PEEP is progressively more frequent applied in intubated and mechanically ventilated patients in the intensive care unit, with an increase in use of PEEP levels > 10 cmH_2O from 28% in the late '90s [28,29] to 40% in a more recent survey across ICUs in Europe and the Americas.[36] Particularly in patients with ARDS higher levels of PEEP are being applied, even though the benefits of higher PEEP levels with or without RM are not unequivocally demonstrated.[28,29,36] Use of higher levels of PEEP and RM could benefit patients with severe ARDS, though .[4,37] Trials investigating the effects of higher levels of PEEP in critically ill patients without ARDS are lacking. The results of the present metaanalysis are in line with results from a previous systematic review suggesting higher levels of PEEP to reduce postoperative atelectasis.[38]

None of the trials included in our metaanalysis analysed the effect of RM separate from the use of higher levels of PEEP. However, one recent randomized controlled trial of cardiac surgery patients shows decrease of alveolar dead–space and increase in arterial oxygenation during surgery when RMs are performed.[39]

An adversity of use of higher levels of PEEP, with or without the use of RM, may lay in an increase in right ventricular afterload as well as a decrease in right ventricular preload. This could cause a decrease in left ventricular preload and reduction in left ventricular stroke volume.[40] It is uncertain whether this causes problems in patients undergoing surgery.

Our study knows several shortcomings. First, it is difficult if not impossible to differentiate between the beneficial effect from lower tidal volumes and that from higher levels of PEEP with or without RM. Most trials included in this metaanalyses compared "conventional ventilation" with higher tidal volumes *and* low levels of PEEP with a "lung-protective" MV strategy with lower tidal volume ventilation *and* higher levels of PEEP (table 1). As a result all trials included in the metaanalysis assessing the effect of higher levels of PEEP and RM is also part of the metaanalysis analysing the effect of lower tidal volumes. Second, the incidence of lung injury could very well be higher than calculated in this metaanalysis, as the clinical picture of ARDS often resembles "suspected" pulmonary infection. ARDS as well as pulmonary infection may present with leucocytosis, fever and pulmonary infiltrates on the chest radiograph. Thus, it could be that ARDS is mistakenly diagnosed as pulmonary infection in some cases. Finally, when interpreting the results of this metaanalysis, the possible occurrence of positive publication bias should be taken into account. Furthermore the use of funnel plots has a limited role, as test for bias when the number of studies included in the analysis is small. Despite these limitations, our metaanalysis provides interesting information which needs further exploration.

Conclusion

Lower tidal volumes, higher levels of PEEP and RM are increasingly used in intensive care unit patients receiving long–term MV. Intraoperative use of lower tidal volumes could reduce the incidence of postoperative lung injury, pulmonary infections and atelectasis. Intraoperative use of higher levels of PEEP and RMs also reduce the incidence of these complications. It is difficult if not impossible to separate the beneficial effects of lower tidal volumes from that of higher levels of PEEP and RM. To better establish the effect of lung–protective intraoperative ventilatory settings we are also in need of well–powered randomized clinical trials. Presently, one large multicentre trial is conducted to identify the effect of intraoperative use of higher levels of PEEP and RM on the incidence of postoperative complications in adult surgical patients.[41]

Key points

1. Intraoperative use of lower tidal volumes may reduce postoperative lung injury, pulmonary infections and atelectasis

2. It is uncertain whether higher levels of PEEP, with or without use of RM, adds to the beneficial effects of intraoperative use of lower tidal volumes

3. We are in need of well–powered randomized controlled trials that test the effect of intraoperative lung–protective ventilatory settings, including tidal volume size, higher levels of PEEP and RM.

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