Review Article

Effects of peep on lung injury, pulmonary function, systemic circulation and mortality in animals with uninjured lungs—a systematic review

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Abstract: It is well-known that positive end-expiratory pressure (PEEP) can prevent ventilator-induced lung injury (VILI) and improve pulmonary physiology in animals with injured lungs. It's uncertain whether PEEP has similar effects in animals with uninjured lungs. A systematic review of randomized controlled trials (RCTs) comparing different PEEP levels in animals with uninjured lungs was performed. Trials in animals with injured lungs were excluded, as were trials that compared ventilation strategies that also differed with respect to other ventilation settings, e.g., tidal volume size. The search identified ten eligible trials in 284 animals, including rodents and small as well as large mammals. Duration of ventilation was highly variable, from 1 to 6 hours and tidal volume size varied from 7 to 60 mL/kg. PEEP ranged from 3 to 20 cmH_2O, and from 0 to 5 cmH_2O, in the 'high PEEP' or 'PEEP' arms, and in the 'low PEEP' or 'no PEEP' arms, respectively. Definitions used for lung injury were quite diverse, as were other outcome measures. The effects of PEEP, at any level, on lung injury was not straightforward, with some trials showing less injury with 'high PEEP' or 'PEEP' and other trials showing no benefit. In most trials, 'high PEEP' or 'PEEP' was associated with improved respiratory system compliance, and better oxygen parameters. However, 'high PEEP' or 'PEEP' was also associated with occurrence of hypotension, a reduction in cardiac output, or development of hyperlactatemia. There were no differences in mortality. The number of trials comparing 'high PEEP' or 'PEEP' with 'low PEEP' or 'no PEEP' in animals with uninjured lungs is limited, and results are difficult to compare. Based on findings of this systematic review it's uncertain whether PEEP, at any level, truly prevents lung injury, while most trials suggest potential harmful effects on the systemic circulation.

Keywords: Animals; uninjured lungs; mechanical ventilation; positive end-expiratory pressure (PEEP); pulmonary physiology

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Introduction

Artificial ventilation is a frequently applied intervention in critically ill patients in need of ventilatory support (1,2), and indispensable in patients under general anesthesia for surgery (3,4). One main side effect of artificial ventilation using positive pressure is alveolar collapse at the end of expiration (5,6). This could not only cause shunt and thus negatively affect arterial oxygenation, but also induce lung injury, through repetitive opening and closing of those lung parts that collapse at the end of expiration—a phenomenon frequently referred to as ventilator-induced lung injury (VILI) (7). Use of positive end-expiratory pressure (PEEP) could prevent alveolar collapse and therefore some level of PEEP is frequently chosen.

There is clear evidence for clinical benefit of 'high PEEP' in patients with acute respiratory distress syndrome (ARDS) (8). One metaanalysis that used individual patient data from three large randomized controlled trials (RCTs) of PEEP (9-11) showed 'high PEEP' to be associated with increased survival. However, it should also be acknowledged that mortality benefit of 'high PEEP' was restricted to patients with moderate or severe ARDS, and 'high PEEP' was even associated with prolonged duration of ventilation in patients classified as having mild ARDS. There is little evidence for benefit of PEEP, at any level, in ICU patients without ARDS (12), and in surgery patients receiving intraoperative ventilation (13). Despite these findings, observational studies show an increase in use of (higher levels of) PEEP in ICU patient without ARDS (1,2), as well as in surgery patients (4,14,15).

One important notion is that PEEP, at any level could cause overdistension of non-dependent lung parts (16-18). Alike repetitive opening and closing, overdistension is considered yet another causal factor for VILI (16,17). PEEP can also negatively impact systemic circulation through its effects on right ventricle loading conditions (19), and afterload (19,20). Indeed, one recent trial of PEEP in surgery patients showed much more episodes of shock during the surgical procedure with the use of higher levels of PEEP (13).

The balance between benefit and harm of (higher levels of) PEEP in the presence of lung injury thus may differ from that in the absence of lung injury. Nevertheless, we hypothesized that PEEP prevents against lung injury and improves pulmonary function, while not affecting non-pulmonary endpoints in mechanical ventilation models using animals with uninjured lungs We performed a systematic review of the literature to search for trials that compared different levels of PEEP in animals with uninjured lungs.

Methods

Search strategy

Two independent investigators performed an unrestricted search in the databases of PubMed and CENTRAL (the Cochrane Library) for relevant articles published up to January 2017, using the following Medical Subject Headings and keywords: 'PEEP' OR 'positive end-expiratory pressure' OR 'positive-end expiratory pressure' OR 'positive end expiratory pressure' AND 'randomized' OR 'RCT'.

All articles returned by this search were screened for eligibility by reading the title and abstract. If considered potentially relevant, the full text was reviewed. References of all these articles as well as reviews and metaanalysis of PEEP were checked for potentially relevant articles missed by the search.

Selection of studies

The single one inclusion criterion was that animals had to be randomized to different levels of PEEP.

The following exclusion criteria were used: (I) animals were subjected to a 'hit' causing lung injury, either before or during ventilation, consisting of (repeated) lung lavage(s), administration of oleic acid, or infection; (II) 'bundles' of ventilation were compared, meaning that animals were randomized to ventilation with different PEEP levels but also differences in other ventilator settings, like tidal volume (V_T) size; (III) when more than one PEEP level was used within an individual animal; and finally (IV) when the trial used immature animals. In case of more than two randomization groups within one trial, we focused one the two groups with the highest and the lowest level of PEEP.

Data extraction

The two investigators extracted the data into a database

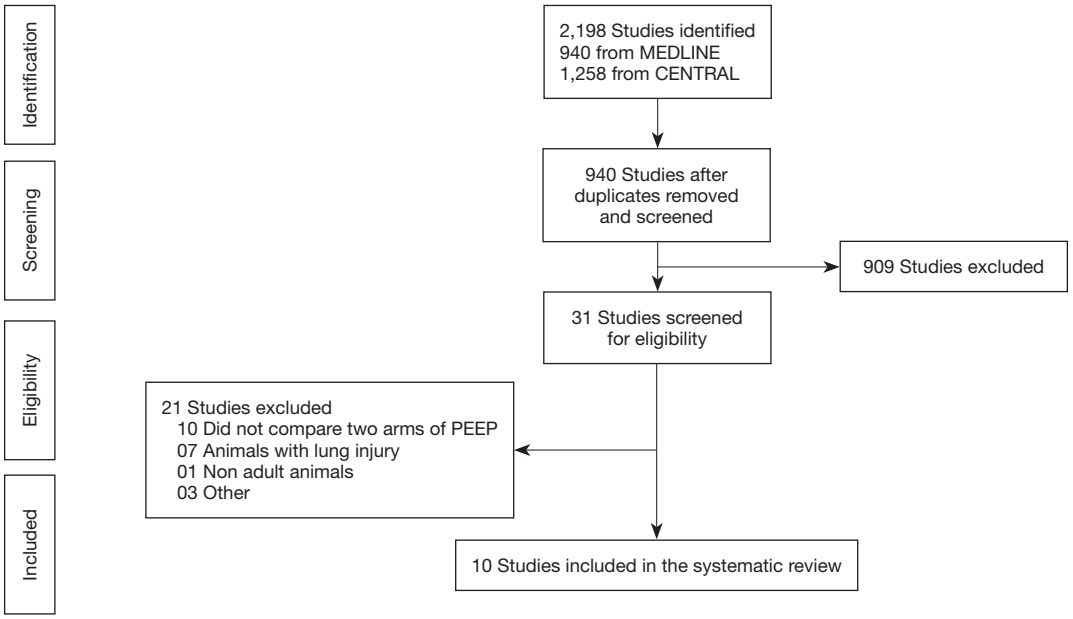

Figure 1 Flowchart of the systematic review.

constructed for this investigation. Any disagreement between investigators on the data extracted was solved by discussion. The following data were extracted: type of animal, age of animal, gender of animal, duration of ventilation before randomization, duration of ventilation, ventilator settings including ventilation mode, tidal volume size, level of PEEP, peak and plateau pressures, fraction of inspired oxygen (FiO_2), pulmonary compliance and if present blood gas analysis results, hemodynamic parameters as reported, such as blood pressure, heart rate, cardiac output or index, and final outcome (e.g., death, if not by sacrifice).

Quality assessment

The same two investigators independently performed quality assessment of the included trials. The SYRCLE's Risk of Bias tool was used to assess the risk of bias of all included studies (21), where again disagreements were settled by discussion.

Definitions

As the set levels of PEEP were quite different between trials, we decided to use the following wording for PEEP levels: 'high PEEP' was used for the PEEP level for trials that compared a higher level of PEEP to a low level of PEEP, where low PEEP was referred to as 'low PEEP'; 'PEEP' was used for trials that compared some level of PEEP to no PEEP, where no PEEP was referred to as 'no PEEP'.

Outcomes

The primary outcome of interest was occurrence or severity of lung injury at the end of the experiment, as assessed and reported by the investigators of the individual trial, which could be histopathology by conventional microscopy or electron microscopy, lung weight or wet-to-dry ratios, or visual inspection. Secondary outcomes included: (I) variables reflecting pulmonary function (e.g., arterial oxygenation, the respiratory system compliance); (II) hemodynamic outcomes (e.g., heart rate, arterial blood pressure, cardiac output or index, and plasma lactate levels) and; (III) mortality at the end of the experiment, if not by sacrifice.

Results

Search results

The search returned 2,198 articles, 940 from MEDLINE and 1,258 from CENTRAL (*Figure 1*). After removal of duplicates, 940 articles were evaluated by reading title and abstracts. Most articles, 909 in total, did not meet the inclusion criterion. After

Table 1 Characteristics of studies

Reference	High PEEP group	Low PEEP group
N, median	8	8
PEEP, cmH_2O	10 [5–10] [3–20]	0 [0–3] [0–5]
Tidal volume, mL/kg	8 [7–8] [7–60]	8 [7–8] [7–50]
Recruitment maneuvers used, %	53	46
Duration of ventilation, minutes	180 [120–180] [60–360]	180 [120–180] [60–360]

Data are shown as median [IQR] [range]. PEEP, positive end-expiratory pressure; IQR, interquartile range.

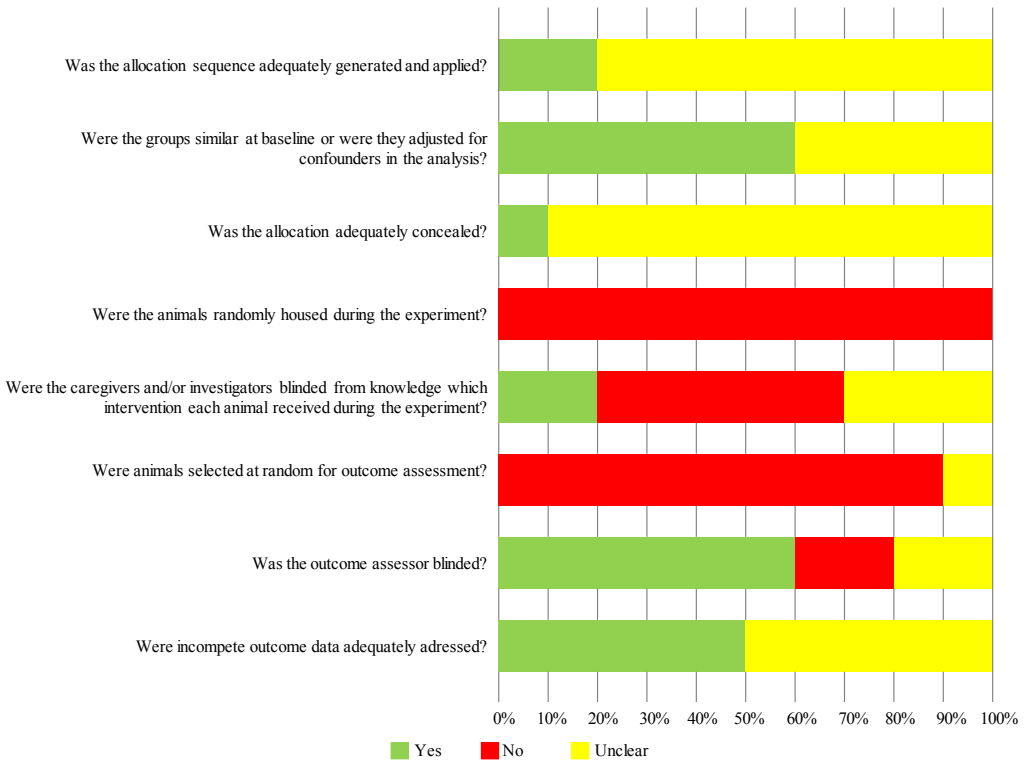

Figure 2 Risk of bias, score (%) per risk of bias item.

carefully assessment of full text of the remaining 31 potentially eligible articles, 21 were excluded for the following reasons: (I) did not compare different PEEP levels (n=10); (II) ventilation in animals with existing lung injury (n=7); (III) immature animals (n=1); and (IV) other reasons (n=3). Thus, 10 trials including 284 animals remained (22-31). *Table 1* summarizes characteristics of the included trials. Three trials used rats (23,25,28), three used pigs (26,27,30), two used rabbits (24,29), one used dogs (22) and one used horses (31). The median included animals were 8 in both PEEP arms.

Quality trials

For the majority of the trials the risk of bias is unclear, since details of the trials were insufficiently provided to assess the risk of bias properly (*Figure 2*). The high risk of bias was in the domains related to housing of the animals, randomly selection of the animals for outcome assessment and blinding of the caregivers and/or investigator to which

Table 2 Effect of PEEP on development of lung injury

Reference	Animal	N in high vs. low PEEP group	Main findings (compared to low PEEP)	Do the findings supports the use of high PEEP*
Nahum *et al.* (22)	Dog	6 *vs*. 6	Less histopathologic changes in lung tissue and lower lung weight	Yes
Verbrugge *et al.* (23)	Rat	16 *vs.* 16	Lower lung weight	Yes
Chu *et al.* (25)	Rat	20 *vs.* 20	Less lung injury	Yes
			Lower MIP-2, TNF-alpha and IL-6 in BAL were not different	
McCaul *et al.* (28)	Rat	9 *vs.* 9	Lower wet-to-dry ratios	Yes
Piccin *et al.* (29)	Rabbit	8 *vs.* 6	More cellular damage; larger areas of haemorrhagic consolidation	No
Madke *et al.* (30)	Pig	6 *vs.* 6	Histopathologic changes in lung tissue were not different	No

*, our interpretation. PEEP, positive end–expiratory pressure; MIP-2, macrophage inflammatory protein-2; TNF-alpha, tumor necrosis factor-alpha; IL-6, interleukin-6; BAL, bronchoalveolar lavage.

intervention each animal received during the experiment.

Ventilation characteristics

Before randomization, in three trials a volume-controlled mode was used (22,26,27), in two a pressure-controlled mode (23,30), and in one a spontaneous breathing mode (31). After randomization, in four trials a volume-controlled mode was used (22,26,27,31), and in two a pressure-controlled mode (23,30). For four trials it remained unclear which ventilation mode was used (24,25,28,29). Duration of ventilation varied widely, from 1 to 6 hours (*Table 1*). In four trials, recruitment maneuvers were used in the 'high PEEP' or 'PEEP' arms (22-25), in three trials recruitment maneuvers were used in both randomization arms (22,23,25). There was a noticeable variation in tidal volume size, from 7 to as high as 60 mL/kg, though tidal volume size was always similar in the 'high PEEP' or 'PEEP' arms and 'low PEEP' or 'no PEEP' arms in the individual trials. Tidal volume size was not reported in three trials (23,26,27).

The levels of PEEP compared

PEEP was most often 10 cmH_2O in the 'high PEEP' or 'PEEP' arms (22,23,26,30), and most often 0 cmH_2O in the 'low PEEP' or 'no PEEP' arms (*Table 1*) (23,25-28). Interestingly, in three trials PEEP was 5 cmH_2O in the 'high PEEP' or 'PEEP' arms (25,27,28), while in three other trials the same level of PEEP was used in the 'low PEEP' arms (29-31). In all trials, PEEP was fixed, except in one trial in which PEEP was titrated from 5 up to 20 cmH_2O in 15 minutes intervals in the 'high PEEP' arm (31).

Outcomes

Lung injury (*Table 2*)—of the six trials investigating the effects of PEEP on lung injury, four showed benefit (22,23,25,28) and two trials showed no benefit in animals ventilated with 'high PEEP' or 'PEEP' (29,30).

All three trials comparing 'PEEP' with 'no PEEP' showed less VILI with 'PEEP' (23,25,28). Of the three trials comparing 'high PEEP' to 'low PEEP', one trial showed less VILI with 'high PEEP' (22), while one found more VILI (29) and another found no differences between the PEEP arms (30).

Pulmonary function (*Table 3*)—of the nine trials investigating the effects of PEEP on the lung parameters, seven trials showed better arterial oxygenation or improved respiratory system compliance with 'high PEEP' or 'PEEP' (23,24,26-28,30,31), while two showed no benefit (22,29).

Of the four trials comparing 'PEEP' with 'no PEEP' (23,26-28), all showed better arterial oxygenation or improved respiratory system compliance in the 'PEEP' arms. Five trials compared 'high PEEP' with 'low PEEP', of which three trials showed improved pulmonary outcomes in the 'high PEEP' arms (24,30,31), and one showed a worsened pulmonary function (29) and another found no

Table 3 Effect of pulmonary function

Reference	Animal	N in high *vs.* low PEEP group	Main findings (compared to low PEEP)	Do the findings supports the use of high PEEP*
Nahum *et al.* (22)	Dog	6 *vs.* 6	Arterial oxygenation was not different	No
Verbrugge *et al*. (23)	Rat	16 *vs.* 16	Better arterial oxygenation	Yes
Mols *et al.* (24)	Rabbit	7 *vs.* 7	Less shunt and less ventilation perfusion mismatch	Yes
Krismer *et al.* (26)	Pig	8 *vs.* 8	Better arterial oxygenation	Yes
Herff *et al.* (27)	Pig	8 *vs.* 8	Better arterial oxygenation	Yes
McCaul *et al.* (28)	Rat	9 *vs.* 9	Better arterial oxygenation and FRC	Yes
Piccin *et al.* (29)	Rabbit	8 *vs.* 6	Lower respiratory system compliance and more atelectasis	No
Madke *et al.* (30)	Pig	6 *vs.* 6	Better respiratory system compliance, arterial oxygenation was not different	Yes
Ambrósio et al. (31)	Horse	7 *vs.* 6	Better arterial oxygenation and respiratory system compliance; less shunt	Yes

*, our interpretation. PEEP, positive end-expiratory pressure; FRC, functional residual capacity.

Table 4 Effect of PEEP on hemodynamic outcomes

Reference	Animal	N in high *vs.* low PEEP group	Main findings (compared to low PEEP)	Argue against the use of high PEEP
Nahum *et al.* (22)	Dog	6 *vs.* 6	CO, BP, HR were not different	No
Krismer *et al.* (26)	Pig	8 *vs.* 8	Lower CO and BP; higher lactate	Yes
Herff *et al.* (27)	Pig	8 *vs.* 8	Lower CO and BP; higher lactate	Yes
McCaul *et al.* (28)	Rat	9 *vs.* 9	Less decrease in LVEDA; no difference in FS	Yes
Piccin *et al.* (29)	Rabbit	8 *vs.* 6	BP, HR and plasma levels lactate were not different	Yes
Madke *et al.* (30)	Pig	6 *vs.* 6	Lower BP, higher HR	Yes
Ambrósio *et al.* (31)	Horse	7 *vs.* 6	Lower CO; BP and HR were not different	Yes

*, our interpretation. PEEP, positive end-expiratory pressure; CO, cardiac output; BP, blood pressure; HR, heart rate; LVEDA, left ventricular end-diastolic area; FS, fractional shortening.

differences (22).

Hemodynamic outcomes (*Table 4*)—of the seven trials that reported on hemodynamic outcomes, in six trials 'high PEEP' or 'PEEP' resulted in a lower cardiac output, hypotension or hyperlactatemia (26-31), while one trial showed no harm (22).

All of the three trials comparing 'PEEP' with 'no PEEP' showed lower cardiac output, hypotension or hyperlactatemia with 'PEEP' (26-28). Of the four trials comparing 'high PEEP' with 'low PEEP', three showed negative effects of 'high PEEP' on the hemodynamic variables (29-31), while one showed no harm (22).

Mortality (*Table 5*)—of the five trials that reported on mortality, two showed higher mortality rates with 'high PEEP' or 'PEEP' (26,27), two trials showed lower mortality rates with 'PEEP' or 'high PEEP' (22,28), and one trial found no differences (30).

Of the three trials comparing 'PEEP' to 'no PEEP' two showed higher mortality rates (26,27), while the other one showed a lower mortality rate with 'PEEP' (28). Of the two trials comparing 'high PEEP' with 'low PEEP', one showed lower mortality rates (22), while the other found no

Table 5 Effect of PEEP on mortality

Reference	Animal	N in high *vs.* low PEEP group	Main findings (compared to low PEEP)	Do the findings supports the use of high PEEP*
Nahum *et al.* (22)	Dog	6 *vs.* 6	Lower mortality	Yes
Krismer *et al.* (26)	Pig	8 *vs.* 8	Higher mortality	No
Herff *et al.* (27)	Pig	8 *vs.* 8	Higher mortality	No
McCaul *et al.* (28)	Rat	9 *vs.* 9	Lower mortality	Yes
Madke *et al.* (30)	Pig	6 *vs.* 6	Similar mortality	No

*, our interpretation. PEEP, positive end-expiratory pressure.

differences (30).

Discussion

The results of this systematic review of trials comparing 'high PEEP' or 'PEEP' with 'low PEEP' or 'no PEEP' in animals with uninjured lungs can be summarized as follows: (I) the number of trials evaluating the effects of PEEP is severely limited; (II) trials are heterogeneous in design and outcomes; (III) the beneficial effect of PEEP on VILI was not found in all trials; (IV) PEEP, at any level, has a clear beneficial effect on pulmonary physiology; (V) PEEP negatively effects systemic circulation; and (VI) the effect of PEEP on mortality is diverse.

To our best knowledge this is the first systematic review investigating the effects of ventilation with different levels of PEEP in animals with uninjured lungs. Strength of this systematic review is that we restricted inclusion to trials that only compared two different levels of PEEP, i.e., trials that compared so-called 'bundles of protective ventilation' were excluded. As such we minimized the risk of confounding effects e.g., differences in tidal volume size. Also, the search strategy was very wide and found a small but reasonable number of trials. Finally, the included trials assessed different types of animals, which could increase generalizability of the findings.

One possible explanation for the fact that some trials showed less lung injury with 'high PEEP' or 'PEEP' while others showed no benefit with respect to development of VILI could be the wide variation of definitions for VILI used. It should also be noticed that some trials used extremely large tidal volumes, high peak inspiratory pressures and plateau pressures, or high FiO_2, which are nowadays considered unsafe. Also, in some trials animals were exposed to long cold ischemic time, or high dosages of epinephrine. It remains uncertain if PEEP has the potential to protect against lung injury under such extreme conditions. Actually, one might wonder if these animals were not having lung injury, but if lung injury was induced during the trial.

One clear finding was that in almost all trials 'high PEEP' or 'PEEP' resulted in better physiologic endpoints, like arterial oxygenation and respiratory system compliance. These findings are very consistent with observations in clinical trials of PEEP, both in trials in ICU patients with ARDS (9-11), and ICU patients without ARDS (32,33). Another clear finding, though, was that ventilation with PEEP negatively affects systemic circulation. Positive pressure ventilation, per se, increases the intrathoracic pressure, decreasing preload and increasing afterload of the right ventricle (34), while it can reduce the afterload of the left ventricle. The present findings echo the results of one recent metaanalysis of clinical trials that compared different levels of PEEP (35), and also the clear finding that PEEP induces shock in one recent clinical trial of intraoperative ventilation (13).

The results of this systematic review add to our knowledge on the effects of PEEP during ventilation in the absence of lung injury. Its results are also in line with those from a recent systematic review and metaanalysis of clinical trials investigating the effects of PEEP in patients without ARDS (35). That investigation suggested no benefit of ventilation with (higher levels of) PEEP with regard to important clinical endpoints, like mortality and duration of mechanical ventilation. That investigation, though, also suggested improved pulmonary function with (higher levels of) PEEP, like a better oxygenation, and there was at least a suggestion that it could negatively affect systemic circulation. These two systematic reviews underline the

need for well-conducted and sufficiently sized clinical, and animal trials investigating the effects of PEEP in patients without ARDS, and in animals without uninjured lungs.

This systematic review has several limitations. First, it should be noted that the trials identified by the search maybe better reflect the clinical scenario of intraoperative ventilation, seen the relative short period of ventilation in all of them. On the other hand, one could also argue that duration of ventilation in the trials reviewed here is very similar to trials of PEEP in animals with lung injury, and these trials have been frequently used in the translation of effects of PEEP from animals to patients with ARDS. Second, the overall quality of the included trials, as with all systemic reviews, influenced the results. The majority of the included trials had an unclear or high risk of bias, and in addition sample sizes were small and not all outcomes were reported in all trials. Third, similar levels of PEEP served as 'high PEEP' or 'low PEEP' across the trials, further complicating the interpretation of the findings. Finally, and as mentioned above, in some trials ventilator settings other than PEEP are by now no longer accepted as 'safe'.

Conclusions

The number of trials comparing different levels of PEEP in animals with uninjured lungs is limited and the results of these trials are difficult to compare. Based on the findings of this systematic review it remains uncertain whether PEEP, at any level, prevents lung injury in animals with uninjured lungs. While (higher levels of) PEEP improves pulmonary function, it also negatively affects systemic circulation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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