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### Lung-protective ventilation in intensive care unit and operation room

*Tidal volume size, level of positive end-expiratory pressure and driving pressure*

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## Chapter 8

### **Ventilation with lower tidal volumes for critically ill patients without the acute respiratory distress syndrome: A systematic translational review and meta-analysis**

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**Abstract**

*Purpose of review:* There is convincing evidence for benefit from lung-protective mechanical ventilation with lower tidal volumes in patients with the acute respiratory distress syndrome (ARDS). It is uncertain whether this strategy benefits critically ill patients without ARDS as well. This manuscript systematically reviews recent preclinical studies of ventilation in animals with uninjured lungs, and clinical trials of ventilation in ICU patients without ARDS on the association between tidal volume size and pulmonary complications and outcome.

*Recent findings:* Successive preclinical studies almost without exception show that ventilation with lower tidal volumes reduces the injurious effects of ventilation in animals with uninjured lungs. This finding is in line with results from recent trials in ICU patients without ARDS, demonstrating that ventilation with lower tidal volumes has a strong potential to prevent development of pulmonary complications and maybe even to improve survival. However, evidence mostly comes from nonrandomized clinical trials, and concerns are expressed regarding unselected use of lower tidal volumes in the ICU, that is, in all ventilated critically ill patients, since this strategy could also increase needs for sedation and/or neuromuscular blockade, and maybe even cause respiratory muscle fatigue. These all then could in fact worsen outcome, possibly counteracting the beneficial effects of ventilation with lower tidal volumes.

*Summary:* Ventilation with lower tidal volumes protects against pulmonary complications, but well-powered randomized controlled trials are urgently needed to determine whether this ventilation strategy truly benefits all ventilated ICU patients without ARDS.

## Introduction

For years ICU physicians understood that positive pressure mechanical ventilation was a life-saving strategy in patients with the acute respiratory distress syndrome (ARDS). Despite increasing awareness of the damaging effects of ventilation in preclinical studies in animals with lung injury, frequently referred to as ventilation-induced lung injury (VILI), the potential harmful effects of traditional use of higher tidal volumes in patients with ARDS were considered unimportant until 15 years ago, when the beneficial effects of ventilation with a lower tidal volume (i.e., 6 ml/kg predicted body weight, PBW) were clearly and convincingly established in a landmark ARDS Network trial in 2000.<sup>1</sup> ICU physicians and ventilation investigators were rather slow to accept these findings, but subsequent trials and a meta-analysis convincingly confirmed the reduction in mortality by using protective ventilation with lower tidal volumes in patients with ARDS.<sup>2</sup> Currently, use of lower tidal volumes is considered standard of care for this complication of critical illness.<sup>3-5</sup>

If ventilation with lower tidal volumes has the potential to improve outcome in patients with ARDS, one could speculate that patients without, or at risk for, ARDS also benefit from a ventilation strategy with lower tidal volumes.<sup>6</sup> One could even consider ARDS as a preventable complication of ventilation.<sup>7</sup> The possible injurious effects of the traditional use of higher tidal volumes in patients without ARDS is not yet widely appreciated, though, even after publication of a randomized controlled trial four years ago showing beneficial effects of ventilation with lower tidal volumes in patients without ARDS on ICU admission.<sup>8</sup> Meanwhile, numerous trials of ventilation during general anesthesia for surgery and one meta-analysis compellingly suggest short-term protective ventilation with lower tidal volumes benefits surgery patients.<sup>9</sup> Currently, use of lower tidal volumes can be considered standard of care in the operation room, but not in the ICU.<sup>10,11</sup>

The aim of this systematic and translational review is to collect and summarize present knowledge on the effects of ventilation with lower tidal volumes in preclinical studies of ventilation in animals without lung injury and clinical trials of ventilation in ICU patients without ARDS. Furthermore, the clinical trials were meta-analyzed with regard to the effects

of ventilation with lower tidal volumes on development of ARDS, mortality, development of pulmonary infections and duration of ventilation.

## Methods

We searched MEDLINE (1966–2013) with the following search terms: 'lower tidal volume' OR 'low tidal volume' OR 'protective ventilation'. Retrieved articles, and cross-referenced studies from those articles, were screened for pertinent information. An article was selected for inclusion if it evaluated at least two ventilation strategies that differed in the size of tidal volumes used. Preclinical studies of ventilation in animals with lung injury and clinical studies of ventilation in patients with ARDS were excluded, as were clinical trials of ventilation for general anesthesia for surgery. Revisions and studies that did not report the outcomes of interest were also excluded. In cases when we found duplicate articles of the same animal study or clinical trial in preliminary abstracts and articles, we analyzed data from the most complete data set. Data were extracted from each article using a data recording form developed for the previously published meta-analysis<sup>9</sup> by the first two authors. After extraction, data were reviewed and compared. Whenever needed, we obtained additional information about a specific study by directly questioning the principal investigator of a specific clinical trial.

Preclinical studies of ventilation in animals without lung injury were stratified as follows: studies in which the tidal volume size but not the positive end-expiratory pressure (PEEP) level differed between the study arms; or studies in which both the tidal volume size and the PEEP level differed. The endpoints assessed in animal studies were: peak pressures (defined as the highest airway pressure level) and/or alveolar strain; severity of inflammation (as by local or systemic levels of cytokines, chemokines or other inflammatory mediators); presence of lung edema [as by (relative) lung weight, or capillary leakage], and lung injury (as by histopathologic examination of lung tissue).

Clinical trials of ventilation in ICU patients without ARDS were not stratified. The endpoints assessed were development of ARDS (as reported by the investigators), mortality,

duration of ventilation, severity of inflammation (as by local or systemic levels of cytokines, chemokines or other inflammatory mediators), and pulmonary infections (as reported by the investigators).

We calculated a pooled estimate of risk ratio (RR) in the individual studies using a random effect model according to Mantel and Haenszel and graphically represented these results using forest plot graphs. Standardized mean difference (SMD), which consists of the difference in means divided by the SD, was used to evaluate the differences in the continuous variables studied across the different situations. Homogeneity assumption was checked and heterogeneity was measured by the  $I^2$  as described before.<sup>9</sup> All analyses were conducted with Review Manager v.5.1.1 and two-sided P-values < 0.05 were considered significant.

## Results

The initial search yielded 1250 articles, 271 on preclinical studies and 979 on clinical studies.

### *Preclinical studies of ventilation in animals without lung injury*

The initial search on preclinical studies yielded 271 articles. After evaluation of abstracts, 230 were excluded because they did not meet the inclusion criteria. After full-text review, 16 articles were excluded because no data on outcomes of interest were described. Two classical articles were excluded because the exact size of tidal volume was not reported.<sup>12,13</sup> Finally, 25 articles were selected for the systematic analysis of the effect of tidal volume size (Figure 1);<sup>14-38</sup> in 19 studies ventilation with lower tidal volumes was compared with ventilation with higher tidal volumes at similar PEEP levels<sup>14-31</sup> (Table 1), and in seven studies ventilation with lower tidal volumes at a higher PEEP level was compared with ventilation with higher tidal volumes without use of PEEP<sup>32-38</sup> (Table 2).

The majority of selected articles reported on preclinical studies in small rodents (e.g., rats and mice). Tidal volume size under the conception of 'lower' tidal volumes varied from 5 ml/kg to as high as 25 ml/kg. Notably, there was a clear trend of tidal volumes becoming

lower over the last decade, both in the 'lower' tidal volume arm and in the 'higher' tidal volume arm.

Ventilation with lower tidal volumes was associated with a decrease in airway pressure,<sup>15,17-19,22,24,26-39</sup> and alveolar strain.<sup>28</sup> Compared with ventilation with higher tidal volumes, ventilation with lower tidal volumes was associated with less inflammation,<sup>15,17,20,21,23,25-27,31</sup> less lung edema or capillary leakage,<sup>13,14,17,18,21,27,31</sup> and less lung injury.<sup>13,15,17,18,20-23,25,26,29,31</sup> Similar results came from studies that compared ventilation with lower tidal volumes at a higher PEEP level with ventilation with higher tidal volumes without PEEP. Compared with ventilation with higher tidal volumes without PEEP, ventilation with lower tidal volumes with higher PEEP levels was associated with less inflammation,<sup>32-37</sup> less lung edema,<sup>33,36</sup> and less lung injury.<sup>32-37</sup>

#### *Clinical trials of ventilation in ICU patients*

The initial search on clinical trials yielded 979 articles. After evaluation of abstracts, 647 were excluded because they did not meet the inclusion criteria. After full-text review, 34 articles were excluded because no data on outcome of interest were described, and 21 articles were excluded because they reported on trials in patients receiving ventilation under general anesthesia for surgery. Finally, six articles were included in the analysis (Figure 1 and Table 3).<sup>8,39-43</sup>

Tidal volume size under the conception of 'lower' tidal volumes varied from 5 to 9 ml/kg PBW. Compared with ventilation with higher tidal volumes, ventilation with lower tidal volumes was associated with less development of ARDS,<sup>8,39,40,42</sup> lower mortality,<sup>42</sup> shorter duration of ventilation,<sup>39,42</sup> less inflammation<sup>8,43</sup> and less pulmonary infection.<sup>39</sup>

#### *Meta-analysis of clinical trials of ventilation in ICU patients*

Thirty-one of 305 patients (10%) ventilated with lower tidal volume and 102 of 386 patients (26%) ventilated with higher tidal volumes developed ARDS during follow-up [RR, 0.42; 95% confidence interval (CI), 0.28 – 0.63] and the analysis displays no sign of heterogeneity ( $I^2 = 15\%$ ) (Figure 2). Mortality was the same in patients receiving ventilation with lower tidal volumes (RR, 0.72; 95% CI, 0.41–1.26) but this analysis showed moderate heterogeneity ( $I^2$

= 60%). The effect of use of lower tidal volumes in the development of pulmonary infection was evaluated only in one study (Figure 2). Duration of the ventilation with lower tidal volumes was the same as with ventilation with higher tidal volumes (SMD, 0.39; 95% CI, – 0.81 to 1.58).

## Discussion

Although the size of tidal volumes used in ventilation has progressively decreased over recent years, predominantly in patients with ARDS,<sup>44</sup> tidal volumes remain more than 6 ml/kg in the general ICU population.<sup>45,46</sup> The main finding of this systematic review is a clear association between tidal volume size and lung injury in uninjured lungs, both in preclinical studies in animals without lung injury and in clinical trials in ICU patients without ARDS.

The results of this investigation expand our knowledge on the potential harmful effects of ventilation. The findings are clearly in line with results from previous investigations in animals and patients. First, the deleterious effects of ventilation with higher tidal volumes in preclinical studies in animals without lung injury reflect results from preceding experiments of ventilation in animals that were challenged with insults causing lung injury before initiation of ventilation.<sup>47</sup> Notably, in these studies increasing lung injury was, in part, dependent on the size of tidal volumes used in ventilation. Second, the association between higher tidal volumes and development of lung injury in the clinical trials in ICU patients without ARDS are in line with findings of a previous systematic review and meta-analysis of clinical trials of ventilation during general anesthesia for surgery.<sup>9,10</sup> Finally, although harm from ventilation seems less extensive in ICU patients without ARDS compared with ICU patients with ARDS,<sup>2</sup> the effects of ventilation with 'higher' tidal volumes go in the same direction. From this, we conclude that mechanical ventilation per se has the potential to cause lung injury.

Several explanations for the benefit of ventilation with lower tidal volumes have been suggested in the literature, all associated with altered alveolar instability and tissue deformation by positive pressure ventilation. Ventilation with lower tidal volume causes less mechanical stress on the alveolar membrane, as it prevents alveolar over-distention<sup>47</sup> and

improves alveolar stability.<sup>48</sup> The latter could, at least in part, be the result of prevention of loss of surfactant with use of lower tidal volumes.<sup>49</sup> Notably, in 1963 Tenney *et al.*<sup>50</sup> showed that for all species of animals the normal tidal volume is approximately 6.3 ml/kg, suggesting that anything above this is unnecessary. This could serve as another argument for using lower tidal volumes, or 'normal tidal volumes', in all ventilated ICU patients.

One important criticism of most preclinical studies of ventilation in animals is the fact that duration of ventilation is short, sometimes even less than 2 h. The same is true for the studies identified in this review. One could argue that the used models better reflect the clinical scenario of patients who require ventilation only for a short time, thus those under general anesthesia for surgery.<sup>34</sup> Ideally, we would use models of ventilation that last longer, preferably days, to mimic the clinical scenario of ICU patients, who usually need ventilation for days. Such models, however, are nonexistent, especially in smaller animals. Markedly, in one preclinical study of animals with healthy lungs identified by the search, mice received ventilation with higher or lower tidal volumes for up to 12 h, compared with ventilation for 6h.<sup>34</sup> This study clearly showed that VILI was dependent on not only tidal volume size, but also duration of ventilation. This could suggest that, compared with patients receiving ventilation under general anesthesia in the operation room, harmful effects could even be more extensive in ICU patients.

Despite the positive result found in the metaanalysis, some limitations in this design of study need to be addressed. Meta-analyses are subject to publication bias, which may exaggerate the study conclusion. Also, only one randomized controlled trial was included in our meta-analysis and most of the results came from observational studies, which weakens the analysis.

It is suggested that any beneficial effect of ventilation with lower tidal volume could be offset by an increased need for sedation and maybe even muscle paralysis with this strategy.<sup>51</sup> Increased use of sedatives and muscle relaxants could increase the incidence of ICU delirium and ICU acquired weakness, and both conditions have the potential to lengthen duration of ventilation and stay in ICU. Furthermore, it is argued that use of lower tidal

volumes is not always possible with spontaneous modes of ventilation, which are most frequently used in ICU patients without ARDS. Consequently, the ICU community calls for more evidence for the alleged beneficial effects and feasibility of ventilation with lower tidal volumes, before extending this strategy to all ICU patients without ARDS.

### **Conclusion**

Preclinical studies of ventilation in animals without lung injury and clinical trials of patients without ARDS show a clear association between ventilation with higher tidal volumes and pulmonary inflammation and injury, and development of ARDS, respectively. Randomized controlled trial evidence is needed to support use of lower tidal volumes with ventilation in all patients without ARDS.

### **Funding**

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**Key points**

- Ventilation-induced inflammation and injury are attenuated with use of lower tidal volumes.
- Ventilation with lower tidal volume decreases the incidence of ARDS in patients who did not suffer from ARDS on admission to the ICU.
- Well-powered randomized controlled trial evidence is needed to confirm the benefits of protective ventilation with lower tidal volumes in patients without ARDS.

**Table 1 – Experimental studies evaluating the effects of ventilation with lower tidal volumes compared to higher tidal volumes in animals without lung injury**

Author [ref]	Year	Animal	Tidal volume size (ml/kg)		PEEP level (cmH <sub>2</sub> O)		Effect of ventilation with lower tidal volumes			
			Lower tidal volume	Higher tidal volume	Lower tidal volume	Higher tidal volume	Peak pressures	Inflammatory mediators	Injury by histopathology	Lung weight
Carlton <i>et al.</i> [14]	1990	Lamb	10.0	48.0	NR	NR	↔	NR	↓	↓
Adkins <i>et al.</i> [15]	1991	Rabbit	20.0	30.0	NR	NR	↔	NR	NR	↓
Caruso <i>et al.</i> [16]	2003	Rat	6.0	24.0	0.0	0.0	↔	↔	NR	NR
Copland <i>et al.</i> [17]	2004	Rat	25.0	40.0	0.0	0.0	↓	↓	↓	↓
Su <i>et al.</i> [18]	2004	Sheep	6.0	12.0	10.0	10.0	↓	NR	↓	↓
Myrianthefs <i>et al.</i> [19]	2006	Swine	10.0	40.0	10.0	10.0	↓	↑	NR	NR
Syrkina <i>et al.</i> [20]	2008	Rat	7.0	20.0	0.0	0.0	NR	↓	↓	NR
Wolthuis <i>et al.</i> [21]	2009	Mice	7.5	15.0	2.0	2.0	NR	↓	↓	↓
Kobr <i>et al.</i> [22]	2010	Piglet	7.0	12.0	5.0	5.0	↓	NR	↓	NR
Hauber <i>et al.</i> [23]	2010	Mice	5.0	10.0	2.0	2.0	NR	↓	↓	NR
Hong <i>et al.</i> [24]	2010	Pig	6.0	15.0	3.0	3.0	↓	↔	↑	NR
Reiss <i>et al.</i> [25]	2011	Mice	8.0	16.0	2.0	2.0	NR	↓	↓	NR
Villar <i>et al.</i> [26]	2011	Mice	6.0	20.0	0.0	0.0	↓	↓	↓	NR
Koshy <i>et al.</i> [27]	2011	Pig	6.0	12.0	5.0	5.0	↓	↓	NR	↓
Kozian <i>et al.</i> [28]	2011	Piglet	5.0	10.0	5.0	5.0	↓	NR	NR	NR
Aikawa <i>et al.</i> [29]	2011	Mice	7.0	10.0	10.0	10.0	↓	NR	↓	NR
Oura <i>et al.</i> [30]	2012	Dog	6.0	15.0	0.0	0.0	↓	NR	NR	NR
Kuipers <i>et al.</i> [31]	2012	Mice	7.5	15.0	2.0	2.0	NR	↓	↓	↓

PEEP: positive end-expiratory pressure

NR: not reported

**Table 2 – Experimental studies evaluating the effects of ventilation with lower tidal volumes and higher positive end-expiratory (PEEP) levels compared to higher tidal volumes and lower PEEP levels in animals without lung injury**

Author [ref]	Year	Animal	Tidal volume size (ml/kg)		PEEP level (cmH <sub>2</sub> O)		Effect of ventilation with lower tidal volumes			
			Lower tidal volume	Higher tidal volume	Lower tidal volume	Higher tidal volume	Peak pressures	Inflammatory mediators	Injury by histopathology	Lung weight
Wilson <i>et al.</i> [32]	2003	Rat	9.0	34.0	3.0	0.0	↓	↓	↓	NR
Ota <i>et al.</i> [33]	2007	Rat	6.0	24.0	3.0	0.0	↓	↓	↓	↓
Fanelli <i>et al.</i> [34]	2009	Mice	6.0	20.0	8.0	0.0	↓	↓	↓	NR
Theroux <i>et al.</i> [35]	2010	Piglet	5.0	10.0	5.0	0.0	↓	↓	↓	NR
Hegeman <i>et al.</i> [36]	2013	Rat	7.0	15.0	3.0	0.0	↓	↓	↓	↓
Vobruba <i>et al.</i> [37]	2013	Pig	7.0	15.0	5.0	0.0	NR	↓	↓	NR
Menendez <i>et al.</i> [38]	2013	Rat	9.0	25.0	5.0	0.0	↓	NR	NR	NR

NR: not reported

**Table 3 – Studies evaluating mechanical ventilation in the ICU patients without acute respiratory distress syndrome**

Author	Year	Tidal volume (ml/kg)		Effect of low tidal volume			
		Low tidal volume	High tidal volume	Duration mechanical ventilation	Mortality	Inflammatory markers	Development of ARDS
Lee <i>et al.</i> [39]	1990	6.0	12.0	↓	↔	NR	↓
Gajic <i>et al.</i> [40]	2004	9.0	12.0	NR	↔	NR	↓
Wolthuis <i>et al.</i> [41]	2007	8.0	10.0	↔	↔	NR	NR
Yilmaz <i>et al.</i> [42]	2007	8.0	11.0	↓	↓	NR	↓
Determann <i>et al.</i> [8]	2010	6.0	10.0	↔	↔	↓	↓
Pinheiro de Oliveira <i>et al.</i> [43]	2010	5.0	12.0	↔	↔	↓	NR

ARDS: acute respiratory distress syndrome

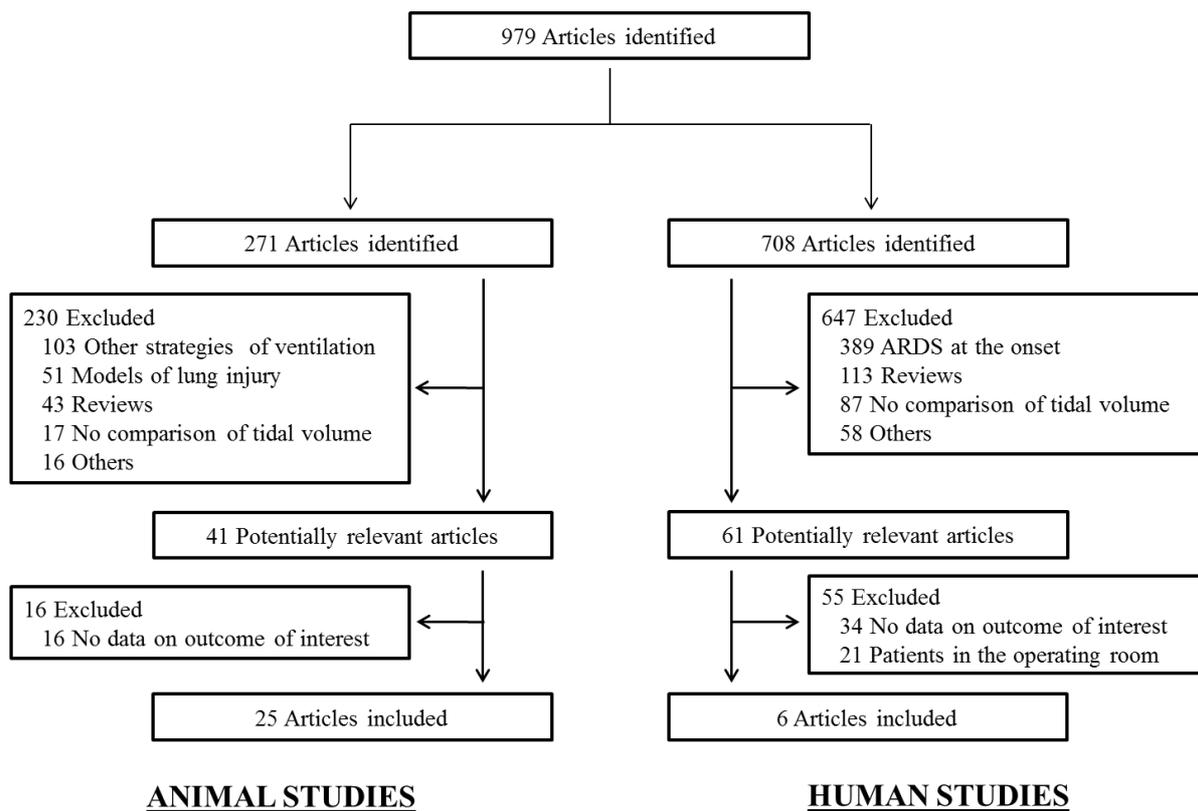
NR: not reported

### **Figure Legends**

Figure 1 – Literature search strategy

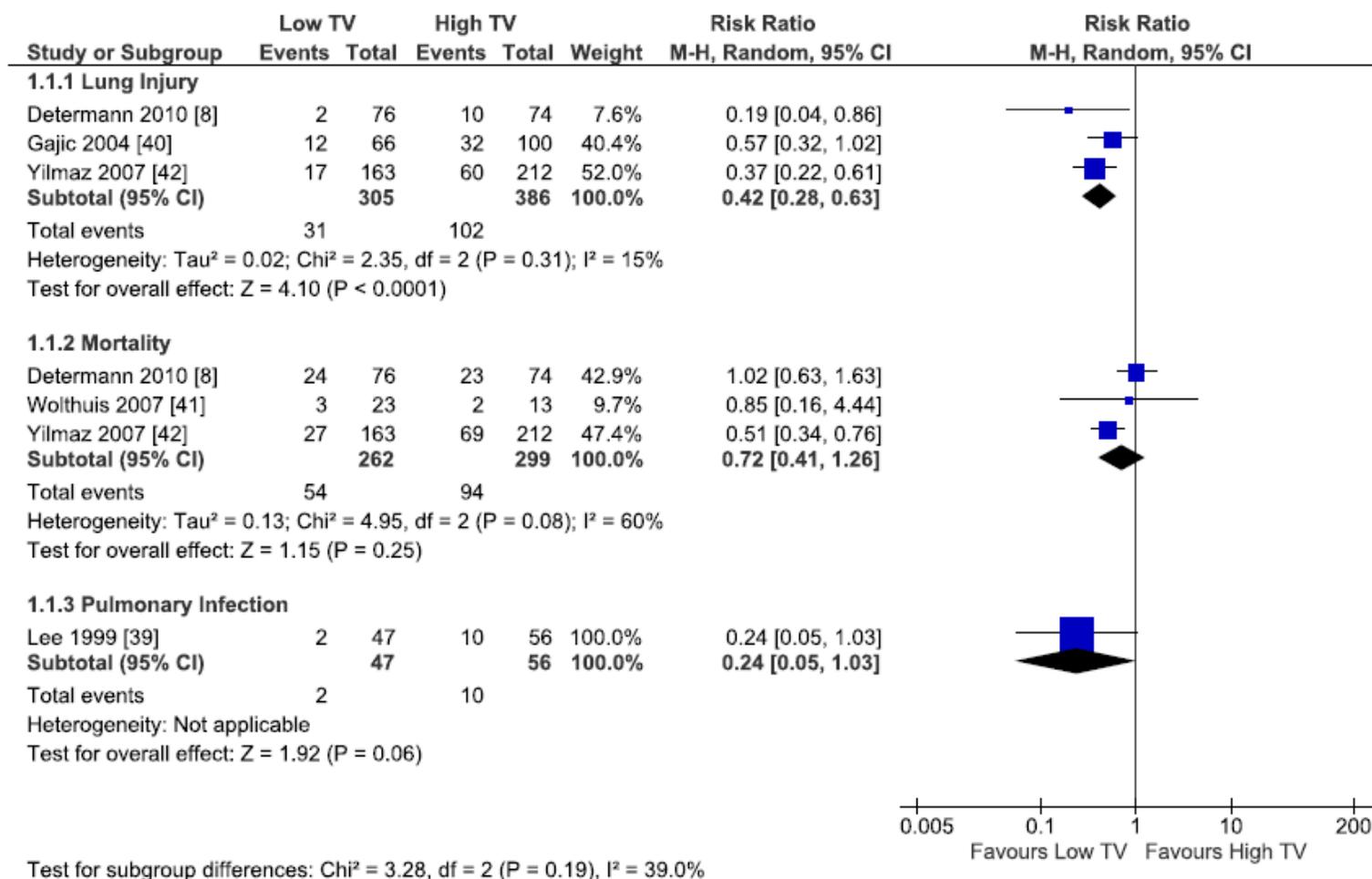
Figure 2 – Forest plot showing the effects of ventilation with lower tidal volumes in ICU patients without acute respiratory distress syndrome (ARDS) under ventilation

**Figure 1 – Literature search strategy**



ARDS, acute respiratory distress syndrome

**Figure 2 – Forest plot showing the effects of ventilation with lower tidal volumes in ICU patients without acute respiratory distress syndrome (ARDS) under ventilation**



A pooled estimate of risk ratio (RR) was calculated in the individual clinical trials of ICU patients without ARDS using a random-effects model according to Mantel and Haenszel. The size of the data markers indicates the weight of the study in the final analyses. CI, confidence interval; TV, tidal volume.

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