

# BMJ Open Optimal plateau pressure for patients with acute respiratory distress syndrome: a protocol for a systematic review and meta-analysis with meta-regression

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## ABSTRACT

**Introduction** Lower tidal volume ventilation in patients with acute respiratory distress syndrome (ARDS) is a strategy to reduce the plateau pressure and driving pressure to limit ventilator-induced lung injury (VILI). Several randomised controlled trials (RCTs) and meta-analyses showed that limiting both the plateau pressure and the tidal volume decreased mortality, but the optimal plateau pressure to demonstrate a benefit is uncertain. The aim of this systematic review is to investigate the optimal upper limit of plateau pressure in patients with ARDS to prevent VILI and improve clinical outcomes using meta-analysis with and without meta-regression.

**Methods and analysis** RCTs comparing two mechanical ventilation strategies will be included, with lower plateau pressure and with higher plateau pressure, among patients with ARDS and acute lung injury. Data sources include MEDLINE via the NCBI Entrez system, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and Ichushi, a database of papers in Japanese. Two of three physicians will independently screen trials obtained by search for eligibility, and extract data from included studies onto standardised data recording forms. For each included trial, the risk of bias and the quality of evidence will be evaluated using the Grading of Recommendation Assessment Development and Evaluation system.

**Ethics and dissemination** This study does not require ethical approval. The results of this systematic review and meta-analysis with and without meta-regression will be disseminated through conference presentation and publication in a peer-reviewed journal.

**Trial registration number** CRD42016041924

## INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a common life-threatening disorder in critically ill patients with 30%–60% mortality.<sup>1–3</sup> ARDS is usually accompanied by short-term and long-term morbidities including prolonged stay in the intensive care unit, prolonged ventilator dependence, various

## Strengths and limitations of this study

- ▶ One strength of this study is that it is a systematic review with meta-regression analysis comparing different plateau pressures to investigate the upper limit of plateau pressure for patients with acute respiratory distress syndrome undergoing mechanical ventilation.
- ▶ One limitation of the study is the paucity of available data regarding the transpulmonary pressure although it is also important to compare the transpulmonary pressure in addition to the plateau pressure. We have to wait for future available studies.
- ▶ This is a protocol article. The results of the subsequent systematic review and meta-analysis with meta-regression analysis will be prepared separately.

neuropsychological impairments (eg, depression, cognitive decline) and decreased quality of life.<sup>2,4,5</sup>

The most critical factor associated with the high mortality in patients with ARDS is ventilator-induced lung injury (VILI)<sup>6</sup> although VILI can also develop in patients with non-injured lung.<sup>7</sup> Patients with ARDS and low lung compliance receiving mechanical ventilation (MV) may develop VILI, including regional alveolar overdistension, repetitive cycling alveolar collapse with shear stress (atelectrauma) aggravated by a high concentration of inspired oxygen.<sup>8–11</sup> VILI can lead to an extended time needed for liberation from MV and an increase in mortality.

For the purpose of minimising VILI, a substantial number of ventilator strategies have been proposed.<sup>12–19</sup> Lower tidal volume (6 mL/kg per predicted body weight) ventilation is a strategy to reduce plateau pressure



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and driving pressure, roughly reflecting the level of alveolar overdistension.<sup>14</sup> Several randomised controlled trials (RCTs) and meta-analyses have shown a beneficial effect of pressure and volume-limited ventilation strategies on clinical outcomes in patients with ARDS.<sup>14 15 20–27</sup> In the Scandinavian clinical practice guideline 2014,<sup>21</sup> developed with a Cochrane systematic review,<sup>20</sup> it is strongly recommended that airway pressure and tidal volume should be limited. In the Surviving Sepsis Campaign Guideline 2012,<sup>28</sup> it is recommended that plateau pressure should be measured and maintained below 30 cmH<sub>2</sub>O during the time of passive pulmonary expansion. However, Villar *et al*<sup>19</sup> have recently reported in an observational study that a plateau pressure above 26 cmH<sub>2</sub>O is harmful, which suggests that appropriate plateau pressure still remains to be investigated.

However, the Cochrane review<sup>20</sup> was a comparison between two lung ventilation strategies, protective and non-protective, not a comparison of different cut-off limits of plateau pressures. All RCTs included in the meta-analysis<sup>16</sup> performed a comparison of higher and lower levels of the upper limits of plateau pressures, but no studies compared various levels of plateau pressures. Also, interactions between the time course and changes in plateau pressure were not considered in the meta-analysis.<sup>16</sup> Furthermore, the relationship between the plateau pressure and mortality in ARDS may not be linear,<sup>29</sup> it may be difficult to investigate the optimal upper limit of plateau pressure by a simple comparison of two different plateau pressures. Therefore, to investigate the optimal upper limit of plateau pressure during the course of ARDS, a simple meta-analysis of RCTs seems to be insufficient. Stratification by the upper limit of plateau pressure and by the day on ventilators along with regression analysis using a meta-regression analysis may be effective.

## OBJECTIVE

The objective of this systematic review is to investigate the optimal limit of plateau pressure on a different day on ventilators to improve clinical outcomes associated with VILI in patients with ARDS.

## METHODS AND ANALYSES

This systematic review is designed following the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statements (see online supplementary material).<sup>30</sup> The logistics and reporting of this protocol will be in compliance with the PRISMA-P. This protocol is registered with PROSPERO prospective register of systematic reviewers (registration number: CRD42016041924).

## STUDY ELIGIBILITY

### Type of studies

We will include only published RCTs, either full scale or as pilot studies.

### Type of participants

The study will include adults with ARDS or acute lung injury (ALI) from any cause, as defined by the North-American-European Consensus Conference on ARDS, aged 18 years or older, undergoing MV.<sup>31</sup>

Type of interventions and comparators: We will include RCTs which compared two different MV strategies, with a lower plateau pressure and a higher plateau pressure, among patients with ARDS and ALI. We will conduct subgroup analyses of the plateau pressures stratified by the day of measuring plateau pressure in addition to a primary meta-analysis which does not consider ventilator day.

### Type of outcomes

The following outcome measures will be evaluated: the primary outcome is short-time mortality ((1) at the end of the follow-up period for each trial, (2) at day 28, and (3) at the hospital discharge), and secondary outcomes are the number of ventilator-free days up to 28 days and barotrauma during hospitalisation.

## INFORMATION SOURCES

We searched MEDLINE via the NCBI Entrez system, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and Ichushi, a database including papers in Japanese.

## SEARCH STRATEGY

We used the search keywords 'Mechanical ventilation' AND 'ARDS', 'adult respiratory distress syndrome', 'ALI' or 'acute lung injury' AND 'tidal volume', 'pressure limited' or 'volume limited'. We also performed a MeSH term search using the following terms: 'respiratory distress syndrome, adult', or 'acute lung injury' AND 'tidal volume', or 'respiration, artificial'. Searches were performed in May or June 2016. The detailed strategy and details of the dates performed are shown in table 1.

### Study records and data management

The literature search results from each database will be extracted into Microsoft Excel files and duplicates will be removed by being sorted alphabetically based on author. The results of all processes (first screening and second screening) are recorded to the same data file. All full-text files will be managed with EndNote (X7) bibliographic software (Thompson Reuters, Philadelphia, Pennsylvania, USA). A meta-analysis will be conducted with the Review Manager (RevMan) software V.5.3.5. All data will be managed by the primary investigator HY.

### Selection process

Two of three physicians (HY, TN, TK) will screen titles and abstracts during the first screening and the full text during the second screening for relevant studies, and will independently extract data from included studies into standardised data forms. Disagreements are resolved by

**Table 1** Search strategy

Number	Searched for
<b>1. MEDLINE (performed on 17 May 2016)</b>	
Component 1. Included patients	
#1	Respiratory distress syndrome, adult[MH] OR shock lung OR acute respiratory distress syndrome OR adult respiratory distress syndrome
#2	Acute lung injury[MH] OR Acute lung injury OR Acute lung injuries
#3	ARDS OR ALI
#4	#1 OR #2 OR #3
Component 2. Ventilator strategies	
#5	Tidal volume[MH] OR Tidal volumes OR Tidal volume
#6	Respiration, Artificial[MH] OR Artificial respiration OR Mechanical ventilation OR Mechanical ventilations
#7	pressure* limited* OR 'volume limited' OR LPVS OR lung protective ventilat*
#8	#5 OR #6 OR #7
#9	#4 AND #8
Component 3. Study design and language limit	
#10	Clinical trial[pt] OR trial[ti] OR randomised controlled trial[pt] OR (controlled clinical trial[pt] OR randomised[tiab]) OR placebo[tiab] OR clinical trials as topic[MH] OR randomly[tiab]
#11	Animals[MH] NOT (Animals[MH] AND Humans[MH])
#12	#10 NOT #11
#13	#9 AND #12
<b>2. CENTRAL (performed on 17 May 2016)</b>	
Component 1. Included patients	
#1	MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees
#2	acute lung injury
#3	Adult Respiratory Distress Syndrome
#4	Acute Respiratory Distress Syndrome
#5	ARDS or ALI
#6	#1 or #2 or #3 or #4 or #5
Component 2. Ventilator strategies	
#7	MeSH descriptor: [Tidal Volume] explode all trees
#8	artificial near ventilation
#9	tidal volume
#10	protective near ventilation
#11	pressure-limited
#12	LPVS
#13	#7 or #8 or #9 or #10 or #11 or #12
#14	#6 and #13
<b>3. EMBASE (performed on 20 June 2016)</b>	
Component 1. Included patients	
#1	EMB.EXACT('adult respiratory distress syndrome') OR ('shock lung' OR 'human ARDS' OR 'acute respiratory distress syndrome' OR 'adult respiratory distress syndrome')

Continued

**Table 1** Continued

Number	Searched for
#2	EMB.EXACT('acute lung injury') OR ('acute lung injuries' OR 'acute lung injury')
#3	TI,AB(ARDS) OR TI,AB(ALI)
#4	#1 OR #2 OR #3
Component 2. Ventilator strategies	
#5	EMB.EXACT.EXPLODE('tidal volume') OR ('tidal volumes' OR 'tidal volume')
#6	EMB.EXACT.EXPLODE('artificial ventilation') OR ('artificial respiration' OR 'mechanical ventilation' OR 'mechanical ventilations')
#7	pressure-limited OR pressure* limited* OR 'volume limited' OR LPVS OR lung protective ventilat*
#8	#5 OR #6 OR #7
#9	#4 AND #8
Component 3. Study design	
#10	(EMB.EXACT('controlled clinical trial') OR EMB.EXACT.EXPLODE('clinical trial (topic)') OR EMB.EXACT('randomized controlled trial')) OR (TI,AB(randomized) OR TI,AB(randomly) OR TI(trial) OR TI,AB(placebo))
#11	#9 AND #10
Component 4. Language limit	
#12	#11 NOT (ANIMAL(YES) NOT HUMAN(YES))
#13	#12 AND PD(>=20150401)
4. Ichushi (performed on 17 May 2016)	
Component 1. Included patients	
#1	呼吸窮迫症候群-急性/TH or ARDS/AL
#2	急性肺損傷/TH or 急性肺損傷/AL
#3	#1 or #2
Component 2. Ventilator strategies	
#4	一回換気量/TH or 一回換気量/AL
#5	人工呼吸/TH or 人工呼吸/AL or レスピレータ装/AL or 機械的換気/AL or 人工換気量/AL or 人工呼吸管理/AL or 人工呼吸法/AL or 人工呼吸療法/AL or 調節呼吸/AL
#6	人工呼吸器/TH or 人工呼吸器/AL or ベンチレータ/AL or ベンチレーター/AL or レスピレータ/AL or レスピレーター/AL or 機械的ベンチレータ/AL or 機械的ベンチレーター/AL or 肺ベンチレータ/AL or 肺ベンチレーター/AL
#7	#4 or #5 or #6
#8	#3 and #7

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; LPVS, lung protective ventilation strategy.

discussion with one of the three physicians who did not screen the study. EN supervises the process of systematic review. TA supervises the process of analysis as a biostatistician. MS, TT and SH are consultants on clinically relevant issues.

### Data collection process

After extracting studies for meta-analyses during the second screening, data will be extracted from each

study by three reviewers (HY, TN, TK) using two tools<sup>1</sup>: the Cochrane Data Collection Form (RCTs only)<sup>32</sup> and<sup>2</sup> Review Manager (RevMan) software V.5.3.5.<sup>33</sup>

### Risk of bias in individual studies

The risk of bias in each included study will be evaluated with the Cochrane Risk of Bias Assessment tool<sup>34 35</sup> with respect to the following seven domains: (1) random sequence generation, (2) allocation concealment, (3)



blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, (6) selective outcome reporting and (7) other sources of bias. Each bias will be graded as either 'low-risk,' 'unclear-risk' or 'high-risk.' Two of three reviewers (HY, TN, TK) will separately grade the bias of each study, and any disagreement will be resolved by a decision from the remaining reviewer.

### Data synthesis

Forest plots will be used for the meta-analysis, and effect size will be expressed as relative risk with 95% CI for categorical data and as weighted mean differences with 95% CI for continuous data. Outcome measures will be pooled using a random effect model to take into account study-specific effects in measures. For all analyses, a two-sided  $p$  value  $<0.05$  is considered significant. In case of missing data, we will attempt to contact the authors of the study for additional data. If a reply from the authors is not obtained, we will classify it as missing data.

Meta-regression analysis will be conducted to evaluate the association between outcome measures and covariates, and to determine the cut-off of the plateau pressure affecting the outcomes adjusted with covariates, such as the different kinds of ventilation methods, the day of plateau pressure measurement and severity of ARDS for the evaluation. Meta-regression analysis will be performed with R V.3.3.2.

### Assessment of heterogeneity

Study heterogeneity between trials for each outcome will be assessed with an  $I^2$  statistic for quantifying inconsistency (RevMan).  $I^2$  values of  $<25\%$ ,  $25\%$ – $50\%$  and  $>50\%$  represent small, medium and large amounts of heterogeneity, respectively.<sup>36</sup> Subgroup analysis, meta-regression analysis and sensitivity analysis will be performed for evaluating possible sources of heterogeneity when sufficient data are available.

### Assessment of reporting bias

A funnel plot will be used to investigate the possibility of publication bias if  $\geq 10$  studies are available (RevMan).<sup>37</sup> To test for funnel plot asymmetry, we will use the Egger test<sup>38</sup> for continuous outcomes and the arcsine test<sup>39</sup> for dichotomous outcomes.

### Subgroup analysis and sensitivity analysis

Subgroup analysis is planned based on the main factors that may cause heterogeneity, which are the levels of plateau pressure. Subgroup analysis will also be performed for different timing of plateau pressure measured during MV. We are also planning subgroup analyses after stratification according to ventilator strategies and modes.

For sensitivity analysis, we will first exclude all studies that are assessed as having a high risk of bias. High risk of bias in each study will be determined when the quality of evidence of each study will be assessed as 'low' or 'very low.' The remaining studies will be used for sensitivity analysis.

### Assessment of confidence in cumulative evidence

We will evaluate the quality of evidence for these studies using the Grading of Recommendation Assessment Development and Evaluation (GRADE) system.<sup>40</sup> The quality of evidence will be decreased by any one of the following limitations: risk of bias, imprecision, inconsistency, indirectness and publication bias. Based on this assessment, the quality of evidence for each outcome will be assessed as 'high', 'moderate', 'low' or 'very low' (GRADEpro, McMaster University, 2014). Two of three reviewers (HY, TN, TK) will separately grade the quality of evidence of each study, and any disagreement will be resolved by a decision of the remaining reviewer.

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**Competing interests** None declared.

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