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Optimal plateau pressure for patients with acute respiratory distress syndrome: A protocol for a systematic review and meta-analysis.

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	acute respiratory distress syndrome, ARDS, mechanical ventilation, plateau pressure

Title

Optimal plateau pressure for patients with acute respiratory distress syndrome: A protocol for a systematic review and meta-analysis.

Registration

Protocol and registration: We registered this protocol to this journal and PROSPERO (registration number is: CRD42016041924).

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Key words: acute respiratory distress syndrome, ARDS, mechanical ventilation, plateau pressure

Abstract

Introduction: Lower tidal volume ventilation in patients with acute respiratory distress syndrome (ARDS) and low lung compliance is one strategy to reduce the plateau pressure in order to prevent ventilator induced lung injury (VILI). Several randomized 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.

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 standardized 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 (GRADE) system.

Ethics and dissemination: This systematic review and meta-analysis does not require ethical approval. The results of this systematic review and meta-analysis will be disseminated through conference presentation and publication in a peer-reviewed journal.

Trial registration number: CRD42016041924

Strengths and limitations of this study

1. This is the first systematic review comparing different plateau pressures and investigating the upper limit of plateau pressure for patients with ARDS undergoing mechanical ventilation to prevent ventilator induced lung injury.
2. This systematic review will only compare clinical outcomes among different plateau pressures, but it will also be important to compare the trans-pulmonary pressure using different mechanical ventilation strategies.
3. This is a protocol article. The results of the subsequent systematic review and

meta-analysis will be prepared separately.

Introduction

Acute respiratory distress syndrome (ARDS) is a common life-threatening disorder in critically ill patients with 30-60% mortality (1-3). ARDS is usually accompanied by short- and long-term morbidities including prolonged stay in the intensive care unit, prolonged ventilator dependence, various neuropsychological impairments (e.g. depression, cognitive decline) and decreased quality of life (2, 4, 5).

The most critical factor associated with the high mortality in patients with ARDS is ventilator induced lung injury (VILI)(6). Patients with ARDS and low lung compliance receiving mechanical ventilation may develop VILI, including regional alveolar over-distension, repetitive cycling alveolar collapse with shear stress (atelectrauma) aggravated by a high concentration of inspired oxygen, (7-10). VILI can lead to not only an extended time needed for liberation from mechanical ventilation, but also an increase in mortality.

For the purpose of minimizing VILI, a substantial number of ventilator strategies have been proposed (11-15). Lower tidal volume (6 ml/kg per predicted body weight) ventilation is a strategy to reduce plateau pressure, the airway pressure during

the end-expiratory pause, roughly reflecting the level of alveolar over-distension (13). Several randomized 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 (13, 14, 16-23). In the Scandinavian clinical practice guideline 2014(17), created using a Cochrane systematic review (16), it is strongly recommended that airway pressure and tidal volume should be limited. In the Surviving Sepsis Campaign Guideline 2012 (24), it is recommended that plateau pressure should be measured and maintained below 30cmH_2O during the time of passive pulmonary expansion. However, these previously published studies and guidelines failed to clearly show an optimal upper limit for plateau pressure. A recent meta-analysis comparing two different ventilator strategies conducted in a Cochrane review (16) was a comparison between two lung protective ventilator strategies, not a comparison of different cutoff limits of plateau pressures.

Therefore, we will conduct a meta-analysis and systematic review to investigate the optimal plateau pressure for patients with ARDS.

Objective

The objective of this systematic review is to investigate the optimal limit of plateau pressure 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 (25). 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 is: 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 (NAECC), age 18years or older, undergoing mechanical ventilation (26).

Type of interventions and comparators: We will include RCTs which compared two different mechanical ventilation strategies, with a lower plateau pressure and a higher plateau pressure, among patients with ARDS and ALI.

Type of outcomes: The following outcome measures will be evaluated: the primary outcome is 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 hospitalization.

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 (Redmond WA USA) 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 standardized data forms.

Disagreements are resolved by 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: (1) the Cochrane Data Collection Form (RCTs only) (27) and (2) Review Manager (RevMan) software V.5.3.5(28).

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 (29, 30) with respect to the following eight domains: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessors, (e) incomplete outcome data, (f) selective outcome reporting and (g) 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% confidence interval [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 because of anticipated significant heterogeneity in included studies. 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.

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 (31). Subgroup analysis and sensitivity analysis will be performed for evaluating possible sources of heterogeneity.

Assessment of reporting bias

A funnel plot will be used to investigate the possibility of publication bias if ≧10 studies are available (RevMan) (32). To test for funnel plot asymmetry, we will use the Egger test (33) for continuous outcomes and the arcsine test (34) 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 mechanical ventilation. 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 (35). 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.

Authors' contributions

HY contributed in the study concept and design, screening for relevant studies, and drafting of the manuscript. TN and TK contributed to the study concept and design, screening for relevant studies. MS contributed to the study concept and design, and critical revision of the manuscript for important intellectual content. AL contributed to critical revision of the manuscript for important intellectual content. EN supervised the process of systematic review. TA supervised the process of analysis as a biostatistician. TT, AL and SH were consultants on clinically relevant issues.

Funding sources/sponsors

None

Conflicts of interest

No one has conflicts of interest in the study.

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Table 1 Search strategy

1. MEDLINE

Performed on 2016/05/17

Number	Searched for
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 randomized controlled trial[pt] OR(controlled clinical trial[pt] OR randomized[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

2. CENTRAL

Performed on 2016/05/17

Number	Searched for
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 tree
#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

2. EMBASE

Performed on 2016/6/20

Number	Searched for
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")
#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)

3. Ichushi

Performed on 2016/05/17

Number	Searched for
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

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	p1	Identify the report as a protocol of a systematic review
Update	-	If the protocol is for an update of a previous systematic review, identify as such
Registration	P1 and p5	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	P2	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	p16	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	-	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	p16	Indicate sources of financial or other support for the review
Sponsor	p16	Provide name for the review funder and/or sponsor
Role of sponsor or funder	p16	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	p7-p8	Describe the rationale for the review in the context of what is already known
Objectives	p9	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	p9	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	p10	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	p10-p11	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	p11	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	p11-p12	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	p12	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	p10	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	p10	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	p12	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	p13	Describe criteria under which study data will be quantitatively synthesised
	p13	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	p14	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	-	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	p13-p14	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	p14-p15	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Secondary Subject Heading:	Evidence based practice, Intensive care
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Key words: acute respiratory distress syndrome, ARDS, mechanical ventilation, plateau pressure

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 randomized 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 standardized 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 (GRADE) 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

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 ARDS undergoing mechanical ventilation.
- One limitation of the study is the paucity of available data regarding the trans-pulmonary pressure although it is also important to compare the trans-pulmonary 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.

Introduction

Acute respiratory distress syndrome (ARDS) is a common life-threatening disorder in critically ill patients with 30-60% mortality (1-3). ARDS is usually accompanied by short- and long-term morbidities including prolonged stay in the intensive care unit, prolonged ventilator dependence, various neuropsychological impairments (e.g. depression, cognitive decline) and decreased quality of life (2, 4, 5).

The most critical factor associated with the high mortality in patients with ARDS is ventilator induced lung injury (VILI)(6) although VILI can also develop in patients with non-injured lung(7). Patients with ARDS and low lung compliance receiving mechanical ventilation (MV) may develop VILI, including regional alveolar over-distension, repetitive cycling alveolar collapse with shear stress (atelectrauma) aggravated by a high concentration of inspired oxygen, (8-11). VILI can lead to not only an extended time needed for liberation from MV, but also an increase in mortality.

For the purpose of minimizing VILI, a substantial number of ventilator strategies have been proposed (12-19). Lower tidal volume (6 ml/kg per predicted body weight) ventilation is a strategy to reduce plateau pressure and driving pressure, roughly reflecting the level of alveolar over-distension (14). Several randomized 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 (14, 15,

20-27). In the Scandinavian clinical practice guideline 2014 (21), developed with a Cochrane systematic review (20), it is strongly recommended that airway pressure and tidal volume should be limited. In the Surviving Sepsis Campaign Guideline 2012 (28), it is recommended that plateau pressure should be measured and maintained below 30cmH_2O during the time of passive pulmonary expansion. However, Villar et al(19) have recently reported in an observational study that a Pplat above 26 cmH_2O is harmful, which suggest that appropriate plateau pressure still remains to be investigated.

However, the Cochrane review (20) was a comparison between two lung ventilation strategies, protective and non-protective, not a comparison of different cutoff limits of plateau pressures. All RCTs included in the meta-analysis (16) 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(16). Furthermore, the relationship between the plateau pressure and mortality in ARDS may not be linear(29), 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 (30). 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 is: 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 (NAECC), age 18years or older, undergoing MV (31).

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 sub-group 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 hospitalization.

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 (Redmond WA USA) 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 standardized data forms. Disagreements are resolved by 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: (1) the Cochrane Data

Collection Form (RCTs only) (32) and (2) Review Manager (RevMan) software V.5.3.5(33).

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 (34, 35) with respect to the following eight domains: (a) random sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessors, (e) incomplete outcome data, (f) selective outcome reporting and (g) 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% confidence interval [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 version 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 (36). 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 ≧10 studies are available (RevMan) (37). To test for funnel plot asymmetry, we will use the Egger test (38) for continuous outcomes and the arcsine test (39) 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 (40). 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.

Authors’ contributions

HY contributed in the study concept and design, screening for relevant studies, and drafting of the manuscript. TN and TK contributed to the study concept and design, screening for relevant studies. MS contributed to the study concept and design, and critical revision of the manuscript for important intellectual content. AKL contributed to critical revision of the manuscript for important intellectual content. EN supervised the process of systematic review. TA supervised the process of analysis as a biostatistician. TT, AKL and SH were consultants on clinically relevant issues.

Funding sources/sponsors

None

Conflicts of interest

No one has conflicts of interest in the study.

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Table 1 Search strategy

1. MEDLINE

Performed on 2016/05/17

Number	Searched for
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 randomized controlled trial[pt] OR(controlled clinical trial[pt] OR randomized[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

2. CENTRAL

Performed on 2016/05/17

Number	Searched for
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 tree
#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

3. EMBASE

Performed on 2016/6/20

Number	Searched for
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")
#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 2016/05/17

Number	Searched for
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

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	p1	Identify the report as a protocol of a systematic review
Update	-	If the protocol is for an update of a previous systematic review, identify as such
Registration	P1 and p5	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	P2	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	p16	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	-	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	p16	Indicate sources of financial or other support for the review
Sponsor	p16	Provide name for the review funder and/or sponsor
Role of sponsor or funder	p16	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	p7-p8	Describe the rationale for the review in the context of what is already known
Objectives	p9	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	p9	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	p10	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	p10-p11	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	p11	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	p11-p12	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	p12	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	p10	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	p10	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	p12	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	p13	Describe criteria under which study data will be quantitatively synthesised
	p13	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	p14	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	-	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	p13-p14	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	p14-p15	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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