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**ADMINISTRATIVE INFORMATION**

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**Review Stage at time of this submission** - Completed but not published.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY2024100115

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 October 2024 and was last updated on 27 October 2024.

**INTRODUCTION**

**Review question / Objective** What are the roles of Mechanosensitive Ion Channels in Ventilation Induced Lung Injury ?

**Condition being studied** Artificial ventilation simulates and supports the breathing, unfortunately, it might simultaneously cause secondary injury, usually called ventilation induced lung injury (VILI), which is particularly obvious in diseased lungs. The reported pathogenetic mechanisms of VILI include volutrauma, atelectrauma, biotrauma, and other doctrines. During artificial ventilation, mechanical force is exerted on the lung. However, how mechanical stimuli are sensed, converted into biological

signals, and cause VILI needs to be elucidated. In recent years, mechanosensitive ion channels (MSICs) have been shown to play an important role in the occurrence of VILI. Animals or pulmonary cell were exposed to mechanical ventilation or mechanical stretch to make VILI model, antagonists ?including gene knockout?or agonists were adopted as the intervention strategy, sham treatments were considered as the control strategy, severity in pathological changes, inflammation, cell death, lung edema and other pathogenesis were considered as the main outcomes. How ever, there was no consensus being reached until now. Therefore, it is necessary to perform a systematic review on the emerging role of MSICs in VILI and their underlying mechanisms reported according to the results from the in vivo, ex vivo and in vitro researches.

## METHODS

**Search strategy** (Mechanosensitive Ion Channel OR Piezo Channel OR TRP channel OR Potassium channel OR sodium channel OR epithelial Na<sup>+</sup> channel) AND (Ventilation Induced Lung Injury OR Ventilator Induced Lung Injury).

**Participant or population** Patients or animals or lung (vascular) cells exposed to injurious mechanical ventilation or mechanical stretch.

**Intervention** Injurious mechanical ventilation or overload mechanical stretch with or without inhibition/trigger strategies of the key signal pathway.

**Comparator** Protective ventilation or Sham.

**Study designs to be included** Any study focused on the role of MSICs in VILI except non original researches, such as guidelines, case reports, thesis, reviews, and editorials.

**Eligibility criteria** (1) Any study focused on the role of MSICs in ventilation induced lung injury independent of animal, cell or tissue; (2) The lung injury model was induced by mechanical ventilation or stretch in vivo, ex vivo or in vitro.

**Information sources** Electronic databases, contact with authors, trial registers, or grey literature.

**Main outcome(s)** changes in inflammation, signal pathway, apoptosis, pyroptosis, oxidative stress.

**Additional outcome(s)** Changes in phosphorylation of key proteins, fibrosis.

**Data management** Records were managed and marked with Endnote Software. Data were managed with specified tables. The main information included the title, author, publication year, participant, intervention/control strategies, main findings (Main pathogenesis, signal pathway).

**Quality assessment / Risk of bias analysis** The Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies 10-item checklist (CAMARADES) is adopted with minor modification to estimate the bias of the included studies, The items are as follows: peer-reviewed publication, control of temperature, random allocation to treatment or control, blinded induction of model, blinded assessment of outcome, use of anesthetic without significant effect on the lung injury, appropriate animal model

or cells, sample size calculation, compliance with animal welfare regulations, and statement of potential conflict of interests. Each item is given one star if the specific study was qualified, otherwise, the star would be deprived; for the item “compliance with animal welfare regulations”, “unclear” is awarded if the ethical review was not mentioned owing to the requirement that all animal experiments should follow the relevant ethics in theory. Two investigators (G.L. and B.D.) independently evaluate the study quality and divergences are well settled through consulting with correspondence author.

**Strategy of data synthesis** For each outcome presented as categorical data or quantitative data, Rate/mean and SD, would be synthesised if it is possible.

**Subgroup analysis** Subgroup will be performed if heterogeneity is significant (P 0.05).

**Sensitivity analysis** Sensitivity is analyzed by excluding individual studies and recalculating the I<sup>2</sup> and odds ratio values to find the source of the heterogeneity.

**Country(ies) involved** China.

**Keywords** Ventilation-induced lung injury, Mechanosensitive ion channels, Mechanical ventilation, Signal pathway.

### Contributions of each author

Author 1 - Gang Liu - perform the electronic searches, analyze the data, and draft the manuscript, plot the figures.

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