Clinical Critical Care

E-ISSN 2774-0048

VOLUME 32 NUMBER 1

JANUARY-DECEMBER 2024

Clinical Critical Care
eISSN 2774-0048

Clinical Critical Care
Volume 32, Article ID e240014, 6 pages
https://doi.org/10.54205/ccc.v32.268588

RESEARCH PROTOCOL

Relationship between strain energy and alveolar overdistension in patients with acute respiratory distress syndrome: The research protocol

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OPEN ACCESS
Citation:
Laikitmongkhon J, Sutherasan Y, Junhasavasdikul D, Gulapa K, Theerawit P. Relationship between strain energy and alveolar overdistension in patients with acute respiratory distress syndrome: The research protocol. Clin Crit Care 2024; 32: e240014.

Received: April 4, 2024
Revised: July 27, 2024
Accepted: August 15, 2024

Data Availability Statement:
The data and code were available upon reasonable request (Pongdhep Theerawit, email address: pongdhep@yahoo.com)

Funding:
The authors declare that there is no funding.

Competing interests:
No potential conflict of interest relevant to this article was reported.

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ABSTRACT:

Background: Energy produced during mechanical ventilation has been established as a contributor to mortality in acute respiratory distress syndrome (ARDS) patients, elucidated through ventilator-induced lung injury (VILI). However, the potential association between strain energy, an engineering-based concept, and the risk of VILI remains unexplored.

Objectives: This study aims to investigate the correlation between strain energy and alveolar overdistension and the relationship between strain energy and single-breath mechanical power (MP) calculated by a simplified formula in patients with ARDS.

Methods: A prospective observational study will be conducted on moderate to severe ARDS patients under sedation and paralysis. We will gradually reduce positive end-expiratory pressure (PEEP) by two cmH_2O every two minutes from 20 to 8 cmH_2O in pressure-controlled ventilation mode. During decremental PEEP titration, patients would be monitored simultaneously for esophageal pressure and electrical impedance tomography (EIT). Data gathered from the mechanical ventilator and EIT during the decrementing PEEP titration were focused on seven PEEP levels: 20, 18, 16, 14, 12, 10, and 8 cmH_2O, providing a dataset of 7 events per patient for analysis. Strain energy and single-breath MP were calculated from ventilator parameters, while EIT provided data on alveolar overdistension.

Hypothesis: We hypothesized that strain energy and single-breath mechanical MP correlate with alveolar overdistension in ARDS patients.

Conclusions: This study aims to assess the correlation between strain energy and alveolar overdistension, as well as the correlation between strain energy and single-breath MP in ARDS patients.

Ethics and dissemination: The study protocol has been approved by the faculty of medicine ethics committee, Ramathibodi Hospital, Mahidol University (COA MURA2023/718).

Trial registration: TCTR20240320001

Keywords: Acute respiratory distress syndrome; Ventilator-induced lung injury; Alveolar overdistension; Mechanical power; Stress; Strain; Strain energy

INTRODUCTION

In the past few decades, concepts and research concerning mechanical ventilation (MV) in line with lung-protective strategies have continuously evolved for patients with acute respiratory distress syndrome (ARDS). It is essential to employ MV strategies that optimize oxygenation and ventilation while preventing ventilator-induced lung injury (VILI), especially in cases of moderate to severe ARDS or when the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) is below 200 mmHg.

To prevent VILI, the MV settings should avoid excessively high pressure and volume. Key parameters for monitoring VILI include airway pressure and lung stress, or transpulmonary pressure (Ptp), which is calculated as airway pressure minus pleural pressure. When monitoring volume, it is crucial to ensure that tidal volume (Vt) and lung strain (volume over functional residual capacity, or FRC) do not lead to airway plateau pressure (Pplat) exceeding 30 cmH_2O and airway driving pressure exceeding 15 cmH_2O, respectively. Additionally, the Ptp or lung stress should not surpass 20-25 cmH_2O, and the lung strain should be limited to 2 [1,2].

As a novel concept, mechanical power (MP) represents the energy delivered by MV to the entire respiratory system (RS) per unit of time. It encompasses the calculation of all factors affecting the energy load on the RS, including airway pressure, Vt, flow rate, and respiratory rate. A high level of MP can contribute to VILI. Subsequent studies have established a direct correlation between MP and mortality in cases of ARDS [3,4].

Gattinoni et al. originally proposed an MP formula based on various parameters measured by MV, using a complex formula [5]. However, recent research has validated simpler formulas for calculating MP that are both reliable and user-friendly. These calculations can be performed at the bedside, offering a more practical approach [6,7]. Alternatively, utilizing main variables such as lung stress, Ptp, and lung strain to calculate the energy generated during breathing by MV yields strain energy [8].

We postulated that the strain energy generated during MV was correlated with alveolar overdistension. An escalation in strain energy likely corresponds to an increase in alveolar overdistension. As no studies have yet explored strain energy, our interest lies in investigating its relationship with alveolar overdistension, particularly among patients with moderate to severe ARDS.

OBJECTIVES

Primary objective

To explore the correlation between strain energy and alveolar overdistension in patients diagnosed with moderate to severe ARDS.

Secondary objective

To explore the correlation between single-breath MP calculated from a simplified equation and alveolar overdistension in patients diagnosed with moderate to severe ARDS.

KEY MESSAGES:

- Strain energy is discussed for the first time in patients with ARDS. The idea is based on strain energy in linear elastic solids, an engineering concept.
- Stress refers to the transpulmonary pressure of the lung, strain refers to the lung volume over the functional residual capacity, and Young's modulus refers to specific lung elastance. The area under a stress-strain curve is strain energy.
- When mechanical ventilation applies transpulmonary pressure to excessive lung strain, alveolar overdistension occurs, leading to ventilation-induced lung injury and, eventually, pneumothorax.

To investigate the relationship between strain energy and single-breath MP calculated from a simplified equation in patients with moderate to severe ARDS.

MATERIALS AND METHODS

Study design

This prospective observational cohort study was conducted from October 2023 to October 2024, focusing on patients with moderate to severe ARDS in the Intensive Care Unit (ICU) at Ramathibodi Hospital. The Institutional Review Board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, approved this study under COA MURA2023/718. Written informed consent will be sought from the patient's next of kin.

Study population

This study will screen for eligible adults (≥18 years old) admitted to the ICU with moderate or severe ARDS based on the Berlin definition [9].

Inclusion criteria

- Patients mechanically ventilated with an esophageal balloon catheter whose primary physicians plan to perform decremental PEEP titration.
- Patients receiving deep sedation and neuromuscular blockade.

Exclusion criteria

- Pregnancy
- On pacemaker
- On intercostal drainage
- Risk for high PEEP: large lung bleb, chronic obstructive lung disease, pneumothorax, pneumomediastinum, profound shock, high dose vasopressor, right-sided heart failure, postcardiac arrest, intracranial hypertension
- Palliative care
- EIT has limitations, particularly for patients with chest or spinal lesions, skin abnormalities, or morbid obesity.

Study protocol

Prior to participating in the research procedures, it is mandatory for all patients to secure consent from their relatives. The patients, while under deep sedation and paralysis, were ventilated in a supine position using Hamilton models G5 or S1. To monitor esophageal pressure, Cooper Surgical Adult set 47-9905 esophageal balloon catheters were individually inserted into the patients and connected to the auxiliary port of the MV. The Baydur occlusion test was employed to confirm proper catheter positioning. Subsequently, a PulmoVista 500 by Dräger EIT belt was affixed to the patients. Continuous recording and exportation of EIT parameters, respiratory mechanics, and esophageal pressure took place from the ventilator for subsequent offline interpretation.

All patients were initially placed on MV using the pressure control ventilation (PCV) mode, with a constant inspiratory pressure of 15 cmH_2O. The inspiratory time was adjusted until zero flow was observed at the end-inspiratory phase (usually 1.2 to 1.5 seconds) to ensure that the corresponding airway pressure closely matched the true Pplat. The PEEP was initially set at 8 cmH_2O, and a respiratory rate of 10-14 breaths per minute was established. Subsequently, we conducted a decremental PEEP titration method, reducing PEEP by 2 cmH_2O every 2 minutes from 20 to 8 cmH_2O.

This protocol closely monitored hemodynamic and respiratory parameters to detect adverse events, including hypotension, arrhythmias, and pneumothorax. In the event of an adverse occurrence, the researcher promptly responds and notifies the attending physician team at the earliest convenience.

Measurement

During the decremental PEEP titration at each PEEP level, the following measurements were conducted: peak inspiratory pressure, PEEP, exhaled Vt, end-inspiratory esophageal pressure, end-expiratory esophageal pressure, and the percentage of alveolar overdistension (%OD). A PEEP analysis tool was employed to determine the %OD at each PEEP level. The calculation of the overdistension percentage from EIT was performed using the formula proposed by Costa et al. [10]

$$Overdistension_{pixel}(\%) = \frac{(Best\ compliance_{pixel} - Current\ compliance_{pixel}) \times 100}{Best\ compliance_{pixel}}$$

The likelihood of alveolar overdistension was classified into high or low potential groups based on the median value of the %OD measured by EIT.

Furthermore, information from bedside monitoring is documented, encompassing vital signs, pulse oximetry, end-tidal carbon dioxide, cardiac output, and pulse pressure variation.

Strain energy

The strain energy was computed using the formula provided below.

$$Strain\ energy = \frac{1}{2} \times lung\ stress \times lung\ strain$$

The lung stress-strain relationship is defined by the formula: lung stress = Esp x lung strain, with Esp is specific lung elastance approximately equal to 12 cm H_2O/ml [2]. The relationship between lung strain and lung stress can be expressed as follows: lung strain = lung stress/12. Consequently, the equation for deriving strain energy is presented below.

$$Strain\ energy = 0.098 \times \frac{1}{2} \times \frac{(lung\ stress)^2}{12}\ (joules)$$

The lung stress was determined using the elastance-derived method [11,12], as expressed in the equation below.

$$Lung\ stress = P_{plat} \times [1 - (\frac{E_{cw}}{E_{rs}})]$$

Single-breath MP

At present, several simplified formulas are available, each designed for different modes of MV. Given the use of the PCV mode, we selected a simplified formula from the study conducted by Chiumello D et al. [6]

$$Single\ breath\ MP = 0.098 \times V_T \times [PEEP + \Delta Pinsp]\ (Joules)$$

Here, the value 0.098 represents the conversion factor from cmH_2O to joules, and ΔP_{insp} denotes the pressure above PEEP or the driving pressure.

OUTCOME

Primary outcome

The correlation between strain energy and alveolar overdistension.

Primary outcome

1. The correlation between single-breath MP and alveolar overdistension.
2. The correlation between strain energy and single-breath MP.
3. The performance analysis of strain energy and single-breath MP for predicting alveolar overdistension.

Timeline

The flowchart of data collection (Figure 1)

DATA ANALYSIS PLAN

Sample size

To conduct a physiologic pilot study, we estimated the participation of 20 individuals.

Statistical analyses

Data gathered from MV and EIT during the decremental PEEP titration were focused on seven PEEP levels: 20, 18, 16, 14, 12, 10, and 8 cmH_2O, providing a dataset of 140 events for analysis.

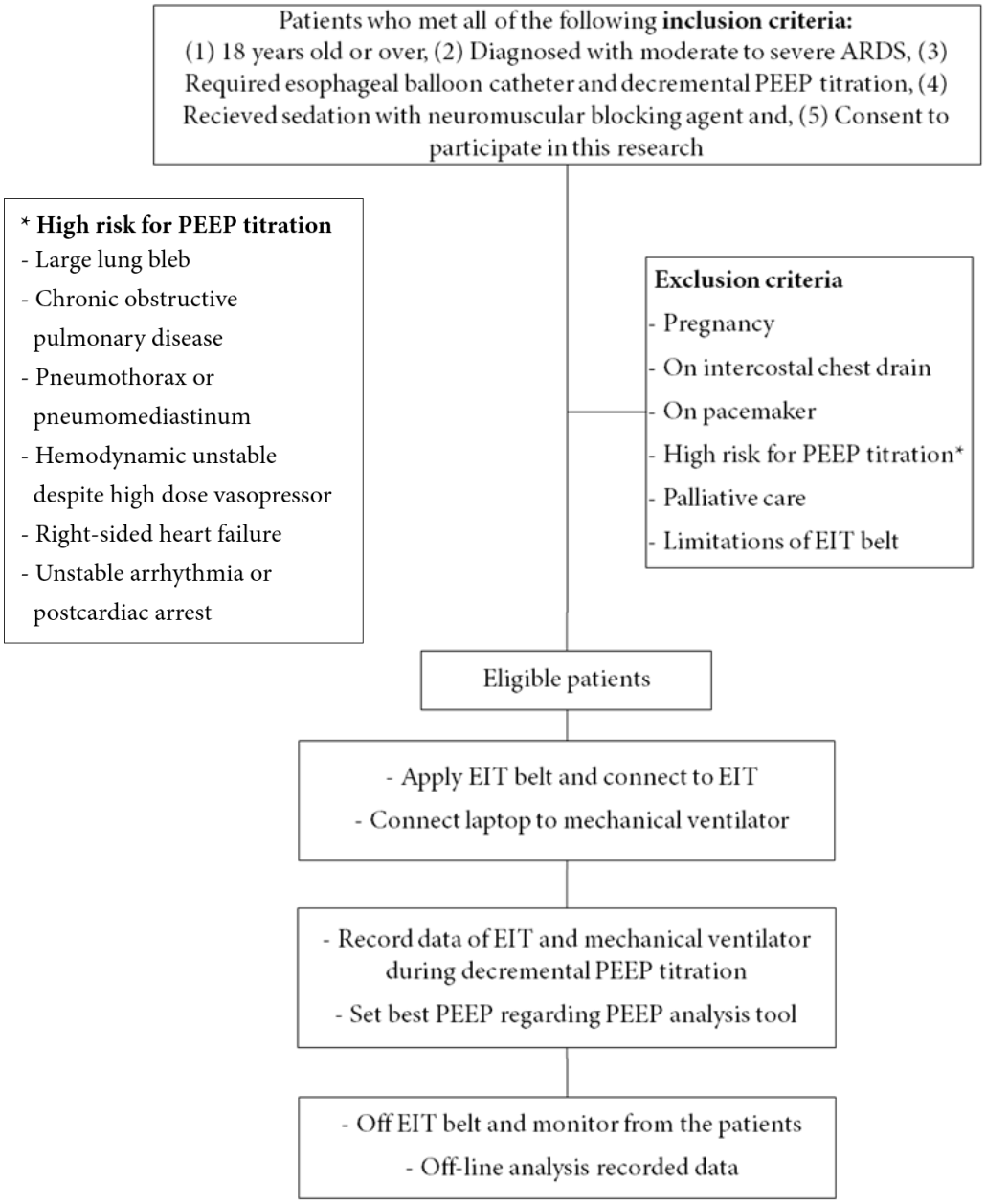

Figure 1. The flow of data collection.

Abbreviations: ARDS: acute respiratory distress syndrome; PEEP: positive end-expiratory pressure; EIT: electrical impedance tomography.

We examined the relationship between two variables using correlation analysis, employing either Pearson's or Spearman's rank correlation test based on the type of data distribution. Additionally, we utilized ROC analysis to assess the predictive performance of variables. Statistical significance was defined as a P-value less than 0.05. All analyses were performed using SPSS statistical software version 22.

DATA MANAGEMENT AND DATA MONITORING

Data collection

The case record form collects the data, including baseline characteristics and respiratory mechanic parameters (Tables 1 and 2). After decremental PEEP titration, we will use data from respiratory compliance, esophageal balloon catheter, and EIT to identify the best PEEP for each patient and report it to their primary physicians. Strain energy and single-breath MP are subsequently calculated and statistically analyzed.

Table 1. Baseline characteristics.

Characteristics	Overall population
Age (years), mean (SD)	
Gender, n (%) Female Male	
Body mass index (kg/m^2), mean (SD)	
Height (cm), mean (SD)	
Cause of ARDS, n (%) Pulmonary origin Extrapulmonary origin	
PaO_2/FiO_2 ratio prior to enrollment (mmHg), mean (SD)	

Abbreviations: n: number; SD:standard deviation; ARDS: acute respiratory distress syndrome; PaO_2/FiO_2 ratio: the ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Table 2. Respiratory Mechanics during decremental PEEP titration.

Respiratory mechanics	Overall population
Optimal PEEP (cmH_2O) based on, mean (SD) RS compliance Zero Ptp at end-expiration EIT	
Strain Energy (joules), mean (SD)	
Single-Breath MP (joules), mean (SD)	

Abbreviations: n: number; SD: standard deviation; PEEP: positive end-expiratory pressure; RS: respiratory system; Ptp: transpulmonary pressure; EIT: electrical impedance tomography; MP: mechanical power.

DISCUSSION

According to the definition of MP, it is energy expended per unit of time, while single-breath MP refers to energy expended per cycle. Our study's simplified calculation of Single-breath MP in PCV mode used the following equation [6].

$$\text{Single-breath MP} = 0.098 \times V_t \times (PEEP + \Delta P_{insp})$$

During assisted breathing, mechanical forces (ΔP_{insp}, PEEP, and volume) in the ventilator can put an energy load (dynamic and static stress) on lung tissue, causing lung strain or alveolar overdistension [8]. Although MP computation has two main variables: ΔP_{insp} and RR, Costa E et al.'s study supports that only ΔP_{insp} was independently associated with VILI and the more significant impact of ΔP_{insp} on mortality [4]. Therefore, it is reasonable to expect a potential correlation between the single-breath MP and alveolar overdistension.

However, MP increases linearly with PEEP and may contribute to VILI. Studies have suggested that PEEP may decrease the lung-dependent cause of VILI [5]. VILI is not directly correlated with any single mechanical breath parameter, such as ΔP_{insp}, PEEP, or Vt, but rather is caused by the combination of parameters that subject the lungs to excessive dynamic strain and energy load [13]. Based on the stress-strain concept, we assumed that strain energy could be a more accurate way to measure alveolar overdistension indirectly.

Concerning the engineering model, the energy present in the lungs affected by ARDS during mechanical inspiration can be analogized to the Elastic Potential Energy of a spring model. This energy is mathematically represented by the following equation, where 'k' is a constant value or Young's modulus, 'l' denotes the extended length of the spring, and 'lo' signifies the original length of the spring.

$$\textit{Elastic potential energy} = \tfrac{1}{2} \times k \times (l - l_0)^2$$

This equation bears a resemblance to the strain energy equation when the 'k' value is substituted with Esp = 12 cmH_2O [2] and the 'Δl' is replaced with lung strain. In this study, strain is defined as the ratio of stress to Esp, so stress/12 or Ptp/12 can be used as a substitute for strain.

From another scientific perspective, considering the principles of physics, there exists a connection between force or pressure and energy. According to this, the product of force (f) and distance (s) results in work (w), which is a manifestation of energy. Given that pressure (p) is defined as force per unit area (a), the equation for work can be expressed as w = p·a·s. When examining Power (P), another manifestation of energy, the equation takes the form presented below.

$$\textit{Power} = (\Delta P \times \Delta V)/\Delta t$$

In the context of this equation, when applied to the lung affected by ARDS, if the change in pressure (ΔP) is substituted with Ptp, representing the authentic distending pressure of the lung, then the change in volume (ΔV) should be regarded as the global lung strain.

Our strengths are pioneering the concept of strain energy, conducting a clinical study on this concept in ARDS patients, and utilizing a robust prospective physiologic cohort design. However, the specific lung elastance, at 12 cm H_2O/ml, is not truly constant but may fluctuate within the range of 12 to 13 cm H_2O/ml. In addition, due to the complexity associated with measuring FRC, lung strain was substituted with elastance-derived lung stress and Esp.

CONCLUSION

This study aims to assess the correlation between strain energy and alveolar overdistension, as well as the correlation between strain energy and single-breath MP in ARDS patients. The novel concept of strain energy presents opportunities for further research to prevent VILI.

CONFIDENTIALITY

Researchers obtained informed consent privately in the ICU. Codes replaced names and numbers for data collection. No personal details were collected. Secure data storage was only on investigators' computers. All information was permanently deleted after the trial.

ACKNOWLEDGEMENT

None

AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Jakkrit Laikitmongkhon, Yuda Sutherasan, Detajin Junhasavasdikul, Kridsanai Gulapa, Pongdhep Theerawit; (II) Data curation: Jakkrit Laikitmomgkhon, Pongdhep Theerawit; (III) Formal analysis: Jakkrit Laikitmomgkhon, Pongdhep Theerawit; (IV) Methodology: Jakkrit Laikitmongkhon, Yuda Sutherasan, Detajin Junhasavasdikul, Kridsanai Gulapa, Pongdhep Theerawit; (V) Project administration: Jakkrit Laikitmomgkhon, Pongdhep Theerawit; (VI) Visualization: Pongdhep Theerawit; (VII) Writing – original draft: Jakkrit Laikitmomgkhon, Pongdhep Theerawit.

SUPPLEMENTARY MATERIALS

None

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