COVER PAGE

Official Title:

The contribution of the combination of transthoracic and transcranial ultrasonography to the titration of positive end-expiratory pressure in patients with acute respiratory distress syndrome and acute brain injury

Brief Title:

The contribution of transthoracic and transcranial ultrasonography to the titration of PEEP in patients with ARDS and ABI

Sponsor/Responsible Party:

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STUDY PROTOCOL

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Background and Rationale

Acute brain injury (ABI)—including traumatic brain injury (TBI), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and acute ischemic stroke (AIS)—primarily affects the central nervous system (CNS) but can also cause multi-organ dysfunction. The lungs are particularly vulnerable due to CNS inflammation, elevated intracranial pressure (ICP), reduced consciousness, and hypothalamic injury, leading to complications such as pneumonia, atelectasis, neurogenic pulmonary edema, and acute respiratory distress syndrome (ARDS). ARDS occurs in up to 30% of TBI, 38% of SAH, 28% of ICH, and 4% of AIS cases, and is associated with higher mortality and poor neurological outcomes.

Positive end-expiratory pressure (PEEP) is a key component of mechanical ventilation (MV) for ARDS, promoting alveolar recruitment and improving oxygenation. In moderate to severe ARDS, PEEP improves survival, but excessive levels can reduce venous return, decrease cardiac output, and cause alveolar overdistension with hypercapnia. In ABI, these effects are particularly concerning, as high PEEP may raise ICP by increasing cerebral blood volume and reduce cerebral perfusion pressure (CPP), leading to ischemia. Consequently, most ABI patients receive PEEP $\leq$ 5 cmH_2O.

Determining optimal PEEP in ABI with ARDS remains challenging, as major ARDS trials excluded such patients. The ESICM consensus suggests applying similar PEEP levels as in non-ABI cases if ICP is PEEP-insensitive. Among proposed methods, lung ultrasound (LUS) offers a non-invasive, bedside approach for PEEP titration, though evidence in ABI remains limited. Transcranial Doppler (TCD) ultrasound can evaluate

cerebral blood flow by measuring the Pulsatility Index (PI) and Diastolic Flow Velocity (FVd), providing real-time insight into cerebral hemodynamics.

This study aims to assess the effect of four levels of PEEP (5, 8, 12 and 16 cmH2O) on LUS scores, respiratory mechanics, arterial blood gas (ABG) and neuromonitoring parameters, in order to determine the optimal PEEP level.

Objectives

Primary Objective:

To determine the difference between the optimal PEEP level identified by LUS (based on the lowest LUS score) and the safest PEEP level determined by TCD (based on PI and FVd measurements), and respiratory mechanics.

Secondary Objective:

To evaluate the association between the difference in PEEP values (optimal for mechanical ventilation vs. safe for cerebral protection) and patient outcomes, including:

- Duration of mechanical ventilation
- ICU length of stay
- ICU mortality
- Hospital mortality

Study Design

- **Type**: Prospective, interventional, single-arm study
- **Setting**: 2nd Intensive Care Unit, George Papanikolaou General Hospital of Thessaloniki, Greece
- **Duration**: Approximately 24 months (including data analysis)
- **Sample size**: Estimated number of participants ~30, determined based on feasibility and expected admissions

Each patient will undergo a stepwise increase in PEEP levels from 5 → 8 → 12 → 16 cmH_2O. At each PEEP level, the following will be performed:

- Lung ultrasound (LUS) to assess lung aeration and calculate LUS score
- Transcranial Doppler to measure PI and FVd
- Measurement of ICP, brain tissue O_2 partial pressure ($PbtO_2$), and MV parameters
- Arterial blood gas (ABG) analysis 20 minutes after each PEEP change

Study Population

Adult patients (≥18 years old) admitted to the ICU with severe ABI who develop ARDS within the first 10 days of ICU stay.

Eligibility Criteria

Inclusion Criteria:

- Age ≥ 18 years
- Severe acute brain injury (e.g., traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke)
- Development of ARDS (according to Berlin criteria) within the first 10 days of ICU admission

Exclusion Criteria:

- Severe chronic brain diseases
- Brain tumor or CNS infection
- Severe chronic pulmonary or cardiovascular disease
- Severe coagulopathy
- Undergoing decompressive craniectomy
- Lack of invasive neuromonitoring
- Withdrawal of life-sustaining treatment
- Poor acoustic window in ultrasound

Intervention Description

A stepwise PEEP titration will be performed at four predefined levels (5, 8, 12, 16 cmH_2O). At each level:

- LUS will be performed to assess lung aeration and calculate the LUS score.
- Transcranial Doppler will be used to determine PI and FVd.
- ICP, $PbtO_2$, and MV parameters (driving pressure, plateau pressure, static respiratory system compliance) will be recorded.
- ABG samples will be taken 20 minutes after each PEEP change.

ICP will be continuously monitored via an intraparenchymal catheter to ensure normal ICP and adequate CPP. If ICP exceeds 22 mmHg despite osmotic therapy, the procedure will be immediately discontinued. During these maneuvers, CPP will be maintained above 60–70 mmHg by increasing mean arterial pressure (MAP) through titration of vasopressor therapy.

Outcome Measures

Primary Outcome:

- Difference between optimal PEEP (based on LUS) and safe PEEP (based on TCD and respiratory mechanics)

Secondary Outcomes:

- Correlation between PEEP difference and patient outcomes (duration of MV, ICU length of stay, ICU/hospital mortality)

Data Collection and Analysis

All variables will be recorded in standardized data collection forms.

In our statistical analysis, we will present continuous numerical variables with means and standard deviations (SD) or medians and interquartile range (IQR) based on normality.

Association of continuous variables for different PEEP levels will be evaluated with repeated measures ANOVA or Friedman test if normality assumption is not met.

We will compare categorical variables with chi-squared or Fisher's exact test according to population characteristics. We will investigate associations of continuous variables with Student's t test or Mann-Whitney U test according to normality of distributions.

A p-value <0.05 will be considered statistically significant.

Ethical Considerations

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

Approval will be obtained from the Ethics Committee of the Aristotle University of Thessaloniki.

Written informed consent will be provided by the patient's legal representative prior to inclusion.

Timeline

Phase	Duration	Activities
Study preparation	1 month	Ethics approval
Patient enrollment	21 months	Data collection
Data analysis	2 months	Statistical analysis and reporting

Investigators

- **Principal Investigator:** Theodoros Schizodimos, 2nd Intensive Care Unit, George Papanikolaou General Hospital of Thessaloniki, Greece
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