UiT

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Pulmonary complications in patients undergoing neurointensive care

Master's Thesis in medicine [MED-3950] – June 2018

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Foreword

The purpose of this thesis is to provide data that could be used to optimize respiratory care for the intubated neurointensive patient. To do so, we wanted both to assess the incidence of pulmonary complications in this group of patients at our hospital, and to assess different ventilator variables used during their stay in the intensive care unit, such as tidal volumes and positive end-expiratory pressures.

The idea behind this project came from my supervisor, who had a long-lasting desire to improve care for the critically ill and brain-injured patient. When looking for a project for my master's thesis, I saw this as an opportunity to learn something from a field of medicine that I had little prior knowledge of. In that respect, I found the combination of respiratory care and brain injury particularly compelling.

A special thank you to Shirin Frisvold, my supervisor, for your valuable time, excellent supervision, interesting discussions and for always being positive though facing different challenges throughout the work with this thesis. And thanks to Lars Bjertnæs, my co-supervisor, who has made crucial contributions both concerning academic content and writing, and even provided very valuable feedback while being on vacation to his mountain cabin.

I also want to address a word of thanks to the University of Tromsø for their financial contributions that made supervision and data collection possible.

Tromsø, June 2018

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Abstract

Introduction

Respiratory complications frequently develop in patients with acute brain injury (ABI), and contribute considerably to poor neurologic outcome and increased mortality in these patients. Several reports have shown that respiratory failure may account for as many as 50% of the deaths after brain injury. We wanted to take a closer look at respiratory complications in patients with ABI at our hospital, and conducted a small study focusing on three aims. These were 1) to assess the incidence of respiratory failure in neurointensive patients of the University Hospital of North Norway (UNN) in Tromsø, 2) to examine whether the PEEP/FiO_2 values used here are similar to the ARDS Network recommendations for PEEP/FiO_2 settings and 3) to assess the tidal volumes (TVs) set to ventilate these patients in controlled ventilator modes.

Materials and methods

The study was conducted as a retrospective observational study. Tracheally intubated patients with acute traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) admitted to the ICU of UNN Tromsø between the 1st of January and the 31st of December 2016 were included.

Results

Eighteen patients with SAH and 12 patients with TBI were identified. Sixteen patients (53%) were diagnosed with any pulmonary complication. Twelve patients (40%) were diagnosed either with pneumonia or were suspected to have developed pneumonia. Seven patients (23%) were diagnosed with atelectasis, while one patient (3%) had a pleural effusion. Compared to the ARDS Network recommendation for PEEP/FiO_2 settings, too low PEEP values for a given FiO_2 were identified in 6 (20%) of the patients. The mean (±SD) TV/actual body weight (n=28) was 6,7 ± 1,1 mL/kg, while the mean (±SD) TV/PBW (n=17) was 7,3 ± 1,0.

Conclusion

The present study found a high incidence of pulmonary complications in ICU patients with ABI, with pneumonia as the most common cause. This finding is consistent with other studies investigating this group of patients. None of the patients in our material were diagnosed with ARDS. The short inclusion time and low number of patients included representing the most likely explanations for this finding. Data on body height could only be found in 57% of the patients, implicating that TVs were set based on other variables than PBW in nearly half of the patients.

Abbreviations

ABI	Acute brain injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CBF	Cerebral blood flow
CPAP	Continuous positive airway pressure
CPP	Cerebral perfusion pressure
CT	Computed tomography
DAI	Diffuse axonal injury
FiO_2	Fraction of inspired oxygen
GCS	Glasgow coma scale
ICP	Intracranial pressure
ICU	Intensive care unit
ISS	Injury severity score
MAP	Mean arterial pressure
OLA	Open lung approach
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
PaO_2	Partial pressure of oxygen in arterial blood
PEEP	Positive end-expiratory pressure
PBW	Predicted body weight
RM	Recruitment maneuver
RR	Risk ratio
SAH	Subarachnoid hemorrhage
TBI	Traumatic brain injury
TV	Tidal volume
UNN	University Hospital of North Norway in Tromsø
VAP	Ventilator-associated pneumonia
VILI	Ventilator-induced lung injury

1 Introduction

Respiratory complications frequently develop in victims of acute brain injury (ABI) and contribute considerably to the poor neurological outcome and increased mortality. Several reports have shown that pulmonary alterations may account for as many as 50% of the deaths after brain injury.[1] Common pulmonary complications in these patients include ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS), atelectasis, pleural effusions, pulmonary edema and pulmonary embolism.[2] Prevention of hypoxemia resulting from lung injury is essential, as hypoxemia may induce secondary brain injury. In a large, prospectively collected data set from the Traumatic Coma Data Bank, hypoxemia in patients with severe traumatic brain injury was associated with significant increases in morbidity and mortality.[3] In spite of a high incidence of pulmonary complications, the optimal strategy for mechanical ventilation of these patients is still unsettled.

1.1 Acute brain injury (ABI)

This study will be focusing on patients with ABI due to subarachnoid hemorrhage (SAH) or traumatic brain injury (TBI). Therefore, in the following emphasize will be put on defining these two disorders.

1.1.1 Subarachnoid hemorrhage (SAH)

Subarachnoid hemorrhage (SAH) is a devastating condition that refers to bleeding in the subarachnoid space, which is located between the arachnoid mater and the pia mater. Despite being a rare condition, accounting for approximately 5% of strokes, the young age of those affected and the high morbidity and mortality makes its effect on years of life lost similar to that of the more common types of stroke, i.e. ischemic stroke and intracerebral hemorrhage.[4] SAH without a preceding trauma is in 80% of cases caused by rupture of an intracranial aneurysm, while causes like vascular malformations and vasculitis are more uncommon.[5] The worldwide incidence of SAH has been estimated to 9,1 per 100 000 person-years.[6] European Standard Population (ESP) standardized incidence of SAH from a ruptured intracranial aneurysm in Norway was estimated to 8,7 per 100 000 person-years between 1984 and 2007.[7] Treatment can be achieved either by an open surgical approach or endovascularly by means of an intra-arterial catheter. The open surgical approach requires opening of the skull (craniotomy) and application of a titanium clip on the neck of the aneurysm, while the endovascular approach involves navigation of the intraarterial catheter to the aneurysm site from a peripheral artery. By applying

the latter procedure, platinum coils are delivered and packed into the lumen of the aneurysm, which slows or prevents blood flow into the aneurysm and leads to thrombus formation.[5]

The brain injury from SAH occurs in two phases.[8] Early brain injury is caused by transient global ischemia and toxic effects of subarachnoid blood. Direct destruction of brain tissue by an intracerebral hemorrhage can also contribute to the damage. The second phase of brain injury typically occurs from 4 to 14 days after rupture of the aneurysm, and involves a clinical syndrome of focal neurologic deficits that develop in one third of the patients.[5] This syndrome is called *delayed cerebral ischemia* and is a major cause of death and disability after SAH. In 70% of patients, narrowing of angiographically visible cerebral arteries—*vasospasms*—is found. The process generally starts 3 to 4 days after aneurysm rupture, peaks at 7 to 10 days, and resolves by 14 to 21 days. Vasospasm has been considered the cause of delayed cerebral ischemia, but its exact role is controversial.[9] Recent evidence suggest that a variety of vascular and neural changes that take place after SAH may contribute to its pathogenesis. Moreover, delayed cerebral ischemia develops in half of the patients with angiographic vasospasm, and ischemia does not occur consistently in the territory supplied by the vessel undergoing spasm.[8]

In two Norwegian cohorts, 40% of the patients had died 6 months after SAH caused by rupture of an intracranial aneurysm.[7] One year after SAH, about 50% of survivors were reported to have sequelae requiring long-term care and rehabilitation.[10] Modifiable risk factors for SAH include smoking, hypertension and excess alcohol intake, which all roughly double the risk individually.[8] Non-modifiable risk factors include increasing age, female sex, family history, and previous history of SAH.

1.1.2 Traumatic brain injury (TBI)

Traumatic brain injury (TBI) is a heterogenous disorder with different forms of presentation. The unifying factor is that brain damage results from external forces, as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object or blast waves from an explosion.[11] Traditionally, TBI is graded as mild, moderate or severe based on Glasgow coma scale (GCS) after resuscitation.[12] Mild TBI with a GCS score of 13-15 is in most cases a concussion, which is followed by full neurological recovery, although many of these patients experience short-term difficulties with memory and concentration. In moderate TBI (GCS 9-13), the patient is lethargic or stuporous. In severe TBI (GCS 3-8) the patient is comatose. Approximately 10-15% of patients with TBI have serious injuries, requiring specialist care.[11] In Scandinavian countries, the incidence of hospital admission due to TBI has been estimated to 200 per 100 000 person-years.[13] TBI is the leading cause of mortality and disability among young individuals in high-

income countries.[11]

TBI can be divided into primary and secondary injury. Primary injury occurs as a consequence of the initial physical insult, while different pathophysiological mechanisms may account for the secondary injury arising hours and days after the initial injury.[11] Primary brain injuries include contusions, intracranial hematomas, cerebral edema, traumatic SAH and diffuse axonal injury (DAI).[14] DAI is characterized by multiple small lesions in white-matter tracts, and often lead to a poor outcome.[11] Secondary brain injury may arise from a multitude of factors such as hypotension, hypoxemia, cerebral ischemia, hydrocephalus, increased intracranial pressure (ICP), hypoglycemia and infection.[3,15]

The most severely affected patients require neurocritical care in an intensive care unit (ICU), where a major focus is to prevent and limit ongoing brain damage and to provide the best conditions for natural brain recovery by reducing brain swelling and raised ICP. As in general intensive care, optimum cerebral perfusion, oxygenation, nutrition as well as glycemic control and temperature controls is also essential.

The Scandinavian Neurotrauma Committee (SMC) has published evidence-based guidelines for initial management of minimal, mild and moderate head injuries in adults (Figure 1).[16] The aim of these guidelines is both to identify patients requiring neurosurgical intervention, and to avoid exposure to ionizing radiation from unnecessary computed tomography (CT) scans. Scandinavian evidence-based guidelines for the pediatric population have also been published.[17] In the 2013 update of the adult guidelines, the brain biomarker S100B was introduced for the first time. Using a low cut-off of 0,10 µg/L, the biomarker has shown considerable ability to predict the absence of CT pathology and injuries requiring neurosurgical intervention.[16] The pediatric guidelines do so far not include the S100B analysis, as the current evidence available for this population has been considered too low.[17]

Regarding severe traumatic brain injuries, evidence-based management guidelines are published by Brain Trauma Foundation.[18] The 4th version of the guidelines was published in 2016, available online at https://www.braintrauma.org/coma/guidelines. As the authors state, they do not intend to produce a 5th version of the guidelines, as they are moving to a model of continuous monitoring of the literature, rapid updates to the evidence review, and revisions to the recommendation as the evidence warrants—a so-called Living Guidelines model.

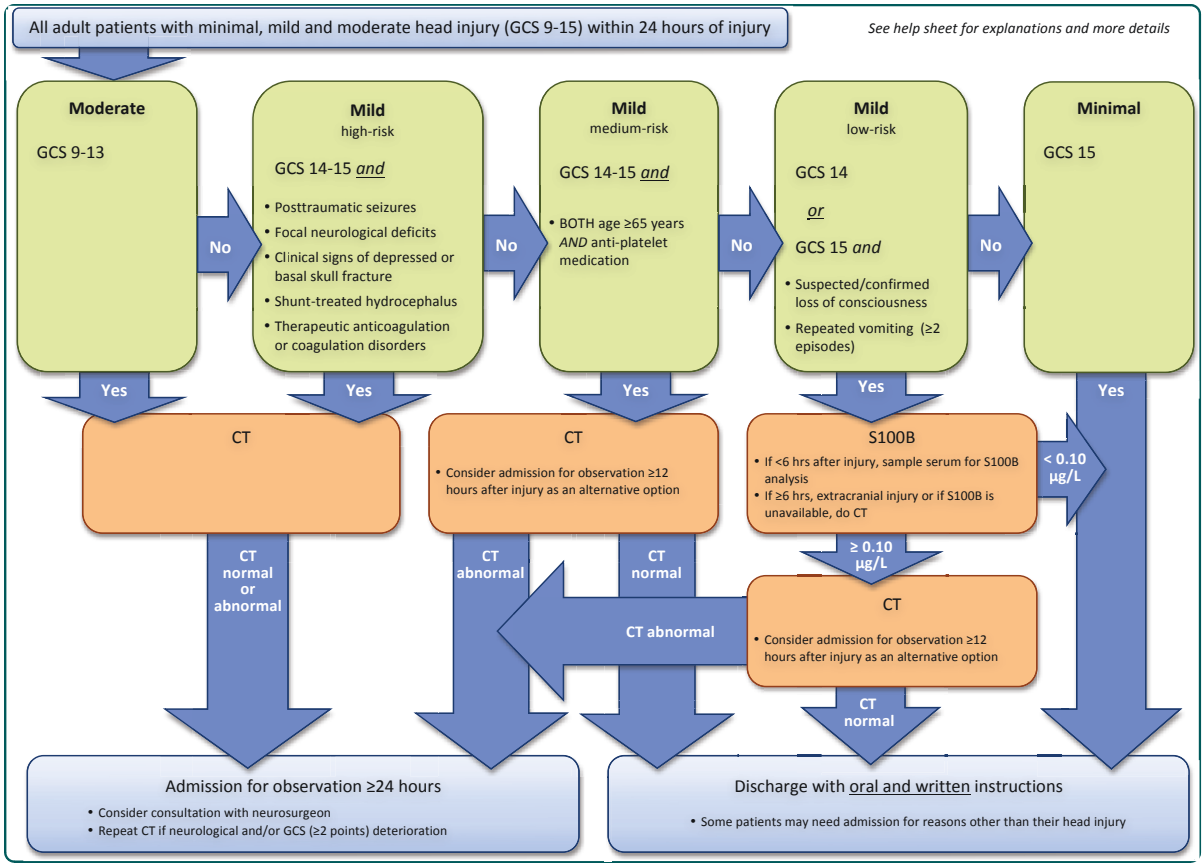


Figure 1. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults. Adopted from Ingebrigtsen T, Romner B, Kock-Jensen C. Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries. J Trauma. 2000;48(4):760-766.

1.2 Acute respiratory failure in ICU patients

1.2.1 Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is a nosocomial pneumonia developing 48 hours or more after tracheal intubation of the patient.[19] The condition often has an early onset and is associated with community-acquired microorganisms. Mechanisms involved in the pathogenesis of VAP are microaspirations of colonized oropharyngeal, tracheobronchial (from a colonized endotracheal tube), or gastric secretions, leading to development of lung microabscesses.

1.2.2 Acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is a severe progressive clinical condition characterized by acute onset of dyspnea and hypoxemia with the appearance of radiographic infiltrates on chest radiography.[20] Due to several limitations of the 1994 Definition of the American-European Consensus Conference on ARDS, an updated definition was proposed in Berlin in 2012 (Table 1).[21] Importantly, the former "acute lung injury" (ALI) term was removed in the 2012 Berlin Definition, and replaced with a comparable term—"mild ARDS".

The clinical picture of ARDS is a manifestation of the alveolar degradation and flooding with a protein-rich edema and cellular debris and a subsequent increases in pulmonary vascular resistance.[20] A complex array of endothelial injury, epithelial injury, neutrophil-mediated damage, cytokine-mediated inflammation and injury, oxidant-mediated injury, ventilator-induced lung injury, and dysregulation of the coagulation and fibrinolytic pathways are all implicated in the development of ARDS (Figure 2). A pro-inflammatory milieu emerges in the pulmonary environment, thus leading to direct parenchymal injury and clinical deterioration. Severe traumatic injury is the epitome of the pro-inflammatory state, and consequently, ARDS occurs with increased incidence in the traumatically injured patient.[20] The major causes of death in ARDS are sepsis and multi organ failure.[19]

Table 1. The Berlin definition of acute respiratory distress syndrome[21]

Timing		Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]		Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema		Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	Mild	26,6 kPa < PaO_2/FIO_2 ≤ 39,9 kPa with PEEP or CPAP ≥5 cm H_2O[c]
	Moderate	13,3 kPa < PaO_2/FiO_2 ≤ 26,6 kPa with PEEP ≥5 cm H_2O
	Severe	PaO_2/FiO_2 ≤ 13,3 kPa with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure.

[a]Chest radiograph or computed tomography scan.

[b]If altitude is higher than 1000 m, the correction factor should be calculated as follows: [PaO_2/FiO_2 × (barometric pressure/760)].

[c]This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

1.2.3 Atelectasis

Atelectasis and lung consolidation are common complications among ICU patients. Contributing factors to atelectasis formation are among others central respiratory depression, hypoventilation due to pain, altered levels of consciousness, obstruction due to mucous plugs or aspiration of particulate matter. Moreover, in traumatized patients, there is a risk for compression of adjacent lung by a pneumothorax, hemothorax or pleural effusion that might promote closure of

dependent small airways[19] Prevention and aggressive treatment of lung collapse with hyperventilation, recruitment maneuvers and aggressive physiotherapy can prevent development of atelectasis and lung infection.

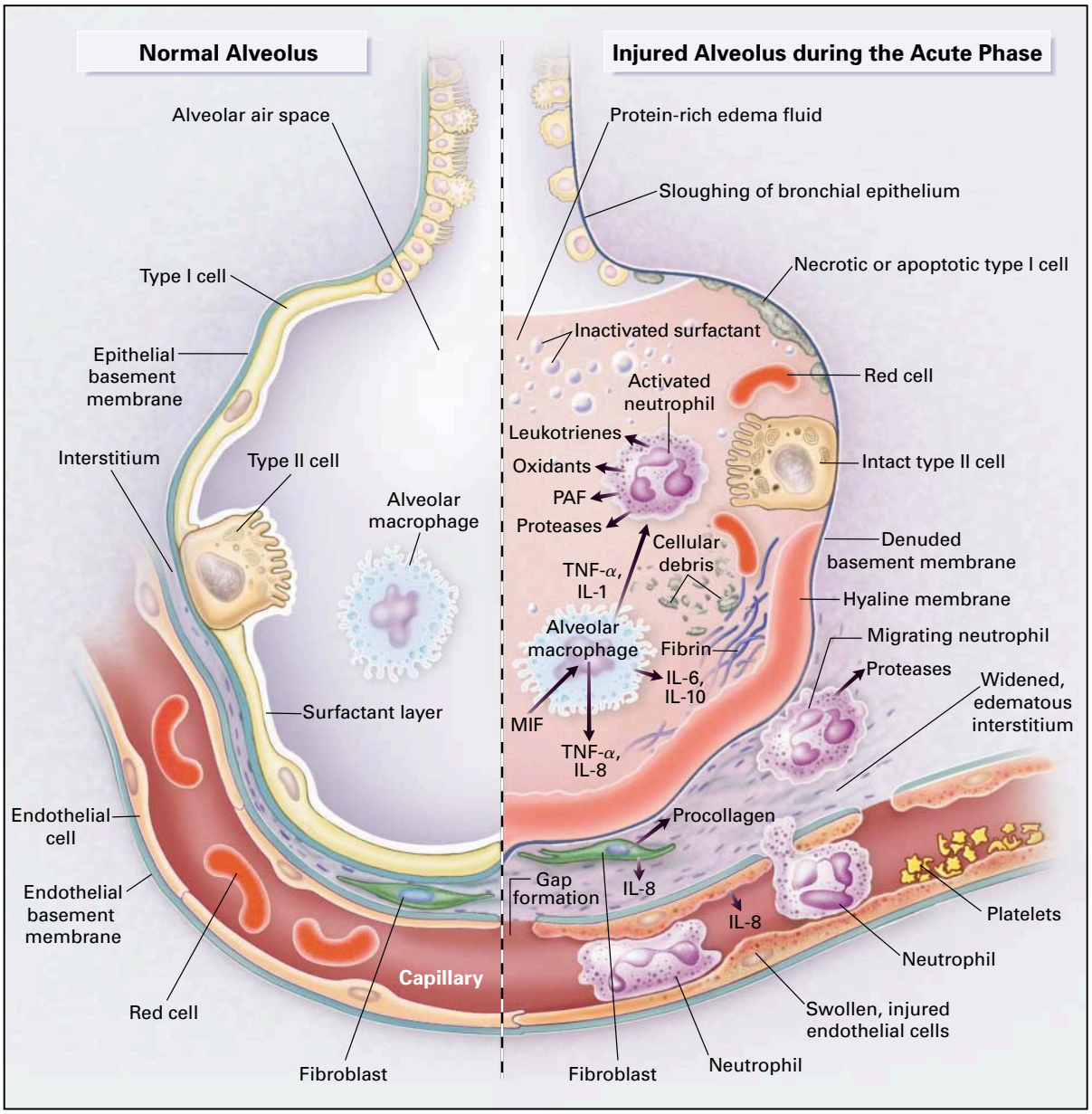


Figure 2. Injured alveolus in the acute phase of the acute respiratory distress syndrome (ARDS). The normal alveolus (left-hand side) and the injured alveolus (right-hand side). In the acute phase of the syndrome, there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and margination through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines, interleukin-1, 6, 8 and 10, (IL-1, 6, 8 and 10) and tumor necrosis factor α (TNF-α), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF denotes macrophage inhibitory factor. Reproduced with permission from Ware LB, Matthay MA. The Acute Respiratory Distress Syndrome. *N Engl J Med*. 2000;342(18):1334-1349. Copyright Massachusetts Medical Society.

1.2.4 Ventilator-induced lung injury (VILI)

In the early days of mechanical ventilation, large tidal volumes (TVs) were applied to prevent atelectasis.[22] Physiological TVs during spontaneous breathing are in the range of 5 to 7 mL/kg of predicted body weight (PBW), while TVs of 10 to 15 mL/kg of PBW became standard during mechanical ventilation. It was later discovered that such high inflation volumes, rather than high inflation pressures, were injurious to the lung causing an inflammatory condition termed ventilator-induced lung injury (VILI).[23] Recent research has shown that too large TVs might induce *volutrauma*, whereas too small TVs might provoke *atelectrauma*. *Barotrauma* occurs following excessive inflation of alveoli, resulting in alveolar rupture and air leaks causing pneumothorax, pneumomediastinum, pneumoperitoneum and subcutaneous emphysema. The term barotrauma can be misleading, as the critical variable leading to air leaks is regional lung over-distension, not high airway pressures per se.[24] In contrast, atelectrauma is associated with a fall in functional residual capacity and closure of dependent small airways at the end of expiration in parallel with a decrease in lung compliance. These changes occur typically in pulmonary edema and ARDS.[22] Atelectrauma can be mitigated by the use of positive end-expiratory pressure (PEEP).

Repetitive opening and closing of small airways during positive pressure ventilation can damage the airway epithelium by generating excessive shear stress. “Stress” is defined as force per unit of area. The associated deformation of the structure is called “strain”, which is defined as the change in size of the lungs. Injurious ventilation affects extracellular matrix and causes fragmentation of components of lung parenchyma, such as hyaluronic acid, which is a well-known trigger of Toll-like receptor (TLR) 4. The latter activates transcription factor NF-Kß, which induces mitochondrial production of cytokines, such as TNF-α. This has the ability to create damage, not only locally in the lungs, but also in remote organs.[25] Thus, changes in ventilation mechanics can activate mediator release both from epithelial and endothelial cells, matrix components and inflammatory cells like polymorphonuclear leucocytes and pulmonary macrophages. This adds still another dimension to the pathophysiological picture of VILI, termed *biotrauma* (Figure 3).[24]

1.2.5 Pulmonary complications in the neurointensive patient

Pulmonary complications are very common in patients with ABI. In an observational cohort of 60 Canadian patients with severe TBI, 45% of them developed VAP[26]—a number far higher than in the general ICU population.[27] The development of VAP was associated with significant morbidity including a longer duration of mechanical ventilation, longer ICU and hospital length of stay, more frequent tracheostomy, and a greater severity of non-neurological organ dysfunction. In

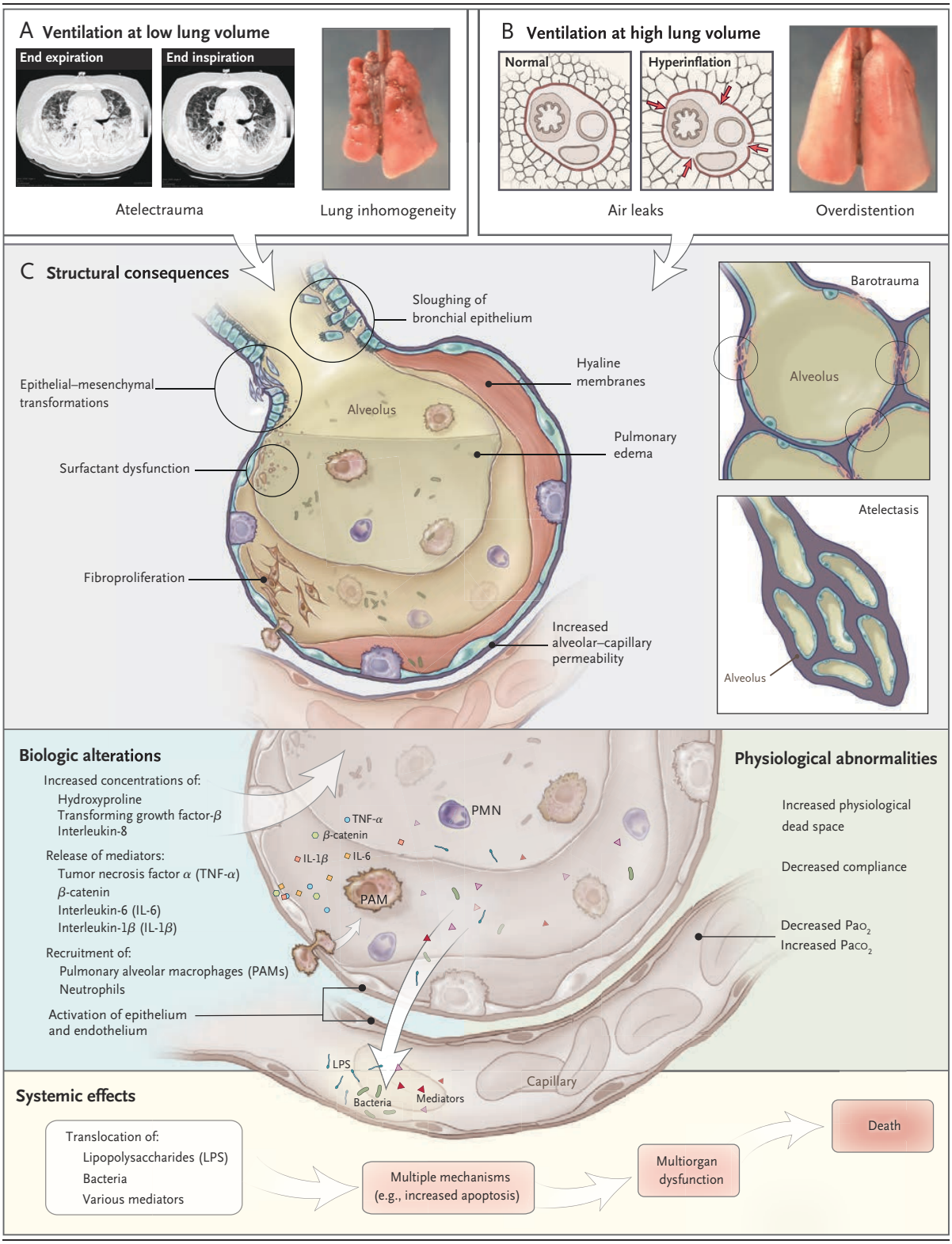


Figure 3. Ventilator-induced lung injury (VILI). The figure shows lung injury caused by forces generated by ventilation at low and high lung volumes. When ventilation occurs at low lung volumes, lung injury can be caused by the opening and closing of lung units (atelectrauma) as well as by other mechanisms. This injury is magnified when there is increased lung inhomogeneity, as shown on CT (Panel A), especially in patients with ARDS who have surfactant dysfunction, pulmonary edema, and atelectasis.[28] In addition, ventilation may be very inhomogeneous, a status that may be partially reversed by the use of positive end-expiratory pressure (PEEP), as shown in a ventilated ex vivo rat lung. At high lung volumes, overdistension can lead to gross barotrauma (air leaks) (Panel B). Overdistension can also lead to increased alveolar-capillary permeability and gross pulmonary edema. Ventilation at both high and low lung volumes has structural physiological, biologic and systemic effects (Panel C). Mediators that are released into the lung can cause further lung

injury, recruit neutrophils to the lung, or set the stage for the development of pulmonary fibrosis. In addition, the increased alveolar-capillary permeability associated with VILI can lead to multiple-organ dysfunction and death. $PaCO_2$ denotes partial pressure of carbon dioxide in arterial blood, PaO_2 partial pressure of oxygen in arterial blood and PMN polymorphonuclear leucocytes. Reproduced with permission from Slutsky AS, Ranieri VM. Ventilator-Induced Lung Injury. *N Engl J Med*. 2013;369(22):2126-2136. Copyright Massachusetts Medical Society.

patients with severe TBI, concomitant thoracic injury, coma upon admission, high injury severity scores (ISS) and advanced age have all been suggested as risk factors.[29]

The incidence of ARDS has also been found to be very high in patients with SAH or severe TBI. Kahn et al. found an incidence of 27% in a retrospective cohort of 620 patients with aneurysmal SAH,[30] and similar figures are also seen in severe TBI.[31–33] Based on the Berlin definition of ARDS, Aisiku et al. found an incidence of 26% in patients with severe TBI,[32] and in an earlier study, development of what was then called ALI resulted in significantly higher mortality, 38% in the ALI group and 15% in the non-ALI group (p = 0,004).[31] Patients with ALI had significantly higher ISS, a greater number of days on the ventilator, and a worse neurologic outcome for those who survived their hospitalization.

In summary, pulmonary complications occur with high incidences in patients with ABI and are independent predictors of poor outcome.

1.3 Mechanical ventilation strategies in acute respiratory failure

Mechanical ventilation is an essential part of life support in acute respiratory failure. Nevertheless, mechanical ventilation may cause or even perpetuate lung injury if alveolar over-distention and repeated alveolar collapse and re-expansion occurs with each breath (ventilator-induced lung injury (VILI)).[34]

Following two landmark randomized controlled trials published around the millennium,[35,36] lung-protective ventilation has been an essential part of ARDS treatment.[20] These trials demonstrated a reduced mortality in patients ventilated with small TVs and low plateau pressures. The application of PEEP as a means of protecting the lung has also been found to increase alveolar recruitment and improve oxygenation.[37] A systematic review and meta-analysis published in 2010 by Briel et al. confirmed the significant reduction in mortality associated with higher PEEP levels compared with lower PEEP levels in ARDS patients without ABI.[38] The mainstays of lung-protective ventilation strategies are therefore (1) to limit TV and driving pressure; (2) limit end-expiratory plateau pressure (P_{plat}); and (3) provide adequate PEEP.[39] PEEP improves oxygenation by increasing functional residual capacity; thereby recruiting small airways and collapsed alveoli and promoting fluid movement from the alveolar to the interstitial space.[40] The best current and practice emphasizes lung protective ventilation with a TV target of 6 mL/kg

PBW in ARDS.[41] The rationale for using PBW in these calculations, is that PBW, a calculation based on body height and sex, rather than actual body weight, better reflects the size of the lung. If instead TV/kg actual body weight were used, it could produce excessive TVs in obese patients or inadequate TVs in underweight patients.

The lower PEEP/higher FiO_2 strategy of the ARDS Network (Table 2) has been a well-established protocol since the ALVEOLI study was published in 2004.[42] In experimental studies, the so-called "open lung approach" (OLA) using higher PEEP values has shown promising results suggesting a reduction in VILI.[43] The OLA aims to achieve high levels of lung aeration in patients with ARDS by first conducting recruitment maneuvers (RMs) to reverse atelectasis and then applying high levels of PEEP to keep recruited alveoli open. Different RMs are in use, but they typically involve a ventilatory approach that transiently increases pulmonary airway pressure to reopen recruitable lung areas. For example, a RM can be conducted by raising inspiratory airway pressures to 50 cm of H_2O for 1 to 2 minutes. Despite promising experimental results, four large randomized trials of higher PEEP and RMs have failed to demonstrate improved clinical outcomes. The last trial was published very recently by the Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators and is the largest trial so far.[44] This randomized trial was conducted in 120 intensive care units from 9 countries and enrolled 1013 patients with moderate to severe ARDS, 501 to the OLA group and 512 to the low-PEEP strategy. In this trial the OLA was associated with a significantly higher 28-day mortality and 6-month morality. Thus, these findings do not support the routine use of lung RMs and PEEP titration in these patients.

Table 2. ARDS Network mechanical ventilation protocol[42]

Lower PEEP/Higher FiO_2														
FiO_2	0,3	0,4	0,4	0,5	0,5	0,6	0,7	0,7	0,7	0,8	0,9	0,9	0,9	1,0
PEEP (cm H_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Higher PEEP/Lower FiO_2														
FiO_2	0,3	0,3	0,3	0,3	0,3	0,4	0,4	0,5	0,5	0,5-0,8	0,8	0,9	1,0	1,0
PEEP (cm H_2O)	5	8	10	12	14	14	16	16	18	20	22	22	22	24

Adopted from the ARDS Clinical Network Mechanical Ventilation Protocol.[42]

Whether a mechanical ventilation strategy with low TVs also should be used in patients without ARDS is still unclear, but evidence for harm from ventilation with a too large TV is rapidly

emerging in other patient groups.[45] A systematic review and individual patient analysis from 2015 by Neto et al. consisting of 2184 ventilated ICU patients without ARDS, found strong evidence for a protective effect of ventilation with low TVs.[46] Patients treated with TVs ≤7 mL/kg PBW developed significantly less pulmonary complications, and the analysis suggested a dose-response relationship between TV size and development of pulmonary complications. Development of pulmonary complications was also associated with a lower number of ICU-free and hospital-free days and alive at day 28 and an increased mortality.

1.4 Mechanical ventilation strategies in ABI

1.4.1 Role of mechanical ventilation in ABI

Due to coma, mechanical ventilation is a lifesaving measure in brain-damaged patients. Patients with severe brain injuries are at risk of pulmonary aspiration or compromised respiratory drive and function and therefore require definitive airway protection.[18] As other patients on mechanical ventilation, patients with ABI are also at risk of developing VILI. Therefore, absence of a lung-protective mechanical ventilation strategy would constitute an additional traumatic factor to the already injured or injury-susceptible lungs of these patients.[47]

As already mentioned, hypoxemia is known to induce secondary brain injury, and is therefore essential to prevent in ABI. This relationship was found in a study by Chesnut et al. where both hypoxemia and hypotension were found to independently contribute to significant increases in morbidity and mortality.[3] Furthermore, therapeutic hyperoxia has not been shown to improve outcome in patients with neurologic injury and is currently not recommended.[48] Careful control of partial pressure of oxygen in arterial blood (PaO_2) is therefore required.

Under normal conditions, partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is the most powerful determinant of cerebral blood flow (CBF).[18] Normal $PaCO_2$ values range from 4,7-6,0 kPa, and within the physiological range (2,7-8,0 kPa), the relationship between $PaCO_2$ and CBF is linear.[49] Low $PaCO_2$ values are known to induce cerebral vasoconstriction, while high $PaCO_2$ values may induce cerebral vasodilation. CBF is important in meeting metabolic demands of the brain. Accordingly, tight control of $PaCO_2$ is an essential part of mechanical ventilation in ABI. In a prospective intervention study enrolling 30 patients with head injury and 10 healthy volunteers, Coles et al. demonstrated that patients treated with hyperventilation, and hence hypocapnia, showed higher ischemia brain volume compared to controls.[50] This was caused by a reduction in CBF and resulted in an increase of oxygen extraction fraction. Hypercapnia should also be avoided as it may result in cerebral hyperemia and high ICP. Cerebral herniation may require

transient hyperventilation to relieve fatal ICP values, but current guidelines do not support prolonged prophylactic hyperventilation.[18]

1.4.2 Relationship between ventilator settings and ICP

Intracranial pressure (ICP) is the limiting factor of cerebral perfusion pressure (CPP) and consequently of cerebral blood flow. CPP is defined as the difference between mean arterial pressure (MAP) and ICP:

CPP = MAP – ICP

Lung-protective ventilation strategies with low TVs have been widely adopted, and have been suggested for all ICU patients.[51] But protection of the lung may not result in protection of the brain. Low TVs may cause a rise in $PaCO_2$, which is accepted in non-brain-injured patients as long as the arterial pH does not fall below 7,30.[22] This strategy is known as *permissive hypercapnia*, but as we have seen, such a strategy in brain-injured patients may increase CBF and ICP. Therefore, choosing the optimal mechanical ventilation strategy in the brain-injured patient remains a challenge to the clinician. That being said, a lung-protective ventilation strategy has been found to be an independent predictor of favorable outcome in brain-damaged patients.[52]

Theoretically, application of PEEP has been thought to increase ICP and thereby lower CPP by increasing the intrathoracic pressure and hence reducing the venous drainage.[53] This relationship has not been subject to extensive research in humans, and so far, studies have yielded conflicting results.[54–56] However, it should be taken into consideration that most of the early studies comprise rather small sample sizes, ranging from 7 to 16 patients. Therefore, caution should be taken when generalizing from these studies. Nevertheless, due to uncertainty concerning the safety of PEEP, mechanical ventilation of patients with ABI traditionally has been applied with great care. This category of patients usually have been excluded from trials examining the effect of lung protective ventilation in ARDS because of the potential adverse effect on ICP.[57] In these patients, Pelosi et al. found that clinicians often institute a ventilation strategy that utilizes larger TVs and lower levels of PEEP as compared to patients without neurologic injury.[58]

A well-designed observational study addressing this special issue was published very recently by Boone et al.[57] This study also constituted the largest analysis of the relationship between PEEP and ICP in the medical literature as yet. Data were collected retrospectively from 341 patients with severe ABI and varying categories of acute lung injury. Severity of lung injury was defined by

applying the ratio of PaO_2 to the fraction of inspired oxygen (FiO_2), the PaO_2/FiO_2-ratio, which was also the oxygenation criterion in the Berlin definition of ARDS (Table 1). Accordingly, patients were stratified into four groups, where the absence of lung injury was classified by a PaO_2/FiO_2 > 39,9 kPa, mild lung injury as PaO_2/FiO_2 > 26,6 kPa and ≤ 39,9 kPa, moderate as PaO_2/FiO_2 > 13,3 kPa and ≤ 26,6 kPa, and severe as PaO_2/FiO_2 < 13,3 kPa. Interestingly, a statistically significant relationship between PEEP and both ICP and CPP was found only in the severe lung injury group. Despite this, a modest increase in ICP was found over the range of applied PEEP values, suggesting a statistically but not clinically meaningful increase. A recently published review concluded that an increase in PEEP apparently can be used safely and even with beneficial effects on the brain in ABI patients, provided that they are normovolemic.[59]

To summarize, in many patients with both brain injury and ARDS, the goals of lung protection can be achieved without threatening cerebral perfusion.[60] However, in patients with more refractory raised ICP the optimal balance concerning mechanical ventilation between brain and lung is not well established. Taking into account all the uncertainty around this issue, a conventional approach with higher TVs and lower PEEP is still used in many patients with a combination of lung and brain injuries.[48,58–60] Further prospective studies are needed to assess the safety and clinical outcomes of applying a lung-protective ventilation strategy to this population of patients. Despite lack of high-quality evidence, the actual consensus is to recommend low TVs (6-8 mL/kg PBW) in ABI patients both for prevention and management of ARDS.[61]

1.5 Aims of the thesis

The primary aim of the thesis is to provide data that can be used to optimize respiratory care for the tracheally intubated neurointensive patient. To do so, we focused on the following aims:

1. Assess the incidence of respiratory failure in neurointensive patients of the University Hospital of North Norway in Tromsø (UNN).
2. Examine whether the PEEP/FiO_2 settings used here are similar to those recommended by the ARDS Network.
3. Assess the TVs set to ventilate these patients in controlled ventilator modes.

2 Materials and methods

2.1 Study design and population

The study was designed and conducted as a retrospective case observation study of neurointensive patients. Tracheally intubated patients with acute traumatic brain injury (TBI) and subarachnoid hemorrhage (SAH) admitted to the ICU of the University Hospital of North Norway in Tromsø (UNN) between the 1st of January and the 31st of December 2016 were included. Some of the patients were transferred to or from intensive care units of community hospitals within an up-take area stretching itself from Mosjøen in the South to Longyearbyen on Spitsbergen Islands in the North. However, only data from their stay in the ICU of UNN were collected.

2.2 Data collection

Data were collected by accessing the patients' electronic health records at UNN. Clinical and ventilator variables were found in handwritten and scanned ICU charts, while other clinical data were identified by going through medical records and x-ray data. All necessary clinical variables and documentation from admission to discharge from the ICU were collected. Some notes from different prehospital care providers notes were also read to assess TBI severity based on Glasgow come scale (GCS) values. The data collection procedure of clinical and ventilator variables was conducted as follows:

TV, ventilator mode, PaO_2, FiO_2 and PEEP values 3 hours after admission to the ICU were collected. Subsequently, TV and ventilator mode from every 12 hours of the stay were noted. To find the lowest PaO_2/FiO_2-ratio in the course of the day, the lowest PaO_2 value that day was first identified. The PEEP value used at the highest FiO_2 during every day was also collected.

In addition to the latter variables, the lowest oxygen saturation value determined with the pulse oximeter (SpO_2) as well as MAP, ICP and CPP in the course of a day were noted. Correspondingly, respiratory rate and ventilator pressures such as peak inspiratory pressure, plateau pressure and driving pressure were noted at fixed intervals every 12 hours. Rough estimates on length of ICU stay and days on ventilator were based on intensive care charts.

Respiratory failure was defined as any pulmonary complication during the ICU stay. Clinical diagnosis of pulmonary complications was identified through medical record and x-ray data. In addition, severity of lung injury was classified by PaO2/FiO2-ratio as done in the aforementioned study by Boone et al.[57] Here, the oxygenation criterion of the Berlin definition of ARDS (Table 1)

was applied in all patients, independent of whether the patient was diagnosed with ARDS or not. Classifying patients this way serves to quantify the degree of oxygenation failure. Accordingly, the absence of lung injury was classified by a PaO2/FiO2 >39,9 kPa, mild lung injury as PaO2/FiO2 >26,6 and ≤39,9 kPa, moderate as PaO2/FiO2 >13,3 and ≤26,6 kPa, and severe as PaO2/FiO2 <13,3 kPa. Patients with at least one PaO2/FiO2 value >26,6 and ≤39,9 kPa were therefore classified as having developed mild lung injury independent of clinical diagnosis found in medical notes. Accordingly, patients with at least one PaO2/FiO2 value >13,3 and ≤26,6 kPa were classified as having developed moderate lung injury, and so forth.

Concerning PEEP values, we were interested in identifying PEEP values that were too low for a given FiO_2 value, as these are the clinically important values to identify. The ARDS Network recommendation for PEEP/FiO_2 settings, which was also reflected in our established protocol, was used as a golden standard (Table 2).[42]

TVs were divided both by actual body weight and predicted body weight (PBW).

Prior to commencing data collection, the project was accepted by the Data Protection Official at UNN.

2.3 Data analysis and statistics

Data are presented as mean ± SD and proportions using descriptive statistical methods. The analyses were performed using SPSS for Mac, version 25 (IBM Corporation, Armonk, NY) and Microsoft Excel for Mac, version 16.13 (Microsoft Corporation, Redmond, WA).

3 Results

3.1 Patients

Eighteen patients with SAH and 12 patients with TBI were included in the study. Patient characteristics are described in Table 3. Patients with TBI were subclassified into groups of TBI severity based on GCS values before tracheal intubation.[12] Of all TBI patients included, 17% of them were classified as having mild TBI, 33% as having moderate TBI and 50% as having severe TBI. Ten (56%) patients with SAH and 1 (8%) patient with TBI died during the stay at UNN or were transferred to their local hospital for terminal care.

Data on body height were only found in 17 (57%) of the patients. Consequently, in nearly half of the patients, we were unable to calculate PBW. The calculations of the length of ICU stay and days on ventilator are rough estimates based on intensive care charts.

Table 3. Patient characteristics

Age at admission, mean (SD), y	52,6 (18,3)
SAH patients	55,4 (16,4)
TBI patients	48,3 (20,9)
Women, No. (%)	18 (60%)
SAH patients	14 (78%)
TBI patients	4 (22%)
Diagnosis, No. (%)	
SAH	18 (60%)
TBI	12 (40%)
Mild TBI (GCS 13-15)	2 (17%)
Moderate TBI (GCS 9-13)	4 (33%)
Severe TBI (GCS ≤8)	6 (50%)
Mortality during hospitalisation, No. (%)	11 (37%)
SAH patients	10 (56%)
TBI patients	1 (8%)
Body weight, mean (SD), kg	
Actual body weight (n=28 (93%))	77,0 (20,1)
Predicted body weight (PBW)[a] (n=17 (57%))	63,4 (10,9)
Length of ICU stay, mean (SD), days	6,2 (7,2)
SAH patients	4,2 (5,1)
TBI patients	9,1 (8,9)
Ventilator days, mean (SD)	5,4 (6,7)
SAH patients	3,6 (4,9)
TBI patients	8,1 (8,1)

Abbreviations: SD, standard deviation; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; ICU, intensive care unit.

[a]Predicted body weight of male patients was calculated as equal to 50+0.91(centimeters of height–152.4); that of female patients was calculated as equal to 45.5+0.91(centimeters of height–152.4).[36]

3.2 Incidence of respiratory failure

In the group of patients with TBI, 4 (33% had developed acute pulmonary complications in the prehospital setting. Two patients were diagnosed with small traumatic pneumothorax, one

patient was diagnosed with pulmonary contusion, and one patient with both pneumo- and hemothorax in addition to pulmonary contusion. Apart from these four patients, none of the other patients were diagnosed with any acute pulmonary complications on admission.

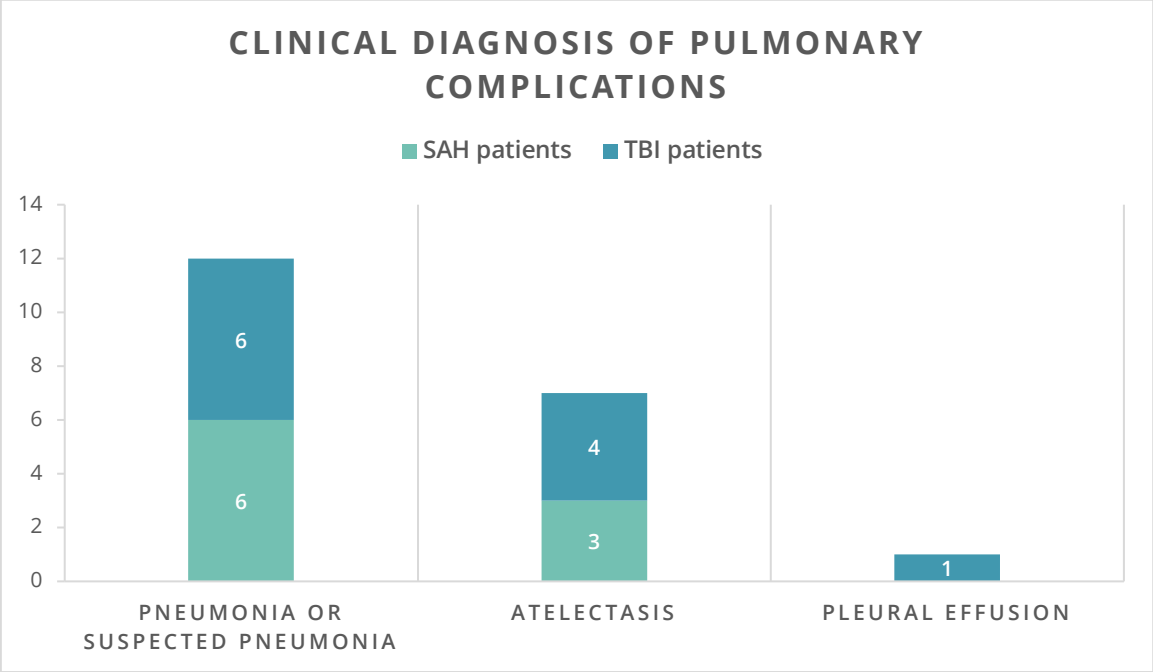


Figure 4. Clinical diagnosis of pulmonary complications during the stay in the ICU.

The number of patients diagnosed with different pulmonary complications during their stay in the ICU is shown in Figure 4. Of all the patients, 16 (53%) were diagnosed with any pulmonary complication. Twelve patients (40%) were diagnosed either with pneumonia or were suspected to have developed pneumonia. Seven patients (23%) were diagnosed with atelectasis, while one patient (3%) had a pleural effusion. Comprising a smaller number of patients, pulmonary complications were observed in 67% of patients with TBI versus 44% of patients with SAH.

Five patients (17%) displayed both pneumonia and other pulmonary complications such as atelectasis and pleural effusion. A patient who developed both pneumonia and atelectasis therefore was included both in the number of patients with pneumonia and in the number of patients with atelectasis. Fourteen patients (47%) were not diagnosed with any pulmonary complication during their stay in the ICU at UNN.

Independent of clinical diagnosis of pulmonary complications, severity of lung injury was also classified by applying the lowest PaO_2/FiO_2 ratio registered during the stay. The result of this classification is shown in Figure 5.

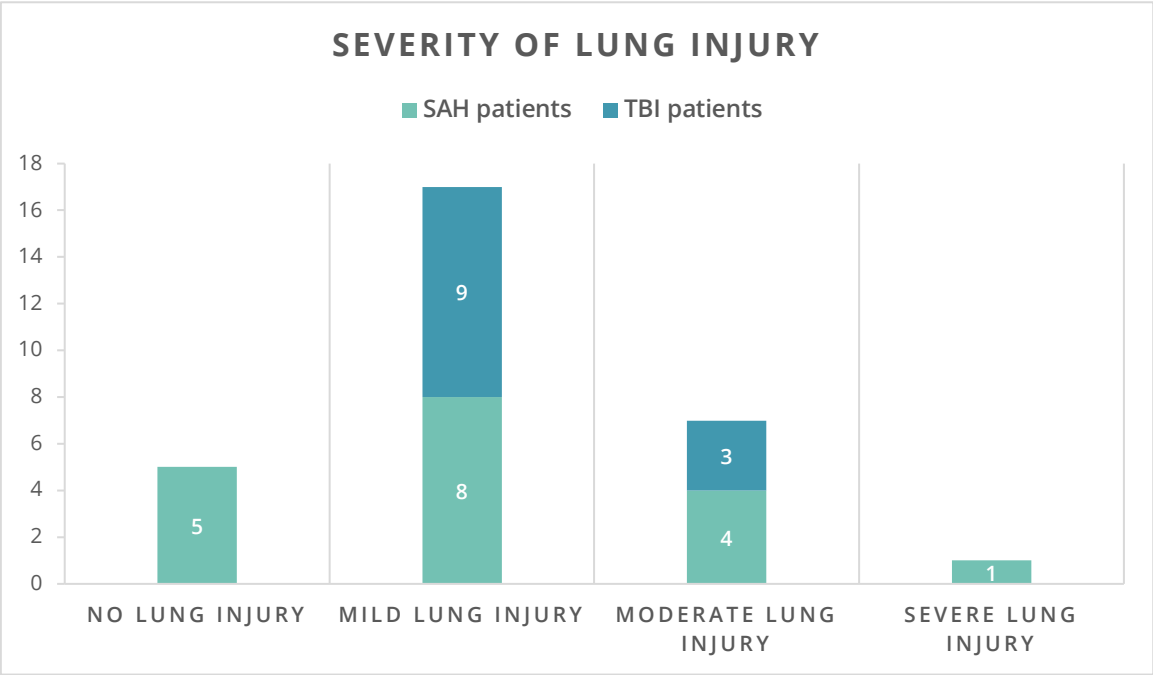


Figure 5. Severity of lung injury. Absence of lung injury was classified by a PaO_2/FiO_2 >39,9 kPa, mild lung injury as PaO_2/FiO_2 >26,6 and ≤39,9 kPa, moderate as PaO_2/FiO_2 >13,3 and ≤26,6 kPa, and severe as PaO_2/FiO_2 <13,3 kPa.

Of all the patients, 25 (83%) of them were registred with a PaO_2/FiO_2 ratio below 39,9 kPa at least once during their stay in the ICU. Consequently, only 5 patients (17%), all belonging to the SAH group, had PaO_2/FiO_2 ratios exclusively >39,9 kPa. Mild lung injury was found in 17 patients (57%), more frequently in the TBI group (75%) than in the SAH group (44%). Moderate lung injury was found in 7 patients (23%). We suspected one patient of having pneumonia, who was later classified with severe lung injury due to a PaO_2/FiO_2 ratio <13,3 kPa. Of all the 7 patients we classified as having moderate lung injury, 3 (43%) of them suffered from pneumonia. We suspected one patient of both pneumonia and atelectasis combined, and one patient to have atelectasis only. In the moderate lung injury group, one patient died within one day of admission, but the clinical diagnosis of the respiratory failure was not made.

3.3 PEEP values

Compared to the ARDS Network recommendation for $PEEP/FiO_2$ settings, too low PEEP values for a given FiO_2 were identified in 6 (20%) of the patients. Of all the collected PEEP values, only 11 of them (5,6%) were found to be too low for the given FiO_2 value. The distribution of all collected FiO_2 values is shown in Figure 6. A relatively small proportion of collected FiO_2 values were in the higher ranges. Totally, we found 14,9% between 0,4 and 0,49 and 6,9% >0,5, respectively.

3.4 Tidal volumes

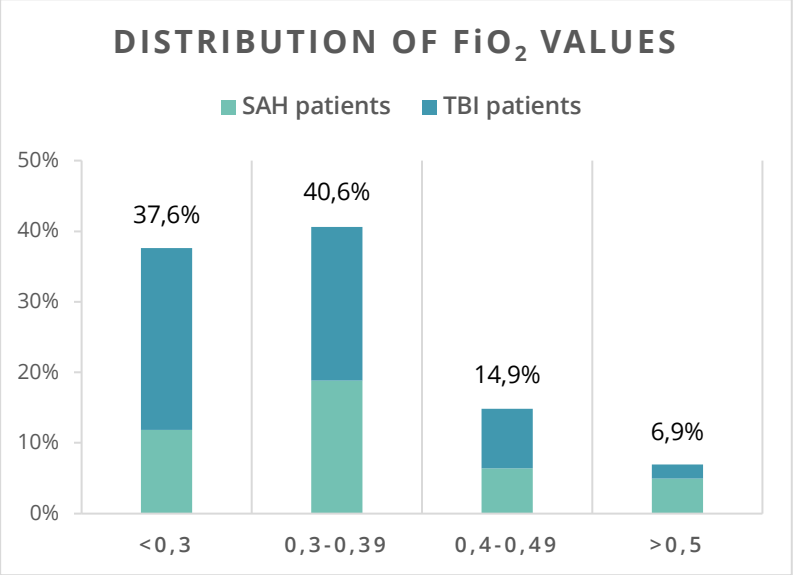


Figure 6. Distribution of FiO_2 values.

Of all 30 patients, information on actual body weight was found in 28 patients (93%), whereas body height was found in 17 patients (57%). Consequently, TV/PBW could only be calculated in this proportion of patients. The mean (±SD) TV/actual body weight was 6,7 ± 1,1 mL/kg, and in 27% of these patients, at least one of the collected TVs was >8 mL/kg actual body weight. Of all TVs/actual body weight collected, 76,1% of them were >6 mL/kg and 11,7% of them were >8 mL/kg. The mean (±SD) TV/PBW was 7,3 ± 1,0, but in 41% of these patients at least one of the collected TVs were >8 mL/kg PBW. Of all TVs/PBW collected, 95,0% were >6 mL/kg and 23,1% were >8 mL/kg.

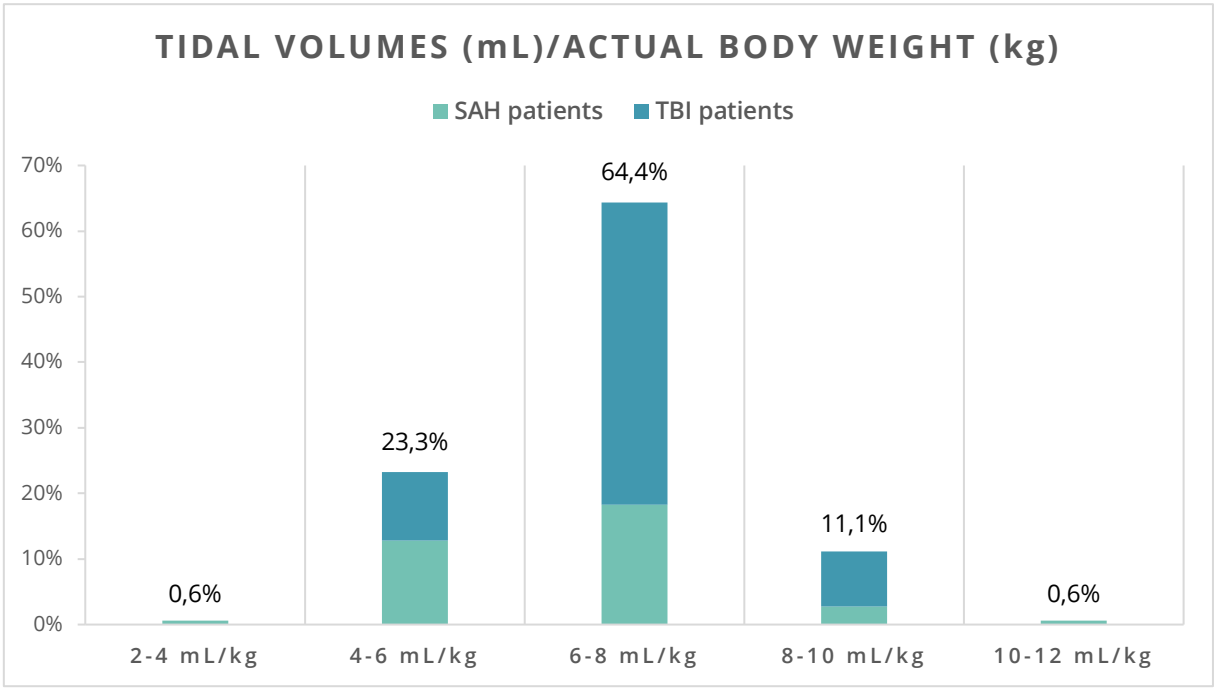


Figure 7. Tidal volumes per actual body weight. The figure shows the distribution of all collected tidal volumes (TVs), divided into different intervals of TVs. TVs in milliliters of actual body weight in kilograms. All TVs were determined during controlled ventilator modes.

To give an impression of exposure over time, all collected TVs on controlled ventilator modes are shown in Figure 7 and Figure 8 as proportions of different TVs/kg. In Figure 7, TVs in mL/kg actual body weight are illustrated, whereas in Figure 8, TVs in mL/kg PBW are shown.

The TBI patients contributed more to the analyses on TVs than did the SAH patients due to more ventilator days. The TBI patients had mean (±SD) 8,1 ± 8,1 ventilator days, while the SAH patients had 3,6 ± 4,9.

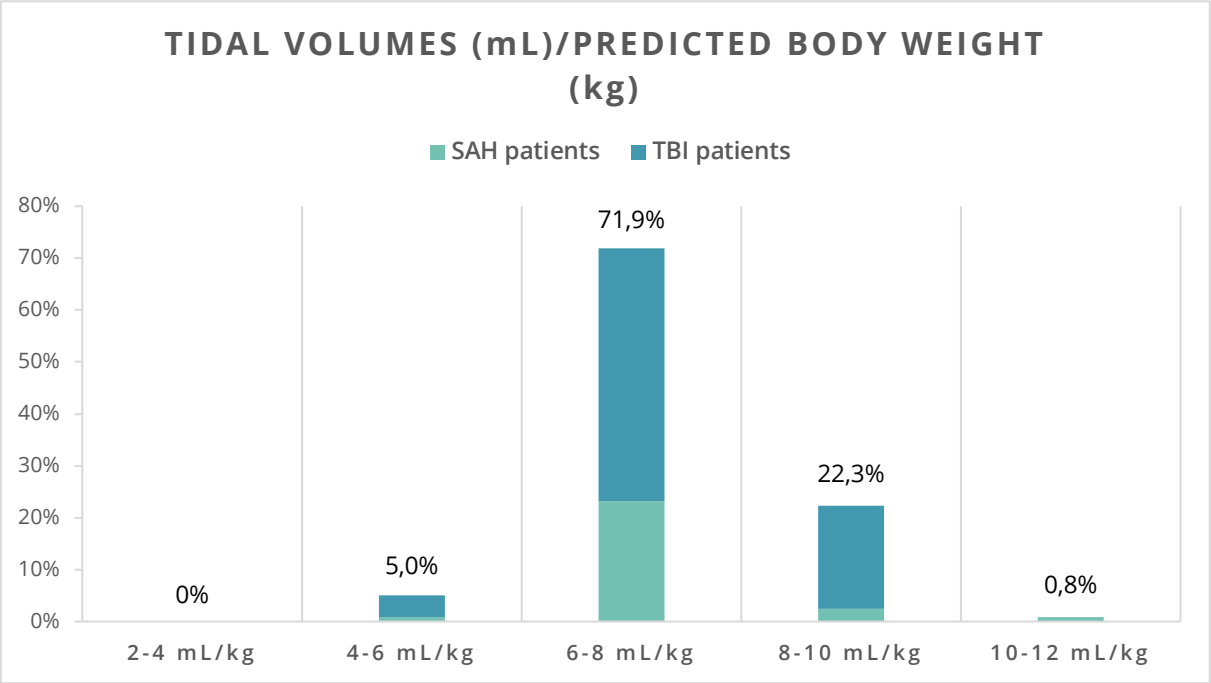


Figure 8. Tidal volumes per predicted body weight. The figure shows the distribution of all collected tidal volumes (TVs), divided into different intervals of TVs. TVs in milliliters of predicted body weight in kilograms. All TVs were determined during controlled ventilator modes.

4 Discussion

The present study demonstrated that 53 % of the ABI patients had pulmonary complications in the ICU, with pneumonia as the most common cause. The finding of high rates of pulmonary complications in neurointensive patients is consistent with the previous studies investigating this group of patients.[26,29–33] Eighty-three per cent of the patients had acute lung injury with low PaO_2/FiO_2, as defined by the Berlin classification for ARDS criteria, at some time point during the ICU course. However, none of the patients in our material were diagnosed with ARDS, while others have reported an incidence of 20-30% in patients with isolated brain injury.[30–33] A study including ICU patients hospitalized between 2012 and 2014 with patient data from the ICUs of the three hospitals comprising the University Hospital of North Norway (Tromsø, Harstad and Narvik) suggested that ARDS is an underdiagnosed condition in the UNN hospitals.[62] When going

through x-ray data and clinical documentation of the patients included, none of them were found to meet all the criteria in the Berlin definition of ARDS, specifically bilateral opacities on chest imaging. The short inclusion time might represent the most likely explanation for fewer patients diagnosed with ARDS in our study as compared with the corresponding results of larger studies.

When considering the PEEP/FiO_2 settings observed, it is close at mind to take a closer a look at the distribution of all collected FiO_2 values (Figure 6). Only a small portion of the patients in our material needed FiO_2 values > 0,4. This study could therefore not demonstrate many PEEP/FiO_2 ratios different from the ARDS Network recommendations for PEEP/FiO_2 settings as presented in Table 2. Consequently, based on these results, no conclusions can be drawn with respect to our second aim regarding the PEEP/FiO_2 settings. Other studies, though, have described low PEEP in ABI, even in the presence of acute respiratory failure. Pelosi et al. conducted a study comparing 552 mechanically ventilated patients with 4030 mixed patients who were ventilated for non-neurologic reasons.[58] They found that more than 80% of the neurologic patients were ventilated with a PEEP of ≤ 5 cm H_2O, despite the fact that a PEEP level of 5 cm H_2O generally is considered the minimum PEEP level during invasive mechanical ventilation.[45]

Concerning TVs, we were only able to calculate TV/PBW in 57% of the patients as information on body height was missing in nearly half of the patients. This may indicate that in many of the patients, the chosen TV was set based on other variables than PBW. This contrasts the recommendation that TVs be set on the basis of PBW because lung size correlate better with body height and sex than actual body weight. Furthermore, the studies investigating the optimal TV in ARDS and other causes of respiratory failure have used TV calculations applying PBW.[35,36,46] Whether body height and PBW was actually assessed and accounted for without writing it down is not known. We can only ascertain that in nearly half of the patients, information on body height was neither found in the ICU chart, the medication chart nor anywhere else in the medical record. In some patients, data on body height was only found by looking at medication charts related to a different admission. If the patient's PBW and corresponding TVs were actually written on the intensive care chart, that could enhance attention to TVs/PBW. As an example, a 183 cm high man would have a PBW of 77,8 kg. The corresponding TV at 6 mL/PBW is 467 mL, while it is 623 mL at a level of 8 mL/PBW. During the work with this thesis, the team at MDCalc, an online medical calculator, was contacted to request the PBW calculator to be included in the collection of available calculators. The MDCalc calculator is available both online at mdcalc.com and as a smartphone app, and is considered the by far most popular online medical calculator.[63] The PBW calculator, if added, would make calculations on PBW easier in a busy clinical practice without

having to find the actual formula.

In 41% of the patients where calculations on PBW could be made, at least one of the collected TVs were >8 mL/kg PBW. Of all TVs/PBW collected, 95,0% of the values were >6 mL/kg and 23,1% were >8 mL/kg. This is not surprising, as the conventional ventilation strategy in patients with ABI uses higher TVs than in non-neurologic patients, and since achievement of desirable $PaCO_2$ values may be challenging using small TVs.[48,59,60] There is a discussion whether all patients receiving mechanical ventilation should receive low TVs around 6 mL/kg PBW. A 2012 meta-analysis synthesizing data from 20 studies involving almost 3000 patients without ARDS found large risk ratios (RRs) favoring lower TVs in terms of lung injury development (RR, 0,33; 95% CI, 0,23-0,47), pulmonary infection (RR, 0,45; 95% CI, 0,22-0,92), and mortality (RR, 0,64; 95% CI, 0,46-0,98).[64] Although these results seem compelling, they must be interpreted with caution. Of the 20 studies included in the meta-analysis, 5 of them were observational (in which inferences of causality may be problematic) and accounted for approximately 85% of both the total number of patients and events in the primary analysis of lung injury prevention.[51] Moreover, the randomized trials included had limitations related to quality and many of them focused on short-term intraoperative ventilation during anesthesia. Generalizability to other clinical situations may therefore be poor. In summary, these findings are not definitive, but rather hypothesis generating and support the need to conduct large randomized trials.

Observational data have found a lung-protective ventilation strategy to be an independent predictor of favorable outcome in brain-damaged patients.[52] But the safety and efficacy of a lung-protective ventilation strategy in patients with ABI also need to be assessed through randomized trials. The medical literature has many examples in which physiological rationale, meta-analyses of small or low-quality studies, or both suggested benefit followed by large trials that refuted these findings or even showed harm.[51] An example of this is steroids for TBI, which had been used to treat head injuries for more than 30 years prior to the so-called CRASH trial.[65] In that large trial enrolling 10 008 adults with head injury, patient recruitment had to be stopped as there was seen an increased mortality in the corticosteroid arm.

Future trials also need to address the safety of PEEP in patients with ABI, and how PEEP affect ICP. In addition, factors contributing to the high number of patients with ABI developing pulmonary complications need to be further explored, and preventing factors need to be elucidated.

4.1 Limitations

This study comprises a small group of patients from only one center covering a short time span. In addition, retrospective studies like this have inherent limitations concerning evidence quality. Consequently, reliable conclusions cannot be drawn from this study alone.

A major limitation of the analyses of PEEP values is the data collection procedure, which consisted in reading scanned handwritten hospital charts. Therefore, these results should be interpreted with caution. As the primary focus of the data collection was to identify the lowest PaO_2/FiO_2 ratio during the course of the day, the lowest PaO_2 value was first identified, and subsequently the corresponding FiO_2 value was noted. The PEEP value identified was the PEEP value at the highest FiO_2 throughout the day, and not necessarily the same FiO_2 value as noticed in the former step. Accordingly, some of the PEEP values do not correspond in time to the FiO_2 values. In retrospect, we would maybe have identified even lower PaO_2/FiO_2 ratios by collecting these values the other way around, i.e. by first identifying the highest FiO_2 value and then calculating the PaO_2/FiO_2 ratio by using the corresponding PaO_2 value. Then we would also be certain that the PEEP value at the highest FiO_2 value during the day corresponded in time. All in all, this seems like a better approach. That being said, the analyses on PEEP values are not totally in vain. The observed PEEP values on the ICU charts were generally set to the same value throughout the day, so the probability that the PEEP and FiO_2 values after all do correspond in time, is high.

Another limitation of the data collection procedure is the manual punching of data from handwritten ICU charts. This procedure could perhaps cause errors in the data set that were not detected. Moreover, some of the handwritten numbers were not easy to interpret, constituting an additional source of potential errors. The fact that TVs only were collected for every 12 hours and other variables only once during the course of a day imply that our data are snapshots of all the actual variables used throughout the ICU stay. Consequently, we cannot be certain that the distribution of observed FiO_2 values shown in Figure 6 and the distribution of TVs in Figure 7 and Figure 8 actually represent the true distribution. Nonetheless, it is plausible to presume that the true distribution lies close to the observed distribution through the snapshots of our material.

The time-consuming data collection procedure related to this study underlines the potential of a digitalized intensive care chart, where study variables more easily can be extracted and analyzed. That would have made both data collection and conduction of studies as a whole more feasible.

The inclusion of patients was based on a list provided by the ICU staff. This list was supposed to include all patients with ABI admitted to the ICU of UNN Tromsø, but by using this method, it is conceivable that some patients that should have been included were not identified.

Another limitation of this study is that we were not able to draw any conclusions with regard to causality between ventilator settings and pulmonary complications. This is both due to the small number of patients included and the observational nature of the study.

5 Conclusion

This study found a high incidence of pulmonary complications in ICU patients with ABI, with pneumonia as the most common cause. This finding is consistent with other studies investigating this group of patients. None of the patients in our material were diagnosed with ARDS. The short inclusion time and the low number of patients included representing the most likely explanations for this finding. The mean (±SD) TV/actual body weight (n=28) was 6,7 ± 1,1 mL/kg, while the mean (±SD) TV/PBW (n=17) was 7,3 ± 1,0. Data on body height could only be found in 57% of the patients, implicating that TVs were set based on other variables than PBW in nearly half of the patients. Randomized trials assessing the safety and efficacy of low TVs and PEEP ventilation in ABI are warranted.

6 References

1. Pelosi P, Severgnini P, Chiaranda M. An integrated approach to prevent and treat respiratory failure in brain-injured patients. *Curr Opin Crit Care*. 2005;11(1):37-42.

2. Borsellino B, Schultz MJ, Gama de Abreu M, Robba C, Bilotta F. Mechanical ventilation in neurocritical care patients: a systematic literature review. *Expert Rev Respir Med*. 2016;10(10):1123-1132. doi:10.1080/17476348.2017.1235976

3. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993;34(2):216-222. http://europepmc.org/abstract/MED/8459458.

4. Johnston SC, Selvin S, Gress DR. The burden, trends, mortality from and demographics of subarachnoid hemorrhage. *Neurology*. 1998;50:1413-1418.

5. Lawton MT, Vates GE. Subarachnoid hemorrhage. *N Engl J Med*. 2017;377(3):257-266. doi:10.1056/NEJMcp1605827

6. De Rooij NK, Linn FHH, Van Der Plas JA, Algra A, Rinkel GJE. Incidence of subarachnoid haemorrhage: A systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78(12):1365-1372. doi:10.1136/jnnp.2007.117655

7. Sandvei MS, Mathiesen EB, Vatten LJ, et al. Incidence and mortality of aneurysmal subarachnoid hemorrhage in two Norwegian cohorts, 1984-2007. *Neurology*. 2011;77(20):1833-1839. doi:10.1212/WNL.0b013e3182377de3

8. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet*. 2017;389(10069):655-666. doi:10.1016/S0140-6736(16)30668-7

9. Lucke-Wold BP, Logsdon AF, Manoranjan B, et al. Aneurysmal subarachnoid hemorrhage and neuroinflammation: A comprehensive review. *Int J Mol Sci*. 2016;17(4):1-17. doi:10.3390/ijms17040497

10. Hackett ML, Anderson CS. Health outcomes 1 year after subarachnoid hemorrhage: An international population-based study. The Australian Cooperative Research on Subarachnoid Hemorrhage Study Group. *Neurology*. 2000;55:658-662.

11. Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol*. 2008;7(8):728-741. doi:10.1016/S1474-4422(08)70164-9

12. Ghajar J. Traumatic brain injury. *Lancet*. 2000;356(9233):923-929. doi:10.1016/S0140-6736(00)02689-1

13. Ingebrigtsen T, Romner B, Kock-Jensen C. Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries. *J Trauma*. 2000;48(4):760-766. doi:10.1097/00005373-200004000-00029

14. Dinsmore J. Traumatic brain injury: an evidence-based review of management. *Contin Educ Anaesthesia, Crit Care Pain*. 2013;13(6):189-195. doi:10.1093/bjaceaccp/mkt010

15. Dombovy ML. Traumatic brain injury. *Contin Lifelong Learn Neurol*. 2011;17(3):584-605.

doi:10.1212/01.CON.0000399074.07686.76

16. Undén J, Ingebrigtsen T, Romner B, Committee N. Scandinavian guidelines for initial management of minimal , mild and moderate head injuries in adults : an evidence and consensus-based update Scandinavian guidelines for initial management of minimal , mild and moderate head injuries in adults : an evide. *BMC Med*. 2013;11(1):50. doi:10.1186/1741-7015-11-50

17. Astrand R, Rosenlund C, Undén J, et al. Scandinavian guidelines for initial management of minor and moderate head trauma in children. *BMC Med*. 2016;14(1). doi:10.1186/s12916-016-0574-x

18. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery*. 2016;24(Suppl 1.):244. doi:10.1227/NEU.0000000000001432

19. Rozet I, Domino KB. Respiratory care. *Best Pract Res Clin Anaesthesiol*. 2007;21(4):465-482. doi:http://doi.org/10.1016/j.bpa.2007.07.001

20. Bakowitz M, Bruns B, McCunn M. Acute lung injury and the acute respiratory distress syndrome in the injured patient. *Scand J Trauma Resusc Emerg Med*. 2012;20(1):54. doi:10.1186/1757-7241-20-54

21. The ARDS Definition Task Force. Acute respiratory distress syndrome: The Berlin Definition. *JAMA*. 2012;307(23):2526-2533. doi:10.1001/jama.2012.5669

22. Marino PL. Chapter 25: Positive pressure ventilation. In: *Marino's The ICU Book*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2014:487-503.

23. Dreyfuss D, Soler P, Basset G, Saumon G. High Inflation Pressure Pulmonary Edema: Respective Effects of High Airway Pressure, High Tidal Volume, and Positive End-expiratory Pressure. *Am Rev Respir Dis*. 1988;137(5):1159-1164. doi:10.1164/ajrccm/137.5.1159

24. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-2136. doi:10.1056/NEJMra1208707

25. Pelosi P, Rocco PR. Effects of mechanical ventilation on the extracellular matrix. *Intensive Care Med*. 2008;34(4):631-639. doi:10.1007/s00134-007-0964-9

26. Zygun DA, Zuege DJ, Boiteau PJE, et al. Ventilator-associated pneumonia in severe traumatic brain injury. *Neurocrit Care*. 2006;5:108-114. doi:10.1385/ncc:5:2:108

27. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: Recent advances in epidemiology and management. *Curr Opin Pulm Med*. 2013;19(3):216-228. doi:10.1097/MCP.0b013e32835f27be

28. Ware LB, Matthay MA. The Acute Respiratory Distress Syndrome. *N Engl J Med*. 2000;342(18):1334-1349. doi:10.1056/NEJM200005043421806

29. Jovanovic B, Milan Z, Markovic-Denic L, et al. Risk factors for ventilator-associated pneumonia in patients with severe traumatic brain injury in a Serbian trauma centre. *Int J Infect Dis*. 2015;38:e46-e51. doi:10.1016/j.ijid.2015.07.005

30. Kahn JM, Caldwell EC, Deem S, Newell DW, Heckbert SR, Rubenfeld GD. Acute lung injury in patients with subarachnoid hemorrhage: incidence, risk factors and outcome. *Crit Care Med*. 2006;34. doi:10.1097/01.CCM.0000194540.44020.8E

31. Holland MC, Mackersie RC, Morabito D, et al. The development of acute lung injury is associated with worse neurologic outcome in patients with severe traumatic brain injury. *J Trauma*. 2003;55(1):106-111. doi:10.1097/01.TA.0000071620.27375.BE

32. Aisiku IP, Yamal JM, Doshi P, et al. The incidence of ARDS and associated mortality in severe TBI using the Berlin definition. *J Trauma Acute Care Surg*. 2016;80(2):308-312. doi:10.1097/TA.0000000000000903

33. Hendrickson CM, Howard BM, Kornblith LZ, et al. The acute respiratory distress syndrome following isolated severe traumatic brain injury. *J Trauma Acute Care Surg*. 2016;80(6):989-997. doi:10.1097/TA.0000000000000982

34. Dreyfuss D, Saumon G. Ventilator-induced lung Injury. *Am J Respir Crit Care Med*. 1998;157(1):294-323. doi:10.1164/ajrccm.157.1.9604014

35. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347-354. doi:10.1056/NEJM199802053380602

36. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308. doi:10.1056/NEJM200005043421801

37. Richard J-C, Brochard L, Vandelet P, et al. Respective effects of end-expiratory and end-inspiratory pressures on alveolar recruitment in acute lung injury. *Crit Care Med*. 2003;31(1). doi:10.1097/01.CCM.0000037960.70104.1E

38. Briel M, Meade M, Mercat A, Al E. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873. doi:10.1001/jama.2010.218

39. Chen H, Xu M, Yang Y-L, et al. Effects of increased positive end-expiratory pressure on intracranial pressure in acute respiratory distress syndrome: a protocol of a prospective physiological study. *BMJ Open*. 2016;6(11). doi:10.1136/bmjopen-2016-012477

40. Lou M, Xue F, Chen L, Xue Y, Wang K. Is high PEEP ventilation strategy safe for acute respiratory distress syndrome after severe traumatic brain injury? *Brain Inj*. 2012;26(6):887-890. doi:10.3109/02699052.2012.660514

41. Linares-Perdomo O, East TD, Brower R, Morris AH. Standardizing predicted body weight equations for mechanical ventilation tidal volume settings. *Chest*. 2015;148(1):73-78. doi:10.1378/chest.14-2843

42. and Blood Institute ARDS Clinical Trials Network TNHL. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351(4):327-336. doi:10.1056/NEJMoa032193

43. Sahetya SK, Brower RG. Lung recruitment and titrated PEEP in moderate to severe ARDS:

Is the door closing on the open lung? *JAMA*. 2017;318(14):1327-1329. doi:10.1001/jama.2017.13695

44. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA*. 2017;318(14):1335-1345. doi:10.1001/jama.2017.14171

45. Neto AS, Schultz MJ. Optimizing the settings on the ventilator: High PEEP for all? *JAMA*. 2017;317(14):1413-1414. http://dx.doi.org/10.1001/jama.2017.2570.

46. Neto AS, Simonis FD, Barbas CS V., et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome. *Crit Care Med*. 2015;43(10):2155-2163. doi:10.1097/CCM.0000000000001189

47. Mascia L. Acute lung injury in patients with severe brain injury: A double hit model. *Neurocrit Care*. 2009;11(3):417-426. doi:10.1007/s12028-009-9242-8

48. Swain A, Bhagat H, Sahni N, Salunke P. Mechanical ventilation in neurological and neurosurgical patients. *Neurol India*. 2016;64(3). doi:10.4103/0028-3886.181585

49. Ngubane T. Mechanical ventilation and the injured brain. *South African J Anaesth Analg*. 2011;17(1):76-80. doi:10.1080/22201173.2011.10872737

50. Coles JP, Fryer TD, Coleman MR, et al. Hyperventilation following head injury: Effect on ischemic burden and cerebral oxidative metabolism. *Crit Care Med*. 2007;35(2):568-578. doi:10.1097/01.CCM.0000254066.37187.88

51. Ferguson ND. Low tidal volumes for all? *JAMA*. 2012;308(16):1689. doi:10.1001/jama.2012.14509

52. Elmer J, Hou P, Wilcox SR, et al. Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage. *Crit Care Med*. 2013;41(8):1992-2001. doi:10.1097/CCM.0b013e31828a3f4d

53. Koutsoukou A, Katsiari M, Orfanos SE, et al. Respiratory mechanics in brain injury: A review. *World J Crit care Med*. 2016;5(1):65-73. doi:10.5492/wjccm.v5.i1.65

54. Frost EAM. Effects of positive end-expiratory pressure on intracranial pressure and compliance in brain-injured patients. *J Neurosurg*. 1977;47(2):195-200. doi:10.3171/jns.1977.47.2.0195

55. Shapiro HM, Marshall LF. Intracranial pressure responses to PEEP in head-injured patients. *J Trauma Acute Care Surg*. 1978;18(4).

56. Burchiel KJ, Steege TD, Wyler AR. Intracranial pressure changes in brain-injured patients requiring positive end-expiratory pressure ventilation. *Neurosurgery*. 1981;8(4).

57. Boone MD, Jinadasa SP, Mueller A, et al. The effect of positive end-expiratory pressure on intracranial pressure and cerebral hemodynamics. *Neurocrit Care*. 2017;26(2):174-181. doi:10.1007/s12028-016-0328-9

58. Pelosi P, Ferguson ND, Frutos-Vivar F, et al. Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med*. 2011;39(6). doi:10.1097/CCM.0b013e31821209a8

59. Asehnoune K, Roquilly A, Cinotti R. Respiratory Management in Patients with Severe Brain Injury. *Crit Care*. 2018;22(1):76. doi:10.1186/s13054-018-1994-0

60. Lowe GJ, Ferguson ND. Lung-protective ventilation in neurosurgical patients. *Curr Opin Crit Care*. 2006;12(1):3-7.

61. Oddo M, Citerio G. ARDS in the brain-injured patient: what's different? *Intensive Care Med*. 2016;42(5):790-793. doi:10.1007/s00134-016-4298-3

62. Moholt A, Hansen HD. Incidence, treatment and survival of ARDS in Northern Norway: preliminary findings [Master's thesis in medicine]. Tromsø: UiT – The Arctic University of North Norway; 2016. 52 pp.

63. Maurer D. MDCalc app, the best online medical calculator is now an app [Internet]. *iMedicalApps*; published 2016 [accessed May 30, 2018]. Available from: https://www.imedicalapps.com/2016/03/mdcalc-medical-calculator-app/

64. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes. *JAMA*. 2012;308(16):1651-1659. doi:10.1001/jama.2012.13730

65. Olldashi F, Muzha I, Filipi N, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): Randomised placebo-controlled trial. *Lancet*. 2004;364(9442):1321-1328. doi:10.1016/S0140-6736(04)17188-2

66. Villar J, Suárez-Sipmann F, Kacmarek RM. Should the ART trial change our practice? *J Thorac Dis*. 2017;9(12):4871-4877. doi:10.21037/jtd.2017.11.01

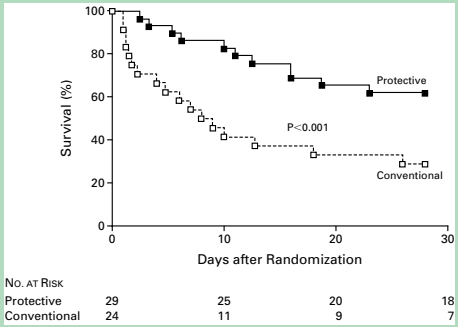
7 GRADE evaluations

In the following pages, GRADE evaluations of five of the cited articles are found. These articles are:

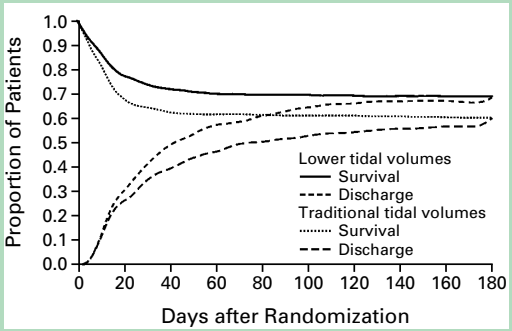
1. Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347-354.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-1308. (ARMA study)
3. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. N Engl J Med. 2004;351(4):327-336. (ALVEOLI study)
4. Neto AS, Simonis FD, Barbas CS V., et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome. Crit Care Med. 2015;43(10):2155-2163.
5. Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA. 2017;318(14):1335-1345. (ART Trial)

Reference: Amato MBP, Barbas CSV, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347-354. doi:10.1056/NEJM199802053380602

Design: RCT	
Evidence level	Ib
GRADE	⊕⊕⊕○ MODERATE

Aim	Materials and methods	Results	Discussion/comments
To determine whether a ventilatory strategy designed to minimize lung injuries could reduce not only pulmonary complications but also mortality at 28 days in patients with the acute respiratory distress syndrome.	53 patients with early acute respiratory distress syndrome, all of whom were receiving identical hemodynamic and general support, were randomly assigned to either conventional or protective mechanical ventilation. Conventional ventilation was based on the strategy of maintaining the lowest positive end-expiratory pressure (PEEP) for acceptable oxygenation, with a tidal volume of 12 ml per kilogram of body weight and normal arterial carbon dioxide levels (35 to 38 mm Hg). Protective ventilation involved end-expiratory pressures above the lower inflection point on the static pressure–volume curve, a tidal volume of less than 6 ml per kilogram, driving pressures of less than 20 cm of water above the PEEP value, permissive hypercapnia, and preferential use of pressure-limited ventilatory modes. The primary end point was survival at 28 days. The secondary end points were survival to hospital discharge, occurrence of clinically detectable barotrauma, and weaning rate adjusted for APACHE II score (Acute Physiology and Chronic Health Evaluation).	After 28 days, 11 of 29 patients (38 percent) in the protective-ventilation group had died, as compared with 17 of 24 (71 percent) in the conventional-ventilation group (P<0.001). The rates of weaning from mechanical ventilation were 66 percent in the protective-ventilation group and 29 percent in the conventional-ventilation group (P=0.005); the rates of clinical barotrauma were 7 percent and 42 percent, respectively (P=0.02), despite the use of higher PEEP and mean airway pressures in the protective-ventilation group. The difference in survival to hospital discharge was not significant; 13 of 29 patients (45 percent) in the protective-ventilation group died in the hospital, as compared with 17 of 24 in the conventional-ventilation group (71 percent, P=0.37).  **Figure 1.** Actuarial 28-Day Survival among 53 Patients with the Acute Respiratory Distress Syndrome Assigned to Protective or Conventional Mechanical Ventilation. The data are based on an intention-to-treat analysis. The P value indicates the effect of ventilatory treatment as estimated by the Cox regression model, with the risk of death associated with the adjusted base-line score on APACHE II included as a covariate.	**Checklist** • Did the trial address a clearly focused issue? **Yes** • Was the assignment of patients to treatments randomised? **Yes** • Were patients, health workers and study personnel 'blind' to treatment? **Unclear/impossible to blind attending physcicians** • Were the groups similar at the start of the trial? **Yes, no significant diffrences between groups** • Aside from the experimental intervention, were the groups treated equally? **Yes** • Were all of the patients who entered the trial properly accounted for at its conclusion? **Yes** • How large and how precise was the treatment effect? **Large difference in 28-day mortality, favoring the protective ventilation group (38% vs 71%, p>0,001), non-significant difference in survival to hospital discharge (p=0,37)** • Can the results be applied to the local population, or in your context? **Yes** • Were all clinically important outcomes considered? **Yes** • Are the benefits worth the harms and costs? **Yes** **Strengths:** Large and significant difference in 28-day mortality. **Limitations:** Small study sample, not impossible to blind attending physicians, minor protocol violations in five patients. Non-significant difference in survival to hospital discharge.
Conclusion As compared with conventional ventilation, the protective strategy was associated with improved survival at 28 days, a higher rate of weaning from mechanical ventilation, and a lower rate of barotrauma in patients with the acute respiratory distress syndrome. Protective ventilation was not associated with a higher rate of survival to hospital discharge.			
Countries Brazil			
Years of data collection 1990 – 1995			

Reference: The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308. doi:10.1056/NEJM200005043421801 (ARMA study)	**Design: RCT**	
	Evidence level	Ib
	GRADE	⊕⊕⊕○ MODERATE

Aim	**Materials and methods**	**Results**	**Discussion/comments**
To determine whether ventilation with lower tidal volumes would improve the clinical outcome in patients with acute lung injury and the acute respiratory distress syndrome. **Conclusion** In this group of patients, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use. **Country** USA **Years of data collection** 1996 – 1999	Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter, randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 ml per kilogram of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 ml per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less. The first primary outcome was death before a patient was discharged home and was breathing without assistance. The second primary outcome was the number of days without ventilator use from day 1 to day 28.	The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent, P=0.007), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean [±SD], 12±11 vs. 10±11; P=0.007). The mean tidal volumes on days 1 to 3 were 6.2±0.8 and 11.8±0.8 ml per kilogram of predicted body weight (P<0.001), respectively, and the mean plateau pressures were 25±6 and 33±8 cm of water (P<0.001), respectively.  **Figure 1.** Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome. The status at 180 days or at the end of the study was known for all but nine patients. Data on these 9 patients and on 22 additional patients who were hospitalized at the time of the fourth interim analysis were censored.	**Checklist** • Did the trial address a clearly focuse issue? **Yes** • Was the assignment of patients to treatments randomised? **Yes** • Were patients, health workers and study personnel 'blind' to treatment? **Unclear/impossible to blind attending physicians** • Were the groups similar at the start of the trial? **Yes, apart from slightly but significantly higher minute ventilation in the lower tidal volume group (p=0,01)** • Aside from the experimental intervention, were the groups treated equally? **Yes, apart from higher plateau pressures in the high tidal volume group and higher PEEP in the low tidal volume group** • Were all of the patients who entered the trial properly accounted for at its conclusion? **Unclear** • How large was the treatment effect? **22% reduced mortality** • How precise was the estimate of the treatment effect? **Statistically significant mortality reduction, but relatively wide confidence interval for difference between groups (p=0,007, 95% CI 2,4–15,3%)** • Can the results be applied to the local population, or in your context? **Yes** • Were all clinically important outcomes considered? **Yes** • Are the benefits worth the harms and costs? **Yes** **Strengths:** Large multi-center randomized trial, significant mortality reduction. **Limitations:** Inconsistency with previous trials, but plausible reasons are given. Risk of performance bias due to unclear blinding procedure.

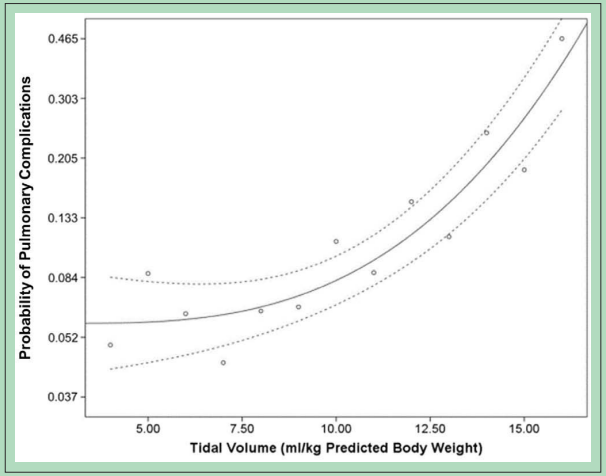
Reference: The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome. *N Engl J Med*. 2004;351(4):327-336. doi:10.1056/NEJMoa032193 (ALVEOLI study)

Design: RCT	
Evidence level	Ib
GRADE	⊕⊕⊕○ MODERATE

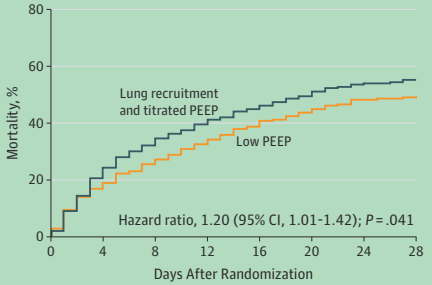
Aim	**Materials and methods**	**Results**	**Discussion/comments**
To compare the effects of higher and lower PEEP levels on clinical outcomes in patients requiring mechanical ventilation for acute lung injury and the acute respiratory distress syndrome.	549 patients with acute lung injury and ARDS were randomly assigned to receive mechanical ventilation with either lower or higher PEEP levels, which were set according to different tables of predetermined combinations of PEEP and fraction of inspired oxygen (refer to Table 2). 23 hospitals across the US participated in the study. The primary outcome measure was the proportion of patients who died before they were discharged home while breathing without assistance. Secondary outcome variables included the number of ventilator-free days (the number of days a patient breathed without assistance for at least 48 consecutive hours from day 1 to day 28), the number of days a patient was not in the intensive care unit (ICU) from day 1 to day 28, and the number of days without organ failure from day 1 to day 28. A centralized interactive voice system was used to randomly assign eligible patients in permuted blocks to either a lower- or a higher-PEEP strategy.	Mean (±SD) PEEP values on days 1 through 4 were 8.3±3.2 cm of water in the lower-PEEP group and 13.2±3.5 cm of water in the higher-PEEP group (P<0.001). The rates of death before hospital discharge were 24.9 percent and 27.5 percent, respectively (P=0.48; 95 percent confidence interval for the difference between groups, –10.0 to 4.7 percent). After adjusting for differences in the baseline variables, the mortality rate was 27.5 percent in the lower-PEEP group and 25.1 percent in the higher-PEEP group (P=0,47; 95 percent confidence interval for the difference between groups, -3.6 to 8.4 percent). From day 1 to day 28, breathing was unassisted for a mean of 14.5±10.4 days in the lower-PEEP group and 13.8±10.6 days in the higher-PEEP group (P=0.50). Table 4. **Main Outcome Variables.*** | Outcome	Lower-PEEP Group	Higher-PEEP Group	P Value
Death before discharge home (%)†			
Unadjusted	24.9	27.5	0.48
Adjusted for differences in baseline covariates	27.5	25.1	0.47
Breathing without assistance by day 28 (%)	72.8	72.3	0.89
No. of ventilator-free days from day 1 to day 28‡	14.5±10.4	13.8±10.6	0.50
No. of days not spent in intensive care unit from day 1 to day 28	12.2±10.4	12.3±10.3	0.83
Barotrauma (%)§	10	11	0.51
No. of days without failure of circulatory, coagulation, hepatic, and renal organs from day 1 to day 28	16±11	16±11	0.82		**Checklist** • Did the trial address a clearly focused issue? **Yes** • Was the assignment of patients to treatments randomised? **Yes** • Were patients, health workers and study personnel 'blind' to treatment? **Unclear/impossible to blind attending physicians** • Were the groups similar at the start of the trial? **Most of the baseline characteristics were similar, but in the higher-PEEP group, mean age was significantly higher (P=0,004), and the mean PaO_2/FiO_2 ratio was significantly lower (P=0,03)** • Aside from the experimental intervention, were the groups treated equally? **Yes, apart from higher plateau pressures in the higher-PEEP group and significant but very small differences in tidal volumes between groups** • Were all of the patients who entered the trial properly accounted for at its conclusion? **Unclear** • How large was the treatment effect? **Non-significant difference in mortality (P=0,48) and in secondary outcomes between groups** • How precise was the estimate of the treatment effect? **Adjusted 95% CI for the difference between groups -3.6 to 8.4 percent** • Can the results be applied to the local population, or in your context? **Yes** • Were all clinically important outcomes considered? **Yes** **Strengths:** Large multi-center randomized trial **Limitations:** Imbalance between groups in some baseline characteristics (age and PaO_2/FiO_2 ratio), unclear blinding.
Conclusion In this group of patients, the results suggest that clinical outcomes are similar whether lower or higher PEEP levels are used.			
Country USA			
Years of data collection 1999 – 2002			

Reference: Neto AS, Simonis FD, Barbas CS V., et al. Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome. Crit Care Med. 2015;43(10):2155-2163. doi:10.1097/CCM.0000000000001189

Design: Systematic review and ind. patient data analysis	
Evidence level	Ia
GRADE	⊕⊕⊕⊕ HIGH

Aim	Materials and methods	Results	Discussion/comments
The aim of this individual patient data analysis was to determine the association between tidal volume and the occurrence of pulmonary complications in ICU patients without acute respiratory distress syndrome and the association between occur- rence of pulmonary complications and outcome in these patients.	**Search strategy:** A sensitive search strategy followed Medical Subject Headings (MESH) and Keywords (protective ventilation OR lower tidal volume OR low tidal volume OR positive end-expiratory pressure OR positive end expiratory pressure OR PEEP). **Selection of studies:** Articles reporting on observational studies or RCTs of "protec- tive ventilation" in ICU patients identified by the search and reporting outcomes of interest were screened for inclusion. Key inclusion criteria were as follows: 1) clear reporting of the size of tidal volume, at least in the first days of ventilation; 2) adult (i.e., age > 18 yr) patients ventilated in the ICU; and 3) without ARDS at the onset of ventilation **Main outcomes:** The primary outcome was a composite of occurrence of ARDS or pneumonia, the two most important pulmonary complications in intubated and ventilated critically ill patients. Secondary outcomes included: 1) duration of stay in ICU and hospital, using the number of ICU-free days and alive and hospital-free days and alive at day 28; 2) in-hospital mortality, defined as death at any time during hospital stay; 3) incidence rate of pulmonary complications, and 4) attributable mor- tality of pulmonary complications.	3 RCTs and 4 observational studies were included. Totally, they comprised 2,184 patients. Based on the tertiles of tidal volume size in the first 2 days of ventilation, patients were assigned to a "low tidal volume group" (tidal volumes ≤ 7 mL/kg predicted body weight), an "intermediate tidal volume group" (> 7 and < 10 mL/kg predicted body weight), and a "high tidal volume group" (≥ 10 mL/kg predicted body weight). Acute respiratory distress syndrome or pneumonia occurred in 23% of patients in the low tidal volume group, in 28% of patients in the intermediate tidal volume group, and in 31% of the patients in the high tidal volume group (adjusted odds ratio [low vs high tidal volume group], 0.72; 95% CI, 0.52–0.98; p = 0.042). Occurrence of pulmonary complications was associated with a lower number of ICU-free and hospital-free days and alive at day 28 (10.0 ± 10.9 vs 13.8 ± 11.6 d; p < 0.01 and 6.1 ± 8.1 vs 8.9 ± 9.4 d; p < 0.01) and an increased hospital mortality (49.5% vs 35.6%; p < 0.01).  **Figure 2.** Probability and unit logistic regression showing the dose-relationship curve between the median tidal volume (mL/kg predicted body weight) used in the first 2 days of ventilation and the probability of pulmonary complications during ICU stay. ***Solid line***, mean quadratic term; ***dashed line***, 95% CI.	**Checklist** • Did the review address a clearly focused issue? **Yes** • Did the authors look for the right type of papers? **Yes** • Do you think all the important, relevant studies were included? **Yes** • Did the review's authors do enough to assess quality of the included studies? **Yes** • If the results of the review have been combined, was it reasonable to do so? **Yes** • What are the overall results of the review? **Significantly lower rates of ARDS and pneumonia in low tidal volume group (adjusted OR [low vs. high tidal volume group] 0,72. No difference in overall mortality between groups.** • How precise are the results? **Wide HR 95% CI for occurrence of pulmonary complications (0,52-0,98)** • Can the results be applied to the local population? **Yes** • Were all important outcomes considered? **Yes** • Are the benefits worth the harms and costs? **Yes** **Strengths:** Large sample size, centers from different parts of the world. Suggested dose-response relationship between tidal volume size and development of pulmonary complications. **Limitations:** 93% of patients came from observational studies. Data from one RCT could not be included as the corresponding author could not be contacted. Subjective diagnostic criteria could lead to misclassification of patients. No studies described how body height was assessed.
Conclusion Ventilation with low tidal volumes is associated with a lower risk of development of pulmonary complications in patients without acute respiratory distress syndrome.			
Countries Netherlands, Brazil, USA and Finland			
Years of publication 2007 – 2013			

Reference: Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: A randomized clinical trial. JAMA. 2017;318(14):1335-1345. doi:10.1001/jama.2017.14171 (ART Trial)	**Design: RCT**	
	Evidence level	**Ib**
	GRADE	⊕⊕⊕○ MODERATE

Aim	Materials and methods	Results	Discussion/comments
To determine if lung recruitment associated with PEEP titration according to the best respiratory-system compliance decreases 28-day mortality of patients with moderate to severe ARDS compared with a conventional low-PEEP strategy. **Conclusion** In patients with moderate to severe ARDS, a strategy with lung recruitment and titrated PEEP compared with low PEEP increased 28-day all-cause mortality. These findings do not support the routine use of lung recruitment maneuver and PEEP titration in these patients. **Countries** Brazil, Argentina, Colombia, Italy, Poland, Portugal, Malaysia, Spain and Uruguay **Years of data collection** 2011 – 2017	A multicenter, randomized trial conducted at 120 intensive care units (ICUs) from 9 countries, enrolling adults with moderate to severe ARDS. **Interventions:** An experimental strategy with a lung recruitment maneuver and PEEP titration according to the best respiratory–system compliance (n = 501; experimental group) or a control strategy of low PEEP (n = 509). All patients received volume-assist control mode until weaning. **Main outcomes and measures:** The primary outcomewas all-cause mortality until 28 days. Secondary outcomeswere length of ICU and hospital stay; ventilator-free days through day 28; pneumothorax requiring drainage within 7 days; barotrauma within 7 days; and ICU, in-hospital, and 6-month mortality.	A total of 1010 patients (37.5% female; mean [SD] age, 50.9 [17.4] years) were enrolled and followed up. At 28 days, 277 of 501 patients (55.3%) in the experimental group and 251 of 509 patients (49.3%) in the control group had died (hazard ratio [HR], 1.20; 95% CI, 1.01 to 1.42; P =0.041). Compared with the control group, the experimental group strategy increased 6-month mortality (65.3%vs 59.9%; HR, 1.18; 95%CI, 1.01 to 1.38; P =0.04), decreased the number of mean ventilator-free days (5.3 vs 6.4; difference, −1.1; 95%CI, −2.1 to −0.1; P = .03), increased the risk of pneumothorax requiring drainage (3.2%vs 1.2%; difference, 2.0%; 95%CI,0.0%to 4.0%; P = .03), and the risk of barotrauma (5.6%vs 1.6%; difference, 4.0%; 95%CI, 1.5%to 6.5%; P = .001). There were no significant differences in the length of ICU stay, length of hospital stay, ICU mortality, and in-hospital mortality. **Figure 2. 28-Day Mortality in the Lung Recruitment Maneuver With Titrated PEEP Group vs the Low-PEEP Group**  No. at risk Lung recruitment and titrated PEEP 501 397 340 303 276 254 233 225 Low PEEP 509 423 378 343 312 286 264 260 PEEP indicates positive end-expiratory pressure.	**Checklist** • Did the trial address a clearly focused issue? **Yes** • Was the assignment of patients to treatments randomised? **Yes** • Were patients, health workers and study personnel 'blind' to treatment? **No, participants, clinicians and outcome assessors were awere of the assigned treatment.** • Were the groups similar at the start of the trial? **Yes** • Aside from the experimental intervention, were the groups treated equally? **Yes, apart from higher rate of neuromuscular blocker use in experimental group** • Were all of the patients who entered the trial properly accounted for at its conclusion? **Yes, three patients were excluded from the analysis due to withdrawal of consent** • How large was the treatment effect? **Adjusted hazard ratio for 28-day mortality in experimental group was 1,22** • How precise was the estimate of the treatment effect? **Wide HR 95% CI for 28-day mortality in experimental group (1,01 to 1,42)** • Can the results be applied to the local population, or in your context? **Yes** • Were all clinically important outcomes considered? **Yes** **Strengths:** Large multi-center randomized trial. Bias was controlled using concealed allocation, intention-to-treat analysis, and by avoiding losses to follow-up. **Limitations:** Not feasible to blind participants, clinicians and outcome assessors. Concerns with study design, methodology, data analyses and results have been raised.[66]