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Effects of positive end-expiratory pressure on intracranial pressure, cerebral perfusion pressure, and brain oxygenation in acute brain injury: Friend or foe? A scoping review

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ABSTRACT

Background: Patients with acute brain injury (ABI) are a peculiar population because ABI does not only affect the brain but also other organs such as the lungs, as theorized in brain–lung crosstalk models. ABI patients often require mechanical ventilation (MV) to avoid the complications of impaired respiratory function that can follow ABI; MV should be settled with meticulousness owing to its effects on the intracranial compartment, especially regarding positive end-expiratory pressure (PEEP). This scoping review aimed to (1) describe the physiological basis and mechanisms related to the effects of PEEP in ABI; (2) examine how clinical research is conducted on this topic; (3) identify methods for setting PEEP in ABI; and (4) investigate the impact of the application of PEEP in ABI on the outcome.

Methods: The five-stage paradigm devised by Peters et al. and expanded by Arksey and O'Malley, Levac et al., and the Joanna Briggs Institute was used for methodology. We also adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension criteria. Inclusion criteria: we compiled all scientific data from peer-reviewed journals and studies that discussed the application of PEEP and its impact on intracranial pressure, cerebral perfusion pressure, and brain oxygenation in adult patients with ABI. Exclusion criteria: studies that only examined a pediatric patient group (those under the age of 18), experiments conducted solely on animals; studies without intracranial pressure and/or cerebral perfusion pressure determinations, and studies with incomplete information. Two authors searched and screened for inclusion in papers published up to July 2023 using the PubMed-indexed online database. Data were presented in narrative and tubular form.

Results: The initial search yielded 330 references on the application of PEEP in ABI, of which 36 met our inclusion criteria. PEEP has recognized beneficial effects on gas exchange, but it produces hemodynamic changes that should be predicted to avoid undesired consequences on cerebral blood flow and intracranial pressure. Moreover, the elastic properties of the lungs influence the transmission of the forces applied by MV over the brain so they should be taken into consideration. Currently, there are no specific tools that can predict the effect of PEEP on the brain, but there is an established need for a comprehensive monitoring approach for these patients, acknowledging the etiology of ABI and the measurable variables to personalize MV.

Conclusion: PEEP can be safely used in patients with ABI to improve gas exchange keeping in mind its potentially harmful effects, which can be predicted with adequate monitoring supported by bedside non-invasive neuromonitoring tools.

Introduction

Acute brain injury (ABI) is frequently followed by systemic complications.[1] Patients affected by ABI may suffer from decreased levels of consciousness with altered airway-protective reflexes and impaired breathing, thus requiring mechanical ventilation (MV) to prevent aspiration, preserve normal gas exchange, and minimize secondary brain damage.[2] MV can influ-

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ence the vulnerability of the lungs to disease following ABI. Up to 30% of patients with ABI manifest acute respiratory distress syndrome (ARDS),[3] as well as ventilator-associated pneumonia (VAP)[1,2] and ventilator-induced lung injury (VILI), suggesting that MV is not free of risks. Several strategies to optimize MV in patients with ABI have been proposed. An appropriate MV, and in particular positive end-expiratory pressure (PEEP) titration, are essential management strategies to maintain adequate oxygen delivery to the brain and minimize lung and brain injury.[3–5]

PEEP can improve systemic oxygenation, ensuring an appropriate gas exchange while preventing lung collapse and overdistention. PEEP can also decrease the carbon dioxide (CO_2) volume exhaled per breath by increasing physiological dead space and decreasing cardiac output (CO).[6] As a consequence, the arterial partial pressure of carbon dioxide ($PaCO_2$) can be increased and arterial intracranial vasodilatation can occur, increasing cerebral blood volume (CBV), with the risk of an increase in intracranial pressure (ICP), especially when intracranial compliance is reduced.[7] Indeed, PEEP can elevate intrathoracic and intra-abdominal pressure and reduce mean arterial pressure (MAP) and CO, thus potentially affecting ICP and cerebral perfusion pressure (CPP). However, the effects of PEEP on the brain have not been fully elucidated.

The aim of this scoping review was to provide an overview of the role and rationale for setting PEEP in patients with ABI. In particular, to (1) describe the physiological basis and mechanisms related to the effects of PEEP in ABI; (2) examine how clinical research is conducted on this topic; (3) identify methods for setting PEEP in ABI; and (4) investigate the impact of the application of PEEP in ABI on the outcome.

Methods

According to the nature of this review, the five-stage paradigm devised by Peters et al.[8,9] and expanded by Arksey and O'Malley,[10] Levac et al.[11] and the Joanna Briggs Institute was used for methodology. For the purpose of a scoping review, we also adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension criteria.[12]

Aims of this scoping review

In this scoping review, we aimed to establish the range or depth of a body of literature on the application of PEEP in patients with ABI, provide a clear indicator of the type of literature and studies that are available, and produce a general and in-depth summary of the literature on this topic.

Selection criteria

Inclusion criteria: we compiled all scientific data from studies published in peer-reviewed journals that discussed the application of PEEP and its impact on ICP, CPP, and brain oxygenation in adult patients with ABI.

Exclusion criteria: (1) studies that only examined a pediatric patient group (those under the age of 18 years); (2) experiments conducted solely on animals; (3) studies without ICP and/or CPP determinations; (4) studies with incomplete information.

Search strategy

Two authors (GZ, DB) searched and screened for papers published up to July 2023 using the PubMed-indexed online database. All disagreements were resolved by consensus. Only publications of studies in adults (defined as older than 18 years) and written in English were selected. The following MESH terms were used "((acute brain injury) OR (neurocritical care patients)) AND ((brain–lung crosstalk) OR (brain–lung interaction OR brain–heart crosstalk) AND (mechanical ventilation in acute brain injury) OR (mechanical ventilation in neurocritical care) OR (effects of PEEP OR consequence of PEEP) AND (guidelines of treatment in acute brain injury) OR (recommendation of treatment))". The literature selection was cross-referenced using a combination of terms to avoid duplicates. Each of the selected articles was analyzed to identify any missed publications.

Data extraction and synthesis

After literature screening, data were presented in narrative and tabular form and included the following information: study population, type of study, level of PEEP, physiological effect, and effect on the outcome.

Results

The initial search yielded 330 references on the application of PEEP in ABI, of which 36 met our inclusion criteria (Figure 1). There were 5 randomized controlled trials (RCTs), 27 non-RCTs (prospective or retrospective), 2 cross-sectional studies, 1 case series, and 1 international survey. Table 1 summarizes the characteristics and results of the studies included in this scoping review.

Discussion

Physiological basis and mechanisms related to the effects of PEEP in ABI

Brain–lung crosstalk

Several mechanisms connect the brain and the lungs and potentially influence the response to the application of PEEP at the molecular level in these organs. These mechanisms are summarized in the so-called "brain–lung crosstalk",[13] which is a complex pathophysiological interaction involving humoral, neural, and cellular pathways.[14–16] Attempts have been made to clarify the pathophysiology of lung injury after ABI and the impact of lung protective ventilation strategies, including PEEP application. However, this mechanism is not completely elucidated. Different theories have been developed, with the first involving a massive release of catecholamines after ABI, which alters the alveolar–capillary membrane and impairs vascular permeability resulting in neurogenic pulmonary edema and respiratory impairment,[1,7] with increased ICP and direct cardiac injury.[17,18] As a result of this mechanism, left atrial, systemic, and pulmonary pressures can increase.[19–22]

Additionally, a release of inflammatory mediators from the intracranial compartment to the systemic circulation via the blood–brain barrier (BBB) triggers inflammatory cascades and generates an inflamed and weaker system (first hit) that is less

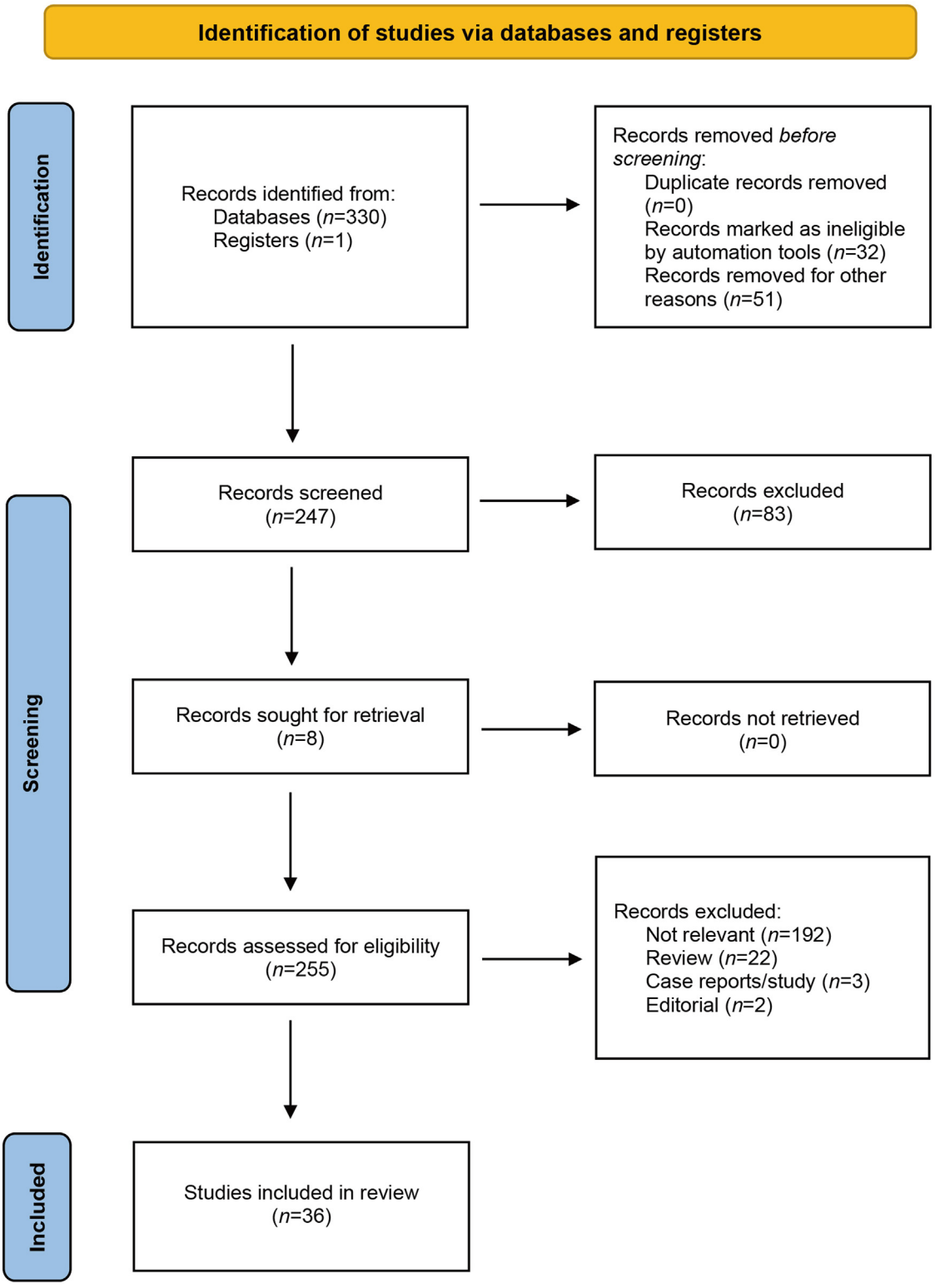

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

able to resist procedures (such as MV) and infections, which become the second hit,[1,7] followed by the release of acute inflammatory mediators in the brain and in the lungs.[23,24] Many experimental and clinical studies have demonstrated that the hypothalamic–pituitary–adrenal axis can be responsible for modulating the inflammatory response after ABI.[25,26]

Conversely, the damaged lungs can influence the brain via humoral, neural, and cellular pathways that promote neuroinflammation, whereas hypoxemia alone is a risk factor for cognitive impairment.[7] Within this context, it is essential to consider that not only primary lung injury, but also inadequate MV settings (including PEEP), can trigger secondary brain dam-

Table 1
Summary of the studies included in the scoping review.

Study	Design	Population	Conclusions
Battaglini et al.[91]	Prospective observational cross-sectional study	10 ABI patients	Patients underwent incremental level of PEEP (from 5 cmH_2O to 15 cmH_2O): no changes in brain oxygenation. Delivery of oxygen, CO_2 consumption and saturation of oxygen significantly correlated with brain oxygenation.
Giardina et al.[56]	Prospective observational study	25 ABI patients (TBI, SAH, ICH)	Patients underwent incremental level of PEEP (from 5 cmH_2O to 15 cmH_2O): CA did not worsen, ICP and CPP changed significantly even if it was clinically irrelevant. Cerebral oxygenation parameters did not change.
Beqiri et al.[66]	Prospective single center randomized interventional study	27 ABI patients (TBI, ICH, SAH)	No differences were seen between the low PEEP (5 cmH_2O) and high PEEP (12 cmH_2O) LPV approaches over ICP and CA. Of interest: baseline ICP and mechanical power can predict the effects of LPV and can help titrate MV.
Zhou et al.[69]	Retrospective observational study	427 ABI patients; 407 non-obese and 220 obese patients	In obese ABI patients, the application of PEEP could induce a modest elevation of ICP seen as the augmentation of 0.19 cmH_2O of ICP and 0.15 mmHg decrease in CPP for every cmH_2O increase in PEEP.
Tas et al.[99]	Prospective study	10 patients with TBI	The PRx variability decreased significantly during the PEEP oscillations with ICP levels <22 mmHg.
Robba et al.[75]	Prospective observational study	30 ABI patients (SAH, TBI, ICH)	LUS score total and LUS score in the posterior lung at baseline could predict the effect of two different levels of PEEP (5 and 15 cmH_2O) over ICP.
Gupta et al.[64]	Prospective study	ABI patients	PEEP can be safely applied until 10 cmH_2O; ONSD and ICP did not significantly increase after PEEP augmentation from 0 to 5 cmH_2O and from 5 to 10 cmH_2O. Differently, the increase of PEEP from 10 to 15 cmH_2O significantly worsens ONSD and ICP.
Robba et al.[80]	Prospective observational study	15 patients with ABI (6 SAH patients, 6 TBI patients, 3 ICH patients)	In patients with ABI, C_{RS}, lower MAP, and lung recruitment are associated with ICP rise following incremental levels of PEEP (two levels of PEEP were tested: 5 and 15 cmH_2O); however, none of those factors was able to predict at baseline the effect of PEEP over ICP.
Jiang et al.[63]	Randomized controlled trial	90 TBI patients who underwent emergency intracranial hematoma evacuation	ONSD (used as ICP change detector method) does not change between patients assisted with traditional MV (V_T 10 mL/kg+ 0 cmH_2O PEEP) and small V_T (8 mL/kg) + 5 cmH_2O PEEP. During a single RM ONSD transiently increased but returned to baseline in 5–10 min, suggesting that RMs could elevate ICP.
Balakrishnan et al.[65]	Prospective study	14 patients with TBI	The application increased level of PEEP (from 5 to 10 cmH_2O) significantly increased ONSD in the pathologic side of the brain.
Li et al.[87]	Prospective cohort study	112 TBI patients	A novel indicator the P_{IC}Gap (the gap between baseline ICP and baseline CVP), proved its efficacy in predicting the effects of PEEP over ICP.
Picetti et al.[81]	International survey	TBI patients	Among clinicians who treat TBI patients, the common high PEEP level was 15 cmH_2O in patients without intracranial hypertension and RF and 10 cmH_2O in patients with intracranial hypertension and RF.
Ruggieri et al.[100]	Randomized controlled trial	32 patients without intracranial hypertension undergoing elective supratentorial brain tumor removal	No significant differences in ICP were noticed between the traditional ventilation approach (9 mL/kg V_T + ZEEP) and protective ventilation (7 mL/kg V_T + PEEP 5 mmHg).
Chen et al.[74]	Prospective study	30 patients with SAH	Lung elastance, chest wall elastance and respiratory system elastance were measured at 5 and 15 cmH_2O PEEP. In patients with higher E_{CW} and E_{CW}/E_{RS} ratio developed higher ICP values in response to PEEP.
Asehnoune et al.[95]	Prospective multicenter before-after trial	744 patients with ABI	Intracranial hypertension did not differ between the pre-intervention period practice (ventilation settings and extubation based on attending physician decision) and intervention period practice (≤7 mL/kg, PEEP, 6–8 cm H_2O and early extubation protocol).
Boone et al.[68]	Retrospective study	341 ABI patients	PEEP is safe in patients with ABI. A significant relationship between PEEP and ICP and PEEP and CPP was found only when severe lung injury occurs. Every centimeter of H_2O increase in PEEP is responsible for 0.31 mmHg ICP increase and 0.85 mmHg decrease in CPP.
Flexman et al.[76]	Randomized control trial	21 patients underwent resection of a supratentorial brain tumor	Patients were randomized to receive RM (30 cmH_2O for 30 s) of a sham RM (5 cmH_2O for 30 s), 90 s of equilibration and then the alternative maneuver (not yet received). Subdural pressure was higher during RM compared to sham RM, MAP further decreased in the RM than in sham RM, CPP decreased of 14 mmHg in the RM.
Lou et al.[82]	Multicenter Cross-sectional Study	Patients with ABI (TBI, AIS, patients who underwent surgery for intracranial tumor, hypoxic-ischemic encephalopathy, intracranial infection, idiopathic epilepsy)	This survey investigated, among others MV parameters, PEEP; in the cohort, the median value of PEEP was 5 cmH_2O and it never exceed 10 cmH_2O.
Nemer et al.[71]	Prospective study	20 patients with TBI and ARDS	ICP and other brain parameters were tested at 3 different PEEP levels (5, 10, and 15 cmH_2O) maintained for 20 min: ICP did not significantly change with the augmentation of PEEP.

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Population	Conclusions
Zhang et al.[72]	Prospective cohort study	9 patients with cerebral injury and lung injury	Patients underwent progressive PEEP augmentation (from 0 to 21 cmH_2O, in steps of 3 cmH_2O each maintained for 3 min) and reduction (in reverse steps); ICP, CPP, and other measurements were taken. ICP and CPP response to PEEP was not uniformly predictable in this cohort, no significant difference was seen with baseline values; however, ICP and MAP monitoring is useful when PEEP is used in those patients.
Nemer et al.[77]	Randomized clinical trial	16 patients with SAH	Patients who underwent CPAP recruitment (35 cmH_2O for 40 s) experienced higher ICP and lower CPP than pressure control RM (15 cm H_2O PEEP and 35 cmH_2O pressure control above PEEP for 2 min).
Yang et al.[78]	Prospective cohort study	6 patients with ABI	Patients underwent RM with pressure control ventilation and crescent levels of PEEP; ICP, CPP, and other variables were monitored, and no significant differences were noticed compared with baseline. ICP monitoring makes the use of RM safer.
Koutsoukou et al.[67]	Randomized clinical trial	21 patients with ABI	Two different levels of PEEP (ZEEP and 8 cmH_2O) were tested, and measurements of different variables were taken and day 1 and day 5. ICP did not significantly differ between the 2 groups.
Mascia et al.[53]	Prospective interventional study	20 patients with ABI and ARDS	Two different PEEP levels (5 and 10 cmH_2O) were applied during MV; when PEEP-induced alveolar recruitment ICP did not change while in the case of hyperinflation significantly increased ICP and $PaCO_2$.
Muench et al.[51]	Prospective study	10 patients with SAH	PEEP was administered in steps of 5 cmH_2O from the baseline (5 or 10 cmH_2O) to 20 cmH_2O. PEEP did not influence ICP nor regional cerebral blood flow directly however, it could have a negative impact on CPP when it influences hemodynamics.
Caricato et al.[52]	Prospective study	21 with SAH or TBI	0, 5, 8 and 12 cmH_2O PEEP were randomly applied to two groups of patients selected on the base of C_{RS} (normal versus C_{RS}). In patients with low C_{RS}, PEEP do not significantly influence ICP.
Huynh et al. [62]	Retrospective study	20 patients with TBI	Regarding PEEP, patients were separated into 3 groups based on 3 PEEP intervals: 0–5 cmH_2O PEEP, 6–10 H_2O PEEP, and 11–15 cmH_2O PEEP. ICP showed a decreasing trend in response to crescent levels of PEEP, significant differences in ICP measurements were seen between the 0–5 cmH_2O and the 11–15 cmH_2O groups.
Wolf et al.[70]	Case series	11 patients with ABI and acute lung injury	Elevated PEEP could lead to moderate ICP increase in patients with a baseline normal ICP; in the case of baseline high ICP, high PEEP does not increase ICP. No significant differences were seen between mean and peak ICP values before and after RMs.
Gamberoni et al.[101]	Prospective study	10 normal patients, 10 ABI patients without RF, 10 ABI patients with ARF	PEEP influences ICP via different mechanisms, moderate levels of PEEP ($\leq$15 cmH_2O) or very high levels can be safely used in ABI when pulmonary compliance is poor.
Bein et al.[79]	Prospective study	11 patients with ABI and acute lung injury	Volume-RM elevated ICP and reduced MAP with following decrease of CPP. jugular venous lactate content difference did not change.
Georgiadis et al.[50]	Prospective study	20 patients with AIS	Three different PEEP levels were applied (4, 8, 12 cmH_2O) while monitoring ICP and MAP; augmentation of PEEP up to 12 cmH_2O did not significantly changed ICP while the changes seen in CPP followed the change in MAP.
Cooper et al.[102]	Prospective Study	33 Patients with a severe head injury	10 cmH_2O PEEP increases ICP slightly because of its effects on hemodynamic (cardiac output) and respiratory (peak inspiratory pressure, $PaCO_2$, and venous admixture) variables although it is clinically inconsequential.
Burchiel et al.[103]	Prospective study	16 patients with ABI and 2 patients with SAH	The volume-pressure response (used as an indicator of intracranial compliance) accurately predicts the effects of PEEP on ICP. A decreased lung compliance mitigates the effect of PEEP on ICP in patients with poor intracranial compliance.
Abbushi et al.[59]	Observational study	10 patients with ABI	Patients mechanically ventilated with PEEP from 0 to 10 cmH_2O could experience a significant ICP rise. A significant ICP decrease has been obtained with 30 degrees head lift.
Shapiro et al.[58]	Observational study	12 patients with a head injury	6 of the 10 patients underwent ICP elevation after administration of 4 to 8 cmH_2O PEEP intending to reduce FiO_2; ICP monitoring should be established during PEEP titration.
Frost[57]	Observational study	7 comatose patients	Increasing PEEP from 5 to 20 cmH_2O did not increase ICP as well as a PEEP of 12 cmH_2O was maintained for 20 h (tested on 1 patient). 40 cmH_2O PEEP was used in 2 patients and a significant raise in ICP was recorded. Abrupt discontinuation of PEEP was not followed by ICP increase except for 2 patients in whom the accumulation of secretion impeded correct ventilation.

ABI: Acute brain injury; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; ARF: Acute respiratory failure; AIS: Acute ischemic stroke; CA: Cerebral autoregulation; CO: Cardiac output; CPAP: Continuous positive airway pressure; CPP: Cerebral perfusion pressure; C_{RS}: Respiratory system compliance; CVP: Central venous pressure; E_{CW}: Chest wall elastance; E_{RS}: Elastance of the respiratory system; FiO_2: Fraction of inspired oxygen; ICH: Intracerebral hemorrhage; ICP: Intracranial pressure; LPV: Lung protective ventilation; LUS: Lung ultrasound; MAP: Mean arterial pressure; MV: Mechanical ventilation; NPO: Neurogenic pulmonary edema; ONSD: Optic nerve sheath diameter; $PaCO_2$: Arterial partial pressure of carbon dioxide; PEEP, Positive end-expiratory pressure; PRx: Cerebral pressure reactivity index; RF: Respiratory frequency; RM: Recruitment maneuver; SAH: Subarachnoid hemorrhage; TBI: Traumatic brain injury; TCD: Transcranial doppler; V_T: Tidal volume; ZEEP: Zero positive end-expiratory pressure.

age. This can be particularly dangerous in patients with ABI where an alteration of the BBB is frequently observed, thus making the brain more susceptible to secondary damage after lung injury.[27] In conclusion, the existence of a brain–lung crosstalk highlights the importance of setting MV, and specifically PEEP, according to both lung and brain physiological needs. The main effects of PEEP on organ crosstalk are shown in Figure 2.

Effects of PEEP on gas exchange

PEEP among ventilator parameters greatly impacts body compartments and organs, including the brain. Owing to its abilities of lung recruitment and oxygenation improvement, PEEP is an essential parameter for the appropriate setting of the ventilator in ABI. PEEP promotes the opening of alveoli, reduces interfaces between open and closed lung regions, and minimizes the injurious effects caused by the continuous opening and closing of alveolar units, hence limiting inflammation and distal organ damage.[28] Accordingly, the application of PEEP improves oxygenation by the augmentation of oxygen (O_2) solubility in the blood, via the augmentation of the pressure in the respiratory system, by Henry's law, and with the reopening of collapsed lung areas increasing alveoli available for ventilation and gas exchange with improvement of the ventilation/perfusion (V/Q) ratio, and reduction of the shunt effect.[29] Over the years, the recruitment properties of PEEP have been demonstrated, especially in the lower lung regions,[30] avoiding the harmful cyclical reopening of the collapsed areas for each breath.[31] PEEP also influences lung edema: during the negative-pressure spontaneous respiration, fluid drainage from the interstitial space is guaranteed by a negative gradient (3–4 mmHg) toward lymphatic vessels, but when MV with PEEP is applied to the respiratory system, the gradient increases to 0 mmHg or even more, counteracting fluid drainage. In contrast, opposite results have been reported, promoting the protective effects of PEEP on lung edema due to the decrease of CO and/or pulmonary blood volume.[28] The establishment of the "best or optimal PEEP" should therefore look for the improvement of arterial oxygenation while also considering the maintenance of the best lung mechanics—that is, with the lung open but not overstretched—and the mitigation of the hemodynamic consequence of PEEP. Moreover, throughout the process, it should be remembered that PEEP can be personalized[32] and VILI should always be avoided; in fact, together with the other components of MV, PEEP could contribute to the stress applied to the lungs and to barotrauma and biotrauma.[33]

Adequate oxygenation is pivotal for the outcome of patients with ABI because hypoxemia (the partial pressure of oxygen [PaO_2] target is between 80 and 120 mmHg)[34] is particularly dangerous because leads to secondary brain insult, which is associated with a 2 fold higher risk of mortality.[1] Similarly, mild to severe hyperoxia (mild: PaO_2 >120 mmHg; severe: PaO_2 >300 mmHg)[35] has possible detrimental effects on the brain, including the risk of delayed ischemia, the triggering or increasing of oxidative stress with potential cellular death and apoptosis, and the higher risk of respiratory tract infections.[36] Different PaO_2 values have been tested to establish which one could define hyperoxia, and although incremental continuous exposure to excessive oxygen was associated with poor outcomes, further studies are needed to define a precise cut-off value. However, the increased oxygenation following PEEP application

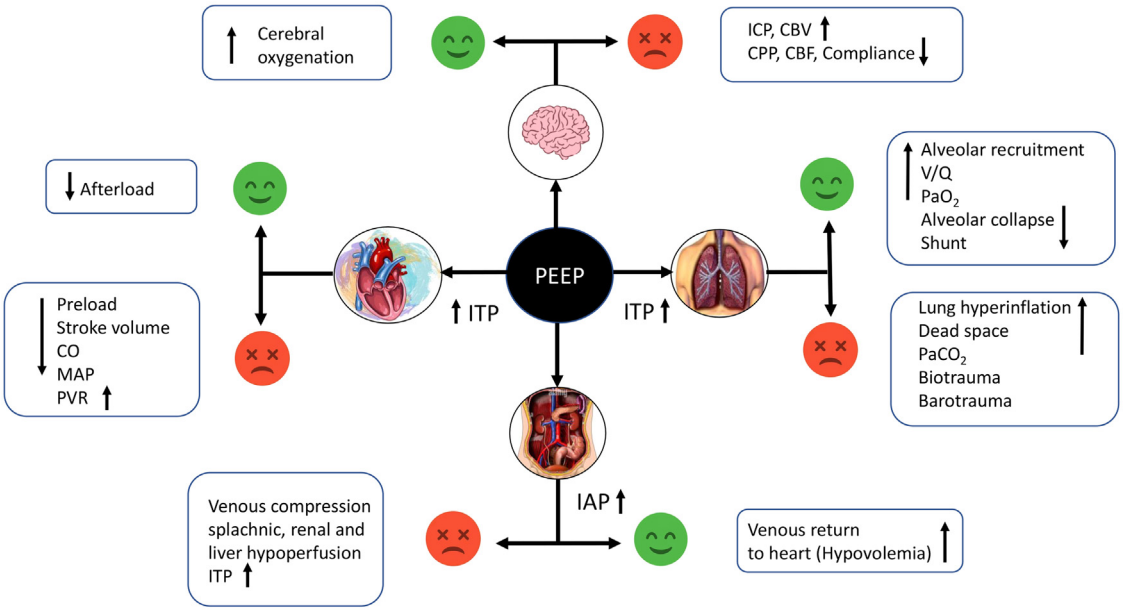

Figure 2. Advantages (green) and Disadvantages (red) of PEEP on different organs. Brain Advantages: improve cerebral oxygenation (as consequence of lung recruitment and improved gas exchange); Disadvantages: increase ICP and CBV (by reducing the venous outflow), reduction of CPP, and reduction of CBF and cerebral compliance (especially when PEEP impaired hemodynamics). Heart Advantages: decreased afterload (by the reduction of left ventricular transmural pressure); Disadvantages: decreased preload, stroke volume, CO, MAP (by hindering venous return), increase of PVR (as a reflex response, to improve venous return and preload). Abdomen Advantages: increase venous return (squeezing the splanchnic vessels); Disadvantages: venous compression; splanchnic, renal, and liver hypoperfusion (when PEEP overcomes the venous pressure); increased ITP and IAP. Lung Advantages: improves PaO_2, V/Q ratio, reduces shunt, and alveolar collapse, when it produces alveolar recruitment. Disadvantages: increase $PaCO_2$ and dead space, lung hyperinflation with barotrauma and biotrauma.
CBF: Cerebral blood flow; CBV: Cerebral blood volume; CO: Cardiac output; CPP: Cerebral perfusion pressure; IAP: Intra-abdominal pressure; ICP: Intracranial pressure; ITP: Intrathoracic pressure; MAP: Mean arterial pressure; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Arterial partial pressure of oxygen; PEEP: Positive end-expiratory pressure; PVR: Peripheric vascular resistance; V/Q: Ratio between ventilation and perfusion of the lungs.

does not always refer to effective alveolar recruitment and reduced shunt, but can be determined by the increased intrathoracic pressure (generated by PEEP), which leads to a reduction of the part of the CO coming from the perfused but not ventilated lung regions.[37] PEEP can reduce the work of breathing with a consequent decrease in $PaCO_2$.[29]

Another important effect of PEEP on the lungs is the decrease of CO_2 volume exhaled per single breath by increasing physiological dead space and decreasing CO.[6] The brain is particularly susceptible to $PaCO_2$ levels. When hypercapnia ($PaCO_2$ >45 mmHg) occurs, brain vessels dilatate with a linear augmentation of the cerebral blood flow (CBF) up to 100%–200% when the $PaCO_2$ exceeds 80 mmHg; consequently, the CBV increases and eventually the ICP rises. Conversely, hypocapnia ($PaCO_2$ <35 mmHg) is followed by vasoconstriction of the arteriolar compartment (which accounts for 30% of the total CBF) and CBF reduction with a mitigating effect on the total CBV and ICP. Both conditions also have humoral effects; hypercapnia produces a catecholamine release with neuronal excitability, seizure, and augmentation of the cerebral metabolism, while in hypocapnia, excitatory amino acids are released with similar effects.[38] Knowledge of the effect of CO_2 on the intracranial compartment could contribute to the MV setting, even if the levels of CO_2 are more influenced by the minute ventilation and all the ventilatory parameters together rather than PEEP alone.[29]

Effects of PEEP on hemodynamics

PEEP also induces hemodynamic effects. Spontaneous breathing generates a negative intrathoracic and pleural pressure transmitted to the right atrium (RA) that facilitates the venous return.[29] However, MV works with positive pressure applied on the respiratory system plus the application of PEEP maintains a positive pressure at the end of an expiration with an increased intrathoracic pressure; this positive pressure is transmitted to the RA and reduces the venous return and consequently the right ventricular (RV) stroke volume and, at least, of the CO because the heart works far from the optimal point of the Frank-Starling's curve.[29,39] Furthermore, PEEP increases the pressure of the pulmonary circulation (extrinsic compression), which is transmitted to the right ventricle, causing deviation of the interventricular septum to the left and contributing to the decrease in stroke volume, MAP, and CO.

The forces that pull the diaphragm toward the abdomen increase intra-abdominal pressure (IAP), squeezing the venous system of the abdominal cavity.[39] An extensive network of superficial (subcutaneous) and deep connections facilitate communication between the abdominal venous system (lumbar veins) and the intrathoracic (azygos system) and cerebral (jugular) venous systems.[40] Functionally, the valve-free venous system allows a bidirectional flow, depending on pressure gradients or hydrostatic and gravitational forces; thus, intravenous pressure changes in the abdomen will influence the intravenous pressure in the neck, thorax, or cranial cavity.[41] Consequently, the increase of IAP in neurocritical patients may provoke ICP elevation.[40] In addition, an increase in IAP negatively enhances brain–gastrointestinal interactions, since it can potentially trigger splanchnic hypoperfusion and ischemic damage of all intra-abdominal viscera and organs.[42]

Positive intrathoracic pressure is transmitted even on the intrathoracic vessels with a reduction of left ventricular (LV) transmural pressure and, as a consequence, the LV afterload decreases, facilitating ventricular emptying and improving CO with less effort to generate peripheric circulation.[43] Nevertheless, a PEEP level <10 cmH_2O is rarely responsible for hemodynamic impairment when volemic status and MAP are normal,[44] but the risk should be considered when a PEEP ≥15 cmH_2O is used in hypovolemic patients.[45] Recently, Lai et al.[46] tested the efficacy of the PEEP-test in patients who underwent MV: this test consisted of a reduction of PEEP from a "high PEEP" level (≥10 cmH_2O) to 5 cmH_2O while monitoring the cardiac index (CI) with the purpose—in patients already known as volume responsive (by a positive passive leg-raising test)—of identifying a significant increase of CI. In the study cohort, the PEEP-test demonstrated its efficacy (seen as an increase of CI ≥8.6%) in predicting the volume responsiveness of MV patients with a PEEP ≥10 cmH_2O (sensitivity of 96.8% and a specificity of 84.9%). The increase of CI is likely due to the decrease of RV afterload plus the increase of cardiac preload induced by PEEP as an influencing factor of the pressure in the intrathoracic compartment of volume-responsive patients.

Effects of PEEP on brain physiology

PEEP can affect intracranial hydrodynamics. Analyzing the previously elucidated mechanisms, PEEP can increase ICP and decrease CPP, fundamentally on the one hand through the increase in intracranial intravenous pressure and volume, consequent to the compromise of cerebral venous drainage and the transmission of increased pressures within the thorax or abdomen. On the other hand, the multiple systemic hemodynamic effects converge in the decrease in MAP. Additionally, the intracranial compliance may decrease owing to the compensatory mechanisms (CBV and cerebrospinal fluid [CSF] displacement) being compromised.

When PEEP produces hemodynamic effects, especially a reduction of MAP, a decrease in the CBF and the CPP occurs.[1] The elevation of intrathoracic pressure due to PEEP also influences the CBV because of the rise of the RA filling pressure that impedes the venous return from the brain vessels with an increase of CBV and a potentially increased ICP.[3,7,47] Patients with increased ICP usually have their head positioned at 30° to let the jugular vein collapse and contrast the transmission of intrathoracic pressure (ITP) to the intracranial compartment (they act as a resistance point, by the Starling resistor model) and partially collect the venous outflow.[48] However, the study of Chapin et al.[49] revealed that increased lung elastance (E_L) and reduced chest wall elastance (E_{CW}) minimize the effects of PEEP over pleural pressure. Therefore, the transmission of PEEP to the intracranial compartment can change and PEEP seems to be associated with ICP elevation when it causes hyperinflation of the lungs, whereas if it recruits the alveolar units, CBF and ICP are stably maintained.[1]

The effects of PEEP on the hemodynamics of the intracranial compartment could also be investigated with the non-invasive transcranial doppler (TCD), which can detect flow velocity of the principal brain vessels. Georgiadis et al.[50] observed the effects of PEEP values of 4, 8, and 12 cmH_2O on the mean flow velocity of the middle cerebral arteries (FV_m MCA) of patients with stroke. In patients with intact cerebral autoregulation (CA), the FV_m MCA did not change after MAP drop due to PEEP, but in cases of impaired CA, PEEP caused MAP drop and cerebral va-

sodilatation. Muench et al.[51] found that increasing PEEP from 5 to 20 cmH_2O in patients with subarachnoid hemorrhage (SAH) significantly decreased the regional CBF detected at TCD examination; this change was concomitant with MAP drop and suggested a disturbance in CA. In the study of Caricato et al.[52] patients with SAH and normal respiratory system compliance (C_{RS}) experienced a significant decrease of V_m MCA after high PEEP application, whereas the FV_m MCA did not change in patients with low C_{RS}. FV_m MCA was measured in ABI patients of the cohort studied by Mascia et al.[53] showing that PEEP (raised from 5 to 10 cmH_2O) was responsible for significant increases in FV_m MCA non-recruiters patients (in whom the PEEP actually generated an increased tidal volume [V_T]).

ABI leads to dysregulation of cerebral metabolism and potentially altered cerebral oxygenation, thus its monitoring cerebral oxygenation together with ICP monitoring could improve the management of ABI and avoid secondary brain damage.[54] However, it should be noted that the effects of positive airway pressure on the cerebral oxygenation of ABI patients are still the subject of debate in the literature.[55] Muench et al.[51] observed in severe SAH patients that the increase of PEEP from 5 to 20 cmH_2O was responsible for a significant decrease of MAP and regional CBF associated with a significant decrease of brain tissue oxygenation ($PtiO_2$); however, with normalization of MAP, the $PtiO_2$ was restored. The jugular oxygen saturation ($SvjO_2$) remained constant in ABI patients identified as recruiters after PEEP augmentation from 5 to 10 cmH_2O, whereas it significantly increased in the non-recruiters group.[53] The effects of PEEP on cerebral oxygenation parameters have been recently investigated in the prospective study of Giardina et al.[56] on mechanically ventilated patients with ABI; PEEP titration from 5 to 15 cmH_2O (gradually achieved in steps of 2 cmH_2O) improved the systemic PaO_2 and C_{RS}, but did not change the cerebral oxygenation parameters (detected with near-infrared spectroscopy [NIRS]) with the exception of the total hemoglobin content.

Clinical research on the application of PEEP in ABI

The appropriate setting of PEEP in patients with ABI is still under debate. As previously mentioned, PEEP can induce marked changes in brain physiology, especially when the hemodynamic status is altered. However, clinical studies investigating the effects of PEEP on brain physiology have reached different conclusions.

Effects of PEEP on brain physiology in ABI patients without lung injury

Effects of PEEP on invasive intracranial pressure and CPP

The relationship of PEEP with ICP has always been a field of study for those who treated neurocritical patients. In 1997, Frost et al.[57] observed in comatose patients that a PEEP level up to 20 cmH_2O did not induce the ICP elevation that was seen when PEEP was set and maintained at 40 cmH_2O. Other studies reported opposite results,[58,59] highlighting the complexity of the matter and the possible variables in play. Changes in ICP and CPP were analyzed in a mixed population of ABI patients with normal and increased ICP (>15 mmHg). PEEP at 5 cmH_2O had no effect in the group with normal ICP, but at 10 and 15 cmH_2O produced a significant increase in ICP (P <0.05). In the group with ICP >15 mmHg, no significant change in ICP occurred at any of the PEEP levels. In both groups, CPP remained unchanged.[60]

According to the etiology of brain injury, in a series of patients with severe traumatic brain injury (TBI) and hemorrhagic strokes, PEEP was raised from 5 to 15 cmH_2O in steps of 5 cmH_2O. PEEP at 10 and 15 cmH_2O produced a significant increase in ICP (P <0.05), however, no significant change was observed in CPP.[61] In the retrospective analysis of Huynh et al.[62] on severe TBI patients, ICP showed a decreasing trend following PEEP augmentation and significant differences in ICP were detected between the 0–5 cmH_2O and the 11–15 cmH_2O PEEP groups; simultaneously, CPP improved significantly.

Georgiadis et al.[50] applied incremental PEEP levels (4, 8, and 12 cmH_2O) to patients in the intensive care unit (ICU) affected by stroke, and demonstrated that PEEP does not influence ICP and can be safely used, providing attention is paid to maintaining adequate MAP and consequently CPP.

In patients with severe SAH, the augmentation of PEEP until 20 cmH_2O did not alter ICP and CBF; however, further increases in PEEP did influence those parameters and CPP when they simultaneously impacted the hemodynamic systemic variables (i.e., decreased MAP) above all when CA impairment is present.[51]

Effects of PEEP on non-invasive intracranial pressure and CPP

Optic nerve sheath diameter (ONSD) is a bedside non-invasive technique for monitoring changes in ICP. Jiang et al.[63] measured ONSD in TBI patients managed with two different approaches: traditional MV (V_T 10 mL/kg + 0 cmH_2O PEEP) and small V_T (8 mL/kg) + 5 cmH_2O PEEP; no significant differences were seen in ONDS and consequently in the MV approach regarding ICP. During a single recruitment maneuver (RM) (maintain an airway pressure of 30 cmH_2O for 30 s), the ONSD increased and returned to baseline after 5–10 min. Gupta et al.[64] studied the effect of different levels of PEEP (0, 5, 10, and 15 cmH_2O) in patients with ABI, recording the ONSD measurements and ICP. Increasing PEEP from 0 to 5 cmH_2O and from 5 to 10 cmH_2O did not produce changes in ONSD and ICP, but when PEEP was increased from 10 to 15 cmH_2O, the ONSD and ICP significantly worsened. Moreover, in a cohort of TBI patients, Balakrishnan et al.[65] showed that the augmentation of PEEP from 5 to 10 cmH_2O significantly increases ONSD, specifically in the pathologic side of the brain.

Effects of PEEP on cerebral autoregulation in ABI patients

Beqiri et al.[66] compared ICP levels and CA capacity in ABI patients without intracranial hypertension but with lung injury managed with protective ventilation at two different PEEP levels (5 and 12 cmH_2O), and no differences were seen in the analyzed parameters. The RCT conducted by Koutsoukou et al.[67] on ABI without lung compromise studied the effects of 0 and 8 cmH_2O PEEP, and proved the absence of ICP and CPP significant variations. Recently, Giardina et al.[56] showed how PEEP rising from 5 to 15 cmH_2O did not affect CA, and even if a significant change in ICP and CPP was detected, it did not reach clinical relevance in terms of absolute values (ICP: 11.11 mmHg–13.43 mmHg, P=0.003; CPP: 72.94 mmHg–66.22 mmHg, P=0.004).

Effects of PEEP on brain physiology in ABI patients with lung injury

Effects of PEEP on invasive intracranial pressure and CPP

In a series of patients with simultaneous acute brain and lung injury, PEEP levels of 5 and 10 cmH_2O were applied and the patients were monitored with ICP, $SvjO_2$, TCD, and respiratory system mechanics and gas exchange. In the group of individuals who improved their gas exchange parameters and pulmonary compliance when applying PEEP (recruiters), the ICP remained constant. However, when PEEP induced pulmonary overdistension and an increase in $PaCO_2$ (non-recruiters), the ICP increased significantly (P <0.0001)[53]; CPP is impacted by PEEP, especially when PEEP has a hemodynamic impact.[50,51]

Boone et al.[68] revealed that in ABI and concomitant lung injury, for every 1 cmH_2O increase in PEEP, there was a 0.31 mmHg increase in ICP (95% CI: 0.07 to 0.54; P=0.04) and a 0.85 mmHg decrease in CPP (95% CI: −1.48 to −0.22; P=0.02), whereas the analysis conducted by Zhou et al.[69] concluded that 1 cmH_2O PEEP produced a 0.15 mmHg decrease in CPP in obese ABI patients. Moreover, Wolf et al.[70] evidenced how in patients with ABI and acute respiratory distress syndrome (ARDS), when the baseline ICP was normal, the PEEP could induce a moderate increase of ICP; in the case of a high baseline ICP value, PEEP did not increase ICP. In contrast, in a series of severe TBI and ARDS patients, Nemer et al.[71] did not observe ICP or CPP changes between 5, 10, and 15 cmH_2O PEEP.

The effects of PEEP on ICP and CPP are not always predictable.[72] However, a PEEP maintained between 5 and 8 cmH_2O usually guarantees appropriate oxygenation and prevents alveolar collapse,[45,73] and some studies proved that PEEP can be safely used up to 10–12 cmH_2O when the hemodynamics are stably maintained.[3,64]

An important contribution to the effects of PEEP on brain physiology comes from the elastic properties of the lung. Caricato et al.[52] investigated the contribution of the C_{RS} on ICP: patients with a normal C_{RS} (>45 mL/cmH_2O) experienced higher central venous pressure (CVP) and bulbar jugular pressure and a drop of MAP, CPP, and FV_m MCA values after PEEP augmentation, whereas these parameters did not change significantly in patients with lower C_{RS} (<45 mL/cmH_2O). ICP and pulmonary compliance did not change in both groups.[62]

Chen et al.[74] furthered the analysis of the elastic properties of the respiratory system. Pressure measurements were provided by an esophageal balloon, extrapolating respiratory system elastance (E_{RS}), E_L, and E_{CW} at two different PEEP levels (5 and 15 cmH_2O) while monitoring ICP. The results showed that SAH patients with higher E_{CW} and E_{CW}/E_{RS} ratios developed higher ICP values in response to PEEP. Therefore, monitoring the elastic properties of the respiratory system has relevance in the prediction of the effects of PEEP on the intracranial compartment, especially in patients with concomitant ARDS where PEEP is used to improve oxygenation, facilitate lung recruitment, and prevent alveolar collapse. Mascia et al.[53] studied individuals with ABI and ARDS coexistence, and demonstrated that if PEEP produces hyperinflation with worsening of $PaCO_2$ levels and lung compliance, ICP levels significantly rise, which is a phenomenon that has been seen in patients with acute ischemic stroke.[73]

Lung ultrasound (LUS) patterns could help in predicting the effect of PEEP on ICP. Robba et al.[75] demonstrated that if PEEP induces hyperinflation without alveolar recruitment (especially in the posterior regions of the lungs) and ICP increases consequently to the C_{RS} decrease, then there is a significant correlation between the baseline LUS score of the lung (based on the identification of lung patterns on six regions for each hemithorax) and ICP augmentation after PEEP application.

Effects of RM on brain physiology in ABI patients

The use of RMs in patients with ABI are controversial since their effects on ICP and other cerebral parameters differ among the studies.

In a prospective crossover study, Flexman et al.[76] compared the effects of a RM on subdural pressure (SBP), brain swelling, and MAP in 21 patients scheduled for supratentorial tumor resection. Patients underwent RM (30 cmH_2O for 30 s) or a "sham" maneuver (5 cmH_2O for 30 s), 90 s of stabilization, and then the maneuver not yet used; SBP, brain swelling (with a brain relaxation score [BRS]), and MAP were measured in each phase and compared. The results showed that RM was responsible for increasing SBP and lowering MAP and CPP, while BRS did not change.

Nemer et al.[77] randomized 16 patients with SAH and ARDS into two different RM methods: continuous positive airway pressure RM (as 35 cmH_2O for 40 s) and pressure control RM (15 cmH_2O PEEP and 35 cmH_2O pressure control above PEEP for 2 min), showing that higher ICP and lower CPP values were measured in the first approach. The PaO_2/ fraction of inspired oxygen (FiO_2) ratio was measured before the RM and after 1 h and was significantly increased only in the pressure control RM group.

Yang et al.[78] performed RM on patients with ABI with pressure control ventilation with a crescent level of PEEP, and showed no significant alteration in ICP and CPP.

Wolf et al.[70] did not find any difference in mean and peak ICP values after RM, which consisted of elevation of PEEP at least of 5 cmH_2O above the previous setting and 2–3 breaths with an inspiratory pressure of 40 mmHg above PEEP and then a decrease to a maximum of 15 mmHg. Bein et al.[79] investigated the effect of a RM on a population of 11 patients with ABI and respiratory failure. The RM consisted of a 30 s increase of peak pressure until 60 cmH_2O, which was then maintained for 30 s; hemodynamics, ICP, CPP, $SvjO_2$, and arterial minus jugular venous lactate content difference (AJDL) were reported before, during, and after the RM. The results showed significant ICP increase (P <0.05), MAP and CPP reduction (P <0.01), and $SvjO_2$ deterioration (P <0.05) at the end of RM, with values returning to normal in the period after the RM; the arterial oxygenation improved at the end of the RM without maintenance in the following period. The group concluded that the tested RM induced a minimal oxygenation improvement at cost of deterioration of cerebral hemodynamics, therefore the technique could not be recommended.

A recent prospective, observational study of a mixed population of ABI patients found that reduced C_{RS}, lower MAP, lung recruitment maneuvers (evaluated with changes in computed tomography [CT] scan), and increased $PaCO_2$ levels were determinants of increased ICP correlated to PEEP augmentation. However, these factors were not able to predict the effect of PEEP on ICP at baseline.[80]

How to set PEEP in ABI

In patients with ABI, the use of MV should be considered a pivotal part of the treatment and should be carefully monitored according to its impact on brain function. PEEP should optimize gas exchange and keep the lungs open but not overstretched, avoiding hemodynamic impairment.[32]

The VENTILO survey of the European Society of Intensive Care Medicine (ESICM) reported that currently clinicians set a low level of PEEP (5–10 cmH_2O) in ABI patients with raised ICP, suggesting some safety concerns about the hemodynamic consequences of PEEP; in cases with normal ICP, higher levels of PEEP are used.[81] Another multicenter survey conducted in 47 ICUs in China that treated neuro-patients reported that the median value of PEEP used in this population was 5 cmH_2O, and the PEEP never rose above 10 cmH_2O.[82]

However, there is still no univocal and recommended strategy to select the optimal PEEP in ABI. Several methods to set "best" PEEP exist, including (1) lung imaging at different pressures (LUS, CT scan, chest X-ray, electrical impedance tomography), (2) PaO_2/FiO_2 table at low and high PEEP, (3) higher delta changes in PaO_2, (4) optimal driving pressure finding the best elastance of the respiratory system, (5) optimal recruitment-to-inflation ratio, (6) optimal dead space (ventilatory ratio or volumetric capnography), (7) transpulmonary pressure at end expiration, (8) express method, and (9) optimal oxygen delivery.[37,83,84]

Monitoring tools for a safe PEEP setting in ABI patients

Simultaneous monitoring of changes in systemic and intracranial hemodynamics seems a good approach for setting PEEP in ABI patients. A PEEP level >15 cmH_2O could lead to CBF and CA impairment, especially in hypovolemic patients,[45] so euvolemia is encouraged in ABI patients undergoing MV.[1,51] MAP is a parameter that could not be ignored during PEEP setting and its management should precede PEEP titration; setting PEEP at 5–8 cmH_2O usually ensures oxygenation and avoids alveolar collapse,[45,73] and when MAP is maintained, PEEP levels up to 15 cmH_2O[71] do not significantly alter ICP and are safe to use. In contrast, PEEP can have negative effects on ICP as proved by other trials,[68,69] especially when it causes hyperinflation in the lungs and elevation of the $PaCO_2$ levels.[53,73] The PEEP level should be lower than the baseline ICP, and when selected, it should recruit lung units and improve oxygenation;[53] in addition, 0 cmH_2O PEEP should be avoided.[2] Based on the current evidence, RMs have contrasting effects on ICP; pressure control ventilation appears to be the safer approach.[77,78] However, the observed unpredictable effects of RMs on ICP means RMs should be conducted under close monitoring.[78] Knowledge of the elastic properties of the respiratory system could predict the amount of transmission of the PEEP to the intracranial compartment; in the case of normal C_{RS}, there is increased transmission of PEEP compared with that in the case of lung damage with a C_{RS} >45 mmHg.[52] Even if reduced C_{RS}, lower MAP, and increased $PaCO_2$ could not predict at baseline the effect of PEEP on ICP, they were determinant in the ICP rise following PEEP in a cohort of ABI patients, suggesting that their values and trends should be maintained under surveillance during PEEP use in ABI patients.[80] Moreover, in the recent RCT of Beqiri et al.[66] a high baseline ICP value was associated with a hazardous and persistent rise of ICP above 22 mmHg when PEEP was increased from 5 to 12 cmH_2O. This suggests that close attention should be paid to the baseline ICP value.

The use of multimodal neuromonitoring has been recently proposed to monitor PEEP and help in setting PEEP. An example is the use of NIRS, which works as a good surrogate of cerebral oxygenation and has been used to predict cerebral response to PEEP application or application of RMs.[80,85,86] Performing ONSD in ABI patients could help in monitoring ICP as it could be used as an indicator of significant changes in ICP when PEEP is applied, especially in patients for whom ICP monitoring is not indicated or available.[64,65,75,80]

LUS performed at baseline could predict the effect of PEEP on ICP, helping with the detection of the lung patterns that could respond to PEEP with undesired overinflation and C_{RS} decrease, worsening ICP.[75]

Starting from the hypothesis that the CVP could act as a mediator between PEEP and ICP, Li et al.[87] developed a new indicator called intracranial-to-central venous pressure gap (P_{IC}Gap), which consists of the difference between ICP and CVP (measured at initial PEEP), and tested its efficiency in predicting the responsiveness of ICP to PEEP. Patients were separated into responders and non-responders, and many variables were measured at different PEEP levels (3, 10, and 15 cmH_2O). The P_{IC}Gap was a stronger predictor of responsiveness compared with ICP and CVP values alone at baseline, with a sensitivity of 95.24%, a specificity of 87.6%, and a cut-off value of 2.5 mmHg. The P_{IC}Gap seemed to be a good predictor of the PEEP effect and should be implemented in the management of ABI patients to prove its efficacy.

Head positioning at 30° can help maintain stable pressure and blood outflow of the cerebral compartment, contributing to ICP maintenance.[48] Owing to their effects on cerebral parenchyma and vessels, PaO_2 and $PaCO_2$ levels should not be forgotten, and monitoring gas exchange is fundamental: the optimal PaO_2 target is 80–120 mmHg,[34] normocapnia (35–45 mmHg) should be pursued in cases of normal ICP, and short-term hyperventilation is suggested in cases of brain herniation but its use in cases of ICP elevation is not supported by evidence.[34]

PEEP setting based on the evidence for bedside decisions

Subpopulations of ABI patients exist based on different etiologies, and specific recommendation should be considered for such groups.[2]

The ESICM consensus statement[34] recommends that in ABI patients without ICP elevation, the PEEP level should be the same as in patients without ABI, as well as in ABI patients with ICP elevation but who are PEEP-insensitive (in whom ICP does not rise after PEEP elevation). Lung protective ventilation is recommended in ABI patients with ARDS and normal ICP. The same guidelines cannot provide a recommendation about MV in ABI patients with significant ICP elevation (rather than the coexistence of ARDS or not).[34] Recently, Robba et al.[88] designed a stepwise approach for TBI patients with ARDS, in terms of PEEP titration, which suggests starting from 5 cmH_2O PEEP and increasing this to improve oxygenation (monitoring plateau pressure and driving pressure), with the support of strategies to manage ICP and its possible elevation. The mnemonic "GHOST-CAP" and "THE MANTLE" acronym should always be kept in mind for good general management of all ABI patients.[89,90]

Thus, to properly set PEEP, monitoring the hemodynamic status, and the elastic properties of the respiratory system are fundamental, especially when there are no specific indicators able to predict the effect of PEEP.[3] Nevertheless, there is no univocal agreement on which method to apply, especially in ABI patients. In this context, the use of multimodal PEEP setting, accounting for hemodynamic status (i.e., using oxygen delivery), systemic and brain needs (i.e., using PaO_2, NIRS, and invasive/non-invasive ICP monitoring), and elastic properties of the respiratory system, could be the most intriguing and complete strategy. A pilot study found good correlation between systemic oxygen delivery and brain oxygenation after PEEP rise from 5 to 15 cmH_2O in patients with ABI, suggesting that systemic indicators of oxygen status are suitable targets to set PEEP in patients with ABI. However, given the limited information and pilot results, further larger studies are warranted to confirm these findings.[91]

To support physicians in the use of PEEP in ABI patients, we propose a new acronym, "DEPARTMENT" (Figure 3), which organizes valuable consequences of PEEP and evidence-based suggestions for PEEP application. This acronym aims to summarize—in a simple, practical, and easy-to-remember way at the bedside—the key points to consider when PEEP is applied in the context of ABI.

Multimodal monitoring provides the opportunity for safe, effective, and personalized PEEP titration through the possibility of measuring different variables. This approach allows different goals to be achieved simultaneously; Figure 4 serves to remind clinicians of how all organs are affected by PEEP and the safety goals for each one.[34,41,89,90]

The impact of the application of PEEP in ABI on the outcome

Little is known about the impact of PEEP on the outcome of ABI patients. Even if not significant, the mortality was lower in the patients with ABI who underwent RM in pressure control (15 cmH_2O PEEP and 35 cmH_2O pressure control above PEEP) compared with those who underwent 35 cmH_2O RM for 30 s.[77] A systematic review from Yuan et al.[92]concluded that mortality did not significantly change between patients with ICP monitoring and those without, although clinical studies included in the review and published after 2012 suggested lower mortality in patients who underwent ICP monitoring. Patients with ABI managed with lung protective ventilation did not experience higher mortality.[82] In cases of ARDS aggravating ABI, mortality increased.[93,94] Despite growing evidence, the impact of PEEP on mortality outcome remains unclear.

ICU length of stay was not negatively impacted by lung protective ventilation (≤6 mL/kg V_T and a peak airway pressure <30 cmH_2O)[82] but worsened in the case of concomitant ARDS.[94] Lung protective ventilation did not worsen the number of days of MV in the survey of Luo et al.,[82] and in the prospective before–after trial of Asehnoune et al.,[95] no difference was seen in the number of ventilation-free days between two different MV approaches. The compliance to treatment was an independent factor associated with the reduction of MV days, and the application of 6–8 cm H_2O PEEP was not directly associated with an improvement in outcome, but significantly contributed to the improvement of the PaO_2/FiO_2 ratio.

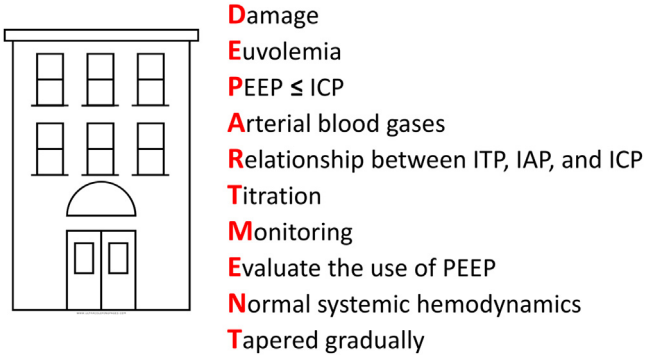

Figure 3. The DEPARTMENT acronym. Damage: as a general rule, supported by clinical and experimental studies, the greater the lung damage, the lower the transmission of pressures from the thoracic cavity to the intracranial compartment.[1,49] Euvolemia: is fundamental to ensure euvolemia before PEEP titration[44] to avoid the hemodynamic harmful consequence of PEEP, especially when high PEEP (>15 cmH_2O) is necessary.[45] The PEEP-test of Lai et al.[46] could help with predicting volume responsiveness. PEEP lower than ICP: PEEP should be kept under the baseline ICP value[53] (0 cmH_2O PEEP should be avoided).[2] Arterial blood gasses: PEEP as part of the management of ABI patients has the goal to reach and maintain safe blood gas levels of O_2 (PaO_2 target: 80–120 mmHg) and CO_2 ($PaCO_2$ target: 35–45 mmHg).[34] Relationship: PEEP could impact other organs and their equilibrium, thus the relationship between PEEP and ICP, ITP, and IAP should always be considered to prevent undesirable consequences.[39–41,43] Titration: PEEP should be a personalized ventilatory parameter[32]; in ABI patients, close attention should be given to baseline ICP and its change during PEEP setting as well as systemic and cerebral hemodynamic parameters. Avoid 0 cmH_2O PEEP[2] and start from 5 cmH_2O PEEP and increase the level to improve oxygenation (pay attention to plateau and driving pressure).[88] Monitoring: PEEP should always be used under close systemic and multimodal neuromonitoring. Even if invasive ICP remains the gold standard, non-invasive tools like TCD,[50–53]ONDS,[63–65] and LUS[75] are gaining reliability when invasive ICP is not available. Methods to monitor cerebral oxygenation (NIRS, $PtiO_2$, $SvjO_2$) should be implemented in clinical practice.[90] Evaluate: PEEP is not contraindicated in ABI and its use is safe under close multimodal monitoring[3,34]and comprehensive monitoring of the elastic properties of the respiratory system.[48,49,80] Normal systemic hemodynamics: ensuring hemodynamic stability as part of a good general approach[89,90] is fundamental in ABI patients; preventing the decrease of CBF and CPP following PEEP and ensuring the stability of MAP is pivotal,[1] thus when properly settled, PEEP could support CO and peripheric circulation.[43] Tapered gradually: PEEP should be decreased gradually. The lung has a viscoelastic property, meaning that the applied stress is not constant during a sustained strain. The deformation of the tissue is expressed as strain, which is the ratio between the applied tidal volume and the end-expiratory lung volume. Increased lung damage has been found with sustained inflation followed by abrupt deflation of PEEP levels, which led to hemodynamic impairment and increased lung microvascular pressure.[96] In a recent animal study, Rocha et al.[97] demonstrated that an abrupt versus gradual release of PEEP associated with standard or high fluid volume status causes epithelial cell damage and increased pulmonary arterial pressure. Detrimental effects of an abrupt increase of PEEP were also assumed to affect the brain.[98] ABI: Acute brain injury; CBF: Cerebral blood flow; CO: Cardiac output; CPP: Cerebral perfusion pressure; IAP: Intra-abdominal pressure; ICP: Intracranial pressure; ITP: Intrathoracic pressure; LUS: Lung ultrasound; MAP: Mean arterial pressure; NIRS: Near infrared spectroscopy; ONDS: Optic nerve sheath diameter; PaO_2: Arterial partial pressure of oxygen; PEEP: Positive end-expiratory pressure; $PtiO_2$: Brain tissue oxygen tension; $SvjO_2$: Venous jugular saturation of oxygen; TCD: Transcranial doppler.

According to the literature available, lung protective ventilation with application of PEEP does not worsen the outcomes in ABI patients,[82] thus it should be considered safe. However, its potentially beneficial effects need further research. New studies are investigating the physiological effect of PEEP on the brain, but the consequences on outcome still need to be validated.[91]

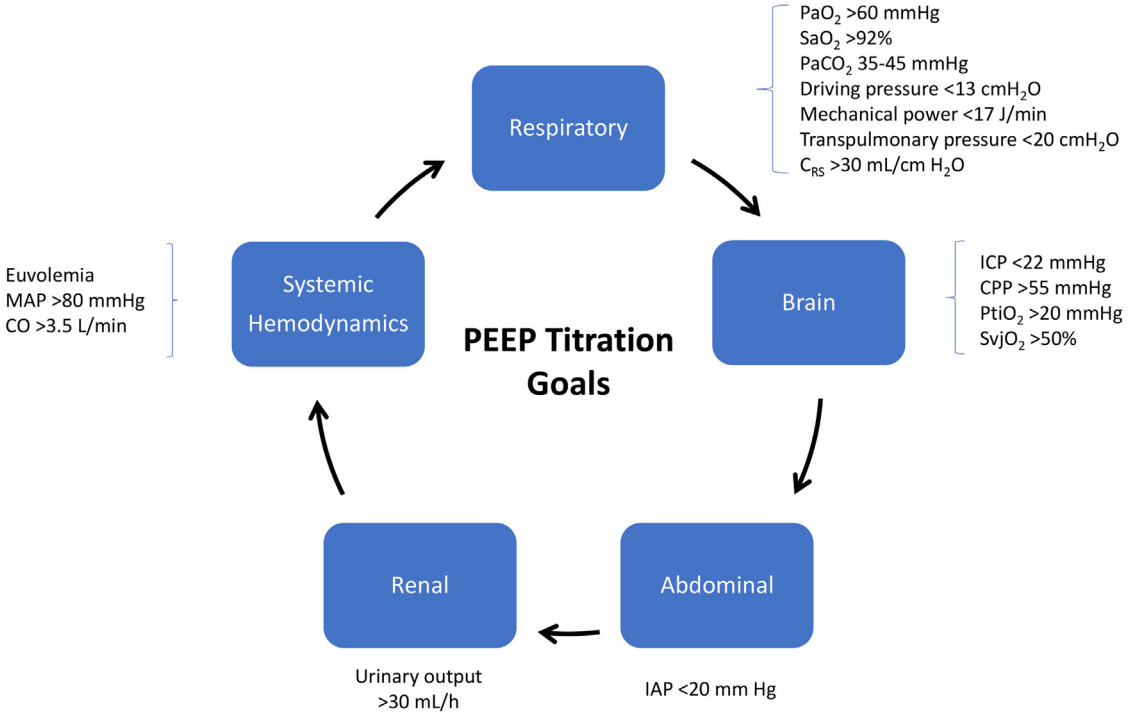

Figure 4. Safety goals during PEEP titration. The figurative circular diagram stresses the importance of continuous monitoring in support of organ (and systemic) stability.
CO: Cardiac output; CPP: Cerebral perfusion pressure; C_{RS}: Compliance of the respiratory system; IAP: Intra-abdominal pressure; ICP: Intracranial pressure; MAP: Mean arterial pressure; $PaCO_2$: Arterial partial pressure of carbon dioxide; PaO_2: Arterial partial pressure of oxygen; PEEP: Positive end-expiratory pressure; $PtiO_2$: Brain tissue oxygenation; SaO_2: Saturation of oxygen; $SvjO_2$: Venous jugular oxygen saturation.

Limitations

Scoping studies help review new information when it is not clear what other, more specific questions can be presented and beneficially addressed by a more precise systematic review. Among the studies included in this scoping review, the most frequent design was the prospective (or retrospective) observational one, whereas the RCT represented the minority. Randomized trials on PEEP in ABI patients are lacking in the literature. All study populations in this research field are often small in dimension and heterogeneous as ABI identifies a group of patients composed by different etiological subpopulations (TBI, SAH, intracerebral hemorrhage, etc.), which could respond slightly differently to PEEP. Monitoring methods are different among the studies, and this could contribute to difficulties in the estimation of the real consequences of PEEP in ABI; moreover, methods to monitor the lung elastic properties and cerebral oxygenation are poorly investigated.

Conclusions

Patients with ABI are a population with peculiarities and the setting of MV should take into consideration the lung–brain interactions. PEEP can be safely used to improve gas exchange keeping in mind its potentially harmful effects, which could be predicted with adequate monitoring supported by bedside non-invasive neuromonitoring tools such as NIRS and LUS. New indicators are needed to predict the effects of PEEP before its use, starting from measurable characteristics of the patient and the etiology of ABI. In addition, the literature underlines that these patients should undergo a good general intensive care approach and multimodal monitoring.

Author Contributions

Greta Zunino and **Denise Battaglini** wrote and edited the manuscript. **Daniel Agustin Godoy** edited the manuscript. All authors read and approved the submitted version.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Not applicable.

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