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PII: S2667-100X(26)00159-3
DOI: https://doi.org/10.1016/j.jointm.2026.09.007
Reference: JOINTM 333

To appear in: *Journal of Intensive Medicine*

Received date: 29 April 2026
Revised date: 25 September 2026
Accepted date: 25 September 2026

Please cite this article as: Shaurya Taran , Emanuele Rezoagli , Sarah Wahlster , John G. Laffey , Giuseppe Citerio , Ventilating the injured brain: Balancing lung protection and cerebral physiology, *Journal of Intensive Medicine* (2026), doi: https://doi.org/10.1016/j.jointm.2026.09.007

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Review

Ventilating the injured brain: Balancing lung protection and cerebral physiology

Shaurya Taran[1,2,*], Emanuele Rezoagli[3], Sarah Wahlster[4,5,6], John G. Laffey[7,8], Giuseppe Citerio[3,9]

[1]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto M4N 3M5, ON, Canada;

[2]Division of Respirology and Critical Care, Toronto Western Hospital, University of Toronto, Toronto M5T 2S8, ON, Canada;

[3]Fondazione IRCCS San Gerardo Dei Tintori, Monza 20900, Italy;

[4]Department of Neurology, University of Washington, Seattle 98195-6465, WA, USA;

[5]Department of Neurological Surgery, University of Washington, Seattle 98195-6470, WA, USA;

[6]Department of Anesthesiology and Pain Medicine, University of Washington, Seattle 98195-6540, WA, USA;

[7]Anesthesia and Intensive Care Medicine, School of Medicine, University of Galway, Galway H91 TK33, Ireland;

[8]Department of Anesthesia and Intensive Care Medicine, University Hospital Galway, Galway H91 YR71, Ireland;

[9]School of Medicine and Surgery, University of Milano-Bicocca, Milan 20126, Italy.

***Corresponding author:** Shaurya Taran, Division of Respirology and Critical Care, Toronto Western Hospital, Office 411-L, 2nd Floor McLaughlin, 399 Bathurst Street, Toronto M5T 2S8, ON, Canada.

E-mail address: shaurya.taran@mail.utoronto.ca

Shaurya Taran: 0000-0001-7639-0365

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Abstract

This review summarizes mechanical ventilation in acute brain injury (ABI) through the lens of integrated brain–lung interactions, with a focus on how gas exchange, ventilatory mechanics, and hemodynamics influence cerebral physiology and clinical outcomes. Among these interactions, the effects of arterial blood gases on the cerebral circulation are particularly important. Carbon dioxide is a key determinant of cerebrovascular tone. Hypocapnia reduces cerebral blood flow (CBF), blood volume, and intracranial pressure (ICP), whereas hypercapnia increases CBF and may exacerbate intracranial hypertension. Observational data demonstrate a U-shaped association between arterial partial pressure of carbon dioxide ($PaCO_2$) and mortality, with increased risk at both low and high values. Current evidence supports targeting normocapnia (approximately 35–45 mm Hg) in most patients, with transient hypocapnia reserved for short-term management of intracranial hypertension. Oxygenation is similarly associated with outcomes. Hypoxemia is consistently associated with increased mortality and worse neurological outcomes, while hyperoxemia leads to oxidative injury and is associated with adverse outcomes in observational studies. Data from large cohorts suggest lowest mortality at intermediate arterial partial pressure of oxygen (PaO_2) levels. Beyond gas exchange, ventilatory mechanics may also influence cerebral physiology. Positive pressure ventilation affects intracranial dynamics through changes in pleural pressure, venous return, and cardiac output. The effect of positive end-expiratory pressure (PEEP) on ICP is variable and depends on lung and chest wall compliance, intracranial compliance, and hemodynamic status. Despite these physiologic considerations, evidence for specific ventilator targets in ABI remains limited. Observational studies suggest associations between higher tidal volume (Vt), plateau pressure (Pplat), driving pressure (ΔP), and mechanical power (MP) with increased mortality; however, randomized data are sparse, and results are heterogeneous. In patients with concomitant acute respiratory distress syndrome (ARDS), lung-protective ventilation strategies

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improve respiratory outcomes but may influence cerebral physiology, particularly through effects on $PaCO_2$ and intrathoracic pressure. Future research should focus on integrating multimodal neuromonitoring with respiratory physiology to define patient-specific ventilatory targets and evaluate their impact on neurological outcomes in prospective studies.

Keywords: Acute brain injury; Acute respiratory distress syndrome; Mechanical ventilation; Lung-protective ventilation

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Introduction

Critically ill patients with acute brain injury (ABI), including traumatic brain injury (TBI), aneurysmal subarachnoid hemorrhage (aSAH), intracerebral hemorrhage (ICH), and acute ischemic stroke (AIS), frequently require mechanical ventilation during their intensive care unit (ICU) course, often for reasons that extend beyond respiratory failure. Indications for ventilatory support include depressed consciousness with loss of airway protection, impaired respiratory drive, need for controlled ventilation during management of intracranial hypertension or refractory seizures, and facilitation of neuroimaging and neuromonitoring.[1,2] Pulmonary complications such as aspiration, pneumonia, neurogenic pulmonary edema, and acute respiratory distress syndrome (ARDS) also contribute to the need for mechanical ventilation.[3–5]

Although ABI subtypes differ substantially in their underlying pathophysiology, they share common ventilatory challenges related to gas exchange, intracranial dynamics, and cardiopulmonary interactions. Changes in arterial carbon dioxide tension alter cerebrovascular tone and cerebral blood flow (CBF). At the same time, positive pressure ventilation influences intrathoracic pressure, venous return, and cardiac output, with downstream effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP).[6,7] These interactions frequently generate competing physiologic priorities. Lung-protective strategies, such as low tidal volume (Vt) ventilation and higher positive end-expiratory pressure (PEEP), may alter arterial partial pressure of carbon dioxide ($PaCO_2$), pleural pressure, and systemic hemodynamics in ways that affect ICP and CPP.[8] Conversely, approaches historically used to control ICP, such as higher Vt and low PEEP strategies, may contribute to lung injury and increase the risk of pulmonary complications.[9] This tension is increasingly relevant with the widespread adoption of lung-protective ventilation in general

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critical care, where strategies that benefit the lungs may not translate directly to patients with competing cerebral priorities.

This review synthesizes current evidence on mechanical ventilation in ABI through the lens of integrated brain-lung interactions. We first review gas-exchange targets, focusing on how carbon dioxide and oxygen affect cerebral physiology. We then examine the physiologic interactions between positive pressure ventilation and the injured brain, with specific emphasis on the effects of Vt and PEEP. We subsequently evaluate evidence for key ventilatory targets, including Vt, plateau pressure (Pplat), driving pressure (ΔP), and mechanical power (MP), followed by considerations in patients with concurrent ARDS. We conclude by highlighting emerging research priorities focused on defining patient-specific ventilatory strategies that preserve both lung and brain homeostasis. This review primarily addresses the acute phase of invasive mechanical ventilation, when ventilatory management is directed toward preventing secondary brain injury through optimization of gas exchange, respiratory mechanics, systemic hemodynamics, and intracranial physiology. Weaning, liberation from mechanical ventilation, and extubation are not covered. Hypoxic-ischemic brain injury following cardiac arrest is also beyond the scope of this review.

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Gas Exchange Targets in ABI: Carbon Dioxide and Oxygen Management

Oxygen and carbon dioxide exert powerful effects on CBF, ICP, and metabolic homeostasis. Yet, defining optimal targets in ABI remains challenging, and current practice relies on physiological principles, observational evidence, and expert consensus rather than on clinical trial data.

Carbon dioxide, CBF, and ICP

Carbon dioxide is one of the most potent regulators of cerebral vascular tone and CBF. Cerebral resistance arterioles contract in response to hypocapnia and dilate with hypercapnia – a phenomenon termed cerebrovascular CO_2 reactivity.[10–12] This response is pH-mediated: CO_2 diffusion alters perivascular pH, promoting vasodilation at lower pH and vasoconstriction at higher pH.[11] Each 1 mm Hg increase or decrease in $PaCO_2$ leads to a 4–8% increase, or 1–4% decrease, in CBF, respectively.[13,14] CO_2 reactivity may be impaired with increasing age and among patients with severe ABI, such that changes in $PaCO_2$ may produce little to no change in CBF. The CBF response to $PaCO_2$ is also modulated by mean arterial pressure (MAP). When MAP is severely reduced, cerebral vasodilatation is maximal, and hypercapnia exerts little further augmentation of CBF, whereas hypocapnia leads to limited vasoconstriction and little to no additional reduction in CBF.[15]

Prophylactic hyperventilation was found in a randomized controlled trial (RCT) to lead to worse outcomes following severe head injury, and is not recommended[16]; however, therapeutic hyperventilation remains a potent short-term rescue therapy for intracranial hypertension.[17] Caution is required as the accompanying reduction in CBF may trigger anaerobic metabolism,[18,19] especially at $PaCO_2$ levels near 25 mm Hg in the first 24–36 h after ABI.[20] The vasoconstrictive effect of hypocapnia is transient because local buffering normalizes perivascular pH within hours, rendering prolonged hyperventilation ineffective[2,10,11]; moreover, rebound ICP elevation may occur when CO_2 is normalized. Conversely, hypercapnia can also be problematic because excess CO_2 increases cerebral blood volume (CBV) and may exacerbate intracranial hypertension. Accordingly, normocapnia (35–45 mm Hg) should be considered the default target, while hypocapnia should be reserved as a short-term rescue strategy in the setting of acute intracranial hypertension.

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A CENTER-TBI study found that deviations from normocapnia during the first week of ventilation were common, with only 53% of patients having at least half of all recorded $PaCO_2$ values in the normocapnic range.[21] In a secondary analysis of the ENIO cohort, a U-shaped relationship between $PaCO_2$ and mortality was observed, with increased risk at $PaCO_2$ values below approximately 32 mm Hg and above 45 mm Hg.[22] International consensus recommends maintaining $PaCO_2$ between 35 mm Hg and 45 mm Hg in patients without significant ICP elevation, reserving short-term hyperventilation (never below 30 mm Hg) only for imminent herniation as a bridge to definitive therapy.[23,24] Ideally, arterial blood gas (ABG) analysis (as opposed to end-tidal CO_2 [$EtCO_2$]) should be used to guide CO_2 management. Large $PaCO_2$–$EtCO_2$ gradients have been described and are associated with increased mortality, highlighting the need for ABG targeting during early and acute phases of ABI.[25,26] Taken together, $PaCO_2$ should not be interpreted as a static target, but as a dynamic determinant of cerebral hemodynamics, whose optimal range varies across patients depending on intracranial compliance, blood pressure, and metabolic demand.

Oxygen tension

Systemic hypoxemia impairs mitochondrial oxidative phosphorylation, promotes excitotoxicity, and amplifies neuronal cell death.[27] Following ABI, brief episodes of PaO_2 below 60 mm Hg have been associated with higher mortality and worse neurological outcomes.[28] Accordingly, the American College of Surgeons trauma quality improvement program (ACS TQIP) Best Practices Guidelines for the Management of Traumatic Brain Injury emphasize strict avoidance of hypoxemia, recommending maintenance of arterial oxygen saturation ≥94% and arterial partial pressure of oxygen (PaO_2) ≥60 mm Hg throughout the acute phase.[29]

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Moreover, the long-standing assumption that higher oxygen levels are protective has been progressively challenged. Excess oxygen delivery promotes oxidative stress, mitochondrial dysfunction, and cerebral vasoconstriction.[30] An analysis of the CENTER-TBI and OzENTER-TBI data found that higher PaO_2 values and greater exposure to supplemental oxygen during the first week in ICU were independently associated with increased 6-month mortality in TBI.[31] In the ENIO study, the lowest mortality was observed within an intermediate PaO_2 range.[32] These findings align with the ESICM consensus recommendations, which advocate avoidance of both hypoxemia and hyperoxemia and suggest targeting a PaO_2 range of approximately 80–120 mm Hg in patients with ABI, irrespective of ICP status.[24]

Another key parameter is the brain tissue oxygen tension ($PbtO_2$), which is influenced by hemoglobin concentration, microcirculatory integrity, and tissue diffusion, in addition to PaO_2 and SpO_2.[33] In the BOOST-II trial, management protocols incorporating $PbtO_2$ monitoring reduced the proportion of time with brain hypoxia.[34] Direct brain oxygenation monitoring may also detect occult cerebral hypoxia despite “acceptable” PaO_2 and SpO_2.[35] While the recent OXY-TC trial showed no difference in clinical outcomes when $PbtO_2$ monitoring was added to ICP monitoring in patients with severe TBI,[36] two additional randomized trials investigating the role of a $PbtO_2$-guided strategy are nearing completion and will further inform this question (NCT03754114; ACTRN12619001328167).

Collectively, current evidence suggests that oxygen should be titrated to avoid both hypoxemia and hyperoxemia, while recognizing that normal systemic oxygenation does not guarantee adequate cerebral oxygen delivery. These observations support a shift away from uniform oxygenation targets toward individualized strategies, in which systemic and cerebral oxygenation are jointly considered rather than assumed to be concordant.

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Physiologic Interactions Between Mechanical Ventilation and the Injured Brain

Mechanical ventilation in patients with ABI produces a complex bidirectional interplay between the lungs and the central nervous system.[8,37] Positive pressure ventilation, particularly with high PEEP and low Vt, can have important effects on CBF, ICP, and CPP. The magnitude of these effects depends heavily on cardiac function, volume status, respiratory system compliance, and cerebral autoregulation. Understanding how ventilator-induced changes in gas exchange, intrathoracic pressure, and systemic hemodynamics translate to cerebral physiology is essential for avoiding secondary brain injury.[6]

Low Vt ventilation in ABI

Low Vt ventilation can influence cerebral physiology through several interdependent mechanisms and should not be regarded as an isolated intervention. Its net physiological effect depends on the respiratory rate (RR), minute ventilation, dead-space fraction, lung mechanics, PEEP, sedation, patient–ventilator synchrony, and $PaCO_2$ control. Reducing Vt also leads to hypercapnia if minute ventilation is not adequately maintained; this risk is more pronounced when the dead space fraction is high (e.g., pneumonia, ARDS). The increase in $PaCO_2$ may not be clinically relevant in most ICU patients, but among those with ABI, even small elevations in $PaCO_2$ can increase CBF, CBV, and ICP – effects that are amplified in patients with reduced intracranial compliance.[38] On the other hand, compensatory increases in RR to preserve normocapnia can lead to dynamic hyperinflation if expiratory time is insufficient, increasing intrathoracic pressure, with the potential to impede cerebral venous outflow. A higher RR also increases the frequency with which energy is delivered to the respiratory system and may therefore increase MP despite a lower Vt. Moreover, very low Vt may promote atelectasis or derecruitment when PEEP is insufficient and may require deeper sedation or neuromuscular blockade to maintain patient–ventilator synchrony. Thus, the

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cerebral and pulmonary consequences of lowering Vt depend on the accompanying ventilatory and supportive strategy. These trade-offs also illustrate why low-Vt ventilation in ABI cannot be interpreted solely through a pulmonary lens.

PEEP–ICP–CPP interactions

The impact of PEEP on ICP and CPP is determined by the degree to which airway pressure is transmitted to the pleural space and how this interacts with jugular venous drainage, cardiac output, and MAP. The overall effects are nuanced and not always easily predictable. In a prospective study of ventilated patients with ABI, slow incremental PEEP increases from 5 cm H_2O to 15 cm H_2O produced clinically modest ICP rises (median ≈2 mm Hg) without triggering interventions, and did not worsen autoregulation indices.[39] Li et al.[40] found that the ICP to central venous pressure (CVP) gap (ICP–CVP) was a strong predictor of the ICP response to increasing PEEP. A baseline gap of <2.5 mm Hg predicted with high sensitivity and specificity a clinically relevant increase in ICP when PEEP was increased from 3 cm H_2O to 15 cm H_2O; this parameter was a better predictor of ICP increase than the baseline ICP or CVP alone. The supine position also increases ICP through the loss of gravity-dependent drainage from the jugular veins, meaning that for the same level of PEEP, the impact on ICP is often higher when supine.[7]

The effect of PEEP on CPP is mediated primarily by changes in MAP. Georgiadis et al.[41] showed that increasing PEEP led to little change in CPP as long as MAP was maintained, whereas when PEEP augmentation led to a reduction in MAP, CPP also decreased. These observations highlight the importance of ensuring stable MAP to reduce the risk of cerebral ischemia whenever PEEP is manipulated.

Role of lung and chest wall compliance

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The effect of PEEP on intracranial dynamics is further modulated by lung and chest wall mechanics. PEEP that recruits collapsed alveoli improves lung compliance and primarily increases transpulmonary pressure rather than pleural pressure, resulting in minimal ICP effects. As the latter creates the gradient for jugular venous drainage, ICP is relatively unimpacted because cerebral venous outflow is maintained.[39] On the other hand, PEEP that causes overdistension with minimal alveolar recruitment increases pleural pressure, obstructing venous outflow and raising ICP. For example, in patients with normal lungs and poor chest wall compliance (e.g., morbid obesity and intra-abdominal hypertension), PEEP often leads to significant increases in ICP owing to the large increase in pleural pressure.[7]

Influence of autoregulation

PEEP-mediated changes in intracranial dynamics also depend in part on the integrity of cerebral autoregulation. When cerebral autoregulation is intact, modest reductions in CPP secondary to PEEP augmentation can elicit compensatory cerebral vasodilation that maintains CBF but increases CBV and may increase ICP, especially when cerebral compliance is impaired. Conversely, when autoregulation is impaired, CBF becomes passively dependent on perfusion pressure, such that reductions in CPP may reduce CBF with heightened risk of ischemia. The pressure reactivity index (PRx), a correlation between slow waves in arterial pressure and ICP, can be used to assess autoregulatory function and identify patients who are unlikely to tolerate aggressive PEEP increases.[42]

Importance of individual patient physiology

Taken together, these mechanisms highlight that the cerebral effects of mechanical ventilation are not determined by individual ventilator settings alone. Furthermore, there is no universally “brain-safe” ventilator strategy, and the interplay among $PaCO_2$, PEEP, hemodynamics, and autoregulation status is highly patient-specific. Nevertheless, the general

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framework presented here – which considers arterial inflow, venous outflow, and respiratory/chest wall mechanics – can be used as a starting point to understand the impacts of key ventilator manipulations on intracranial dynamics (Figure 1). This integrated approach is essential to identifying the least injurious compromise between lung protection and preservation of cerebral physiology.[24]

Evidence for Lung-Protective Mechanical Ventilation in ABI

Over the past two decades, lung-protective ventilation strategies centered on low Vt ventilation, appropriate PEEP, and limitation of ΔP have become standard in critical care. In patients with isolated ABI and normal lung function, the principal objective of mechanical ventilation is optimization of cerebral physiology rather than treatment of respiratory failure, whereas patients with coexisting ABI and ARDS require a more balanced approach that simultaneously prioritizes lung protection and prevention of secondary brain injury. These considerations have been increasingly examined in registry data, observational studies, and randomized trials.

Vt

Low Vt ventilation close to 6 mL/kg predicted body weight (PBW) is a cornerstone of modern critical care, supported by evidence demonstrating reduced mortality across ARDS and non-ARDS populations.[43,44] These data have partly driven the observed reduction in delivered Vt over time.[45] Among patients with ABI, global practice has similarly shifted toward lower Vt ventilation.[46,47] A longitudinal multinational study of 4152 patients with ABI found that mean delivered Vt was 9.1 mL/kg PBW in 2004, whereas by 2016 it had decreased to 8 mL/kg PBW.[46] In the VENTIBRAIN study, which recruited 2095 patients with ABI from 26 countries between 2020 and 2023, median Vt at admission was 6.5 mL/kg PBW.[48]

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The optimal approach to Vt selection in patients with ABI has not been clearly established. A meta-analysis of eight observational studies found no clear benefit of Vt <8 mL/kg PBW in ABI,[49] whereas a recent observational study found a reduction in mortality with sustained delivery of Vt ≤8 mL/kg PBW (compared with > 8 mL/kg PBW) over the first 7 days of mechanical ventilation.[50] In contrast, the PROLABI randomized trial of 190 patients with ABI showed harm with more aggressive Vt reduction (≤6 mL/kg PBW) combined with higher PEEP.[51] The VENTIBRAIN observational study also found that lower Vt was linearly associated with higher mortality, although caution is warranted given the observational nature of this study and the possibility of residual confounding.[48] Direct comparisons between these studies are challenging because of differences in designs, analytic approaches, proportion of ABI subtypes, and Vt thresholds. While it is plausible that very low Vt should be approached with caution (e.g., due to hypercapnia, excess sedation to abolish asynchrony, and alveolar derecruitment), a safety threshold has not been established. Current data are further limited by the inclusion of heterogeneous ABI populations and limited applicability to patients with coexisting ABI and ARDS. In addition, the treatment group in the PROLABI trial received lower Vt together with a higher PEEP strategy, making it difficult to determine whether the reported harm was attributable to Vt itself or to concomitant interventions such as increased PEEP, sedation, neuromuscular blockade, or other aspects of ventilatory management.

Taken together, it is unlikely that a single universal Vt target will be appropriate for all ABI conditions across all phases of injury. For example, the Vt strategy must also consider the need to avoid hypocapnia in patients with large ischemic penumbra (e.g., following AIS) or active delayed cerebral ischemia (e.g., following a SAH). A practical clinical suggestion is therefore to initiate ventilation near 6–8 mL/kg PBW, with further individualization based on patient-specific considerations and evolving physiology (e.g., high ICP, imminent herniation,

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severe ARDS).[6,25] Caution with Vt lower than 6 mL/kg PBW may be appropriate until further evidence becomes available.

Pplat and PEEP

Pplat represents the pressure in the small airways and alveoli during the inspiratory phase of mechanical ventilation. A secondary analysis of the LUNG SAFE study in ARDS found a significant increase in the slope of the Pplat-mortality association curve above Pplat of 20 cm H_2O and again above 30 cm H_2O.[52] ARDS guidelines recommend maintaining Pplat below 30 cm H_2O.[53,54] Data are sparser in the ABI population, and the ESICM consensus statement does not specifically mention a target for Pplat.[24] The VENTIBRAIN study found a linear association between Pplat and ICU mortality (hazard ratio 1.5; 95% CI, 1.3–1.8 comparing the 75th percentile with the 25th percentile)[48]; importantly, however, a safety threshold was not examined.

The role of PEEP in ABI has been more challenging to clarify due to concerns regarding ICP elevation. The VENTIBRAIN study found a U-shaped association between PEEP and mortality, with the lowest mortality at approximately 8 cm H_2O of PEEP.[48] However, the optimal PEEP likely depends on multiple patient-specific factors (e.g., ARDS, potential for lung recruitment, ICP impact). Reluctance to use higher PEEP in patients with ABI is common: a registry-based cohort study found that PEEP was significantly lower in ABI (*vs.* non-ABI) patients, including in patients with $PaO_2/FiO_2 \leq 150$ where higher PEEP may be especially important.[47] These findings suggest that concern about cerebral effects may sometimes lead to underuse of potentially beneficial PEEP.

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ΔP, defined as Pplat minus PEEP, incorporates the interaction between Vt and respiratory system compliance. A landmark analysis of nine ARDS trials demonstrated a strong association between higher ΔP and mortality (relative risk 1.41 per one-standard-deviation increase in ΔP, 95% CI 1.31–1.51) with an inflection point at 15 cm H_2O; furthermore, in this analysis, reductions in Vt or increases in PEEP were associated with improved survival only when accompanied by a reduction in ΔP.[55] A Bayesian analysis of five ARDS RCTs demonstrated that the mortality impact of low Vt depended on respiratory system elastance (posterior probability: 93%), effectively implicating ΔP rather than Vt as the causal driver of outcomes.[56]

In ABI, evidence for ΔP-limited ventilation is less well-established. A secondary analysis of the ENIO study found that a one-standard-deviation increase in ΔP (corresponding to ≈14 cm H_2O) on day 3 (compared with the median ΔP of 10 cm H_2O) was associated with increased in-hospital mortality.[57] The VENTIBRAIN study found that higher ΔP was linearly associated with increased ICU mortality, 6-month mortality, and worse neurologic outcome at 6 months.[48] A prespecified secondary analysis of VENTIBRAIN found a tight association between higher time-varying dynamic ΔP (peak pressure minus PEEP) and mortality; furthermore, patients with lower PaO_2/FiO_2 and lower Glasgow Coma Scores had worse outcomes for the same level of dynamic ΔP.[58] Although causality cannot be inferred from these observational data, ΔP is increasingly recognized as an important marker of ventilatory intensity in ABI, even if it is not yet a formal target in current consensus statements.[24]

MP

MP integrates Vt, ΔP, RR, flow, and PEEP into a composite measure of the total energy delivered to the lung per unit time. This concept is particularly relevant in ABI, where permissive hypercapnia is often undesirable, and maintenance of normocapnia with lower Vt

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may necessitate higher RRs (especially in the presence of increased physiological dead space), potentially increasing MP despite unchanged Vt. MP may represent an important determinant of outcome in ARDS and general critical care populations,[59–61] but no randomized trials have evaluated MP–guided ventilation; moreover, its specific role in ABI remains to be defined. A secondary analysis of ENIO (*n*=1217 patients) found that higher MP on days 1, 3, and 7 of mechanical ventilation was associated with higher hospital mortality, increased reintubation, and higher tracheostomy placement, whereas higher MP on days 1 and 3 was also associated with increased ARDS.[62] Associations with clinical outcomes were similar for a related formula based on $4 \times \Delta P + RR$.[57] Importantly, ABI consensus recommendations do not address MP,[24] and the incremental predictive value of this composite variable beyond its individual components has not been definitively established.[63]

Management of ARDS and ABI

The challenge of competing ventilatory priorities is exemplified in patients with coexisting ABI and ARDS. ARDS develops in 20–48% of patients with ABI[64–67] and is associated with increased mortality, worse neurologic outcomes, and longer durations of mechanical ventilation and ICU length of stay.[65,68] Concomitant ARDS and ABI poses several challenges. Patients with ABI, particularly those with intracranial hypertension, were excluded in several landmark ARDS trials,[44,69–71] resulting in limited direct evidence to guide decision-making. Moreover, clinicians may need to balance competing management priorities, as lung-protective strategies for ARDS may induce secondary brain injury, while attempts to optimize cerebral physiology may worsen pulmonary injury. Key areas of potential brain-lung conflict include: (1) low Vt, PEEP titration, and optimization of Pplat and ΔP; (2) prone position ventilation; (3) use of extracorporeal membrane oxygenation (ECMO) in refractory cardiorespiratory failure; and (4) use of a conservative fluid management strategy.

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In patients with coexisting ARDS and ABI without ICP elevation, the ESICM consensus statement recommends standard lung-protective ventilation, including low Vt, standard PEEP (same as in patients without ABI), and prone-position ventilation. However, no recommendations are provided for patients with ARDS and clinically significant ICP elevations.[24] When using low Vt in ARDS and ABI, vigilant monitoring of $PaCO_2$ is warranted. Of note, the daily mean $PaCO_2$ in the low Vt (4–6 mL/kg/PBW) arm in the ARMA trial ranged between 40 mm Hg and 44 mm Hg,[44] suggesting that normocapnia may be feasible. When there is strong clinical concern for elevated ICP, and hypercapnia is unavoidable, invasive and non-invasive measures of brain physiology can help determine individualized $PaCO_2$ thresholds.

Similarly, PEEP titration should be deliberate, accounting for lung compliance and hemodynamic effects while strictly avoiding alveolar hyperinflation. Concerns about intracranial hypertension can be mitigated by optimizing cerebral venous drainage and maintaining MAP to preserve CPP.[41,72] Lung ultrasonography can also help to individualize PEEP titration in ABI. A study of 30 patients showed that the effect of PEEP on ICP could be predicted by the lung ultrasound score. Specifically, improvement in the lung ultrasound score following PEEP augmentation from 5 cm H_2O to 15 cm H_2O correlated with a significant reduction (or no change) in ICP.[73] Prolonged recruitment maneuvers should generally be avoided in patients with ABI, as elevations in intrathoracic pressure may impair cerebral venous drainage and increase ICP without established clinical benefit.[74,75] If considered for refractory hypoxemia, recruitment maneuvers should be brief and reserved for carefully selected patients with close monitoring of ICP, CPP, and systemic hemodynamics.

Prone-position ventilation improves survival in moderate to severe ARDS, with the PROSEVA trial demonstrating a 17% absolute reduction in 28-day mortality with ≥16 h/day

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of proning among patients with $PaO_2/FiO_2 \leq 150$.[69] Proning also results in substantial improvements in arterial oxygenation, P/F ratio, and $PbtO_2$.[76,77] Despite these benefits, prone positioning remains under-utilized in ABI,[78] largely due to concerns regarding its effects on ICP. Studies have reported median ICP increases from 3 mm Hg to 12.7 mm Hg during proning[76,77,79,80]; patients with a higher baseline ICP appear to be at greater risk.[77] However, a recent study of 30 patients with aSAH found that only 5/97 proning sessions were terminated due to medically refractory ICP crises.[81] Overall, available evidence suggests that prone-position ventilation is feasible in carefully selected patients with close neuromonitoring. Strategies to mitigate intracranial hypertension during proning include positioning techniques that preserve cerebral venous outflow (e.g., reverse Trendelenburg or orienting the dominant jugular vein superiorly) and minimize intra-abdominal pressure (e.g., padding the shoulders and hips).[82,83] ICP can be treated before or during proning, and CPP can be preserved via blood pressure augmentation.

ECMO represents a potential rescue strategy to manage carefully selected patients with severe ARDS and ABI who remain refractory to conventional lung-protective ventilation. While ABI has historically been considered a relative contraindication for ECMO, improvements in circuit technology have expanded its use. Heparin-bonded circuits and polymethylpentene oxygenators may allow for VV-ECMO support, potentially with minimal systemic anticoagulation, in carefully selected ABI patients or those at risk for hemorrhagic conversion.[84] Femoral access can mitigate concerns regarding impaired cerebral venous drainage related to neck cannulation. In addition, careful control of sweep gas can avoid rapid $PaCO_2$ correction and the attendant risk of cerebral ischemia due to vasoconstriction.[85,86]

In parallel with respiratory support, fluid management must also be carefully considered. Both hypo- and hypervolemia have been associated with worse outcomes in ABI,[87–89] and a

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strategy targeting euvolemia is generally appropriate. Among patients with ARDS, the FACTT trial found that fluid restriction led to improved lung function and shorter duration of mechanical ventilation compared to liberal fluid management[90]; however, this strategy should be balanced against the risk of compromising cerebral perfusion in patients with concomitant ABI. In patients with cerebral vasospasm or acute large vessel occlusion, even transient hypovolemia may precipitate ischemia, necessitating caution with diuresis. Fluid administration and volume status should ideally be guided using a combination of dynamic indices of fluid responsiveness, bedside echocardiography to assess cardiac output and preload, and integration with neuromonitoring parameters such as ICP, CPP, and $PbtO_2$ when available. Furthermore, because the hemodynamic effects of positive-pressure ventilation are highly dependent on intravascular volume status, optimization of preload, cardiac output, and MAP should accompany ventilatory adjustments to preserve both cerebral oxygen delivery and perfusion.

In practice, ventilatory priorities in patients with concomitant ABI and ARDS should be dynamically adjusted according to the dominant physiological threat at a given time. In the presence of intracranial hypertension or impaired cerebral compliance, strict control of $PaCO_2$ may take precedence. When cerebral autoregulation is impaired, particular attention should be paid to maintaining stable MAP to preserve CBF. Conversely, in severe hypoxemia, optimization of oxygenation and limitation of ventilator-induced lung injury (VILI) become primary goals. This context-dependent prioritization underscores the need for integrated brain–lung monitoring rather than fixed ventilatory targets.

Strategies to Promote Best Ventilation Practices

Recent literature increasingly advocates for individualization of patient management guided by advanced monitoring strategies. Integration of multimodal neuromonitoring with

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respiratory mechanics and gas exchange allows clinicians to balance cerebral and pulmonary goals in real time.[37,91,92] Electrical impedance tomography and transpulmonary pressure measurements may further refine Vt and PEEP selection.[93,94] Esophageal manometry may help identify patients in whom higher airway pressures do not translate into harmful transpulmonary pressures, thereby allowing safer application of lung-protective strategies in the setting of ABI.

Careful sedation management and optimizing ventilator synchrony also play a pivotal role.[95,96] Excessive sedation may prevent accurate neurological assessment, whereas inadequate control of patient–ventilator interaction can increase cerebral metabolic demand. Protocolized sedation strategies and early mobilization, when feasible, may help mitigate these risks.[97] Adjuncts such as short-term neuromuscular blockade may be considered in selected patients with severe ventilator dyssynchrony or refractory hypoxemia, although their use must be balanced against the need for ongoing neurologic assessment.[24,54] Ventilator modes that improve synchrony (e.g., proportional assist ventilation or neutrally adjusted ventilatory assist) may offer advantages in reducing patient effort, although data in ABI populations remain sparse.

Finally, implementation science is essential to translate these insights into practice. Variability in clinician behavior and local resources and economic status remain major barriers in clinical practice, as highlighted by recent surveys and cohort studies.[98,99] Standardized care pathways that integrate neurologic and respiratory targets (e.g., paired ICP/CPP and ventilatory goals) may reduce practice variability and improve consistency in bedside decision-making.[100] Audit-and-feedback frameworks and incorporation of ventilation metrics (e.g., ΔP, MP) into routine quality dashboards may further facilitate implementation at the institutional level.[101]

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Future Directions and Research Priorities

Future research in mechanical ventilation for ABI should move beyond "one-size-fits-all" strategies toward a precision physiology-based approach. Rather than defining universal ventilatory targets, the field should aim to identify patient-specific thresholds for $PaCO_2$, oxygenation, and ventilatory intensity based on intracranial compliance, perfusion, cerebral autoregulation, and cerebral metabolic demand.

A key priority will be the integration of multimodal invasive and non-invasive neuromonitoring with advanced respiratory metrics to define individualized "safe operating zones," within which both lung and brain homeostasis can be preserved (Figure 2). In parallel, future studies should account for heterogeneity across major neurological conditions, including TBI, ICH, aSAH, and AIS, while also identifying biologically and physiologically distinct sub-phenotypes within each disease that may differ in their tolerance to ventilatory interventions. The concept of "ventilator-associated brain injury" also warrants further investigation and its potential impact on long-term neurological outcomes.[102,103] Prospective trials integrating both pulmonary and neurological endpoints and accounting for patient-centered outcomes will be essential to validate these strategies.

Conclusion

Mechanical ventilation in ABI should be understood not simply as respiratory support, but as a dynamic intervention that simultaneously modulates pulmonary mechanics, systemic hemodynamics, and cerebral physiology. Within this framework, $PaCO_2$ should be treated as a dynamic determinant of CBF rather than a static target, while PaO_2 should be titrated to avoid both hypoxemia and hyperoxemia, recognizing that systemic oxygenation may not reflect brain tissue oxygen tension. Similarly, Vt, PEEP, and other ventilatory targets should be individualized according to their effects on gas exchange and intracranial physiology.

These principles support a shift away from fixed ventilatory strategies based on thresholds and ranges, toward integrated, physiology-guided strategies informed by real-time neuromonitoring and cardiopulmonary mechanics. Future progress will depend on the ability to align ventilatory intensity with individual cerebral responses, thus transforming ventilation from a standardized protocol into a precision tool to improve neurologic recovery.

Acknowledgments

No funding sources to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Statement

Not applicable.

Conflict of Interest

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

Data Availability

N/A: This narrative review did not use primary data.

Disclosures

AI was used for Figure generation (ChatGPT; GPT-5.6 Sol; OpenAI; San Francisco, CA, USA).

References

Journal Pre-proof

[1] Stevens RD, Lazaridis C, Chalela JA. The role of mechanical ventilation in acute brain injury. Neurol Clin 2008;26(2):543–563,x. doi: 10.1016/j.ncl.2008.03.014.

[2] Taran S, McCredie VA, Goligher EC. Noninvasive and invasive mechanical ventilation for neurologic disorders. Handb Clin Neurol 2022;189:361–86. doi: 10.1016/b978-0-323-91532-8.00015-x.

[3] Li Y, Liu C, Xiao W, Song T, Wang S. Incidence, risk factors, and outcomes of ventilator-associated pneumonia in traumatic brain injury: a meta-analysis. Neurocrit Care 2020;32(1):272–85. doi: 10.1007/s12028-019-00773-w.

[4] Rogers FB, Shackford SR, Trevisani GT, Davis JW, Mackersie RC, Hoyt DB. Neurogenic pulmonary edema in fatal and nonfatal head injuries. J Trauma 1995;39(5):860–866;discussion 866–8. doi: 10.1097/00005373-199511000-00009.

[5] Taran S, Hamad DM, von Düring S, Malhotra AK, Veroniki AA, McCredie VA, et al. Factors associated with acute respiratory distress syndrome in brain-injured patients: a systematic review and meta-analysis. J Crit Care 2023;77:154341. doi: 10.1016/j.jcrc.2023.154341.

[6] Taran S, Wahlster S, Robba C. Ventilatory targets following brain injury. Curr Opin Crit Care 2023;29(2):41–9. doi: 10.1097/mcc.0000000000001018.

[7] Georgopoulos D, Taran S, Bolaki M, Akoumianaki E. Mechanical ventilation in patients with acute brain injuries: a pathophysiology-based approach. Am J Respir Crit Care Med 2025;211(6):932–45. doi: 10.1164/rccm.202409-1813SO.

[8] Mazzeo AT, Fanelli V, Mascia L. Brain-lung crosstalk in critical care: how protective mechanical ventilation can affect the brain homeostasis. Minerva Anestesiol 2013;79(3):299–

Journal Pre-proof

309.

[9] Mascia L, Zavala E, Bosma K, Pasero D, Decaroli D, Andrews P, et al. High tidal volume is associated with the development of acute lung injury after severe brain injury: an international observational study. Crit Care Med 2007;35(8):1815–20. doi: 10.1097/01.Ccm.0000275269.77467.Df.

[10] Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. Crit Care Med 2010;38(5):1348–59. doi: 10.1097/CCM.0b013e3181d8cf2b.

[11] Laffey JG, Kavanagh BP. Hypocapnia. N Engl J Med 2002;347(1):43–53. doi: 10.1056/NEJMra012457.

[12] Taran S, Sekhon M, Robba C. Carbon dioxide pathophysiology and targets following acute brain injury. Intensive Care Med 2025;51(7):1256–9. doi: 10.1007/s00134-025-07913-1.

[13] Willie CK, Macleod DB, Shaw AD, Smith KJ, Tzeng YC, Eves ND, et al. Regional brain blood flow in man during acute changes in arterial blood gases. J Physiol 2012;590(14):3261–75. doi: 10.1113/jphysiol.2012.228551.

[14] Kety SS, Schmidt CF. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J Clin Invest 1948;27(4):484–92. doi: 10.1172/jci101995.

[15] Iwabuchi T, Kutsuzawa T, Ikeda K, Nakamura T. Effects of blood gases on the pressure-flow relationships in canine cerebral circulation. Stroke 1973;4(1):65–72. doi: 10.1161/01.str.4.1.65.

Journal Pre-proof

[16] Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. J Neurosurg 1991;75(5):731–9. doi: 10.3171/jns.1991.75.5.0731.

[17] Gouvea Bogossian E, Peluso L, Creteur J, Taccone FS. Hyperventilation in adult TBI patients: how to approach it? Front Neurol 2021;11:580859. doi: 10.3389/fneur.2020.580859.

[18] Coles JP, Fryer TD, Coleman MR, Smielewski P, Gupta AK, Minhas PS, et al. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. Crit Care Med 2007;35(2):568–78. doi: 10.1097/01.Ccm.0000254066.37187.88.

[19] Coles JP, Minhas PS, Fryer TD, Smielewski P, Aigbirihio F, Donovan T, et al. Effect of hyperventilation on cerebral blood flow in traumatic head injury: clinical relevance and monitoring correlates. Crit Care Med 2002;30(9):1950–9. doi: 10.1097/00003246-200209000-00002.

[20] Marion DW, Puccio A, Wisniewski SR, Kochanek P, Dixon CE, Bullian L, et al. Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury. Crit Care Med 2002;30(12):2619–25. doi: 10.1097/00003246-200212000-00001.

[21] Citerio G, Robba C, Rebora P, Petrosino M, Rossi E, Malgeri L, et al. Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: results from the CENTER-TBI study. Intensive Care Med 2021;47(9):961–73. doi: 10.1007/s00134-021-06470-7.

[22] Robba C, Battaglini D, Abbas A, Sarrió E, Cinotti R, Asehnoune K, et al. Clinical practice and effect of carbon dioxide on outcomes in mechanically ventilated acute brain-

Journal Pre-proof

injured patients: a secondary analysis of the ENIO Study. Intensive Care Med 2024;50(2):234–46. doi: 10.1007/s00134-023-07305-3.

[23] Hawryluk GWJ, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med 2019;45(12):1783–94. doi: 10.1007/s00134-019-05805-9.

[24] Robba C, Poole D, McNett M, Asehnoune K, Bösel J, Bruder N, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. Intensive Care Med 2020;46(12):2397–410. doi: 10.1007/s00134-020-06283-0.

[25] Cinotti R, Taran S, Stevens RD. Setting the ventilator in acute brain injury. Intensive Care Med 2024;50(9):1513–5. doi: 10.1007/s00134-024-07476-7.

[26] Sardesai N, Hibberd O, Price J, Ercole A, Barnard EBG. Agreement between arterial and end-tidal carbon dioxide in adult patients admitted with serious traumatic brain injury. PLoS One 2024;19(2):e0297113. doi: 10.1371/journal.pone.0297113.

[27] Piantadosi CA, Zhang J. Mitochondrial generation of reactive oxygen species after brain ischemia in the rat. Stroke 1996;27(2):327–331;discussion 332. doi: 10.1161/01.str.27.2.327.

[28] Wu H, Gong L, Gu JC, Xing HW, Qian ZX, Mao Q. Proper partial pressure of arterial oxygen for patients with traumatic brain injury. Med Sci Monit 2021;27:e932318. doi: 10.12659/MSM.932318.

[29] American College of Surgeons trauma quality improvement program: best practices in the management of traumatic brain injury. American College of Surgeons. [Last accessed on

Journal Pre-proof

2026 March 21].

[30] Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside review: the effects of hyperoxia during critical illness. Crit Care 2015;19(1):284. doi: 10.1186/s13054-015-0996-4.

[31] Rezoagli E, Petrosino M, Rebora P, Menon DK, Mondello S, Cooper DJ, et al. High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI. Intensive Care Med 2022;48(12):1709–25. doi: 10.1007/s00134-022-06884-x.

[32] Robba C, Battaglini D, Cinotti R, Asehnoune K, Stevens R, Taccone FS, et al. Individualized thresholds of hypoxemia and hyperoxemia and their effect on outcome in acute brain injured patients: a secondary analysis of the ENIO Study. Neurocrit Care 2024;40(2):515–28. doi: 10.1007/s12028-023-01761-x.

[33] Rosenthal G, Hemphill JC 3rd, Sorani M, Martin C, Morabito D, Obrist WD, et al. Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. Crit Care Med 2008;36(6):1917–24. doi: 10.1097/CCM.0b013e3181743d77.

[34] Okonkwo DO, Shutter LA, Moore C, Temkin NR, Puccio AM, Madden CJ, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. Crit Care Med 2017;45(11):1907–14. doi: 10.1097/ccm.0000000000002619.

[35] Hays LMC, Udy A, Adamides AA, Anstey JR, Bailey M, Bellapart J, et al. Effects of brain tissue oxygen ($PbtO_2$) guided management on patient outcomes following severe traumatic brain injury: a systematic review and meta-analysis. J Clin Neurosci 2022;99:349–

Journal Pre-proof

58. doi: 10.1016/j.jocn.2022.03.017.

[36] Payen JF, Launey Y, Chabanne R, Gay S, Francony G, Gergele L, et al. Intracranial pressure monitoring with and without brain tissue oxygen pressure monitoring for severe traumatic brain injury in France (OXY-TC): an open-label, randomised controlled superiority trial. Lancet Neurol 2023;22(11):1005–14. doi: 10.1016/s1474-4422(23)00290-9.

[37] Matin N, Sarhadi K, Crooks CP, Lele AV, Srinivasan V, Johnson NJ, et al. Brain-lung crosstalk: management of concomitant severe acute brain injury and acute respiratory distress syndrome. Curr Treat Options Neurol 2022;24(9):383–408. doi: 10.1007/s11940-022-00726-3.

[38] Beqiri E, Smielewski P, Guérin C, Czosnyka M, Robba C, Bjertnæs L, et al. Neurological and respiratory effects of lung protective ventilation in acute brain injury patients without lung injury: brain vent, a single centre randomized interventional study. Crit Care 2023;27(1):115. doi: 10.1186/s13054-023-04383-z.

[39] Giardina A, Cardim D, Ciliberti P, Battaglini D, Ball L, Kasprowicz M, et al. Effects of positive end-expiratory pressure on cerebral haemodynamics in acute brain injury patients. Front Physiol 2023;14:1139658. doi: 10.3389/fphys.2023.1139658.

[40] Li HP, Lin YN, Cheng ZH, Qu W, Zhang L, Li QY. Intracranial-to-central venous pressure gap predicts the responsiveness of intracranial pressure to PEEP in patients with traumatic brain injury: a prospective cohort study. BMC Neurol 2020;20(1):234. doi: 10.1186/s12883-020-01764-7.

[41] Georgiadis D, Schwarz S, Baumgartner RW, Veltkamp R, Schwab S. Influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in

Journal Pre-proof

patients with acute stroke. Stroke 2001;32(9):2088–92. doi: 10.1161/hs0901.095406.

[42] Riemann L, Beqiri E, Younsi A, Czosnyka M, Smielewski P. Predictive and discriminative power of pressure reactivity indices in traumatic brain injury. Neurosurgery 2020;87(4):655–63. doi: 10.1093/neuros/nyaa039.

[43] Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci Mde O, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA 2012;308(16):1651–9. doi: 10.1001/jama.2012.13730.

[44] Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. 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):1301–8. doi: 10.1056/nejm200005043421801.

[45] Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Peñuelas O, Abraira V, et al. Evolution of mortality over time in patients receiving mechanical ventilation. Am J Respir Crit Care Med 2013;188(2):220–30. doi: 10.1164/rccm.201212-2169OC.

[46] Tejerina EE, Pelosi P, Robba C, Peñuelas O, Muriel A, Barrios D, et al. Evolution over time of ventilatory management and outcome of patients with neurologic disease. Crit Care Med 2021;49(7):1095–106. doi: 10.1097/ccm.0000000000004921.

[47] Lu YTL, Taran S, Fan E, McCredie VA, Angriman F, Telias I, et al. Approaches to mechanical ventilation in patients with and without acute brain injury: a registry-based cohort study. Crit Care Med 2026; 54(1):1-11. doi: 10.1097/ccm.0000000000006931.

[48] Robba C, Giardiello D, Almondo C, Asehnoune K, Badenes R, Cinotti R, et al.

Journal Pre-proof

Ventilation practices in acute brain injured patients and association with outcomes: the VENTIBRAIN multicenter observational study. Intensive Care Med 2025;51(2):318–31. doi: 10.1007/s00134-025-07808-1.

[49] Asehnoune K, Rooze P, Robba C, Bouras M, Mascia L, Cinotti R, et al. Mechanical ventilation in patients with acute brain injury: a systematic review with meta-analysis. Crit Care 2023;27(1):221. doi: 10.1186/s13054-023-04509-3.

[50] Daza JF, Hamad DM, Urner M, Liu K, Wahlster S, Robba C, et al. Low-tidal-volume ventilation and mortality in patients with acute brain injury: a secondary analysis of an international observational study. Chest 2025;168(5):1141–51. doi: 10.1016/j.chest.2025.06.042.

[51] Mascia L, Fanelli V, Mistretta A, Filippini M, Zanin M, Berardino M, et al. Lung protective mechanical ventilation in patients with severe acute brain injury: a multicenter, randomized clinical trial (PROLABI). Am J Respir Crit Care Med 2024; 210(9):1123 – 31. doi: 10.1164/rccm.202402-0375OC.

[52] Laffey JG, Bellani G, Pham T, Fan E, Madotto F, Bajwa EK, et al. Potentially modifiable factors contributing to outcome from acute respiratory distress syndrome: the LUNG SAFE study. Intensive Care Med 2016;42(12):1865–76. doi: 10.1007/s00134-016-4571-5.

[53] Qadir N, Sahetya S, Munshi L, Summers C, Abrams D, Beitler J, et al. An update on management of adult patients with acute respiratory distress syndrome: an Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 2024;209(1):24–36. doi: 10.1164/rccm.202311-2011ST.

Journal Pre-proof

[54] Grasselli G, Calfee CS, Camporota L, Poole D, Amato MBP, Antonelli M, et al. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med 2023;49(7):727–59. doi: 10.1007/s00134-023-07050-7.

[55] Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747–55. doi: 10.1056/NEJMsa1410639.

[56] Goligher EC, Costa ELV, Yarnell CJ, Brochard LJ, Stewart TE, Tomlinson G, et al. Effect of lowering Vt on mortality in acute respiratory distress syndrome varies with respiratory system elastance. Am J Respir Crit Care Med 2021;203(11):1378–85. doi: 10.1164/rccm.202009-3536OC.

[57] Wahlster S, Sharma M, Taran S, Town JA, Stevens RD, Cinotti R, et al. Associations between driving pressure and clinical outcomes in acute brain injury: a subanalysis of ENIO. Am J Respir Crit Care Med 2024;209(11):1400–4. doi: 10.1164/rccm.202402-0402LE.

[58] Taran S, Citerio G, Taccone FS, Rezoagli E, Liu K, McCredie VA, et al. Dynamic driving pressure and clinical outcomes in mechanically ventilated patients with acute brain injury: a secondary analysis of the VENTIBRAIN study. Intensive Care Med 2026;52(1):31–41. doi: 10.1007/s00134-025-08241-0.

[59] Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016;42(10):1567–75. doi: 10.1007/s00134-016-4505-2.

[60] Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, et al.

Journal Pre-proof

Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med 2018;44(11):1914–22. doi: 10.1007/s00134-018-5375-6.

[61] Urner M, Jüni P, Hansen B, Wettstein MS, Ferguson ND, Fan E. Time-varying intensity of mechanical ventilation and mortality in patients with acute respiratory failure: a registry-based, prospective cohort study. Lancet Respir Med 2020;8(9):905–13. doi: 10.1016/s2213-2600(20)30325-8.

[62] Wahlster S, Sharma M, Taran S, Town JA, Stevens RD, Cinotti R, et al. Utilization of mechanical power and associations with clinical outcomes in brain injured patients: a secondary analysis of the extubation strategies in neuro-intensive care unit patients and associations with outcome (ENIO) trial. Crit Care 2023;27(1):156. doi: 10.1186/s13054-023-04410-z.

[63] Rezoagli E, Laffey JG, Madotto F, Protti A, Pham T, Pesenti A, et al. Prognostic value of disease severity and mechanical ventilation intensity in acute respiratory distress syndrome: analysis of the LUNG SAFE cohort. Eur Respir J 2026;67(1):2500742. doi: 10.1183/13993003.00742-2025.

[64] Aisiku IP, Yamal JM, Doshi P, Rubin ML, Benoit JS, Hannay J, et al. The incidence of ARDS and associated mortality in severe TBI using the Berlin definition. J Trauma Acute Care Surg 2016;80(2):308–12. doi: 10.1097/ta.0000000000000903.

[65] Holland MC, Mackersie RC, Morabito D, Campbell AR, Kivett VA, Patel R, 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):106–11. doi: 10.1097/01.Ta.0000071620.27375.Be.

Journal Pre-proof

[66] 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(1):196–202. doi: 10.1097/01.ccm.0000194540.44020.8e.

[67] Elmer J, Hou P, Wilcox SR, Chang Y, Schreiber H, Okechukwu I, et al. Acute respiratory distress syndrome after spontaneous intracerebral hemorrhage*. Crit Care Med 2013;41(8):1992–2001. doi: 10.1097/CCM.0b013e31828a3f4d.

[68] Taran S, Stevens RD, Perrot B, McCredie VA, Cinotti R, Asehnoune K, et al. Incidence and outcomes of acute respiratory distress syndrome in brain-injured patients receiving invasive ventilation: a secondary analysis of the ENIO Study. J Intensive Care Med 2023; 39(2):136-145. doi: 10.1177/08850666231194532.

[69] Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–68. doi: 10.1056/NEJMoa1214103.

[70] Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010;363(12):1107–16. doi: 10.1056/NEJMoa1005372.

[71] National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380(21):1997–2008. doi: 10.1056/NEJMoa1901686.

[72] Robba C, Ball L, Nogas S, Battaglini D, Messina A, Brunetti I, et al. Effects of positive end-expiratory pressure on lung recruitment, respiratory mechanics, and intracranial pressure

Journal Pre-proof

in mechanically ventilated brain-injured patients. Front Physiol 2021;12:711273. doi: 10.3389/fphys.2021.711273.

[73] Robba C, Ball L, Battaglini D, Iannuzzi F, Brunetti I, Fiaschi P, et al. Effects of positive end-expiratory pressure on lung ultrasound patterns and their correlation with intracranial pressure in mechanically ventilated brain injured patients. Crit Care 2022;26(1):31. doi: 10.1186/s13054-022-03903-7.

[74] Sanfilippo F, Uryga A, Ball L, Battaglini D, Iavarone IG, Smielewski P, et al. The effect of recruitment maneuvers on cerebrovascular dynamics and right ventricular function in patients with acute brain injury: a single-center prospective study. Neurocrit Care 2024;41(1):38–48. doi: 10.1007/s12028-024-01939-x.

[75] Bein T, Kuhr LP, Bele S, Ploner F, Keyl C, Taeger K. Lung recruitment maneuver in patients with cerebral injury: effects on intracranial pressure and cerebral metabolism. Intensive Care Med 2002;28(5):554–8. doi: 10.1007/s00134-002-1273-y.

[76] Reinprecht A, Greher M, Wolfsberger S, Dietrich W, Illievich UM, Gruber A. Prone position in subarachnoid hemorrhage patients with acute respiratory distress syndrome: effects on cerebral tissue oxygenation and intracranial pressure. Crit Care Med 2003;31(6):1831–8. doi: 10.1097/01.Ccm.0000063453.93855.0a.

[77] Roth C, Ferbert A, Deinsberger W, Kleffmann J, Kästner S, Godau J, et al. Does prone positioning increase intracranial pressure? A retrospective analysis of patients with acute brain injury and acute respiratory failure. Neurocrit Care 2014;21(2):186–91. doi: 10.1007/s12028-014-0004-x.

[78] Picetti E, Pelosi P, Taccone FS, Citerio G, Mancebo J, Robba C, et al. VENTILatOry

Journal Pre-proof

strategies in patients with severe traumatic brain injury: the VENTILO Survey of the European Society of Intensive Care Medicine (ESICM). Crit Care 2020;24(1):158. doi: 10.1186/s13054-020-02875-w.

[79] Beuret P, Carton MJ, Nourdine K, Kaaki M, Tramoni G, Ducreux JC. Prone position as prevention of lung injury in comatose patients: a prospective, randomized, controlled study. Intensive Care Med 2002;28(5):564–9. doi: 10.1007/s00134-002-1266-x.

[80] Nekludov M, Bellander BM, Mure M. Oxygenation and cerebral perfusion pressure improved in the prone position. Acta Anaesthesiol Scand 2006;50(8):932–6. doi: 10.1111/j.1399-6576.2006.01099.x.

[81] Leppert J, Ditz C, Souayah N, Behrens C, Tronnier VM, Küchler J. Limitations of prone positioning in patients with aneurysmal subarachnoid hemorrhage and concomitant respiratory failure. Clin Neurol Neurosurg 2023;232:107878. doi: 10.1016/j.clineuro.2023.107878.

[82] Brunetti DJ, Leonardis F, Frisardi F, Dauri M, Deana C, Aspide R, et al. Effects of ‘head up’ prone position on transcranial color Doppler-based estimators of intracranial pressure in moderate to severe acute respiratory distress syndrome without brain injury: a cross-over, longitudinal, physiological study. Neurocrit Care 2025;43(2):446–57. doi: 10.1007/s12028-025-02240-1.

[83] Dabrowski W, Siwicka-Gieroba D, Robba C, Badenes R, Malbrain M. The prone position must accommodate changes in IAP in traumatic brain injury patients. Crit Care 2021;25(1):132. doi: 10.1186/s13054-021-03506-8.

[84] Kurihara C, Walter JM, Karim A, Thakkar S, Saine M, Odell DD, et al. Feasibility of

Journal Pre-proof

venovenous extracorporeal membrane oxygenation without systemic anticoagulation. Ann Thorac Surg 2020;110(4):1209–15. doi: 10.1016/j.athoracsur.2020.02.011.

[85] Lorusso R, Barili F, Mauro MD, Gelsomino S, Parise O, Rycus PT, et al. In-hospital neurologic complications in adult patients undergoing venoarterial extracorporeal membrane oxygenation: results from the Extracorporeal Life Support Organization registry. Crit Care Med 2016;44(10):e964–972. doi: 10.1097/ccm.0000000000001865.

[86] Chen X, Xie J, Wang Y, Du Z, Luo X, Zeng Z, et al. Impact of early $PaCO_2$ and pH fluctuations on neurological outcomes in ARDS patients receiving VV ECMO: a retrospective cohort study from the CSECLS registry. Ann Intensive Care 2025;15(1):143. doi: 10.1186/s13613-025-01570-9.

[87] Zhao Z, Wang D, Jia Y, Tian Y, Wang Y, Wei Y, et al. Analysis of the association of fluid balance and short-term outcome in traumatic brain injury. J Neurol Sci 2016;364:12–8. doi: 10.1016/j.jns.2016.03.007.

[88] Clifton GL, Miller ER, Choi SC, Levin HS. Fluid thresholds and outcome from severe brain injury. Crit Care Med 2002;30(4):739–45. doi: 10.1097/00003246-200204000-00003.

[89] Wiegers EJA, Lingsma HF, Huijben JA, Cooper DJ, Citerio G, Frisvold S, et al. Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study. Lancet Neurol 2021;20(8):627–38. doi: 10.1016/s1474-4422(21)00162-9.

[90] National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med

Journal Pre-proof

2006;354(24):2564–75. doi: 10.1056/NEJMoa062200.

[91] Baker MS Jr, Carpenter KLH, Helmy A, Hutchinson PJ. Multimodality monitoring for the management of severe traumatic brain injury. Neurosurg Clin N Am 2025;36(3):343–54. doi: 10.1016/j.nec.2025.03.013.

[92] Robba C, Graziano F, Rebora P, Elli F, Giussani C, Oddo M, et al. Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU): an international, prospective observational cohort study. Lancet Neurol 2021;20(7):548–58. doi: 10.1016/s1474-4422(21)00138-1.

[93] Bronco A, Grassi A, Meroni V, Giovannoni C, Rabboni F, Rezoagli E, et al. Clinical value of electrical impedance tomography (EIT) in the management of patients with acute respiratory failure: a single centre experience. Physiol Meas 2021;42(7). doi: 10.1088/1361-6579/ac0e85.

[94] Rezoagli E, Bellani G. How I set up positive end-expiratory pressure: evidence- and physiology-based! Crit Care 2019;23(1):412. doi: 10.1186/s13054-019-2695-z.

[95] Feng SN, Laws LH, Diaz-Cruz C, Cinotti R, Schultz MJ, Asehnoune K, et al. Sedation practices in mechanically ventilated neurocritical care patients from 19 countries: an international cohort study. Neurocrit Care 2025;43(1):232–42. doi: 10.1007/s12028-024-02200-1.

[96] Luo XY, He X, Zhou YM, Wang YM, Chen JR, Chen GQ, et al. Patient-ventilator asynchrony in acute brain-injured patients: a prospective observational study. Ann Intensive Care 2020;10(1):144. doi: 10.1186/s13613-020-00763-8.

[97] Chanques G, Constantin JM, Devlin JW, Ely EW, Fraser GL, Gélinas C, et al. Analgesia

Journal Pre-proof

and sedation in patients with ARDS. Intensive Care Med 2020;46(12):2342–56. doi: 10.1007/s00134-020-06307-9.

[98] Prabhakar H, Mahajan C, Kapoor I, Shrestha GS, Picetti E, Robba C, et al. VENTIlatory strategies for patients with severe traumatic brain injury in the LOw- and Middle-Income CountrieS. The VENTILOMICS survey. Crit Care Sci 2025;37:e20250062. doi: 10.62675/2965-2774.20250062.

[99] Feng SN, Diaz-Cruz C, Cinotti R, Asehnoune K, Schultz MJ, Shrestha GS, et al. Impact of country income level on outcomes in patients with acute brain injury requiring invasive mechanical ventilation: a secondary analysis of the ENIO Study. Neurocrit Care 2025;43(1):243–53. doi: 10.1007/s12028-024-02198-6.

[100] Ouyang M, Allende MI, Anderson CS. Timely delivery of care in neurological emergencies: can standardized management protocols help? Curr Opin Crit Care 2025;31(2):149–54. doi: 10.1097/mcc.0000000000001240.

[101] Murali M, Ni M, Karbing DS, Rees SE, Komorowski M, Marshall D, et al. Clinical practice, decision-making, and use of clinical decision support systems in invasive mechanical ventilation: a narrative review. Br J Anaesth 2024;133(1):164–77. doi: 10.1016/j.bja.2024.03.011.

[102] Bassi T, Taran S, Girard TD, Robba C, Goligher EC. Ventilator-associated brain injury: a new priority for research in mechanical ventilation. Am J Respir Crit Care Med 2024;209(10):1186–8. doi: 10.1164/rccm.202401-0069VP.

[103] Van Hollebeke M, Shi Z, Dres M. Ventilator-induced brain injury: another iatrogenic complication of mechanical ventilation. Curr Opin Crit Care 2026;32(1):34–41. doi:

Journal Pre-proof

10.1097/mcc.0000000000001347.

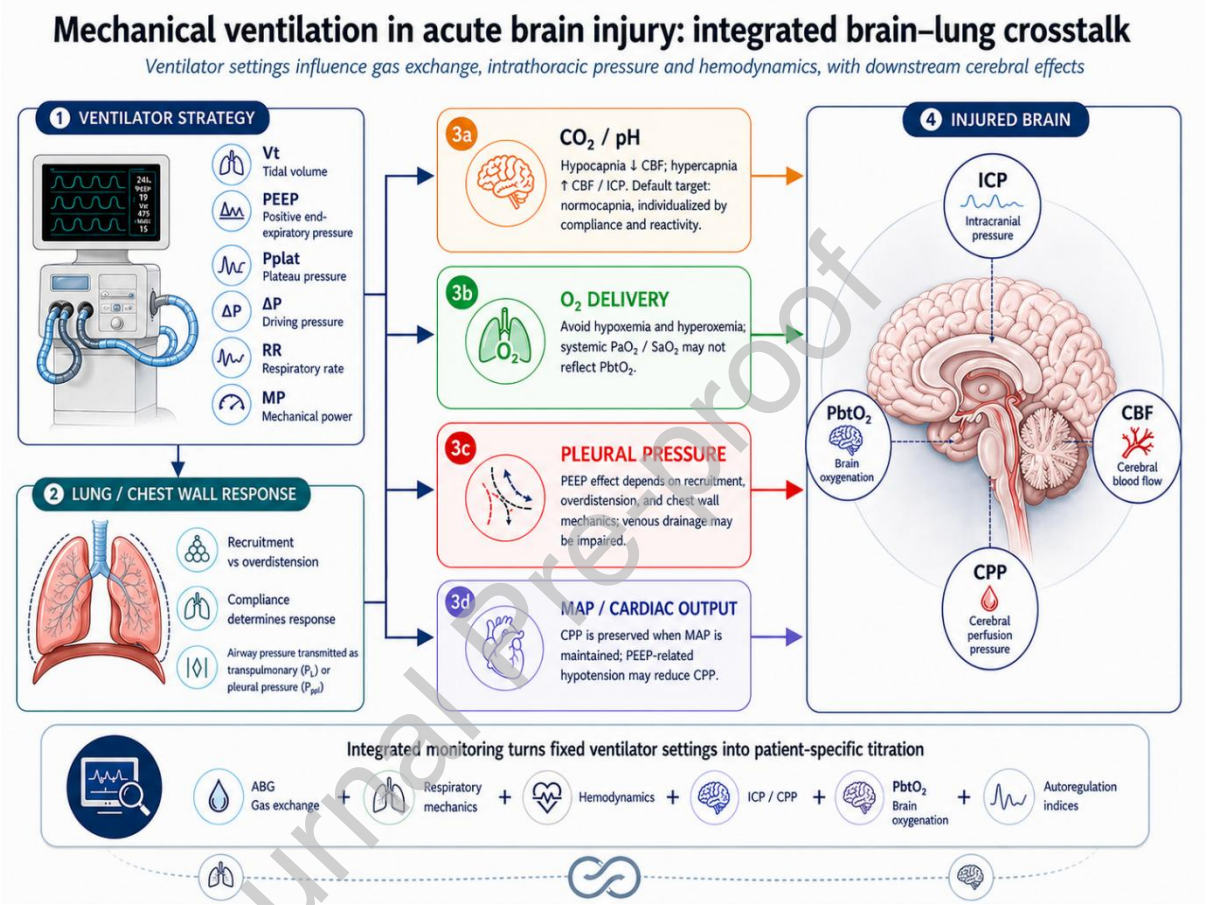


Figure 1: Integrated brain–lung crosstalk during mechanical ventilation in ABI. Mechanical ventilation in ABI should be interpreted as an integrated physiological intervention with impacts on both the lungs and brain. Ventilatory variables, including Vt, PEEP, Pplat, ΔP, RR and MP, interact with respiratory system mechanics and chest wall properties. These interactions modulate carbon dioxide homeostasis, oxygen delivery, pleural pressure transmission and systemic hemodynamics, with downstream effects on ICP, CPP, CBF and brain tissue oxygen tension ($PbtO_2$). Integrated monitoring of ABGs, respiratory mechanics, hemodynamics, ICP/CPP, $PbtO_2$, and autoregulation indices may support patient-specific

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titration aimed at minimizing both VILI and secondary brain injury. ABGs: Arterial blood gases; ABI: Acute brain injury; CBF: Cerebral blood flow; CPP: Cerebral perfusion pressure; ICP: Intracranial pressure; MP: Mechanical power; PEEP: Positive end-expiratory pressure; Pplat: Plateau pressure; RR: Respiratory rate; VILI: Ventilator-induced lung injury; Vt: Tidal volume; ΔP: Driving pressure.

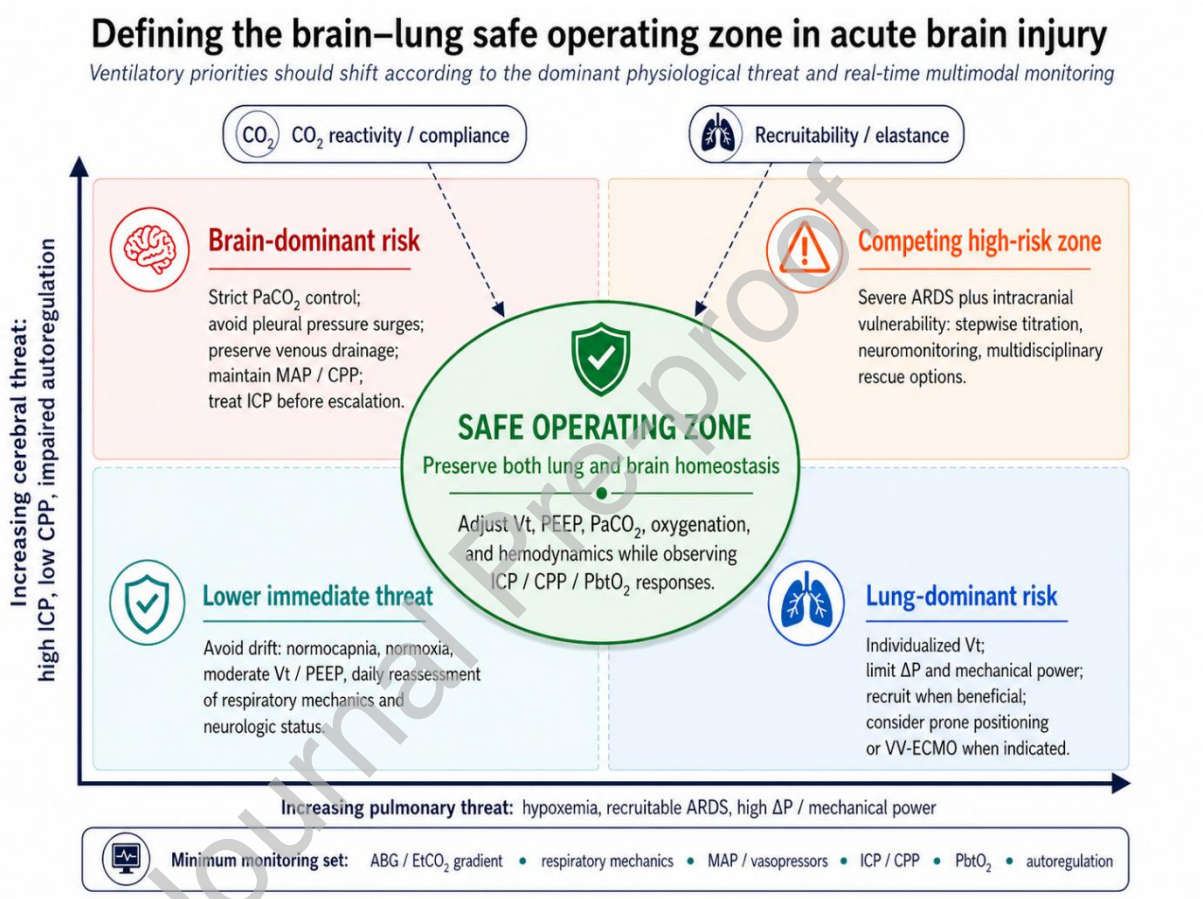


Figure 2: Conceptual brain–lung "safe operating zone" for ventilatory management in ABI. The optimal ventilation strategy in ABI depends on the balance between cerebral and pulmonary threats rather than on fixed universal thresholds. When cerebral vulnerability predominates, such as in patients with intracranial hypertension, low CPP, or impaired autoregulation, priority should be given to $PaCO_2$ control, preservation of venous drainage, and support of MAP/CPP. When pulmonary injury predominates, such as in severe hypoxemia, recruitable ARDS, or high ventilatory intensity, priority shifts toward limiting

VILI through individualized Vt, limitation of ΔP and MP, and physiologically guided recruitment strategies. Patients with both high cerebral and pulmonary risk require stepwise titration guided by neuromonitoring and respiratory mechanics. The central "safe operating zone" represents a dynamic physiological range in which lung and brain homeostasis are jointly preserved through real-time reassessment, not a fixed treatment algorithm. ABI: Acute brain injury; ARDS: Acute respiratory distress syndrome; CPP: Cerebral perfusion pressure; MAP: Mean arterial pressure; MP: Mechanical power; $PaCO_2$: Arterial partial pressure of carbon dioxide; VILI: Ventilator-induced lung injury; Vt: Tidal volume; ΔP: Driving pressure.

Conflicts of interest:
ST: None
ER: None
SW: None
JGL: None
GC: None

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