Brain-Lung Crosstalk: Management of Concomitant Severe Acute Brain Injury and Acute Respiratory Distress Syndrome

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Abstract

**Purpose of Review** To summarize pathophysiology, key conflicts, and therapeutic approaches in managing concomitant severe acute brain injury (SABI) and acute respiratory distress syndrome (ARDS).

**Recent Findings** ARDS is common in SABI and independently associated with worse outcomes in all SABI subtypes. Most landmark ARDS trials excluded patients with SABI, and evidence to guide decisions is limited in this population. Potential areas of conflict in the management of patients with both SABI and ARDS are (1) risk of intracranial pressure (ICP) elevation with high levels of positive end-expiratory pressure (PEEP), permissive hypercapnia due to lung protective ventilation (LPV), or prone ventilation; (2) balancing a conservative fluid management strategy with ensuring adequate cerebral perfusion, particularly in patients with symptomatic vasospasm or impaired cerebrovascular blood flow; and (3) uncertainty about the benefit and harm of corticosteroids in this population, with a mortality benefit in ARDS, increased mortality shown in TBI, and conflicting data in other SABI subtypes. Also, the widely adapted partial pressure of oxygen (P\textsubscript{a}O\textsubscript{2}) target of >55 mmHg for ARDS may exacerbate secondary brain injury, and recent guidelines recommend higher goals of 80–120 mmHg in SABI. Distinct pathophysiology and trajectories among different SABI subtypes need to be considered.

**Summary** The management of SABI with ARDS is highly complex, and conventional ARDS management strategies may result in increased ICP and decreased cerebral perfusion. A crucial aspect of concurrent management is to recognize the risk of secondary brain injury in the individual patient, monitor with vigilance, and adjust management during critical time windows. The care of these patients requires meticulous attention to oxygenation and ventilation, hemodynamics, temperature management, and the neurological exam. LPV and prone ventilation should be utilized, and supplemented with invasive ICP monitoring if there is concern for cerebral edema and increased ICP. PEEP titration should be deliberate, involving measures of hemodynamic, pulmonary, and brain physiology. Serial volume status assessments should be performed in SABI and ARDS, and fluid management should be individualized based on measures of brain perfusion, the neurological exam, and cardio-pulmonary status. More research is needed to define risks and benefits in corticosteroids in this population.

Introduction

Acute respiratory distress syndrome (ARDS) is commonly encountered in severe acute brain injury (SABI). Among subtypes of SABI, ARDS has been reported in up to 30% of patients with traumatic brain injury (TBI) [1–5], 38% of patients with non-traumatic subarachnoid hemorrhage (SAH) [6–9], 28% of patients with spontaneous intracranial hemorrhage (sICH) [10], 4% of patients with acute ischemic stroke (AIS) [11, 12], and 48% of patients after cardiac arrest [13, 14]. Given the high prevalence of ARDS and a wide range of reported neurological manifestations with COVID-19 [15–18], the concurrent occurrence of SABI and ARDS will likely rise further. ARDS is independently associated with increased mortality and poor...
neurological outcome in all SABI subtypes [2, 3, 5, 6, 8, 13, 14, 19].

In critically ill patients with SABI, pathophysiological interactions between the brain and lungs are complex (Fig. 1). SABI can induce and worsen ARDS via multiple pathways [20–22]; conversely, hypoxemia and systemic inflammatory responses encountered in ARDS can further precipitate secondary brain injury. Cognitive deficits and mood disorders are frequently encountered as long-term sequelae of ARDS [23–25], even in the absence of known SABI. Strategies for managing SABI and ARDS may conflict. Ventilatory and hemodynamic targets considered

standard ARDS care may insufficiently support or even harm the acutely injured brain. Most major randomized controlled trials (RCTs) supporting ARDS treatment strategies excluded patients with neurological injury or elevated intracranial pressure (ICP) [26•, 27•, 28–31], and the results of these studies are not generalizable to this population.

In this article, we review key principles and evidence in the treatment of SABI and ARDS, and provide [32] guidance on how to approach conflicts in managing concomitant SABI and ARDS based on the available literature and practical considerations.

**Fig. 1** Pathophysiological interactions between the brain and lungs
Mechanical ventilation targets in SABI

Mechanical ventilation (MV) in SABI is typically indicated due to impaired consciousness, resulting in loss of airway protective reflexes and decreased respiratory drive or in the context of secondary respiratory events, such as aspiration pneumonia, pulmonary contusions, pulmonary edema, pulmonary embolism, or ARDS. On occasions, MV is deemed necessary when deep sedation is required to treat status epilepticus, elevated ICP, extreme agitation, or to facilitate emergent neuroimaging studies. However, the optimal \( P_{\text{O}_2} \) and \( P_{\text{CO}_2} \) targets are not yet established.

Hypoxemia has shown to be detrimental in SABI [33–36], due to secondary ischemic injury and reflexive cerebral vasodilation resulting in increased ICP. Hyperoxemia (\( P_{\text{O}_2} > 300 \) mmHg) may also be potentially harmful due to the creation of reactive oxygen species and exacerbation of inflammation and cellular injury [34, 35, 37, 38]. Several large trials in a general ICU population demonstrated no difference between conservative and liberal oxygen therapy [39–41], though questions remain about the subgroup of patients with brain injury in these trials. A recent ESICM consensus statement recommended higher \( P_{\text{O}_2} \) targets of 80–120 mmHg in SABI and strict avoidance of hypoxemia [42•]. Ideally, targets would be individualized based on the type and extent of brain injury. Also, the optimal hemoglobin goal to optimize oxygen-carrying capacity and cerebral oxygen delivery remains under investigation. Both anemia and blood transfusions have been associated with worse neurological outcomes in SABI [43–46]. Based on evidence in the general ICU population [47–49], hemoglobin goals around 7 gm/dl and conservative transfusion strategies have been widely adopted. However, patients with SABI were underrepresented in these studies. A RCT in TBI showed higher adverse events with hemoglobin goals > 10 gm/dl with no improvement in neurological outcome [50]. SAH guidelines recommend transfusing to a hemoglobin goal of 8–10 gm/dl in patients at risk for delayed cerebral ischemia (DCI) [51], but the impact on neurological outcomes remains to be established, and a large RCT comparing transfusion strategies is ongoing [52]. The value of adjusting hemodynamic and ventilator parameters based on brain tissue oxygen (\( P_{\text{btO}_2} \)) is being investigated. Observational studies in TBI and SAH have shown higher mortality in association with decreased \( P_{\text{btO}_2} \) levels and suggested outcome benefits with \( P_{\text{btO}_2} \)-directed therapy [53–58]. The Brain Oxygen Optimization in Severe TBI (BOOST-3) trial, a phase 3 RCT, is assessing the potential to improve neurological outcomes in TBI by comparing ICU care guided by ICP monitoring only against an ICP plus \( P_{\text{btO}_2} \)-guided management strategy [59].

Partial pressure of carbon dioxide (\( P_{\text{CO}_2} \)) acts as a fundamental regulator of cerebral blood flow (CBF) [60]. Hypercapnia causes dilatation of the cerebral vasculature and can result in ICP elevations. Lowering \( P_{\text{CO}_2} \) via therapeutic hyperventilation is a rapid, effective measure to treat elevated ICP, but the effect diminishes over 6–24 h, and hypocapnia can cause cerebral vasoconstriction and cerebral ischemia [61–63]. Also, normocapnia following hypocapnia can result in rebound ICP spikes. Due to these concerns, the
use of therapeutic hyperventilation remains controversial and should only be considered as a short-term rescue strategy. Both hypo- and hypercapnia are associated with higher mortality and poor outcomes in TBI, AIS, and PCABI [64•, 65, 66]. Mild hypocapnia (30–35 mmHg) can be considered in patients with elevated ICPs. Potential benefits of mild hypercarbia in restoring cerebral perfusion after cardiac arrest are being investigated [67–69]. In most patients with SABI, vigilant monitoring and avoidance of extreme $P_aCO_2$ fluctuations are recommended [42•].

The optimal tidal volume (Vt), respiratory rate (RR), positive end-expiratory pressure (PEEP), and preferred mode of ventilation in SABI remain unknown. Many patients who require MV due to the loss of airway protective reflexes often retain their ventilatory drive. If safely tolerated, a spontaneous mode may diminish the need for sedation. An assisted mode will ensure tighter control of ventilation and $P_aCO_2$. Abnormal breathing patterns are commonly encountered in SABI [69], and changes in respiratory drive may further exacerbate ventilator dyssynchrony, requiring nuanced management of sedation to minimize barotrauma and avoid $P_aCO_2$ derangements.

**Overview of ARDS**

ARDS is defined by four components: (1) acute onset within 7 days of a clinical insult, (2) hypoxemia ($P_aO_2;FiO_2 \leq 300$), (3) radiographic bilateral pulmonary opacities, and (4) findings not fully explained by fluid overload or heart failure [70]. The Berlin definition stratifies ARDS into three categories based on hypoxemia severity (mild: P:F ratio 201–300 mmHg, moderate: 101–200 mmHg, severe: $\leq 100$ mmHg with PEEP $\geq 5$ cm H$_2$O) [71].

The most common contributing risk factors, accounting for approximately 85% of ARDS cases, are pneumonia, non-pulmonary sepsis, and aspiration of gastric contents [72]. A wide range of other pulmonary and non-pulmonary etiologies, including major trauma, intracranial hypertension, pulmonary contusions, pancreatitis, inhalation and drowning injuries, severe burns, non-cardiogenic shock, blood transfusions, pulmonary vasculitis, and drug overdoses, have been associated with ARDS [72, 73].

Despite advances in understanding the pathophysiology and development of therapeutic interventions, ARDS remains a common and lethal condition. In a study of nearly 30,000 patients from 50 countries, 23% of mechanically ventilated patients and 10% of patients admitted to an ICU had ARDS [74]. Mortality ranged from 35% in patients with mild ARDS to 46% in the subgroup with severe ARDS. Since this study, the prevalence of ARDS has dramatically increased due to the COVID-19 pandemic. Mortality from COVID-19-related ARDS ranges widely (12–78%), and limited comparative data suggests similar outcomes between COVID-19-related ARDS and non-COVID-ARDS [75, 76].

The main therapeutic pillars of ARDS consist of treatment of the underlying cause, lung protective ventilation (LPV), PEEP titration, neuromuscular blockade (NMB), prone positioning (PP), conservative fluid management,
corticosteroids, and extracorporeal membrane oxygenation (ECMO). A detailed overview of physiological benefits and evidence for these treatments is provided in Table 1. Within the broad consensus definition of ARDS, there is substantial heterogeneity among the population, and further investigation of ARDS subphenotypes may allow for more nuanced, tailored treatment strategies in the future [77].

Management of brain-lung conflicts in concurrent SABI and ARDS

An overview of potential conflicts arising in SABI with various ARDS management principles and strategies to balance brain and lung pathology is provided in Fig. 2. Figure 3 delineates an algorithm with specific considerations for ARDS with SABI. Key considerations in the management of ARDS and SABI based on the available evidence are highlighted below.

Lung protective ventilation

LPV, defined as low tidal volume ventilation coupled with PEEP optimization and minimization of barotrauma, is the standard of care for patients with ARDS. The landmark ARMA trial was stopped early after demonstrating a 9% decrease in mortality and fewer days of MV with Vt of 4–6 cc/kg of predicted body weight (PBW) compared to 12 cc/kg PBW [26•]. Further evidence to support the use of LPV in ARDS has emerged since, and studies have suggested that LPV may reduce progression to acute lung injury (ALI) or ARDS in ventilated patients without ARDS [78–80]. Moreover, studies have identified high Vt as a predictor of ARDS in various subtypes of SABI [10, 81–83].

While permissive hypercapnia with LPV is commonly tolerated in patients with ARDS and no known brain injury, a rising PaCO2 can result in elevated ICPs, and poor neurological outcomes in SABI [64•, 65]. Also, the widely adapted PaO2 goal target of >55 mmHg in ARDS based on the ARMA study protocol may be insufficient in SABI and exacerbate secondary brain injury.

Overall, LPV should be utilized in concurrent SABI and ARDS, with vigilant monitoring of PaCO2 and higher PaO2 goals of 80–120 mmHg. The balance between lung protection and PaCO2 control should be determined based on ARDS severity, lung compliance, and concern for worsening brain edema and herniation. If hypercarbia is unavoidable in patients at high risk for neurological decompensation due to elevated ICP, direct measures of brain physiology should be considered. Invasive ICP and PbtO2 monitoring, and cerebral autoregulation with CO2 reactivity studies can be valuable in determining if higher PaCO2 values are tolerated from a cerebral pressure and localized perfusion standpoint.
| SABI subtype | Commonly encountered critical issues | Critical time windows | Hemodynamic goals | Evidence of corticosteroids |
|--------------|--------------------------------------|-----------------------|------------------|---------------------------|
| **TBI**      | ↑ ICP: EDH, SDH, contusion, hydrocephalus, vasogenic, and cytotoxic edema, impaired autoregulation | **Edema:** mostly within 7 days Bimodal distribution Early (<72 h): peak at day 4 Late (>72 h): peak at day 7 | **Age-based BP targets** [148]: SBP ≥ 100 mmHg for age 50–69, SBP ≥ 110 mmHg for age 15–49 or >70 | Large RCT (MRC CRASH) 48-h methylprednisolone infusion ↑ in death at 2 weeks and 6 months. Etiology of increased mortality remains unclear [153, 154•] Meta-analysis of RCTs also showed ↑ in mortality (driven by large number of patients in MRC CRASH) |
|              | ↓ Cerebral perfusion: impaired autoregulation, BCVI | **Blossoming of contusions:** majority within 24–48 h, most within <7 d | **CPP 60–70 mmHg, ICP <20 mmHg** Avoid hypovolemia | **BTF guidelines:** do not recommend high-dose steroids due to harm |
|              | ↑ ICP: mass effect from SAH/IPH, hydrocephalus, ischemic infarcts cytotoxic edema, retraction edema after clipping | **Rebleeding:** 4% day 1, then 1–2% per day until aneurysm secured | **Unsecured vascular lesion:** avoid extreme HTN to prevent re-rupture, maintain CPP, ideal goal not established, consider pre-morbid baseline BP, guidelines suggest SBP goal < 160 mmHg | Two systematic reviews and meta-analyses [156, 157]: limited by heterogeneity, overall inconclusive. ↓ in natriuresis and hypovolemia. Trend towards ↓ in symptomatic vasospasm, overall no significant change in neurological outcomes |
|              | ↓ Cerebral perfusion: vasospasm, DCI, distal microthrombi, neurogenic cardiomyopathy and cardiogenic shock, CSW | **Acute hydrocephalus:** first 3 days (subacute 4–14 d, late > 2 weeks) | **Secured vascular lesion:** during the vasospasm period, avoid hypotension, permisive HTN, consider BP augmentation case-by-case, maintain strict intravascular euvoeleva | **NCS guidelines:** not recommended (lack of evidence and harm in other SABI and SCI trials) |
| **SAH**      | ↑ ICP: mass effect from SAH/IPH, hydrocephalus, ischemic infarcts cytotoxic edema, retraction edema after clipping | **Rebleeding:** 4% day 1, then 1–2% per day until aneurysm secured | **Unsecured vascular lesion:** avoid extreme HTN to prevent re-rupture, maintain CPP, ideal goal not established, consider pre-morbid baseline BP, guidelines suggest SBP goal < 160 mmHg | Two systematic reviews and meta-analyses [156, 157]: limited by heterogeneity, overall inconclusive. ↓ in natriuresis and hypovolemia. Trend towards ↓ in symptomatic vasospasm, overall no significant change in neurological outcomes |
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| SABI subtype | Commonly encountered critical issues | Critical time windows | Hemodynamic goals | Evidence of corticosteroids |
|--------------|-------------------------------------|----------------------|-------------------|----------------------------|
| sICH         | ↑ ICP: ICH expansion, intra-/perihematomal (vasogenic>cytotoxic) edema, hydrocephalus (IVH, external ventricular distortion) | Edema: ↑ within 24 h, peak days 2–4, decreases > day 7 Second peak can occur days 10–14 (often coupled with ↓ in Na) | Exact target unclear, avoid extreme HTN and large BP drops, consider pre-morbid BP and renal failure Upper BP limit < 140–180 mmHg | Pooled analyses showed no difference in mortality or neurological outcome, but higher adverse effect rate, one RCT terminated early due to ↑ infections [158] Pre-admission use: ↑ mortality AHA guidelines: not recommended due to lack of evidence of efficacy and risk of adverse events |
| AIS          | ↑ ICP: cytotoxic>vasogenic edema (malignant MCA), hydrocephalus (ventricular compression), hemorrhagic transformation, reperfusion injury | Edema: ↑ within 24 h, peak days 3–5, decreases > day 7 (younger patients tend to swell earlier than elder patients) | BP goals: ideal goals unknown and vary case-by-case, consider presence, degree and chronicity of occlusions, stenoses, collateralization and recanalization status, hemorrhagic conversion and reperfusion Avoid hypotension after acute stroke, instead permissive HTN. No evidence in favor of induced HTN, can consider case-by-case | Meta-analysis (8 RCTs of corticosteroids within 48 h) showed no difference in mortality or neurological outcome, inconsistent results between trials, small numbers of GIB [155] Pre-admission use: ↑ mortality AHA guidelines: not recommended due to lack of evidence of efficacy and potential complications |
|             | ↓ Cerebral perfusion: vascular compression by ICH |                       |                   |                           |
|             | ↓ Cerebral perfusion: LVO, cervical stenosis/occlusion, intracranial atherosclerosis, dissection | Hemorrhagic transformation: 2–14 days, mostly within 7 days (more common in larger infarcts) | Perfusion dependence: 24 h–7 days | Volume status: avoid intravascular hypovolemia |
|             | |                       |                   |                           |
| SABI subtype | Commonly encountered critical issues | Critical time windows | Hemodynamic goals | Evidence of corticosteroids |
|--------------|-------------------------------------|-----------------------|-------------------|-----------------------------|
| PCABI        | ↑ ICP: Vasogenic and cytotoxic edema | Edema: ↑ within 24 h, peak days 2–5, decreased days 7–10 | BP goals: avoid hypotension: SBP>90 mmHg, MAP>65 mmHg | Vasopressin-epinephrine and methylprednisolone during CPR and stress-dose hydrocortisone for post resuscitation shock: improved survival to discharge with favorable neurological outcome compared to epinephrine alone [159] |
|              | ↓ Cerebral perfusion: shock, decreased cardiac output, right-shifted or narrow cerebral autoregulation, microvascular dysfunction, transient hyperemia delayed hypoperfusion | ↑ Risk of herniation during rewarming from therapeutic hypothermia Brain tissue hypoxia nadir at 13–40 h post arrest | Volume status based on presence and type of shock | Methylprednisolone and vasopressin during CPR ↑ ROSC, no change in survival and neurological outcome [160] |

AHA American Heart Association, AIS acute ischemic stroke, BCVI blunt cerebrovascular injury, BP blood pressure, BTF Brain Trauma Foundation, CPP cerebral perfusion pressure, CPR cardiopulmonary resuscitation, CSW cerebral salt wasting, DCI delayed cerebral ischemia, EDH epidural hematoma, GIB gastrointestinal bleeding, HTN hypertension, ICP intracranial pressure, IHCA in-hospital cardiac arrest, IVH intraventricular hemorrhage, LVO large vessel occlusion, MRC CRASH Medical Research Council Corticosteroid Randomization After Significant Head Injury, MT mechanical thrombectomy, PCABI post-cardiac arrest brain injury, RCT randomized clinical trial, ROSC return of spontaneous circulation, SABI severe acute brain injury, SAH subarachnoid hemorrhage, SBP systolic blood pressure, SCI spinal cord injury, SDH subdural hematoma, sICH symptomatic intracranial hemorrhage, TBI traumatic brain injury
High positive end-expiratory pressure

PEEP is often utilized in patients with severe ARDS to optimize lung recruitment, thereby improving oxygenation and maximizing compliance. PEEP is adjusted based on various measures, including empirical titration tables, pressure–volume loops, esophageal manometry to estimate transpulmonary pressure, and optimization of driving pressure [84–86]. Several RCTs have compared high versus low PEEP strategies in ARDS. No individual trial demonstrated improved mortality with a higher PEEP strategy, but some did note improved oxygenation [87–89]. A subsequent meta-analysis demonstrated possible benefit in moderate-severe ARDS with higher PEEP [90]. Lower driving pressure, defined as the difference between the static pressure and PEEP in a volume-controlled ventilator mode, is associated with reduced mortality [91].

The use of high PEEP is controversial in SABI. PEEP increases intrathoracic and right atrial pressures, and may subsequently cause elevated ICPs by impeding cerebral venous drainage. Higher PEEP may also decrease cerebral perfusion pressure (CPP) in patients with impaired cerebral autoregulation.
Studies in SABI show mixed results regarding the effect of PEEP on ICP [92, 93, 94*, 95–97]. Small studies in TBI, SAH, ICH, and AIS did not observe a significant effect on CPP when increasing PEEP up to 15 cmH2O [93, 95, 98]. Other studies suggested that a principal mechanism resulting in ICP elevations and CPP reductions appeared to be a PEEP-dependent decrease in mean arterial pressure (MAP) [96, 97], with ICP and CPP improving once MAP was restored. High PEEP was more likely to affect CPP when cerebral autoregulation was impaired [92]. One study suggested that intrathoracic pressure augmentation would only impact ICP when PEEP values exceeded ICP [98]. A small prospective study of patients with SABI and ALI found substantial differences in the effect of PEEP on ICP depending on whether increasing PEEP resulted in alveolar recruitment or hyperinflation based on static volume-pressure curves, with only the latter group showing a rise in PaCO2 and ICP [99]. Recent studies have also shown an association between decreased respiratory compliance and PEEP-mediated ICP elevations [94*, 100].

Based on these findings, the use of increased PEEP to treat ARDS is reasonable and likely safe in most patients with SABI [42*]. PEEP titration should be
deliberate based on lung compliance, and MAP should be strictly maintained. Non-invasive methods such as transcranial Doppler (TCD), pupillometry, and optic nerve sheath diameter (ONSD) may be helpful while titrating PEEP or during recruitment maneuvers, and should be considered in patients at risk for elevated ICP or impaired autoregulation. Simultaneous use of lung and brain ultrasound and a lung ultrasound score to guide PEEP titration in SABI have been described [94•, 101].

**Prone positioning**

Since the PROSEVA trial demonstrated a 17% absolute mortality reduction with ≥16 h/day of PP in patients with P/F ratio < 150 [27•], this therapy has become standard of care in moderate and severe ARDS and has been widely utilized during the COVID-19 pandemic [102].

While considered one of the most effective interventions in the management of moderate-severe ARDS, the impact of PP on ICP, CPP, and neurological outcomes in SABI is not fully understood, and PROSEVA excluded patients with ICP > 30 mmHg. PP in SABI also raises numerous logistical concerns (Table 2): worsening of concomitant cervical spine instability in TBI, positioning in patients with cranial bone flaps, accidental displacement of invasive brain monitors, and inadequate cerebral spinal fluid (CSF) drainage from external ventricular drains (EVD).

PP can result in ICP elevations due to decreased head elevation, increased abdominal pressure, and compression of neck veins affecting cerebral venous drainage. Most studies investigating the effect of PP on ICPs are small with fewer than 30 patients, included mixed types of brain injuries, did not assess long-term neurological outcome, and used varying degrees of head elevation [103–105]. Also, duration of PP in these studies was shorter (1–8 h), a criticism of negative PP trials before PROSEVA. Many of these studies demonstrated statistically significant transient elevations in ICP by 5–15 mmHg, with mixed effects on CPP, and overall substantial improvement of \( P_{\text{O}_2} \) and PbT\( O_2 \) [106, 107]. The clinical relevance of these findings is not clear. The largest study including 111 patients showed a significant increase in ICP, and decrease in CPP when ICP exceeded 20 mmHg, the mean \( P_{\text{O}_2}/\text{FiO}_2 \) ratio improved from 135 to 340 [107]. The only prospective RCT included 51 patients but excluded those with ICP > 20 and \( P_{\text{O}_2}/\text{FiO}_2 \) ratio < 150, limiting the applicability to patients with elevated ICPs and severe ARDS. PP for 4 h daily resulted in significantly improved hypoxemia and initially elevated ICPs that gradually down-trended over 4 h [108•]. Overall, in most studies, the benefit on oxygenation and hemodynamics appeared to outweigh transient rises in ICP.

Given the substantial mortality benefit and potential impact on cerebral oxygen delivery, PP should be utilized in patients with SABI and moderate-severe ARDS. In those with concern for elevated ICP, invasive neuromonitoring is particularly important in the absence of the ability to follow a neurological examination. Elevating the head, positioning to minimize neck
compression, aggressive bowel regimens and padding to decrease abdominal pressure, prophylactic and therapeutic ICP treatment with hyperosmolar therapy (HT) or CSF diversion, and MAP elevations with vasopressors are strategies to optimize CPP. The prone angle can also be modified to facilitate serial neurological assessments.

Sedation and neuromuscular blockade

Patients with ARDS often require deep sedation and NMB to facilitate ventilator synchrony, especially in patients requiring LPV. Both sedation and NMB are also thought to reduce global oxygen consumption. The ACURASYS trial demonstrated a mortality benefit for continuous infusion of NMB in moderate-severe ARDS [28], but the subsequent ROSE trial found no such benefit [29]. Importantly, no significant harm was demonstrated in either trial.

In patients with SABI, sedatives are used as a strategy to treat increased ICP by decreasing cerebral metabolism and oxygen consumption. NMB can also be used to optimize ICP and CPP, typically in cases when ventilator dyssynchrony is felt to worsen ICPs. However, the ability to perform serial neurological assessments becomes impaired. In addition, side effects of sedative medications, such as hypotension and reduced cardiac output, may affect CPP. Deep prolonged sedation may also compound neurocognitive sequelae and result in protracted recovery in critically ill patients.

In general, short-acting agents such as propofol are preferred to allow for intermittent neurological assessments and reduce the risk of delirium [109, 110]. The need to utilize sedation for ICP control has to be considered and reassessed over time. When the neurological exam is limited by deep sedation, additional neuromonitoring such as pupillometry, quantitative electroencephalography (EEG), invasive and non-invasive ICP monitoring, and serial imaging should be considered in patients at risk for acute neurological deterioration.

Inhaled pulmonary vasodilators

Inhaled pulmonary vasodilators (IPV), typically inhaled prostacyclins or nitric oxide (NO), have been shown to improve oxygenation and reduce pulmonary arterial pressures, but have not demonstrated a survival benefit in ARDS [111–113]. As a result, they are not routinely recommended in ARDS, but rather used selectively as a bridge to other treatments in truly refractory hypoxemia, or in specific populations. Potential benefits include improvement of right ventricular dysfunction, acute or chronic pulmonary hypertension, and right-to-left shunting, and adverse effects include worsening renal failure or inhibition of platelet function. Pre-clinical studies have implicated impaired NO metabolism in the pathogenesis of various SABI subtypes and suggested both deleterious and neuroprotective effects of inhaled NO [114].
While thought to potentially improve cerebral blood flow and oxygenation, a better understanding of NO pathways in the brain is needed to establish benefits or harms in different SABI subtypes [115–118]. In patients with ICH at increased risk of bleeding, close monitoring for hematoma expansion could be considered due to the theoretical risk of platelet inhibition.

### Extracorporeal membrane oxygenation

ECMO provides circulatory support and gas exchange for patients experiencing profound cardiopulmonary failure. Venovenous (VV)-ECMO can be an effective rescue therapy in patients with severe ARDS refractory to conventional therapies. The CESAR trial demonstrated lower mortality and improved outcomes in patients with ARDS who were transferred to an ECMO Center [30]; the subsequent EOLIA trial showed a trend towards improved outcome with VV-ECMO that was not statistically significant [31], though a high probability for benefit was indicated in subsequent Bayesian analysis [119]. The utilization of ECMO has increased substantially over the past two decades, and has increased even further due to the COVID-19 pandemic [120].

Historically, SABI has been considered a relative contraindication for ECMO. Concerns include the risk of hematoma expansion or hemorrhagic conversion with therapeutic anticoagulation, decreased cerebral venous return with large venous cannulas placed in the internal jugular vein, and extreme fluctuations in PaCO2 which can result in ICH [121]. However, major recent technological advances have allowed for increased ECMO utilization in SABI. Heparin-bonded circuits and polymethylpentene oxygenators have allowed for extended VV-ECMO support with low-dose or no systemic anticoagulation without premature oxygenator failure or excessive thrombotic complications [122, 123]. Femoral access for cannulation avoids concerns regarding impaired cerebral venous drainage. Initial low sweep gas rates and titration can avoid overly rapid PaCO2 correction. Overall, ECMO is feasible in highly selected patients with SABI, and may be considered on a case-by-case basis, with anticipated neurological prognosis weighing heavily in patient selection.

### Fluid and hemodynamic management

The FACTT trial and a large meta-analysis demonstrated a decrease in MV duration, ICU length of stay, and improved gas exchange, but no change in mortality with a conservative fluid management strategy in ARDS [124, 125]. While initial volume resuscitation may be indicated in patients with hypovolemic or septic shock, hypervolemia is strictly avoided in ARDS to minimize alveolar capillary hydrostatic pressure and pulmonary edema.

However, hypotension and hypovolemia may result in decreased CPP and precipitate or exacerbate brain injury. Concerns about adequate cerebral perfusion are particularly high in patients with symptomatic vasospasm,
acute cerebrovascular occlusions or high-grade stenoses, or impaired cerebral autoregulation.

Hypotension is associated with higher mortality and worse outcomes in all SABI subtypes [126–132]. While there is limited evidence for induced hypertension, higher BP targets and even BP augmentation may be considered in scenarios with high concern for cerebral perfusion. There is limited evidence to guide volume management in SABI. Low fluid balance in the first days is associated with worse neurological outcomes in TBI [133, 134]. Fluid restriction has shown to result in higher risk of cerebral infarction in SAH [135] and may cause watershed infarcts in patients with preexisting cervical vascular stenoses. However, fluid balance does not always reflect intravascular volume status. Hypervolemia can augment cerebral edema in patients with blood–brain barrier (BBB) disruption, exacerbate heart failure, cardiogenic shock, and pulmonary edema, and is also associated with high ICU mortality and worse outcomes in SABI [133, 136, 137]. Guidelines recommend targeting intravascular euvoled and avoiding a restrictive or negative fluid balance in SABI [138].

The use of HT to treat elevated ICP may have differential effects on intravascular volume status depending on the type of HT used and the patient's organ function. Mannitol causes an osmotic diuresis and may lead to decreased preload and cardiac output, and also precipitate or exacerbate acute kidney injury. Hypertonic saline may contribute to hypervolemia and pulmonary edema.

For patients with concurrent ARDS and SABI, a tailored fluid strategy utilizing serial multimodal volume status assessments is critical in guiding the optimal strategy for the individual patient. For most patients, targeting normotension and intravascular euvoled is appropriate. Hypotension and intravascular hypovolemia should be strictly avoided in patients with impaired cerebral perfusion, and the use of diuretics may have to be limited during critical time windows. Measures of cerebral perfusion, such as TCD or CT-angiogram (CT-A) and CT-perfusion (CT-P), can help guide BP and volume targets.

**Corticosteroids**

Following decades of inconclusive and negative clinical trials [139–141], several recent RCTs have demonstrated benefits of corticosteroids in ARDS. The DEXA-ARDS study showed lower mortality and reduced duration of MV in patients with moderate-severe ARDS who received a 10-day course of corticosteroids after 24 h of disease onset [142]. Delayed corticosteroids within ≥7 days of onset have not shown a benefit, with higher mortality at ≥14 days [141]. Several studies from the COVID-19 era have suggested benefits of corticosteroids; the RECOVERY trial demonstrated a mortality reduction by one-third in ventilated patients with COVID-19 [143], and a meta-analysis of 7 RCTs also showed a significant mortality reduction [144]. Treatment with corticosteroids has since become commonplace in ARDS.
However, distinct ARDS subgroups may have varying responses to corticosteroids based on hypo- or hyperinflammatory phenotypes or the presence of infectious organisms, and future research is needed to establish benefits and harmful effects and effects of dosing in different sub-populations.

Corticosteroids can reduce cerebral vasogenic edema by decreasing BBB permeability [145], with benefits noted in the treatment of brain tumors [146] and subtypes of meningitis [147]. However, corticosteroids have not proven to be effective in SABI and might be harmful. Specifically, the Brain Trauma Foundation (BTF) guidelines state that corticosteroids are not recommended in TBI for ICP control, and high-dose steroids are contraindicated (level 1 recommendation) [148]. After several inconclusive RCTs [149–152], a large multicenter RCT (MRC CRASH) stopped early after showing higher mortality at 2 weeks [153] and 6 months [154•] with a 48-h high-dose methylprednisolone infusion. Disability at 6 months did not differ, and reasons for the increased mortality remain unclear with no substantial difference in infections or gastrointestinal bleeding. Studies in AIS [155], SAH [156, 157], and ICH [158] have not demonstrated a significant improvement in survival or neurological outcome but have suggested adverse systemic effects. In cardiac arrest, some studies have suggested an association with increased return of spontaneous circulation when used in combination with vasopressin during cardiopulmonary resuscitation, with no benefit on long-term neurological outcomes [159, 160]. Two systematic reviews have not found a benefit with corticosteroids alone [161, 162].

With insufficient evidence to guide management in concurrent ARDS and SABI, decisions may be guided by ARDS severity, ARDS and SABI etiologies, underlying infectious etiologies, potential for iatrogenic harm (e.g., risk for hyperglycemia, infection, and myopathy), and time from ARDS onset. Steroids should generally be avoided when TBI is the dominant clinical problem. Given the mortality benefit in ARDS, they should be considered in other SABI subtypes and may be beneficial in some SAH and post-cardiac arrest populations. More data is needed to establish the overall benefit or harm in various ARDS and SABI subtypes.

### Specific considerations in SABI subtypes

The different subtypes of SABI have very distinct underlying pathophysiology and clinical trajectories. Specific concerns related to increased ICP, impaired cerebral perfusion, and critical time windows are summarized in Table 1. Key neuroprotective strategies to minimize secondary brain injury in all SABI subtypes encompass maintaining physiological homeostasis; avoiding derangements in temperature, oxygenation, and ventilation; optimizing cerebral perfusions; averting detrimental ICP elevations and decreased CPP; and early recognition and treatment of seizures and status epilepticus.

In patients with TBI, the BTF has developed evidence-based guidelines, and a multiterritory algorithm has been adopted to minimize secondary injury [148]. While there is large heterogeneity within TBI, these principles
should be applied to patients with concomitant ARDS. In patients with clinical concerns for elevated ICP, invasive multimodal monitoring should be strongly considered, and target ICP < 20 mmHg, CPP 60–70 mmHg, $P_a CO_2$ 35–40 mmHg, and $PbtO_2$ > 20 mmHg.

The main challenge in concurrent SAH and ARDS is the prevention of DCI while minimizing volume overload. While DCI is thought to be multifactorial, the only known potentially reversible etiology is vasospasm. Radiographic vasospasm occurs in 70% of patients with SAH, and 30% of patients with radiographic vasospasm develop cerebral ischemia [163, 164]. Also, a subset of patients with SAH develop cerebral salt wasting syndrome and natriuresis, which can lead to acute intravascular hypovolemia. The currently recommended management approach during the vasospasm period (3–21 days, peak day 7–10, <5% after day 14) is to maintain intravascular euvolemia and a combination of permissive and induced hypertension. Hypovolemia and fluid restriction have been associated with increased risk of cerebral infarction and poor outcomes [165]. However, induced hypervolemia and hemodilution have not demonstrated an outcome benefit and are associated with worsening pulmonary edema [44, 166–168]. In addition, up to 30% of patients with SAH can develop neurogenic heart failure [163]. Daily multimodal volume status assessments are recommended; while there is clinical concern for DCI, strict intravascular euvolemia should be targeted and diuresis should be minimized. TCD, CT-A, and CT-P can help stratify and reassess the risk for vasospasm.

A crucial part of sICH management is serial monitoring of the neurological exam and hemodynamic status to ensure early recognition and treatment of ICH expansion, hydrocephalus, and herniation [169]. If deep sedation and NMB are required for ARDS management during a critical time period, serial imaging or invasive ICP monitoring should be considered in patients with high clinical concerns for neurological deterioration. With regard to ventilatory and hemodynamic targets, a large retrospective cohort in mechanically ventilated patients with ICH identified high Vt as the strongest risk factor for ARDS development and in-hospital mortality, other modifiable risk factors included high fluid balance, hypoxemia, and transfusions [10].

The management of AIS revolves around ensuring adequate cerebral perfusion and salvaging the ischemic penumbra. The degree of concern is based on the presence and chronicity of occlusions and stenoses, revascularization and collateral status, and concern for reperfusion injury and hemorrhagic conversion [13]. BP and volume targets need to be determined based on these factors and weighed against ARDS severity as well as presence of cardiopulmonary disease as a common stroke risk factor. Concerns about ICPs crises and herniation are high in patients with large middle cerebral artery infarctions, or cerebellar infarcts resulting in mass effect on the brainstem or obliteration of the fourth ventricle, and close neurological monitoring is warranted in these patients.

The post-cardiac arrest syndrome is characterized by a systemic inflammatory state, and there is substantial overlap in pathophysiological mechanisms encountered in ARDS. Interventions that have shown to impact
outcomes include temperature management, hemodynamic optimization (MAP > 65 mmHg), adequate oxygenation and ventilation with $P_aO_2$ and $PCO_2$ goals in a physiological range, and appropriate neuroprognostication [13, 170–172]. Studies have suggested decreased occurrence of ARDS, more ventilator-free days, and improved neurological outcomes with LPV after cardiac arrest [173]. Seizures are common after cardiac arrest [174], and may be another potentially modifiable target in minimizing secondary brain injury. Cerebral edema and elevated ICP have been described in up to 22% [175], and are associated with worse outcomes [176]. The use of invasive ICP monitoring is controversial and less established in this population and its utility remains under investigation.

**Conclusions**

ARDS is common and associated with higher mortality and worse neurological outcomes in SABI. ARDS and SABI management strategies may conflict. High PEEP, permissive hypercapnia due to LPV, and prone ventilation may result in increased ICP and decreased CPP. Measures to enhance cerebral perfusion, including volume resuscitation, BP augmentation, and HT, can interfere with the conservative fluid management strategy recommended in ARDS. More research is needed to determine risks and benefits in corticosteroids, especially in light of conflicting data about mortality in ARDS and TBI.

The care of patients with SABI and ARDS requires meticulous attention to oxygenation and ventilation, hemodynamics and volume status, temperature management, and the neurological exam. In general, LPV and PP should be utilized, and PEEP titration should be deliberate based on measures of lung and brain physiology. Intravascular euvoolemia and normotension should be targeted in SABI, particularly for patients at risk for brain ischemia due to impaired cerebral perfusion. In patients with high concern for increased ICP and insufficient cerebral perfusion, multimodal monitoring and serial hemodynamic assessments can help determine individualized targets to support the acutely injured brain 177.

**Compliance with Ethical Standard**

**Conflict of Interest**

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