

# Acute respiratory distress syndrome in traumatic brain injury: how do we manage it?

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**Abstract:** Traumatic brain injury (TBI) is an important cause of morbidity and mortality worldwide. TBI patients frequently suffer from lung complications and acute respiratory distress syndrome (ARDS), which is associated with poor clinical outcomes. Moreover, the association between TBI and ARDS in trauma patients is well recognized. Mechanical ventilation of patients with a concomitance of acute brain injury and lung injury can present significant challenges. Frequently, guidelines recommending management strategies for patients with traumatic brain injuries come into conflict with what is now considered best ventilator practice. In this review, we will explore the strategies of the best practice in the ventilatory management of patients with ARDS and TBI, concentrating on those areas in which a conflict exists. We will discuss the use of ventilator strategies such as protective ventilation, high positive end expiratory pressure (PEEP), prone position, recruitment maneuvers (RMs), as well as techniques which at present are used for 'rescue' in ARDS (including extracorporeal membrane oxygenation) in patients with TBI. Furthermore, general principles of fluid, haemodynamic and hemoglobin management will be discussed. Currently, there are inadequate data addressing the safety or efficacy of ventilator strategies used in ARDS in adult patients with TBI. At present, choice of ventilator rescue strategies is best decided on a case-by-case basis in conjunction with local expertise.

**Keywords:** Traumatic brain injury (TBI); acute respiratory distress syndrome (ARDS); positive end expiratory pressure (PEEP); extra corporeal membrane oxygenation (ECMO)

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## Introduction

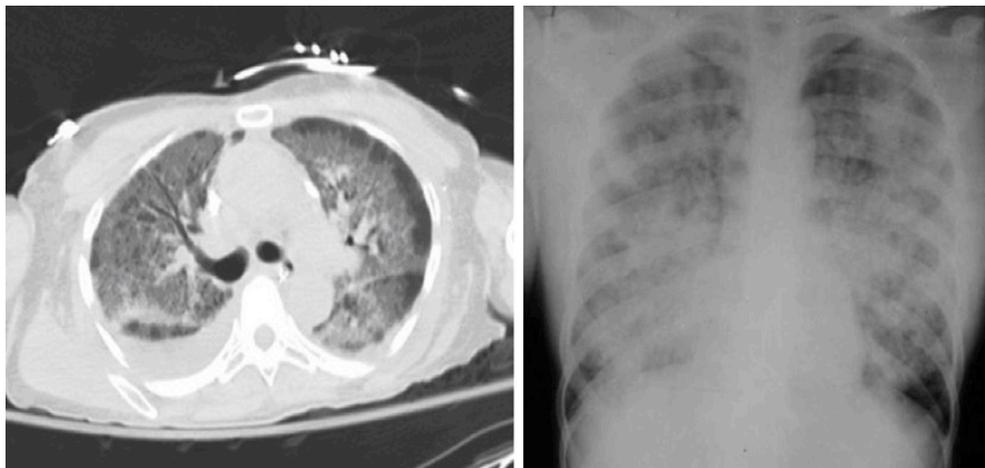
Acute respiratory distress syndrome (ARDS) is a life threatening condition characterized by refractory hypoxemia and stiff lungs (1-3). According to the recent *Berlin Definition* (4), ARDS is defined as an acute hypoxemic respiratory distress syndrome, not fully explained by cardiac failure occurring within one week of a known clinical

insult or new or worsening respiratory symptoms, with bilateral opacities on chest X-ray (*Table 1, Figure 1*). A major component of ARDS is lung tissue inflammation.

In the *Berlin Definition* there is no more use of the term acute lung injury (ALI) and the wedge pressure measurement was abandoned because ARDS may coexist with hydrostatic oedema caused by cardiac failure or fluid overload, furthermore

**Table 1** ARDS Berlin Definition

Timing	Acute onset: within one week of a known clinical insult or new/worsening respiratory symptoms
Chest imaging	Bilateral opacities visible (on chest radiograph or computed tomography scan), not fully explained by effusions, nodules, masses, or lobar/lung collapse
Origin of edema	Respiratory failure associated to known risk factors and not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	200 mmHg < PaO <sub>2</sub> /FiO <sub>2</sub> <300 mmHg with PEEP >5 cmH <sub>2</sub> O
Moderate	100 mmHg < PaO <sub>2</sub> /FiO <sub>2</sub> <200 mmHg with PEEP >5 cmH <sub>2</sub> O
Severe	PaO <sub>2</sub> /FiO <sub>2</sub> <100 mmHg with PEEP >5 cmH <sub>2</sub> O

**Figure 1** Computed tomography (left panel), and chest X-ray (right side) of a patient with ARDS.

the value of using pulmonary artery catheterization was questioned due to insertion risk (4) (*Table 2*).

Several ventilatory strategies have been demonstrated to be useful in ARDS population, including the use of protective ventilation by using low tidal volume (TV) ventilation and limiting plateau pressure no more than 30 cmH<sub>2</sub>O with allowing permissive hypercapnia, prone positioning, the use of high positive end expiratory pressure (PEEP), recruitment manoeuvres (RM), extra corporeal membrane oxygenation (ECMO) and extra corporeal carbon dioxide removal (ECCO<sub>2</sub>R) (5-7).

The utility of these strategies has been proved in several groups of patients, both during anaesthesia and in critical care (8,9); however, their use in neurocritical care patients is still uncertain, as most of these lung protective ventilatory strategies are associated with an increased risk of intracranial hypertension (9).

There are tight interactions between cerebral and respiratory dynamics, so mechanical ventilation can have effect on cerebral perfusion and represent a potential burden for iatrogenic secondary brain damage (10). ARDS is common in neurocritical care patients (11-13) and lung injury is associated with worse outcome (12) and longer ICU length of stay (14).

Traumatic brain injury (TBI) is a major cause of mortality and morbidity and it is the most common cause of death under the age of 40 (15-17) (*Figure 2*).

According to the recently published *Brain Trauma Foundation Guidelines*, the main targets in TBI population are to avoid hypoxia and cerebral hypoperfusion (18). In particular, the central goal is the prevention of hypoxic secondary insults through the maintenance of an adequate cerebral perfusion pressure (CPP) and cerebral oxygen delivery.

**Table 2** The American European Consensus Conference (AECC) definition of acute lung injury and acute respiratory distress syndrome (ARDS) [1994]

Diagnostic criteria for acute lung injury (ALI)

Time: acute onset

Oxygenation:  $\text{PaO}_2/\text{FiO}_2 \leq 300$  mmHg (regardless of PEEP level used)

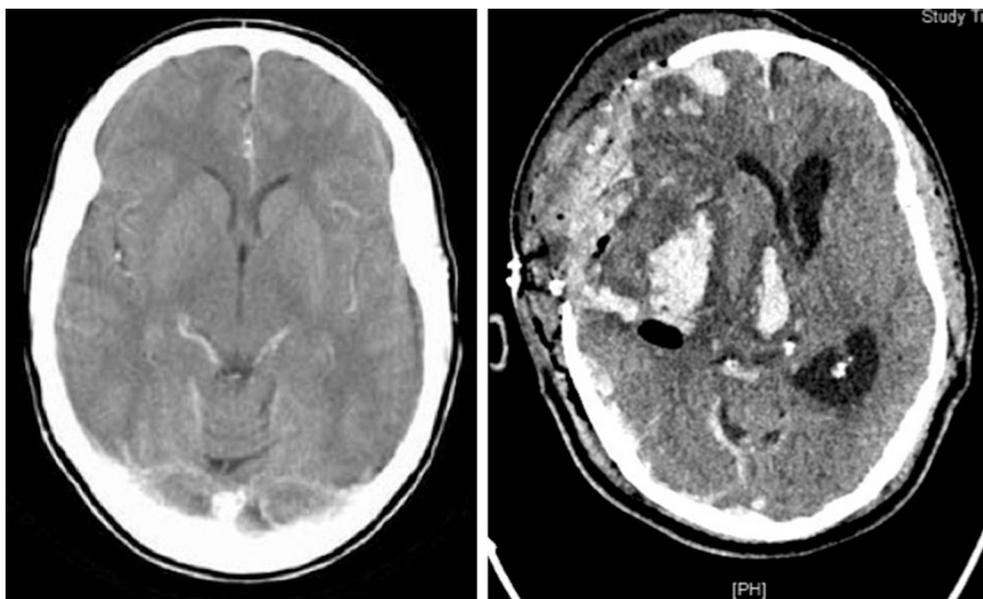
CXR: bilateral infiltrates

Pulmonary capillary pressure  $\leq 18$  mmHg/No evidence of left atrial hypertension

Diagnostic criteria for ARDS

Same as ALI, except for oxygenation:  $\text{PaO}_2/\text{FiO}_2 \leq 200$  mmHg

PEEP, positive end expiratory pressure; CXR, chest X-ray.



**Figure 2** Computed tomography in two patients with traumatic brain injury (TBI). (A) diffuse brain swelling with traumatic subarachnoid haemorrhage; (B) devastating traumatic brain injury with multiple intracerebral haemorrhages after decompressive craniectomy.

Mechanical ventilation is very often necessary in the brain-injured patient and respiratory failure can be multi etiological [aspiration pneumonia, pulmonary contusion related to chest trauma, neurogenic pulmonary oedema, transfusion-related acute lung injury (TRALI) etc.].

When a concomitance of TBI and ARDS occurs, the ventilatory management can be very challenging as ventilatory targets are often in conflict in these two pathologies.

Recruitment maneuvers (RMs), prone positioning and the use of high PEEP can improve pulmonary gas exchange and respiratory mechanics by reducing ventilation—perfusion mismatch, and by opening collapsed alveoli

reducing intrapulmonary shunt (19,20). However, they may be associated with the development of intracranial hypertension (21) by impairing jugular venous outflow and by impeding cerebral venous return to the right atrium. Moreover, they can increase ICP and decrease mean arterial pressure, both resulting in decreased CPP (22).

Literature is lacking regarding the management of patients with a concomitance of TBI and ARDS, and there is therefore need of a pragmatic approach to this group of patients.

The aim of this manuscript is to review and describe the different ventilatory strategies in patients with a concomitance of TBI and ARDS.

**Table 3** TBI and ARDS: ventilatory targets and strategies

Ventilatory	TBI	ARDS
PaO <sub>2</sub>	Normoxia: PaO <sub>2</sub> >60 mmHg (Brain Trauma Foundation); PaO <sub>2</sub> >97 mmHg (UK Transfer Guidelines)	PaO <sub>2</sub> 55–88 mmHg (ARDS network)
PaCO <sub>2</sub>	Normocapnia PaCO <sub>2</sub> ranges from 35–45 mmHg; prolonged prophylactic hyperventilation with PaCO <sub>2</sub> ≤25 mmHg is not recommended	pH >7.30, permissive hypercapnia accepted
PEEP	PEEP < ICP, provide MAP is maintained	Incremental FiO <sub>2</sub> /PEEP combination
Plateau Pressure	≤30 cmH <sub>2</sub> O	≤30 cmH <sub>2</sub> O
Prone positioning	Reasonable to attempt when severe hypoxemia, with strict neuromonitoring	Improve PaO <sub>2</sub> /FiO <sub>2</sub> ratio; suggestion to use prone position when P/F <150 mmHg [Guérin <i>et al.</i> , (23)]
Recruitment maneuvers	Reasonable to attempt when severe hypoxemia, with strict neuromonitoring	Incremental FiO <sub>2</sub> /PEEP combination
iNO	No evidence of benefit	Limited evidence available, rescue therapy?
ECCO2R	Rescue therapy, could be considered individually (limited evidence available)	Rescue therapy, could be considered individually (limited evidence available)
ECMO	Reasonable to attempt in selected cases; use of heparin needs further studies	Improves outcome in patients referred to ECMO centers

TBI, traumatic brain injury; ARDS, acute respiratory distress syndrome; PaO<sub>2</sub>, arterial oxygen partial pressure; PaCO<sub>2</sub>, arterial carbon dioxide partial tension; PEEP, positive end expiratory pressure; ICP, intra cranial pressure; MAP, mean arterial pressure; ECCO2R, extracorporeal carbon dioxide removal.

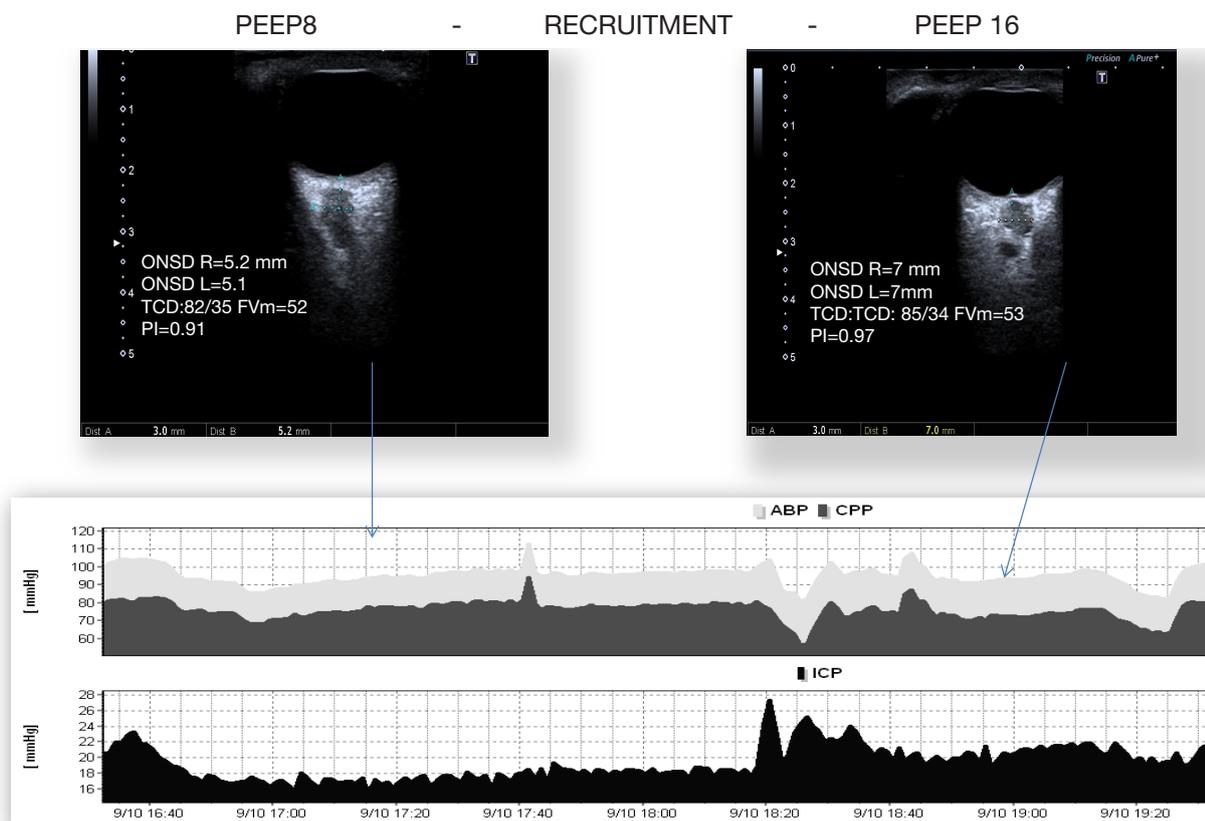
## Ventilatory targets (Table 3)

### Arterial oxygen partial pressure (PaO<sub>2</sub>)

What really matters to the brain after TBI is to avoid hypoxemia, which has long been identified as a significant secondary insult following TBI and associated with poor outcome (24,25). PaO<sub>2</sub> target can be efficiently directed on brain tissue oxygen tension (PbO<sub>2</sub>) or on jugular venous saturation (SjvO<sub>2</sub> of <50%) (18). The effect on mortality and poor outcome of hypoxemia in TBI has been confirmed by the analysis of the IMPACT study database, a cohort of more than 9,000 patients with TBI recruited to randomized controlled trials and series dating back to the 1980s (26). The IMPACT analysis showed that arterial hypoxemia results in a decreased cerebral oxygen delivery, which causes cerebral vasodilatation, and an increase in ICP. A transcranial Doppler study in healthy volunteers found that the inflection point of cerebral vasodilatation is at PaO<sub>2</sub> =58 mmHg or SpO<sub>2</sub> of 90% (27). Current guidelines recommend avoidance of PaO<sub>2</sub> <60 mmHg and maintenance of normoxia (18–22,24–28). The ARDSNet target of PaO<sub>2</sub> is 55–80 mmHg seems therefore to be too low to be safely applied to patients with TBI (29).

### PaCO<sub>2</sub> and TV

The ARDSNet trial (29) demonstrated a decreased mortality and days of mechanical ventilation in patients with ARDS ventilated with TV of 6 mL/Kg compared to patients ventilated with 12 mL/kg (29). As expected, patients ventilated with lower TV had a higher mean PaCO<sub>2</sub> than those in the traditional group (44 *vs.* 40 mmHg), and permissive hypercapnia as a consequence of protective ventilation is commonly accepted in patients with ARDS. However, hypercapnia is associated with cerebral vasodilation and consequent increased ICP, and can be dangerous in patients with TBI, and hypocapnia has been suggested to be a useful strategy to reduce ICP. According to the *Brain Trauma Foundation Guidelines* (18), prolonged prophylactic hyperventilation with PaCO<sub>2</sub> of <25 mmHg is not recommended as first line therapy to reduce ICP, and hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced. Hyperventilation can be detrimental, as severe hypocapnia and consequent cerebral vasoconstriction can determine brain tissue hypoxia and compromise compliance and blood flow velocities (30,31);



**Figure 3** Invasive (through ICP Bolt) and non invasive ICP (through optic nerve sheath diameter) monitoring in a patient with TBI and ARDS during recruitment manoeuvres and increased levels of PEEP. Initially, ICP is below 20 mmHg (mean ONSD =5.2), with PEEP =8, with stable arterial blood pressure (ABP) and cerebral perfusion pressure (CPP). After recruitment manoeuvres and setting PEEP at 16, ICP spikes up >20 mmHg, with ABP and CPP increase (ONSD =7 mm). PaCO<sub>2</sub> remained constant during the procedure and the patients remained haemodynamically stable.

if hyperventilation is used, oxygen jugular saturation (SjO<sub>2</sub>) or brain tissue oxygen partial pressure (BtpO<sub>2</sub>) measurement are recommended to monitor oxygen delivery (IIB recommendation) (17). Grubb *et al.* (32) demonstrated that cerebral blood volume (CBV) is linearly related to PaCO<sub>2</sub>. Therefore, in TBI patients the standard of care is to ventilate to low normocapnia (17) (PaCO<sub>2</sub> between 33.75 and 37.5 mmHg, equivalent to 4.5 to 5 KPa), but this may be a challenge in ARDS patients. Furthermore, high TV ventilation in patient with TBI has been associated with development of ARDS (14), as it has been shown that the proportion of induced ARDS increases with the higher initial TV, in particular with mean TV ≥10 mL/Kg (14).

All in, when ARDS and TBI coexist, a balance needs to be found between CO<sub>2</sub> control and lung protection. Potentially, there are not absolute contraindications to

the use of protective ventilation in TBI; the PaCO<sub>2</sub> values should be set case by case according to ICP. Moreover, multimodal brain monitoring such as microdialysis catheters or brain parenchymal oxygen electrode may allow intensivists to tolerate a higher PaCO<sub>2</sub>, if cerebral metabolism remains intact.

#### *Positive end-expiratory pressure*

The use of PEEP has been considered very controversial in TBI patients, because the raised mean intrathoracic pressure related to PEEP can reduce cerebral venous return and consequently increase ICP (*Figure 3*). Cerebral perfusion during increased ICP is better described by a Starling Resistor (collapsible tube) than by Hagen-Poiseuille' law (rigid tube). Accordingly, the water-fall

principle best describes venous outflow; this means that cerebral venous downstream pressure is limited by CVP only when CVP exceeds ICP (the edge of the waterfall). If PEEP and CVP are lower than ICP, they don't influence effective downstream pressure. Some authors (33) found that if PEEP values are below ICP values, then the associated augmentation of intrathoracic pressure doesn't result in increased ICP. Observational studies found that high PEEP in patients with acute stroke and subarachnoidal haemorrhage (SAH) was associated with a reduced CPP and a decrease in CBF when cerebral autoregulation was impaired (34,35). However, they demonstrated that the principal mechanism responsible for reduction in CPP was a decrease in MAP, PEEP dependently. In all the cases, when MAP was restored, CPP and CBF returned to their baselines (35). Marcia *et al.* (36) demonstrated that when increased PEEP was applied to brain injured patients with ARDS, there was a substantial difference in the effects on ICP, depending on whether the application of PEEP caused alveolar hyperinflation or alveolar recruitment. When PEEP determines alveolar recruitment, the main effect is reduction in PaCO<sub>2</sub> with subsequently reduction in ICP. The effect is opposite when PEEP causes alveolar hyperinflation (36).

In a prospective study higher levels of PEEP were applied on patients with severe head injury or SAH with normal or low respiratory system compliance (37). In the group with normal respiratory compliance the increase of PEEP caused increased CVP, but reduced MAP, CPP and mean velocity of middle cerebral arteries. The authors concluded that monitoring respiratory system compliance may be useful to avoid negative effect of PEEP on ICP (37).

The optimal level of PEEP is still uncertain in ARDS patients. An ARDSnet study published in 2004 (38) found no benefit from higher PEEP strategy when compared with the standard ARDSnet ventilation protocol (39). At present, therefore, the use of PEEP to treat ARDS may be appropriate in TBI patients, provided that MAP is maintained and a strict close attention needs to be paid to any changes in CPP and ICP. When a decision of increasing PEEP in a TBI patient is made, it is necessary to ensure MAP stability and a close monitoring of cerebral parameters, mainly ICP and CPP.

### **RM**s

RMs are useful strategies able to improve oxygenation, alveolar recruitment, and optimize ventilation-perfusion mismatch (1,20). However, RMs can have dangerous effect

on ICP, as they can cause a significant elevation of ICP in patients with altered cerebral autoregulation, by impairing jugular blood outflow and increasing intrathoracic pressure, central venous pressure (CVP) and impeding cerebral venous return to the right atrium (*Figure 3*) (40).

Nemer *et al.* studied the effects of RMs in a RCT including patients with SAH and TBI who developed ARDS (40) and found that pressure control recruitment maneuver doesn't impair ICP or CPP, while it improves oxygenation (40). This suggests that RMs can be used with caution in patients with TBI, ensuring hemodynamic stability and a close monitoring of cerebral parameters.

### **Prone positioning**

Prone ventilation is known to improve PaO<sub>2</sub>/FiO<sub>2</sub> ratio in ARDS (41). Recently published data from a large multicenter prospective randomised study (PROSEVA trial) showed a significant reduction of mortality after 28 and 90 days in ARDS treated with prone positioning compared to supine positioning (23). This recent meta-analysis by Guérin *et al.* (23) suggested use of prone position in ARDS patients with P/F <150 mmHg. These data followed a study conducted by Mancebo *et al.*, which demonstrated a decrease in mortality from 58% to 43% with proning of patients for a more prolonged period (mean 17 hours) (42). In TBI patients there are serious concerns over the effect on ICP of prone positioning and also technical difficulties can be present, such as risks of removal or displacements of ICP Bolt and drains and practical difficulties in positioning neuromonitoring. The recommended position for patients with TBI is a 30 head up tilt combined with a straight head position (17). Therefore, this cohort of patients has previously been excluded in studies with utilization of prone position to improve oxygenation (43,44). Thelandersson *et al.* in their pilot study (45) demonstrated that prone positioning is not associated with adverse effect on ICP. In this study, the authors enrolled 12 patients mechanically ventilated and with an ICP probe inserted; the patients were placed in prone position for 3 hours and then turned them back to supine position. They demonstrated that positioning patients with TBI and reduced intracranial compliance in prone position significantly improved PaO<sub>2</sub>, SpO<sub>2</sub> and respiratory system compliance, without altering intracranial parameters (45).

Nekludo *et al.* (46) discovered an improvement in oxygenation, a slightly increase of ICP and a moderate increase of MAP in TBI patients during treatment with

prone position. As MAP increased to a greater extent than ICP, this resulted in an improved CPP in prone position. In their cohort of patients the authors also observed that the ARDS cases of extrapulmonary origin seem to respond better to the prone position, compared with pulmonary ARDS (46). In a more recent study conducted by Roth *et al.* (47) a moderate but significant elevation of ICP during prone positioning was demonstrated. However, the oxygenation during and after prone positioning shows a significant improvement and the achieved increase of oxygenation and  $PbO_2$  by far exceeds and the changes in ICP (47). In conclusion, there is no clear evidence to aid intensivists when deciding whether or not proning a patient when there is co-existence of ARDS and TBI; however, it doesn't seem unreasonable to attempt prone ventilation when hypoxemia is refractory to conventional ventilation. The effect of proning on ICP should be observed in real continuous time, with additional treatments for increased ICP or deescalation to a different ventilatory strategy if ICP increases too much. We would not recommend proning in patients with frontal contusions, where the increased local pressure directly related to prone position may compromise the perfusion in the perilesional areas.

### **Nitric oxide (NO)**

Inhaled NO has been proposed to treat refractory hypoxemia by reestablishing an adequate ventilation perfusion matching because of its pulmonary vasodilator effects. In both randomized clinical trials (48,49) and meta analyses (50-52), NO has been shown to improve oxygenation over a 24 hour period of treatment, but there have never been any convincing data on improving outcome and mortality. In addition, detrimental effects on kidney function have been documented (53). Papadimos *et al.* (54) demonstrated anti-inflammatory effects of inhaled nitric oxide beyond the respiratory system and hypothesized that it may be of benefit when TBI and ARDS coexist. However, the role of nitric oxide after cerebral injury appears to be complex and linked with three different isoforms of enzyme NO synthase: iNO, eNO and nNO (55). In the acute phase nitric oxide released from infiltrating leucocytes or produced by induced nitric oxide synthase contributes to secondary injury mechanisms, for example increasing the production of free radicals (56). Later, nitric oxide seems to have protective effects by improving CBF (56). The available evidence suggest that NO derives from eNOS is neuroprotective after brain injury, whereas NO synthesized

by iNOS contributes to further damage.

Despite the controversies surrounding NO dysfunction after brain injury, there is animal evidence that increasing cerebral NO levels either directly using inhaled NO or indirectly using NO donors has neuroprotective effects (57). Better understanding of the role of NO pathway may lead to the development of new pharmacotherapies.

### **Extracorporeal membrane CO<sub>2</sub> removal (ECCO<sub>2</sub>R)**

The use of low TV (6 mLs/kg—predicted body weight) and maximum End Inspiratory Plateau Pressure of 30 cmH<sub>2</sub>O in ARDS patients (58), can determine hyperinflation and hypercapnia (59,60). Those results support the concept of ECCO<sub>2</sub>R as possible integrated tool to conventional ventilation to adjust respiratory acidosis (61). Although using an ECCO<sub>2</sub>R can provide a lower level of CO<sub>2</sub> reached with less injurious ventilatory strategies, evidence from randomized control trials is lacking. The largest case series included 90 patients and demonstrated improvement in oxygenation and reduction of PaCO<sub>2</sub> with the use of Arterio-Venous (AV) ECCO<sub>2</sub>R (62). There has been a small case series published describing the use of AV ECCO<sub>2</sub>R in five patients with TBI (63): in all of them PaO<sub>2</sub>/FiO<sub>2</sub> ratio improved and PaCO<sub>2</sub> decreased, and in some of them there was also a concomitant increase in ICP. The dose of anticoagulant required to run the extracorporeal circuit is lower than the one used for ECMO; however, there is still a significant risk of intracranial bleeding (63). In a pilot study of patients with TBI treated with ECCO<sub>2</sub>R (64), no complications (cerebral or extracerebral) attributable to anticoagulation were seen. Furthermore, this system can be run without additional heparin, as the components are heparin bonded, although the CO<sub>2</sub> exchanger will need to be replaced more frequently (65). However, because of the small number of patients included in this analysis, larger prospective trials are warranted to further elucidate application of these devices in neurocritical care patients.

### **Extracorporeal membrane oxygenation (ECMO)**

Veno-venous ECMO provides gas exchange across a semi permeable membrane and minimizes the trauma caused by mechanical ventilation allowing the lungs to rest (66,67). ECMO can be an effective strategy in patients with severe respiratory failure refractory to conventional ventilation (68,69). To avoid clotting of the circuit the patient needs to be anticoagulated with a bolus of heparin before

cannulation (70) and then with heparin infusion to maintain ACT 180–200 s or PTT 40–50 s. Therefore, the main complication of ECMO is bleeding, which occurs in 17% to 21.3% of cases (71). Technical improvements of the ECMO devices, such as centrifugal pump techniques and full heparin-coated circuits have led to a significant reduction of bleeding complications (72); however, ECMO is still considered contraindicated in patient with intracranial or active bleeding (73,74). There are several cases report published on successful craniotomy under ECMO treatment in multiple traumatized patients with severe thoracic and brain injuries, which reported good neurological outcomes (75,76). In the case report presented by Yen *et al.*, the patient was not anticoagulated with systemic heparin for the running of the ECMO and a heparin bonded circuit was utilized (76). Robba *et al.* (77) presented a case series of four trauma patients managed with ECMO with no ECMO related complications. Mullenbach *et al.* (78) also recommended the use of heparin free ECMO in multiple injured patients with respiratory failure impossible to control by lung protective ventilation, even if severe TBI is present. Nowadays ECMO is feasible only in a limited number of centers, but despite the large number of complications associated with this treatment (bleeding, haemorrhage, acquired von-Willebrand disease during ECMO), it should be considered as rescue therapy for management of refractory respiratory failure even in trauma patients. Future larger studies should focus on the indications, management, and the use of heparine in this cohort of patients.

### **Steroids**

The development and severity of ARDS are related to dysregulated inflammation and the outcomes are related to persistent inflammation and abnormal fibroproliferation (79,80). Corticosteroids are potent modulators of inflammation and inhibitors of fibrosis that have been used since the description of ARDS in attempts to improve outcome (81). Certainly there is no evidence to suggest that a short course of high dose steroids is helpful for either prevention, as demonstrated by four randomized controlled trials (82–85) or treatment of ARDS (86). Clinical trials regarding the use of steroids in the late stage of ARDS gave controversial results (87–89); therefore, work still needs to be done to determine if there are benefits to prolonged treatment with low dose corticosteroids for unresolving ARDS. However, ARDS

is heterogeneous; steroids may be beneficial for some etiologies of ARDS, and not for others. ARDS associated with *Pneumocystis carinii*, for example, should be treated with steroids, since high quality randomized controlled trials have demonstrated that steroid treatment decreases both the risk of respiratory failure and death (90). Unfortunately, this level of evidence is lacking for most other etiologies of ARDS. Despite significant interest in the use of steroids in treatment of pandemic H1N1 influenza-associated ARDS, most reports from careful observation cohort studies suggest that such treatment was associated with harm (91,92). For TBI patients there has been a similar long interest in the use of steroids to modulate the disease process. However, now the use of steroids is not recommended for improving outcome or reducing ICP and in patients with severe TBI high dose methylprednisolone was associated with increased mortality and is contraindicated. (Level 1 Recommendation, *Guidelines for the Management of Severe TBI*, 4th edition) (17). The Corticosteroid Randomization after Significant Head Injury Trial (CRASH) (93) was designed to provide high quality of evidence on the impact of steroids on TBI patients. This was a large multicenter trial which studied over 10,000 patients with TBI. Participants were randomized to receive either 2 g intravenous methylprednisolone followed by 0.4 mg/h for 48 h, or placebo. Data from CRASH study showed a deleterious effect of methylprednisolone, higher mortality and more corticosteroid-treated subjects in the unfavorable outcomes group (death and severe disability) compared with the favorable group (94).

### **Fluid balance and hemoglobin target**

An association between positive fluid balance and worse outcome in patients with ARDS has been demonstrated in a number of studies (95,96). Data from the ARDS Network Fluids and Catheter Treatment Trial (97) support the use of a conservative fluid management strategy in ARDS, having demonstrated improvement of the oxygenation index and the lung injury score, reduction of ventilator-free days and length of stay in ICU. However, in some patients, particularly those with severe ARDS requiring high mean airway pressures for oxygenation, hypovolaemia may exacerbate hypoxaemia by virtue of increased intrapulmonary shunt, and clinical benefit may result from the careful administration of fluid boluses (98). Zhao *et al.* (99) were the first to test the effect of fluid balance on short term TBI outcome and they demonstrated that both high

and low fluid balances were associated with poor short-term outcome and unstable ICP in TBI patients. Patients at the low (<637 mL fluid balance calculated at midnight) and upper (>3,673 mL calculated at midnight) tertiles of fluid balance were associated with poor outcomes. Those in the upper tertile also had a higher incidence of acute kidney injury and refractory intracranial hypertension. There was a negative correlation between the cumulative fluid balance and the short-term outcome for patients in the low tertile and a positive correlation between the cumulative fluid balance and the short-term outcome in the upper fluid balance group (99). High fluid balance is independently associated with poor short-term outcomes including acute kidney injury and refractory intracranial hypertension in patients with TBI. An insufficient fluid in the early stage of critical illness may lead to tissue hypoperfusion and ischemia (100) whereas excessive intravenous fluid contributes to the development of tissue edema. An optimal volume of fluid at any given time maintains tissue viability (101). These data suggest the critical importance of maintaining an appropriate fluid balance for TBI patients. Excessive fluid balance may exacerbate secondary brain injuries such as edema, intracranial hypertension and the disruption of the blood-brain barrier, leading to worse outcome. However, fluid therapy is necessary for volume resuscitation, maintenance of CPP and the prevention of secondary brain injury (102). Anemia is highly prevalent in the intensive care unit (ICU) with up to 95% critically ill patients developing subnormal haemoglobin (Hb) level by day 3 (103). Likewise, 20% to 53% of patients receive red blood cell (RBC) transfusions to correct anemia during their ICU stay (104). However, allogenic RBC transfusions carry risks that may adversely affect clinical outcomes (105,106). Evidence suggests that it is safe to adopt a lower transfusion threshold for the general medical/surgical ICU population (107-109). This has led to a paradigm shift concerning RBC transfusions in the ICU, with most guidelines now recommending hemoglobin levels around 70 g/L for transfusion in patients without significant comorbidities to minimize exposure to allogenic blood (110-112). However, specific patient populations, such as neurocritically ill patients, were underrepresented in these studies and results could thus not be applied to them. Neurocritically ill patients may represent an exception to the rationale for using low transfusion triggers because impaired oxygen delivery is a crucial modifiable factor in brain ischemia

and secondary brain injury (113,114). The optimal Hb level for cerebral oxygen delivery in TBI patients is still unknown (115). Two guidelines in neurocritically ill patient population (subarachnoid hemorrhage) were recently published; one recommending to treat anemia but without mention to threshold, and the other one recommending transfusion in order to reach hemoglobin levels of 80 to 100 g/L (116,117). Interestingly, guidelines for the management of patients with TBI did not cover this topic (18). Moreover, data on which clinicians have to rely in decision making is discordant, as both anemia and RBC transfusion have been observed to be associated with unfavorable clinical outcomes in neurocritically ill patients (118,119). Anemia has repeatedly shown to be associated with unfavorable outcomes in patients with TBI (118-120), although other studies have not confirmed this relationship (121,122). Recent microdialysis studies showed that cerebral metabolism of subjects affected by SAH and TBI becomes impaired at Hb values lower than 90 g/L (123), but RBC transfusions are known to improve physiologic measures such as brain oxygen tension in a majority of patients with TBI (124-126).

## Conclusions

The lung and brain interaction poses important challenges to ventilator management of patients with TBI and ARDS. The beneficial effect of protective lung ventilation and respiratory strategies is well established both in intensive care and in the operating room. However, the application of these techniques on neurocritical care patients is contrasting because of the specific needs and ventilator targets in this group of patients. Moreover, haemodynamic and general management (including Hb target and fluid balance) can be contrasting in this group of patients. The use of cerebral multimodal monitoring can be useful to assess cerebral hemodynamic and to evaluate the effects of ventilator strategies commonly used in ARDS patients. It would be desirable a concomitant cerebral and respiratory system monitoring in these patients, mainly in the more severe ones, in order to allow the best approach to these patients and avoid complications.

Further studies will be necessary to create shared diagnostic and therapeutic guidelines based on available evidence and that can contribute to improve patients' clinical outcome.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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