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WHAT'S NEW IN INTENSIVE CARE

ARDS in the brain-injured patient: what's different?

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Management of ARDS in patients with acute brain injury (ABI) differs in several ways from non-neurological subjects. Ventilation must be doubly protective, for the lung and the brain. Adjustment of ventilator settings is dictated by the interactions of positive-pressure ventilation with intracranial circulation, brain compliance, and cerebral autoregulatory reserve, aiming to avoid intracranial pressure (ICP) increase and inadequate cerebral blood flow (CBF). Established therapies of refractory hypoxemia such as prone positioning appear feasible but require rigorous control of ICP. Clinical data on the use of extracorporeal decarboxylation to control hypercapnia in patients with ABI and intracranial hypertension and to manage refractory hypoxemia with extracorporeal membrane oxygenation (ECMO) remain limited. ABI-related ARDS has distinct mechanisms, determined by a cross talk between neuroinflammation, sympathetic activation, and systemic immune response, and may be exacerbated by specific neurointensive care interventions, such as CBF augmentation (Fig. 1). These differences justify a different approach to ARDS after ABI and explain why brain-injured patients are generally excluded from randomized controlled trials of ARDS.

Brain–lung interactions

Recent experimental data suggest divergent inflammatory pathways between neurogenic and non-neurogenic ARDS. In a mouse model of TBI-ARDS, activation of adenosine A_{2A} receptor (A2AR), known to have anti-inflammatory properties in the traditional oleic acid-induced ARDS model, exerted instead a pro-inflammatory effect that aggravated lung damage [1]. Activation of the sympathetic nervous system is an important pathogenic determinant of ABI-related ARDS [2]. It induces secondary immune suppression, thereby increasing the risk of pulmonary infections. Sympathetic hyperactivity also triggers α-adrenergic discharge with subsequent hydrostatic pulmonary edema (neurogenic pulmonary edema), a distinct entity from ARDS that generally occurs earlier (within 24 h of ABI) and has been often described following high-grade subarachnoid hemorrhage. Finally, intracranial hypertension might directly increase regional, systemic, and lung inflammation and exacerbate pre-existing damage [3].

Lung–brain interactions

Ventilation: control of tidal volume, CO_2, and ICP

Modest $PaCO_2$ increases may translate into higher cerebral blood volume (CBV) and ICP, which, under conditions of poor brain compliance, may decompensate intracranial hypertension. On the basis of this strong physiologic notion, ABI patients were traditionally ventilated to maintain tight CO_2 control. This notion was challenged by clinical data showing that aggressive hypocapnia ($PaCO_2$ 25–30 mmHg) may lead to secondary cerebral ischemia and that even moderate hypocapnia may be harmful in unselected ABI patients [4]. A less restrictive CO_2 control seems preferable after ABI in general, aiming to keep normocapnia and to tolerate mild hypercapnia in certain conditions, such as after post-anoxic coma.

Traditional ventilation aiming for tight CO_2 control also led to high tidal volumes (>9 mL/kg of predicted body weight, PBW), which were later demonstrated to exacerbate lung injury. Lung-protective ventilation with

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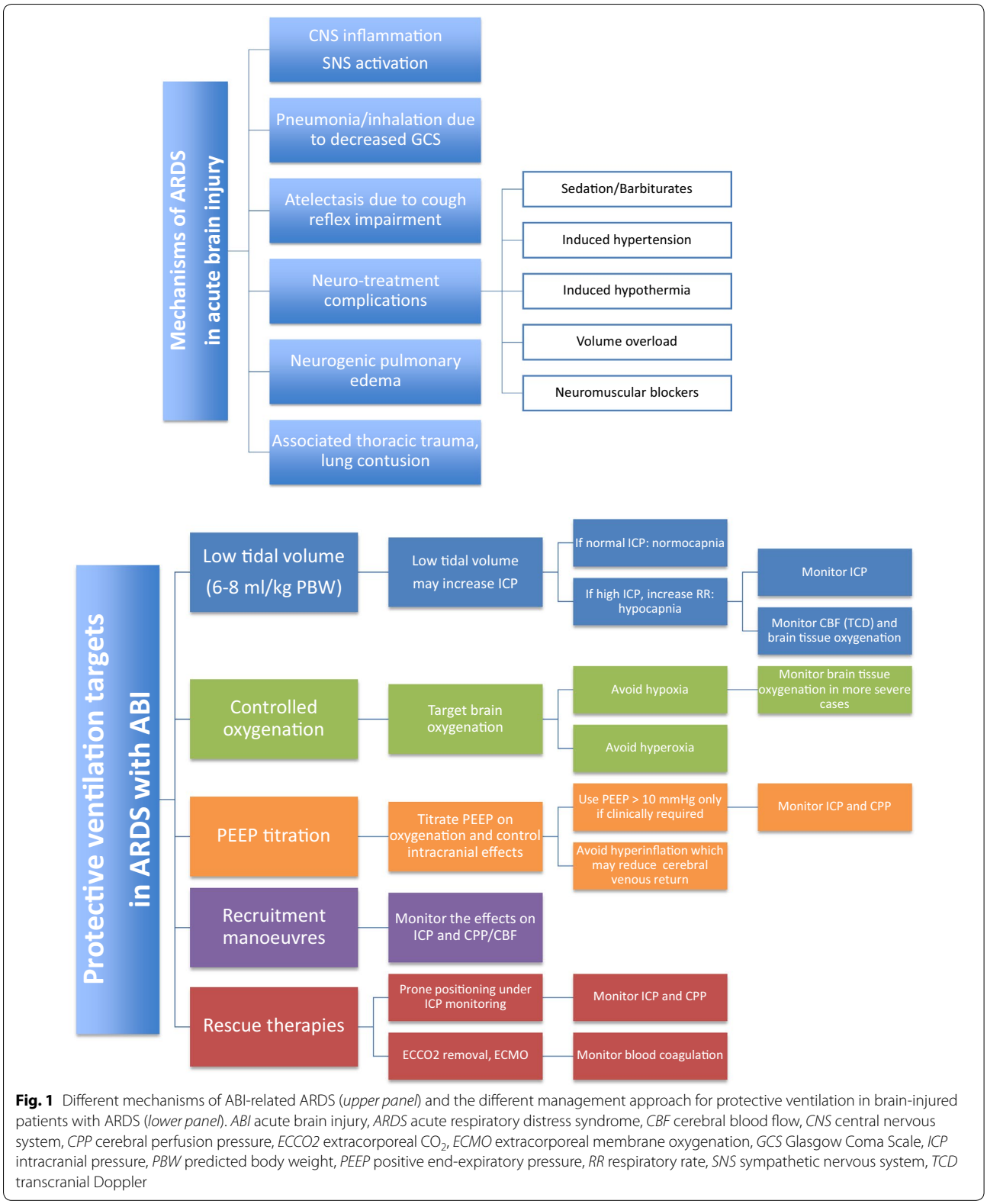

Fig. 1 Different mechanisms of ABI-related ARDS (*upper panel*) and the different management approach for protective ventilation in brain-injured patients with ARDS (*lower panel*). *ABI* acute brain injury, *ARDS* acute respiratory distress syndrome, *CBF* cerebral blood flow, *CNS* central nervous system, *CPP* cerebral perfusion pressure, *ECCO2* extracorporeal CO_2, *ECMO* extracorporeal membrane oxygenation, *GCS* Glasgow Coma Scale, *ICP* intracranial pressure, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *RR* respiratory rate, *SNS* sympathetic nervous system, *TCD* transcranial Doppler

low tidal volumes (6 mL/kg of PBW) achieves greater neurophysiologic protection than high tidal volume ventilation in animal models [5, 6]. Despite lack of high-quality evidence, the actual consensus is to recommend lung protective low tidal volume ventilation (6–8 mL/kg PBW) in ABI patients for the prevention and the management of ARDS.

Oxygenation: effects of positive-pressure ventilation on cerebral circulation

PEEP may improve cerebral and systemic oxygenation, limit the utilization of high FiO_2—which may in turn worsen outcome after ABI—and prevent cyclic lung recruitment/derecruitment, which can impair cerebral microcirculation [7].

Favorable effects of PEEP application must be balanced with its potential side effects on cerebral circulation. First, on the basis of the principle of the Starling resistor, increasing PEEP may impede cerebral venous outflow, thereby leading to ICP increase. In ABI patients with ARDS, however, the consequences of PEEP on ICP and brain circulation appear less relevant because of the reduced compliance of the respiratory system. Poorly compliant lung acts as an isolator: in this context, PEEP increase (up to 15 cmH_2O) does not translate into clinically relevant ICP increase [6]. ICP elevations may, however, be significant if PEEP does not achieve effective alveolar recruitment but rather causes lung hyperinflation and thus impediment to cerebral venous return [8]. Second, even if ICP remains stable, PEEP may reduce systemic venous return and MAP, eventually leading to CPP decrease, mainly in patients with impaired cerebral autoregulation [9]. Maintenance of adequate volume expansion and MAP is essential to prevent cerebral hypoperfusion.

Rescue therapies

When tighter CO_2 control is required to manage intracranial hypertension, pumpless extracorporeal lung assist for CO_2 removal could be a safe option [10]. The use of prone positioning to manage refractory hypoxemia is feasible and efficacious to improve oxygenation providing ICP is normal. Prone positioning, however, leads to ICP elevation and CPP decrease [11]; therefore, careful ICP/CPP monitoring is mandatory.

Data on the use of venovenous ECMO for refractory hypoxemia in ABI patients remain limited to case reports [12].

External factors

The association between increased vasopressors to augment CPP and lung injury was found for epinephrine and dopamine, which were both strong independent risk factors for ARDS in TBI patients [13]. Instead of epinephrine and dopamine, norepinephrine or phenylephrine is nowadays mostly used for CBF augmentation; therefore, the putative causal role of the last agents on lung injury remains unclear. Volume resuscitation might lead to positive fluid balance which in turn aggravates ARDS.

Monitoring

Given the complex interactions of the respiratory system with brain compliance and cerebral circulation, multimodal monitoring by way of invasive ICP monitoring and, ideally, brain tissue PO_2 is suggested to optimize protective ventilation in ABI patients with ARDS [14]. Careful analysis of the ICP curve and of ICP–MAP interactions helps in assessing cerebral autoregulation [15], and identifying patients in whom side effects of PEEP and recruitment maneuvers on CPP may be more relevant.

Monitoring of preload and cardiac output (echocardiography, transpulmonary thermodilution) also allows titration of fluid resuscitation and vasopressors, thereby preventing low CBF and secondary exacerbation of lung damage (e.g., by excessive fluid overload) [14].

Summary

ARDS after ABI has different mechanisms and requires a different management approach, aiming to achieve dual lung and brain protection. Standard protective ventilation strategies include:

- "Controlled" oxygenation (aiming to avoid both hypoxia and hyperoxia)
- Low tidal volumes
- Tolerance of higher $PaCO_2$ than has been traditionally accepted
- Moderate PEEP

Brain multimodal and hemodynamic monitoring allows optimization of care guided to patient-specific intracerebral physiology. Choice of rescue therapies (prone positioning, extracorporeal CO_2 removal, ECMO) may be decided on a case-by-case basis and according to local expertise.

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