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UNDERSTANDING THE DISEASE

What respiratory targets should be recommended in patients with brain injury and respiratory failure?

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Introduction

Acute brain injury (ABI) as a consequence of hypoxia, trauma, or stroke is a major cause of disability and death. Mechanical ventilation (MV) affects cerebral hemodynamics viadifferent mechanisms. First, it can optimize the blood level of oxygen and the arterial partial pressure of carbon dioxide ($PaCO_2$), which is a potent modulator of intracranial pressure (ICP) owing to its effect on cerebrovascular tone and consequently cerebral perfusion pressure. Hypercapnia mainly triggers vasodilatation and increases ICP whereas hypocapnia causes vasoconstriction. Second, increased intrathoracic pressure caused by application of positive end-expiratory pressure (PEEP) may impair venous return, thus reducing mean arterial pressure and/or increasing ICP. Consequently, in ABI patients, it has become traditional to target a combination of high tidal volume (Vt) (> 9 ml/kg) and low PEEP [1]. Concurrent acute respiratory failure or acute respiratory distress syndrome (ARDS) in ABI is multifactorial, its causes including aspiration, chest trauma, ABI-induced lung inflammation with reduced pulmonary compliance, and ventilator-induced lung injury (VILI), and it is associated with a worse outcome [2]. VILI is a modifiable risk factor, amenable to the use of lung protective ventilation (LPV), an approach that includes the application of low Vt and high PEEP levels [3]. Clearly, therefore, in cases where ABI and respiratory failure coexist, it is necessary to determine which is the optimal ventilator strategy. The aim of this editorial is to review briefly the current evidence on the use of ventilator settings to achieve respiratory targets (including oxygen and $PaCO_2$ levels) in patients with ABI and acute respiratory failure or ARDS.

Oxygen and carbon dioxide targets

The oxygen and $PaCO_2$ targets applied in ABI are different from the levels targeted in patients with ARDS. In the latter group, modest oxygenation targets and permissive hypercapnia are accepted as consequences of the MV settings required by LPV strategies [3] (Fig. 1). By contrast, in ABI, hypoxia must be avoided, or promptly treated, as it can cause secondary brain injury. It instead remains to be established whether hyperoxia plays a role, although a recent study comparing normoxia and mild hyperoxia in cardiac arrest patients did not demonstrate any difference in neurological outcome [4].

As a result of the risk of cerebral ischemia, hypocapnia should be avoided or used only briefly in emergency settings in the presence of intracranial hypertension, possibly in combination with brain tissue oxygen monitoring [5]. Hypercapnia, too, should be avoided, in this case because of the risk of vasodilation and increased ICP. Interestingly, in hypoxic ABI, moderate hypercapnia (52 mmHg) was not associated with increased hospital mortality, as long as pH remained in the normal range [6].

Ventilatory settings

Maintaining normoxia and normocapnia in ABI patients being treated with LPV can be challenging. Most randomized controlled trials comparing MV strategies in ARDS have excluded patients with comorbid ABI. In patients suffering from ARDS, it is recommended to

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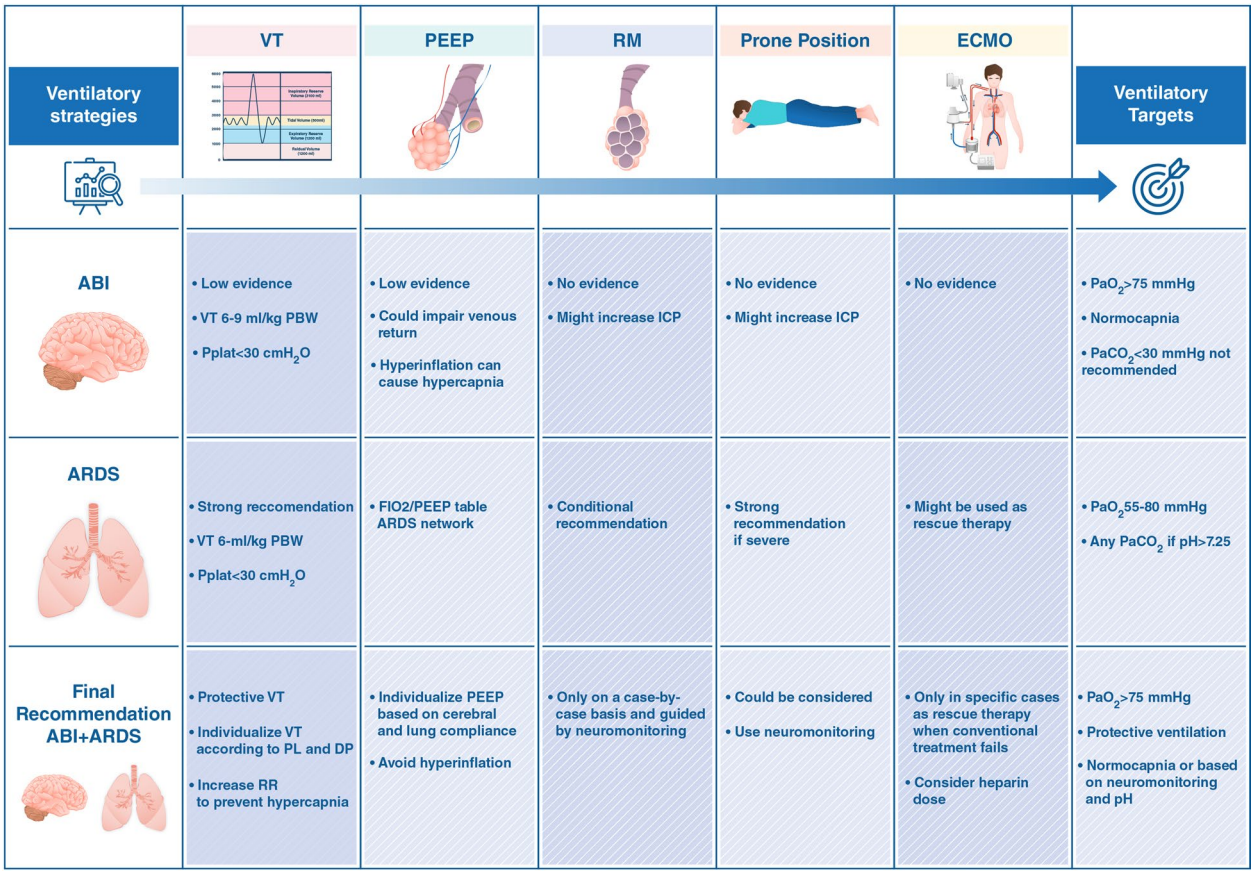

Fig. 1 Summary of ventilatory strategies and respiratory targets in patients with ABI and ARDS. In ABI, normoxia (>75 mmHg) should be the target as the role of hyperoxia in different neurological conditions has not yet been determined. Mild hypocapnia (30–35 mmHg) should be considered only if there is a risk of high ICP, whereas aggressive hypocapnia is not recommended except in situations of life-threatening brain herniation. Respiratory targets in ARDS include PaO_2 50–80 mmHg and permissive hypercapnia. In patients presenting with both brain injury and respiratory failure it is therefore suggested to reach normoxia and $PaCO_2$ levels according to multimodal neuromonitoring. If transpulmonary pressure measurement is not available, we suggest that Vt levels of up to 9 ml/kg might be acceptable in ABI patients with normal lungs [9], but recommend LPV with Vt 6 ml/kg in the presence of ARDS. RM and prone positioning might be used in ABI patients with severe ARDS under continuous neuromonitoring owing to an overall favorable risk–benefit ratio. Extracorporeal membrane oxygenation should be used only in selected life-threatening cases when conventional methods have failed. ABI acute brain injury, MV mechanical ventilation, $PaCO_2$ arterial partial pressure of carbon dioxide, ICP intracranial pressure, PEEP positive end-expiratory pressure, Vt tidal volume, ARDS acute respiratory distress syndrome, VILI ventilator-induced lung injury, LPV lung protective ventilation, PBW predicted body weight, RM recruitment maneuvers

target a Vt of 6 ml/kg predicted body weight (PBW) [3] and keep the plateau pressure < 30 cmH_2O [3]. In non-ARDS patients receiving invasive MV, a large clinical trial comparing 4–6 ml/kg and 8–10 ml/kg PBW found no benefit from the lower Vt settings [7]. Notably, in patients with ABI, Vt >9 ml/kg PBW has been identified as a risk factor for ARDS [8]; other authors failed to confirm this association between Vt and ARDS, although they found high driving pressures to be associated with the development of ARDS [9]. Recently, a multifaceted ventilation strategy, consisting of Vt 7 ml/kg, PEEP 6–8 mmHg, and early extubation, was found to reduce days of MV and mortality in ABI patients [10]. To date, however, no study has unequivocally shown that MV with high Vt per se increases ICP. Consequently, the optimal Vt value in ABI remains to be established. Outside dedicated trials, it is suggested to titrate Vt according to the size of the residual intact lung, using driving pressure and end-inspiratory transpulmonary pressure settings to minimize overdistention.

To avoid hypercapnia as a possible consequence of lower Vt during MV, reducing apparatus dead space or increasing respiratory rate might be warranted. However, a higher respiratory rate is also associated with poor outcome in ABI patients [8], most likely mediated by increased mechanical power.

PEEP is another component of LPV, with high PEEP levels (≥ 15 cmH_2O) recommended only in cases of moderate to severe ARDS [3]. Improved arterial and brain tissue oxygenation have been described in ABI patients with ARDS submitted to progressively increasing PEEP levels [11]. In ABI patients, the effect of PEEP on ICP seems to depend mainly on PEEP-related hemodynamic effects and respiratory system compliance [12]. However, no distinction was made between lung and chest wall compliance.

Similarly, the use of recruitment maneuvers (RM) may potentially have a detrimental effect on ICP. In ABI patients with ARDS, lung recruitment has a transient positive effect on arterial oxygenation but can worsen cerebral hemodynamics and cerebral oxygenation during the procedure [13]. The Alveolar Recruitment for ARDS trial showed a worsening effect of the maximal recruitment strategy on patient survival [14]. However, there may be subgroups of patients that benefit from RM with improvement of oxygenation. We therefore suggest that RM may be performed under neuromonitoring, taking into account the benefit-to-risk ratio.

Rescue therapies

Prone positioning has been shown to improve outcome in severe ARDS patients [3], but no evidence exists in patients with elevated ICP, who have been consistently excluded from trials. A single-center controlled trial in comatose patients documented that short prone position sessions prevented worsening of respiratory failure, although an increase in ICP was observed [15].

However, since the detrimental effect of prone positioning on ICP remains to be clarified, prone positioning should still be considered in cases of refractory hypoxia.

There may be a role for veno-venous extracorporeal membrane oxygenation in severe ARDS, but as yet there is no evidence of its effect in ABI, probably because extracorporeal membrane oxygenation could potentially increase the risk of intracerebral hemorrhage due to anticoagulation.

In conclusion, no strong evidence exists regarding the use of LPV strategies in ABI patients. The traditional approach, namely that of combining intermediately sized Vt with low PEEP, is not contraindicated in patients with ABI and healthy lungs, while ABI patients with concurrent respiratory failure or ARDS can derive beneficial effects from LPV, which should therefore be taken into consideration in this population. Ventilatory targets and settings should be titrated individually under close neuromonitoring of brain physiology and lung mechanics, bearing in mind the old dictum, primum non nocere!

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Compliance with ethical standards

Ethical approval
An approval by an ethics committee was not applicable.

Conflicts of interest
Shirin Frisvold and Claude Guérin declare no conflicts of interest. Chiara Robba is a junior editor of *Intensive Care Medicine*.

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