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UNDERSTANDING THE DISEASE

Acute respiratory distress syndrome complicating traumatic brain injury. Can opposite strategies converge?

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Acute respiratory distress syndrome (ARDS) is a clinical-pathological condition associated with an increased morbidity and mortality [1], in part attributable to mechanical ventilation [1].

Different respiratory support strategies have been demonstrated to improve outcomes in ARDS patients [2], particularly when delivered in such a way to minimize lung stress and strain, and the consequent risk of ventilatory-induced lung injury (VILI) [1].

These 'lung protective strategies', which are increasingly becoming the standard of care in the intensive care unit (ICU) [2], include: low tidal volume (TV) and plateau pressure (Pplat) with permissive hypercapnia, prone positioning, and the application of levels of positive end-expiratory pressure (PEEP) appropriate to the severity of disease and to the proportion of atelectatic lung tissue (potential for lung recruitment) [2].

The use of these strategies and of neuromuscular blockers, lung recruitment maneuvers (RM), and venous–venous extracorporeal membrane oxygenation (VV-ECMO) have been proposed in severe ARDS from various etiologies [2], although their application in neurocritical care patients is still uncertain and presents important challenges [3].

Indeed, all the trials evaluating lung protective ventilatory strategies have excluded acute brain-injured patients, given the potential risk of worsening intracranial hypertension and cerebral perfusion pressure (CPP), resultant from the increase in intrathoracic pressures (e.g., high PEEP or RM) or from the vasodilatory effect on cerebral vasculature of permissive hypercapnia [4]. Consequently, patients with traumatic brain injury (TBI) have often been ventilated using very low or no PEEP, and high tidal volumes; while prone position, RM and extracorporeal devices have been rarely used [5].

The lack of an evidence-base in this population is particularly important as moderate or severe ARDS is common in TBI patients, with an incidence of ~ 14% [6], and the occurrence of ARDS in this population is associated with worse outcomes and longer ICU length of stay [7]. Furthermore, preliminary nonrandomized trials on small populations of patients with post-anoxic brain injury suggest that the use of protective ventilatory strategies might prevent ARDS and improve outcomes [8, 9].

Therefore, when ARDS occurs in patients with TBI, their ventilatory management can be challenging as the optimal ventilatory targets for the injured lung and the injured brain often diverge, and there is a paucity of clinical studies to offer guidance.

The most recent European Society of Intensive Care Medicine (ESICM) guidelines for the ventilatory management of acute brain injured patients [10], give a "*strong recommendation, but no evidence*" to the use of lung protective strategy for patients with concurrent ARDS and acute brain injury without a significant intracranial pressure (ICP) elevation.

However, there was no consensus on whether lung protective ventilation should be used in patients with ARDS and concurrent brain injury and clinically significant ICP elevation [10]. In addition, ventilatory targets suggested from ESICM Guidelines include a partial pressure of oxygen (PaO_2) of 80–120 mmHg, and partial pressure of carbon dioxide ($PaCO_2$) of 35–45 mmHg in first instance,

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$PaCO_2$ = 35–38 mmHg as tier 1, and 32–35 mmHg as tier 2 strategy. These targets maybe challenging in the presence of ARDS. There is, therefore, a need for a pragmatic approach to ventilation that can guide clinicians in the management of this complex group of patients.

The stepwise approach of TBI and ARDS management and their combination

In TBI patients, the primary aim of ICU management is to minimize the risk of secondary brain damage. In this context, management of raised ICP is paramount [11, 12]. Many ICP-lowering treatments have been proposed, and current clinical guidelines and algorithms suggest applying these strategies in a stepwise fashion, starting with less aggressive and safer treatments, and reserving the more aggressive ones for the refractory cases of intracranial hypertension [13]. The most recent Seattle consensus [13] established 18 interventions grouped in tier 1, 2 and 3. Basic (tier 0) treatment consists only in the maintenance of homeostasis (e.g., avoidance of fever, analgesia and sedation, intubation and mechanical ventilation targeting normoxia and normocapnia). If ICP increases, the use of Tier 1 strategies is suggested. These include the maintenance of CPP of 60–70 mmHg, deeper analgesia and sedation to lower ICP, osmotic therapy, targeted $PaCO_2$ to 35–38 mmHg, and anti-seizure prophylaxis. In patients with persistently increased ICP, Tier 2 treatments such as lower targets of $PaCO_2$ to 32–35 mmHg, neuromuscular blockade, and higher mean arterial pressure to increase CPP can be adopted. Finally, in case of refractory intracranial hypertension, the most aggressive and high risk of complications Tier 3 therapies (e.g., barbiturates, hypothermia, decompressive craniectomy) could be taken into consideration.

Similarly, ARDS management relies on a stepwise approach with more aggressive strategies reserved for patients with more severe and refractory conditions. A consensus of experts [14] provided fifteen recommendations, and a therapeutic algorithm for managing ARDS, recommending the use of low tidal volume, plateau pressure limitation, and PEEP > 5 cmH_2O as initial management. In case of persistent hypoxemia and according to the severity of ARDS, guidelines suggest trying higher values of PEEP and eventually neuromuscular blockade, prone position and other rescue therapies. Finally, in refractory cases, consideration should be given to VV-ECMO.

However, when managing TBI patients with ARDS, climbing one step of the ARDS treatment staircase can lead to worsening ICP, and vice versa.

If the TBI patient has no ARDS, physicians should follow the Seattle consensus [13], apply the different tiers for ICP treatment, and consider the basic respiratory targets and settings recommended by current guidelines [10], with TV 6–8 ml of predicted body weight, PEEP 5 cmH_2O, Pplat < 30 cmH_2O and respiratory rate of 16–22 breaths/minute. On the other hand, in patients with ARDS and TBI without intracranial hypertension and with stable ICP despite lung protective ventilation settings, the latter should be continued while strictly monitoring cerebrovascular function preferably using a multimodal neuromonitoring approach [15].

In case of worsened cerebral and/or respiratory condition, physicians should be ready to adapt the guidelines to clinical needs. Figure 1 presents a pragmatic approach to help clinicians in the decision-making in these situations.

In the case of mild ARDS, with a partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) between 200 and 300 mmHg, Tidal volumes can be adapted and increased provided driving pressure is < 14–15 cmH_2O, and/or respiratory rate can be adapted if hypercapnia is not controlled, according to the clinical picture. If ICP remains elevated (Tier 2 or 3), neuromuscular blockers can be considered. Similarly, if ICP remains unstable and protective ventilation targets cannot be achieved, or respiratory function deteriorates (PaO_2/FiO_2 = 100–200 mmHg), prone positioning should be trialed with close monitoring of ICP, or ECMO if ICP cannot be controlled. In addition to ventilatory settings and eventually prone positioning, decompressive craniectomy, barbiturates and hypothermia should be taken in consideration even in a stage of Tier 2 of the Seattle Guidelines if this can allow to more easily reach ventilatory targets and lung protective strategies settings.

In case of severe ARDS, with PaO_2/FiO_2 < 100 mmHg, more advanced treatment tiers for ARDS and TBI staircase should be discussed.

In this situation, VV-ECMO support to optimize arterial blood gases and minimize the intensity of mechanical ventilation could be used more frequently in patients at low risk of cerebral bleeding, while prone positioning can be tried at any tier, taking in account multimodal neuromonitoring and minimizing the risk of increased ICP.

Finally, fluid administration should be dictated by the clinical requirements, but generally aiming for conservative fluid balance. If cerebral perfusion pressure needs to be increased in patients with TBI, vasopressors should be considered, in the first instance to avoid fluid overload.

Despite the absence of strong evidence on the beneficial effects of lung protective strategies in TBI patients, we believe that recent studies and the results obtained in general ICU ARDS patients would justify the rationale on using these strategies even in this population, in particular if ICP is well controlled. However, if ICP is unstable, the best management strategy remains debated. In fact, in this case, ICP should be aggressively treated as

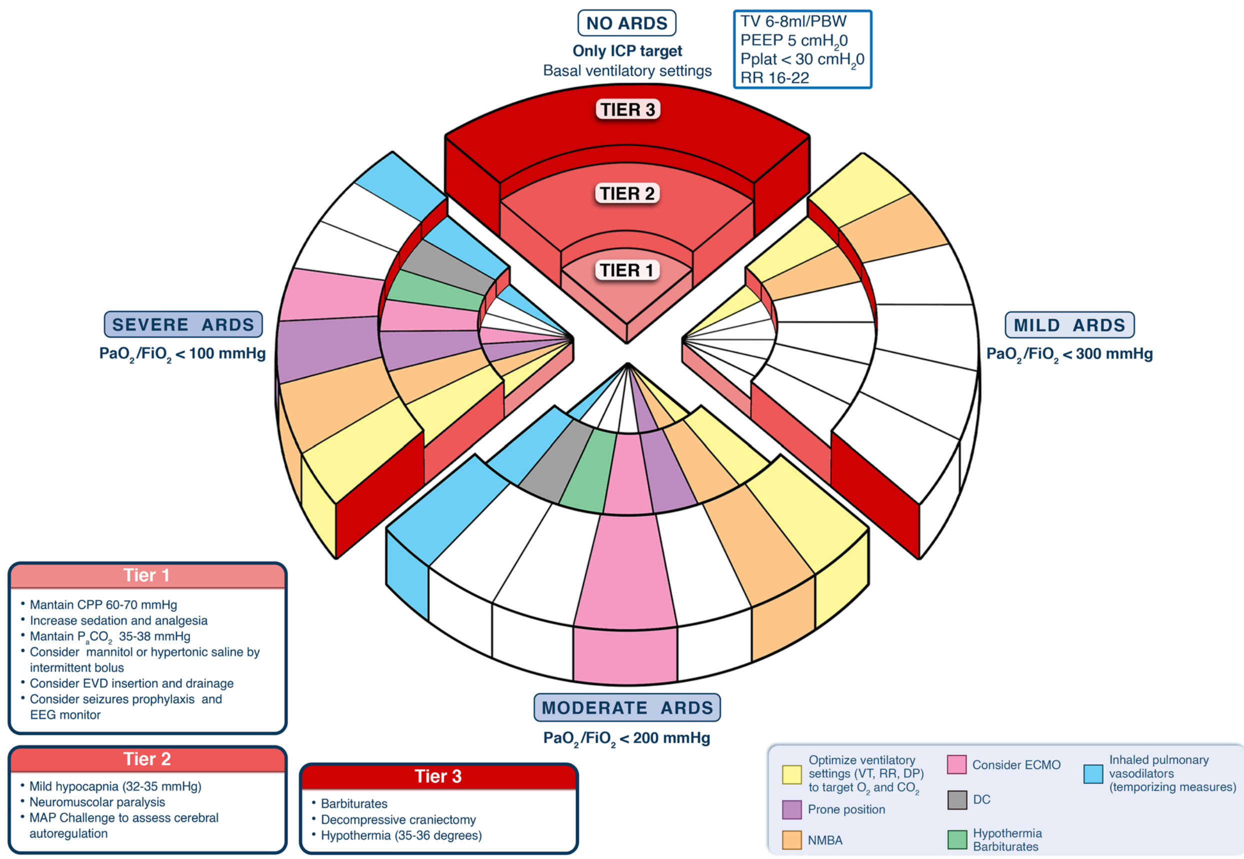

Fig. 1 Pragmatic approach for the management of concomitant acute respiratory distress syndrome (ARDS) and traumatic brain injury (TBI). The representation of the severity of brain injury and of the intracranial pressure (ICP) treatment is shown according to the therapy intensity level (tiers), according to the Seattle consensus [13], which defines the aggressiveness of clinical management to control ICP. The higher is the tier, the higher is the level of treatment required to maintain an ICP < 22 mmHg. Aggressive strategies used for ICP control (barbiturates, hypothermia, decompressive craniectomy) are highlighted in the picture only when used differently from the Seattle consensus (which allocates them to tier three). As first instance, when patients have no ARDS (partial pressure of oxygen, PaO_2, fraction of inspired oxygen, FiO_2 ratio > 300), basal ventilatory settings should be applied, including tidal volume 8 ml/predicted body weight (PBW), provided protective plateau pressure (Pplat) and low-moderate positive end expiratory pressure (PEEP). In this scenario, TBI patients should be managed following the 3 tiers of the Seattle consensus. Mild ARDS: in this scenario, clinicians should in first instance optimize the ventilatory settings, in particular increasing PEEP to improve oxygenation or increase tidal volume (taking in account protective plateau pressure and driving pressure, DP) and respiratory rate (RR) in order to achieve the partial pressure of carbon dioxide ($PaCO_2$) targets required in the different tiers for ICP control. If necessary, neuromuscular block agents (NMBA) can be used in this phase as suggested as Tier 2 strategy for ICP control. Hypothermia, barbiturates and decompressive craniectomy (DC) should be still taken in consideration in case of refractory intracranial hypertension. In case of moderate ARDS, in addition to previous strategies, neuromuscular block can be used even in Tier 1 stage to optimize ventilation. Prone positioning can be applied, especially if the patient is in Tier 1 and 2 stage of Seattle guidelines, but caution should be used in case of refractory intracranial hypertension (Tier 3). If these strategies do not allow to achieve acceptable oxygenation and $PaCO_2$, more aggressive treatments can be taken in consideration; for instance, extracorporeal membrane oxygenation (ECMO) can be discussed in case of severe intracranial hypertension (Tier 2 and 3) or, on the other hand, decompressive craniectomy, barbiturates and hypothermia can be anticipated already at the stage of Tier 2 treatment for ICP. Finally, inhaled pulmonary vasodilators can be taken in consideration regardless ICP as temporized measure. In case of severe ARDS, in addition to the above mentioned strategies, ECMO and prone positioning can be taken in account at any stage of Tier. Additional abbreviations: *CPP* cerebral perfusion pressure; *MAP* mean arterial pressure; *EVD* external ventricular drain; *CSF* cerebrospinal spinal fluid; *EEG* electroencephalography

intracranial hypertension is associated with worse outcomes[11], but at the same time strategies to minimize lung injury and VILI should be adopted.

Therefore, when TBI and ARDS coexist, physicians should be ready to skip some of the steps of the two staircase approaches suggested for these two pathologies separately, to achieve the best compromise between ICP control and lung protection and adequate gas exchange. Given the lack of high-level evidence on this topic, a pragmatic and multidisciplinary approach should guide the often-difficult decision-making.

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Data availability

There are no data in this manuscript.

Conflicts of interest

CR is speaker for Masimo e GE Healthcare. GC reports grants and personal fees as a Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics, all outside the submitted work. LC declares no competing interests.

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