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2020-12

Robba , C , Poole , D , McNett , M , Asehnoune , K , Boesel , J , Bruder , N , Chieregato , A , Cinotti , R , Duranteau , J , Einav , S , Ercole , A , Ferguson , N , Guerin , C , Siempos , I I , Kurtz , P , Juffermans , N P , Mancebo , J , Mascia , L , McCredie , V , Nin , N , Oddo , M , Pelosi , P , Rabinstein , A A , Neto , A S , Seder , D B , Skrifvars , M B , Suarez , J I , Taccone , F S , van der Jagt , M , Citerio , G & Stevens , R D 2020 , ' Mechanical ventilation in patients with acute brain injury : recommendations of the European Society of Intensive Care Medicine consensus ' , Intensive Care Medicine , vol. 46 , no. 12 , pp. 2397-2410 . https://doi.org/10.1007/s001

http://hdl.handle.net/10138/336202
https://doi.org/10.1007/s00134-020-06283-0

acceptedVersion

Intensive Care Med (2020) 46:2397–2410
https://doi.org/10.1007/s00134-020-06283-0

CONFERENCE REPORTS AND EXPERT PANEL

Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus

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Abstract

Purpose: To provide clinical practice recommendations and generate a research agenda on mechanical ventilation and respiratory support in patients with acute brain injury (ABI).

Methods: An international consensus panel was convened including 29 clinician-scientists in intensive care medicine with expertise in acute respiratory failure, neurointensive care, or both, and two non-voting methodologists. The panel was divided into seven subgroups, each addressing a predefined clinical practice domain relevant to patients admitted to the intensive care unit (ICU) with ABI, defined as acute traumatic brain or cerebrovascular injury. The panel conducted systematic searches and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was used to evaluate evidence and formulate questions. A modified Delphi process was implemented with four rounds of voting in which panellists were asked to respond to questions (rounds 1–3) and then recommendation statements (final round). Strong recommendation, weak recommendation, or no recommendation were defined when > 85%, 75–85%, and < 75% of panellists, respectively, agreed with a statement.

Results: The GRADE rating was low, very low, or absent across domains. The consensus produced 36 statements (19 strong recommendations, 6 weak recommendations, 11 no recommendation) regarding airway management, non-invasive respiratory support, strategies for mechanical ventilation, rescue interventions for respiratory failure, ventilator liberation, and tracheostomy in brain-injured patients. Several knowledge gaps were identified to inform future research efforts.

Conclusions: This consensus provides guidance for the care of patients admitted to the ICU with ABI. Evidence was generally insufficient or lacking, and research is needed to demonstrate the feasibility, safety, and efficacy of different management approaches.

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Springer

Keywords: Mechanical ventilation, Respiratory failure, ARDS, Traumatic brain injury, Acute stroke, Subarachnoid hemorrhage

Introduction

Patients with acute brain injury (ABI) admitted to the intensive care unit (ICU) frequently require mechanical ventilation or other forms of respiratory support [1–6]. These patients can experience respiratory failure due to loss of airway protective reflexes or decreased respiratory drive and are at risk for pulmonary complications such as pneumonia and acute respiratory distress syndrome (ARDS) [3–6]. Mechanical ventilation is used as a mechanism to ensure reliable oxygen delivery and modulate cerebral hemodynamics through control of arterial carbon dioxide tension [1–6]. At the same time, mechanical ventilation can exert harmful effects on the brain due to complex physiological interactions between intrathoracic, central venous and intracranial compartments [1–6]. Lung-protective ventilation, widely implemented in critically ill patients, may be withheld from brain-injured patients due to such concerns [1–7]. There is lack of clarity not only about strategies of ventilation but also regarding decisions on tracheal intubation, ventilator liberation, extubation, and tracheostomy in the ABI population [5–9]. Additionally, the safety and efficacy of advanced rescue therapies for severe respiratory failure such as prone positioning, alveolar recruitment maneuvers (ARMs), and extracorporeal membrane oxygenation (ECMO) are not established in this population [5].

To address these questions, we established a consensus panel with two primary tasks. First, to provide evidence-based recommendations on best clinical practices for mechanical ventilation in patients with ABI. And second, to identify knowledge gaps and suggest an agenda for research in this area. The panel addressed seven domains of clinical practice relevant to the target population: (1) indications for endotracheal intubation; (2) non-invasive interventions to ensure oxygenation and ventilation; (3) settings of mechanical ventilation; (4) targets for arterial blood gases; (5) rescue interventions in patients with concurrent ABI and severe respiratory failure; (6) criteria for ventilator liberation and tracheal extubation; and (7) criteria and timing for tracheostomy.

Methods

Panel selection and governance

A multidisciplinary international consensus panel was assembled with 29 intensivists who were selected for their established clinical and scientific expertise in neurointensive care and/or in acute respiratory failure and mechanical ventilation. Additional criteria for panel selection included representation from scientific societies and individuals with proven experience in consensus generation and guideline development. The consensus panel also included two non-voting methodologists who were invited to assist with literature data extraction, methodological rating, and who performed biostatistical tasks including meta-analysis and analysis of voting results.

The consensus was led by two chairpersons (RS, CR) who conceived of the project, established the aims, deliverables, milestones and timeline; engaged with European Society of Intensive Care (ESICM) leadership to obtain endorsement; organized and set the agenda for meetings; ensured communications with the panel; and drafted this report. Leaders in the Neurocritical Care Society participated in the drafting of this manuscript. The chairs worked closely within a six-member steering committee that included two methodologists (DP and MM) and two members of the panel (GC and KA). The consensus panel met by one teleconference and once in person, respectively, in July and in October 2019, the latter organized in conjunction with the ESICM LIVES Conference in Berlin, Germany. The steering committee met monthly by teleconference. The steering committee identified seven domains of clinical practice and generated a list of questions to be addressed by the panel (Table 1).

Consensus subgroups

The consensus panel was divided into seven subgroups, each tasked with one of the domains. Subgroups nominated a lead who served in a coordinating role, and subgroup communications were undertaken by email and teleconferences. Subgroup members refined the proposed question, generated the search strategy, performed the systematic search, and screened titles and abstracts based on predetermined inclusion and exclusion criteria.

Article selection, data extraction and reporting

Systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. A systematic search was performed by two experts in each subgroup, using MEDLINE, up to the dates indicated for each query in the Electronic Supplementary Material

Table 1 Domains addressed by the consensus and recommendations

Domain	Consensus recommendation	Level of recommendation	Level of evidence
1. What are the indications for endotracheal intubation in patients with ABI?	1. **We recommend** that in patients with ABI, the decision to proceed with endotracheal intubation should be guided by a combination of factors including the level of consciousness, severe agitation and combativeness, loss of airway protective reflexes, significant ICP elevation (strong recommendation; no evidence; good practice statement).	Strong recommendation	No evidence
	2. **We recommend** that endotracheal intubation should be considered in patients with ABI who are comatose (GCS $\leq$ 8)	Strong recommendation	No evidence
	3. **We recommend** that endotracheal intubation should be considered in patients with ABI when there is a loss of airway protective reflexes	Strong recommendation	No evidence
	4. **We recommend** that endotracheal intubation should be considered in patients with ABI who have significant elevation in intracranial pressure	Strong recommendation	No evidence
	5. **We recommend** that endotracheal intubation should be considered in patients with ABI who have clinical evidence of brain herniation	Strong recommendation	No evidence
	6. **We recommend** that endotracheal intubation should be considered in patients with ABI who have non-neurological indications for intubation	Strong recommendation	No evidence
	7. **We suggest** that endotracheal intubation should be considered in patients with ABI who have severe agitation and combativeness	Weak recommendation	No evidence
2. Is it safe and effective to use non-invasive respiratory support (e.g., high-flow nasal canula, NIPPV) in patients with ABI?	8. **We are unable to provide a recommendation** on the use of noninvasive positive pressure ventilation in patients with ABI who have hypercapnic or mixed hypercapnic/hypoxemic respiratory insufficiency	No recommendation	Low evidence in favor
	9. **We suggest** that high-flow nasal cannula oxygen therapy may be considered in patients with ABI who have hypoxemic respiratory failure that is refractory to conventional supplemental oxygen, provided there are no contraindications	Weak recommendation	No evidence
3. Should we use specific mechanical ventilation settings (e.g., tidal volume/PBW; PEEP; FiO_2) and target specific respiratory physiologic parameters (e.g., Pplat) in patients with ABI?	10. **We recommend** that in mechanically ventilated patients with ABI who do not have clinically significant ICP elevation, the same level of PEEP should be used as in patients without brain injury	Strong recommendation	Very low evidence in favor
	11. **We recommend** that in mechanically ventilated patients with ABI who have clinically significant ICP elevation that is PEEP-insensitive, the same level of PEEP should be used as in patients without ABI	Strong recommendation	No evidence
	12. **We recommend** that in mechanically ventilated patients with concurrent ABI and ARDS who do not have clinically significant ICP elevation, a strategy of lung protective mechanical ventilation should be used	Strong recommendation	No evidence

Table 1 (continued)

Domain	Consensus recommendation	Level of recommendation	Level of evidence
	13. **We suggest** that in mechanically ventilated patients with ABI without clinically significant ICP elevation, a strategy of lung protective mechanical ventilation should be considered	Weak recommendation	No evidence
	14. **We are unable to provide a recommendation** regarding lung protective mechanical ventilation in mechanically ventilated patients with ABI who have clinically significant ICP elevation	No recommendation	No evidence
	15. **We are unable to provide a recommendation** regarding lung protective mechanical ventilation in mechanically ventilated patients who have concurrent ABI, ARDS, and clinically significant ICP elevation	No recommendation	No evidence
4. Should we target specific values of pH, PaO_2 and $PaCO_2$ in patients with ABI?	16. **We recommend** that the optimal target range of PaO2 in patients with ABI who do not have clinically significant ICP elevation is 80–120 mmHg	Strong recommendation	Contradictory low-quality evidence
	17. **We recommend** that the optimal target range of PaO2 in patients with ABI who have clinically significant ICP elevation is 80–120 mmHg	Strong recommendation	No evidence
	18. **We recommend** that the optimal target range of PaCO2 in patients with ABI who do not have clinically significant ICP elevation is 35–45 mmHg	Strong recommendation	Low-quality evidence
	19. **We recommend** hyperventilation as a therapeutic option in patients with ABI who have brain herniation	No recommendation	No evidence
	20. **We are unable to provide a recommendation** regarding the use of hyperventilation as a therapeutic option in patients with ABI who have clinically significant ICP elevation	Weak recommendation	No evidence
5. Is it safe and effective to use rescue interventions (e.g., neuromuscular blockade, prone positioning, extracorporeal membrane oxygenation) to support respiratory failure in patients with ABI?	21. **We are unable to provide a recommendation** regarding the use of alveolar recruitment maneuvers in mechanically ventilated patients who have concurrent ARDS and ABI who do not have significant ICP elevation	No recommendation	Very low evidence in favor
	22. **We are unable to provide any recommendations** regarding the use of alveolar recruitment maneuvers in mechanically ventilated patients who have concurrent ARDS and ABI who have significant ICP elevation	No recommendation	Very low evidence in favor
	23. **We recommend** that prone positioning may be considered in mechanically ventilated patients who have concurrent ARDS and ABI, but do not have significant ICP elevation	Strong recommendation	Very low evidence in favor
	24. **We are unable to provide any recommendations** regarding the use of prone positioning in mechanically ventilated patients who have concurrent ARDS, ABI and significant ICP elevation	No recommendation	No evidence

Table 1 (continued)

Domain	Consensus recommendation	Level of recommendation	Level of evidence
	25. **We recommend** that short-term treatment with a neuromuscular blocker, in combination with appropriate sedation, may be considered in mechanically ventilated patients who have concurrent ABI and severe ARDS	Strong recommendation	No evidence
	26. **We are unable to provide any recommendations** regarding the use of ECMO in mechanically ventilated patients who have concurrent ARDS and ABI	No recommendation	Very low evidence in favor
	27. **We are unable to provide any recommendations** regarding the use of $ECCO_2R$ in mechanically ventilated patients who have concurrent ARDS and ABI	No recommendation	No evidence
6. What are the criteria for ventilator weaning in patients with brain injury? What are the criteria for extubation in patients with brain injury?	28. **We recommend** that the decision to extubate patients with ABI should be guided by several factors including the expected clinical trajectory of the underlying neurological condition, the level of consciousness, the presence of airway protective reflexes, and factors relevant to the extubation of non-neurological patients	Strong recommendation	Moderate evidence in favor
	29. **We recommend** that the neurological status should be accounted for in making the decision to wean mechanical ventilation in patients with ABI	Strong recommendation	No evidence
	30. **We recommend** that the decision to extubate patients with ABI should account for the expected clinical trajectory of the underlying neurological condition	Strong recommendation	No evidence
	31. **We suggest** that the decision to extubate patients with ABI should account for the level of consciousness	Weak recommendation	No evidence
	32. **We recommend** that the decision to extubate patients with ABI should account for airway protective reflexes (cough, gag, swallowing)	Strong recommendation	No evidence
	33. **We are unable to provide any recommendations** regarding a specific GCS threshold to be considered in the decision to extubate mechanically ventilated acute brain-injured patients.	No recommendation	No evidence
7. What are the indications for tracheostomy in patients with ABI? What is the optimal timing of tracheostomy in in patients with ABI?	34. **We recommend** that tracheostomy should be considered in mechanically ventilated patients with ABI who have failed one or several trials of extubation	Strong recommendation	No evidence
	35. **We recommend** that tracheostomy should be considered in mechanically ventilated patients with ABI who have persistently reduced level of consciousness	Weak recommendation	Contradictory low-quality evidence
	36. **We are unable to provide a recommendation** regarding the optimal timing of tracheostomy in patients with ABI	No recommendation	Contradictory low-quality evidence

ABI acute brain injury, *ARDS* acute respiratory distress syndrome, *ECCO2R* extracorporeal carbon dioxide removal, *ECMO* extracorporeal membrane oxygenation, *ICP* intracranial pressure, *GCS* Glasgow Coma Scale, *LPV* lung protective ventilation, *NMB* neuromuscular blocker, PaO_2 partial pressure of oxygen, $PaCO_2$ partial pressure of carbon dioxide, *PEEP* positive end expiratory pressure

(ESM). The search codes for each subgroup are presented in the ESM. The search was set by including only original studies published in English in peer-review journals. Additionally, reference lists of the pre-screened studies were manually checked, using an iterative approach. Disagreements were discussed with the panel methodologists (DP, MM).

Studies were eligible for inclusion if they reported on adult patients with ABI, defined as an acute cerebral disorder consequent to trauma or to a cerebrovascular event (specifically subarachnoid hemorrhage, intracranial hemorrhage, or acute ischemic stroke). Studies on mechanical ventilation in other critically ill neurological populations (e.g., brain tumor, status epilepticus, anoxic–ischemic brain injury) were excluded. Significant intracranial pressure elevation was defined as > 20 mmHg when invasive monitoring was available, or as clinical or radiological signs of intracranial hypertension [10].

Articles were included in the analysis if they met the following criteria: studies of adults (> 18 years) admitted to the ICU with ABI, defined as above; clearly defined intervention and control groups; reported data on relevant outcome measures, such as clinical endpoints (survival, neurological or cognitive function, functional status) and/or physiological endpoints (intracranial pressure, cerebral oxygenation, cerebral blood flow, cerebral perfusion pressure, measures of lung function). Data from articles selected for full-text analysis were extracted using a standardized electronic form structured according to the population, intervention, comparison, and outcomes (PICO) model. Categorical variables were presented as event rates in treatment arms and controls, and absolute risks, absolute risk reductions, and relative risks computed. Continuous variables were reported as means or medians, standard deviation (SD) or interquartile ranges (IQR). Absolute and relative risks from randomized controlled trials (RCTs) were represented in Forest plots. Reporting on evidence rating, consensus methodology, statistical analysis and generation of the research agenda are in the ESM. Statements were classified as a strong recommendation, weak recommendation, and no recommendation when, respectively, > 85%, 75–85% and < 75% of votes were in favor.

Results

Results of the literature search, article selection, systematic review, GRADE rating and meta-analyses (when possible) for each domain are presented in the ESM. Overall, evidence was of low quality or lacking in nearly all domains and questions studied. The panel generated a total of 36 statements which are described hereafter, grouped according to the preestablished clinical practice domain (Table 1). Based on pre-established voting thresholds (ESM), 19 statements were strong recommendations, 6 were weak recommendations, and 11 were no recommendations. Ten of the 36 statements were based on some level of scientific evidence, while the remaining 26 were expert-determined (Table 1).

1. What are the indications for endotracheal intubation in patients with ABI?

Rationale

Despite the lack of scientific evidence, clinical experience in brain-injured patients and in critically ill patients helped the panel define a composite of factors that should inform the decision to intubate brain-injured patients. There was consensus regarding specific neurological factors as well as general factors such as acute respiratory or circulatory failure.

Recommendations

- We recommend that in patients with ABI, the decision to proceed with endotracheal intubation should be guided by a combination of factors including the level of consciousness, severe agitation and combativeness, loss of airway protective reflexes, significant ICP elevation (strong recommendation; no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who are comatose (Glasgow Coma Scale [GCS] ≤ 8) (strong recommendation; no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI when there is a loss of airway protective reflexes (strong recommendation, no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who have a significant elevation in intracranial pressure (strong recommendation, no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who have clinical evidence of brain herniation (strong recommendation, no evidence; good practice statement).
- We recommend that endotracheal intubation should be considered in patients with ABI who have non-neurological indications for intubation (strong recommendation, no evidence; good practice statement).

- We suggest that endotracheal intubation should be considered in patients with ABI who have severe agitation and combativeness (weak recommendation, no evidence).

2. Is it safe and effective to use non-invasive respiratory support in patients with ABI?

Rationale

The panel noted that the quality of evidence was very low and did not reach consensus on the use of non-invasive ventilation in acute brain-injured patients with TBI. Based on clinical experience and data in other populations, the following was stated:

Recommendations

- We are unable to provide a recommendation on the use of non-invasive positive pressure ventilation in patients with ABI who have hypercapnic or mixed hypercapnic/hypoxemic respiratory insufficiency (no recommendation, low evidence in favor).
-
- We suggest that high-flow nasal cannula oxygen therapy may be considered in patients with ABI who have hypoxemic respiratory failure that is refractory to conventional supplemental oxygen (weak recommendation, no evidence).

3. Should we use specific mechanical ventilation settings in patients with ABI?

Rationale

The aim in this domain was to determine if specific ventilator settings [e.g., tidal volume, positive end expiratory pressure (PEEP)] would be beneficial in patients with ABI. An extensive review of the literature (ESM) revealed only marginal evidence for a specific strategy.

Recommendations

- We recommend that in mechanically ventilated patients with ABI without ARDS who do not have clinically significant ICP elevation, the same level of PEEP should be used as in patients without brain injury (strong recommendation, very low evidence in favor).
- We recommend that in mechanically ventilated patients with ABI without ARDS who have clinically significant ICP elevation that is PEEP-insensitive (patients who do not experience ICP elevation after increase of PEEP), the same level of PEEP should be used as in patients without ABI (strong recommendation, no evidence; good practice statement).
- We recommend that in mechanically ventilated patients with concurrent ABI and ARDS who do not have clinically significant intracranial pressure (ICP) elevation, a strategy of lung protective mechanical ventilation should be used (strong recommendation, no evidence, good practice statement).
- We suggest that in mechanically ventilated patients with ABI without ARDS without clinically significant ICP elevation, a strategy of lung protective mechanical ventilation should be considered (weak recommendation, no evidence).
- We are unable to provide a recommendation regarding lung protective mechanical ventilation in mechanically ventilated patients with ABI without ARDS who have clinically significant ICP elevation (no recommendation, no evidence).
- We are unable to provide a recommendation regarding lung protective mechanical ventilation in mechanically ventilated patients who have concurrent ABI, ARDS, and clinically significant ICP elevation (no recommendation, no evidence).

4. Should we target specific values of partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$) in patients with ABI?

Oxygen levels

Rationale

The panel concluded that there are enough data to suggest that both hypoxemia and hyperoxia should be avoided in ABI patients as both may have an unfavorable impact on clinical outcomes. Although specific targets for PaO2 would optimally need to be individualized on the basis of disease-, context- and patient-specific features, the panel agreed on a general recommendation of normoxia.

Recommendations

- We recommend that the optimal target range of PaO_2 in patients with ABI who do not have clinically significant ICP elevation is 80–120 mmHg (strong recommendation, low-quality evidence).
- We recommend that the optimal target range of PaO_2 in patients with ABI who have clinically sig-

nificant ICP elevation is 80–120 mmHg (strong recommendation, no evidence; good practice statement).

$PaCO_2$ and short-term hyperventilation

Rationale

The panel considered at some length the question of $PaCO_2$ targets in ABI, including existing guidelines which recommend short-term mild hyperventilation in the management of TBI patients who have increased intracranial pressure [29]. Despite the overall low level of evidence on this topic, there was agreement to recommend targeting a normal range of $PaCO_2$ values in the absence of increased ICP and hyperventilation as a therapeutic option in patients with brain herniation. Conversely, panel members expressed differing views regarding hyperventilation as a therapeutic option in patients who have clinically significant ICP elevation, and a consensus was not obtained regarding this question.

Recommendations

- We recommend that the optimal target range of $PaCO_2$ in patients with ABI who do not have clinically significant ICP elevation is 35–45 mmHg (strong recommendation, low-quality evidence).
- We recommend short-term hyperventilation as a therapeutic option in patients with ABI who have brain herniation (weak recommendation, no evidence).
- We are unable to provide a recommendation regarding the use of short-term hyperventilation as a therapeutic option in patients with ABI who have clinically significant ICP elevation (no recommendation, no evidence).

5. Is it safe and effective to use rescue interventions to support severe respiratory failure in patients with ABI?

Alveolar recruitment maneuvers

Rationale

The panel felt that the issue was insufficiently investigated, and attention should be paid to achieving a balance between expected improvements in oxygenation and potentially detrimental effects on ICP and CPP.

Recommendations

- We are unable to provide a recommendation regarding the use of alveolar recruitment maneuvers in mechanically ventilated patients who have concurrent ARDS and ABI who do not have significant ICP elevation (no recommendation, very low evidence in favor).
- We are unable to provide any recommendations regarding the use of alveolar recruitment maneuvers in mechanically ventilated patients who have concurrent ARDS and ABI who have significant ICP elevation (no recommendation, very low evidence in favor).

Prone positioning

Rationale

Despite the low level of evidence, the panel recommended prone positioning when ICP is not increased, given the favorable effect on ARDS outcome and the potentially beneficial increases in brain oxygenation. However, questions remain regarding significant ICP elevation since prone position could mediate detrimental effects on intracranial physiology.

Recommendation

- We recommend that prone positioning may be considered in mechanically ventilated patients who have concurrent moderate or severe ARDS (PaO_2/FiO_2 ratio < 150) and ABI, but do not have significant ICP elevation (strong recommendation, very low evidence in favor).
- We are unable to provide any recommendations regarding the use of prone positioning in mechanically ventilated patients who have concurrent moderate or severe ARDS ($PaO_2/FiO_2 < 150$), ABI and significant ICP elevation (no recommendation, no evidence).

Neuromuscular blockers

Rationale

The panel found no studies on the use of neuromuscular blockers as a rescue therapy for patients with concurrent ABI and ARDS. However, based on evidence suggesting beneficial effects in severe ARDS [11–13], the panel ruled in favor of short-term use of neuromuscular blocker infusions.

Recommendation

We recommend that short-term treatment with a neuromuscular blocker, in combination with appropriate sedation, may be considered in mechanically ventilated patients who have concurrent ABI and severe ARDS (strong recommendation, no evidence; good practice statement).

Extracorporeal life support

Rationale

Experience with ECMO and extracorporeal CO_2 removal ($ECCO_2R$) in ABI with severe respiratory failure patients is limited due to serious concerns regarding the safety of these techniques in patients with, or at risk of, intracranial hemorrhage and cerebral ischemia following ABI. Small case series and case reports were identified evaluating ECMO in patients with both ABI and ARDS, none which reported serious neurological complications [ESM—Group NV5]. However, after discussion, the panel did not reach a consensus on the use of these techniques.

Recommendations

- We are unable to provide a recommendation regarding the use of ECMO in mechanically ventilated patients who have concurrent ARDS and ABI (no recommendation, very low evidence in favor).
- We are unable to provide a recommendation regarding the use of $ECCO_2R$ in mechanically ventilated patients who have concurrent ARDS and ABI (no recommendation, no evidence).

6. What are the criteria for ventilator weaning and extubation in patients with ABI?

Rationale

The panel identified variables that should be considered in the decision to wean and extubate this subpopulation including neurological and non-neurological features. A consensus was not reached regarding a specific GCS threshold to guide the decision to extubate.

Recommendations

- We recommend that the decision to extubate patients with ABI should be guided by several factors including the expected clinical trajectory of the underlying neurological condition, the level of consciousness, the presence of airway protective reflexes, and factors relevant to the extubation of non-neurological patients (strong recommendation, moderate evidence in favor).
- We recommend that the neurological status should be accounted for in making the decision to wean mechanical ventilation in patients with ABI (strong recommendation, no evidence; good practice statement).
- We recommend that the decision to extubate patients with ABI should account for the expected clinical trajectory of the underlying neurological condition (strong recommendation, no evidence; good practice statement).
- We suggest that the decision to extubate patients with ABI should account for the level of consciousness (weak recommendation, no evidence).
- We recommend that the decision to extubate patients with ABI should account for airway protective reflexes (cough, gag, swallowing) (strong recommendation, no evidence; good practice statement).
- We are unable to provide any recommendations regarding a specific GCS threshold to be considered in the decision to extubate mechanically ventilated acute brain-injured patients (no recommendation, no evidence).

7. What are the indications for and optimal timing of tracheostomy in patients with ABI?

Indications for tracheostomy

Rationale

Despite the lack of high-quality evidence, based on clinical experience and on the literature from the general ICU population, the panel determined that a major determinant in the decision to perform tracheostomy should be one or more failed attempts of extubation trials and persistently depressed responsiveness.

Recommendations

- We recommend that tracheostomy should be considered in mechanically ventilated patients with ABI who have failed one or several trials of extubation (strong recommendation, no evidence; good practice statement).
- We suggest that tracheostomy should be considered in mechanically ventilated patients with ABI who have persistently reduced level of consciousness (weak recommendation, contradictory low-level evidence).

Timing of tracheostomy

Rationale

The panel noted that the decision regarding timing of tracheostomy varies considerably across countries and medical institutions and may depend considerably on local practices and policies. Therefore, the panel did not reach a consensus.

Recommendation

We are unable to provide a recommendation regarding the optimal timing of tracheostomy in patients with ABI (no recommendation, contradictory low-quality evidence).

Discussion

The recommendations contained in this document are intended as guidance to clinicians managing patients admitted to the ICU with ABI. These recommendations were generated via a rigorous methodology that included a comprehensive systematic review and grading of available evidence, the engagement of a multidisciplinary, international expert panel, and the iterative refinement of consensus statements using the modified Delphi method. The principal limitation encountered was the paucity or lack of robust scientific evidence on many of the clinical questions posed, which means that several of the recommendations are based on the collective expert opinions of the panel [14–19]. As a corollary of this limitation, several knowledge gaps were identified, which have helped to establish an agenda for research (Table 2).

The decision to intubate a patient with isolated ABI in the absence of intrinsic respiratory failure is very common in emergency and intensive care medicine, yet scientific evidence is lacking to support specific approaches. Intubation is lifesaving in severe ABI patients and not beneficial in milder forms of ABI, yet the role of intubation in intermediate severity ABI remains unclear [18]. Intubation commits patients to a course of mechanical ventilation and sedation, which significantly curtails the ability to clinically assess neurological function at the bedside. Studies are needed to explore strategies (including timing) regarding endotracheal intubation in the ABI population. These studies should be stratified according to ABI etiology (TBI, SAH, ICH, AIS) and consider the relative importance of clinical factors such as neurological severity (e.g., GCS), presence of airway protective reflexes, agitation or combativeness, ICP elevation, predicted clinical trajectory (e.g., likelihood and time-course of neurological worsening, the need for surgery or interventional management), and non-neurological injury or organ failure.

Invasive ventilation is used in patients with severe ABI to counter dysregulated breathing patterns and to maintain PaO_2 and $PaCO_2$ within physiological ranges [19]. This enables effective and reliable oxygen delivery to the brain and provides a mechanism to indirectly control cerebral perfusion via adjustment of minute ventilation and $PaCO_2$. Yet, these principles, well-established in neurointensive care, seem at variance with lung protective strategies which aim to reduce ventilator-induced lung injury (VILI) via settings in which relative hypercapnia and hypoxemia may be permitted. Lung protective ventilation has been associated with significantly higher survival in clinical trials of patients with ARDS [20–24] and with improved outcomes in mechanically ventilated ICU and surgical populations who do not have ARDS [25, 26]. Although patients with ABI have consistently been excluded from these trials, the Consensus recommended that patients with ABI who do not have ICP elevation should receive lung protective ventilation and PEEP as other mechanically ventilated patients would. Clinical trials are needed to determine the safety and efficacy of different lung protective ventilation strategies in ABI patients, both with and without ARDS. These trials should be stratified by ABI etiology and neurological severity and consider a range of different endpoints both proximal (neurophysiological impact, biomarkers of VILI) and more distal (mortality, neurological outcome, duration of mechanical ventilation and stay in the hospital).

Regarding arterial blood gases, the consensus recommended avoidance of hyperoxia and hypoxia, both associated with poor outcome after ABI. The panel recommended maintaining PaO_2 80–120 mmHg, higher compared to the range commonly targeted in the general ICU population (55–80 mmHg)[27]. Overall, research is warranted to identify optimal PaO_2 targets in this population. One approach will be to leverage large-scale multisite observational studies using multivariable modeling, to precisely determine associations between specific PaO_2 thresholds or target ranges and clinically significant outcomes in stratified ABI populations.

The panel recommended normocapnia in ABI patients without ICP elevation. It also recommended short-term hyperventilation in patients with cerebral herniation. However, there was a lack of agreement on the use of short-term mild hyperventilation ($PaCO_2$ target 30–35 mmHg) to treat elevations in ICP. Although it is part of the staircase approach for the management of ICP, hyperventilation causes cerebral vasoconstriction and has been associated with poor outcome in the Lung Safe cohort [28], perhaps due to an increase in mechanical

Table 2 Proposed scientific agenda on mechanical ventilation and respiratory support in ABI

Clinical context	Knowledge gaps	Study design considerations	Endpoints of interest
ABI	Clinical indications for intubation	Pragmatic trials comparing different strategies/algorithms (including timing) regarding intubation in ABI patients stratified by etiology and severity	Mortality, neurological outcome Duration of MV Length of stay in ICU and hospital
	Optimal PaO2 and PaCO2 levels	Adequately powered observational data Pragmatic trials comparing different PaO_2 and $PaCO_2$ targets in selected ABI patients/settings Use of prognostic enrichment strategies	Physiological effects Mortality, neurological outcome
	Role of lung protective ventilation	Explanatory and pragmatic trials comparing LPV with conventional ventilation, or different intensities of LPV, in in ABI patients stratified by etiology and severity	Physiological effects Markers of VILI Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital
	Ventilator liberation	Statistical models exploring factors independently associated with successful extubation Explanatory and pragmatic trials comparing different strategies for ventilator liberation in selected ABI patients/settings	Tracheostomy Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital
	Clinical indications for tracheostomy	Explanatory and pragmatic trials comparing tracheostomy vs extubation strategies in selected ABI patients/settings Use of predictive enrichment strategies to optimize patient selection	Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital
	Timing of tracheostomy	Explanatory and pragmatic trials comparing tracheostomy at different time-points in selected ABI patients/settings	Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital
ABI and ICP elevation	Role of short-term hyperventilation	Analysis of high-resolution physiological time series data Pragmatic trials evaluating hyperventilation strategies/durations for the management of clinically significant ICP elevation	Safety Efficacy in reducing ICP Mortality, neurological outcome
ABI and acute respiratory failure	Role of non-invasive ventilation	Analysis of observational data Pragmatic trials comparing non-invasive ventilation with invasive ventilation in selected ABI patients/settings stratified by etiology and severity Use of predictive enrichment strategies to optimize patient selection	Safety (e.g., risk of aspiration) Physiological effects Conversion to invasive ventilation Mortality, neurological outcome Length of stay in ICU and hospital Sedative use in ICU Barriers to clinical neurological assessment in ICU
	Role of high-flow oxygen therapy	Analysis of observational data Pragmatic trials comparing high-flow oxygen therapy with other invasive ventilation in selected ABI patients/settings Use of predictive enrichment strategies to optimize patient selection	Safety (e.g., risk of aspiration) Physiological effects Conversion to invasive ventilation Mortality, neurological outcome Length of stay in ICU and hospital Sedative use in ICU Barriers to clinical neurological assessment in ICU
ABI and ARDS	Role of lung protective ventilation	Explanatory and pragmatic trials comparing LPV with conventional ventilation, or different intensities of LPV, in in ABI patients stratified by etiology and severity	Physiological effects Sedative use in ICU Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital

Table 2 (continued)

Clinical context	Knowledge gaps	Study design considerations	Endpoints of interest
	Role of neuromuscular blocker therapy	Analysis of observational data Explanatory and pragmatic trials evaluating NMB therapy in selected patients with concurrent ABI and severe ARDS	Physiological effects Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital Barriers to clinical neurological assessment in ICU
	Role of prone positioning	Analysis of observational data Pragmatic trials evaluating prone positioning in selected patients with concurrent ABI and severe ARDS Use of predictive enrichment strategies to optimize patient selection	Safety Physiological effects Mortality, neurological outcome Duration of mechanical ventilation Length of stay in ICU and hospital Sedative use in ICU Barriers to clinical neurological assessment in ICU
	Role of ECMO	Analysis of observational data Pragmatic trials evaluating management with and without ECMO in selected patients with concurrent ABI and severe ARDS Use of predictive enrichment strategies to optimize patient selection	Safety Neurological complications (e.g., intracranial hemorrhage) Physiological effects Mortality, neurological outcome Length of stay in ICU and hospital

ICP intracranial pressure, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *ECCO2R* extracorporeal carbon dioxide removal, *VILI* ventilator-induced lung injury, *LPV* lung protective ventilation, *NMB* neuromuscular blocker

power [29]. While early studies have explored this issue [30], contemporary trials are needed to investigate the effect of short courses of hyperventilation, in conjunction with other measures, on physiological endpoints and clinical outcomes in patients who have intracranial hypertension.

Little is known about how ventilator liberation should be accomplished in the setting of ABI [31]. Available evidence and clinical experience suggest that decisions on ventilator weaning and tracheal extubation must integrate neurological features with other systemic variables, and this is the approach recommended by the panel. Mechanical ventilation may be prolonged unnecessarily, or tracheostomy performed prematurely, in a subset of patients who could have been successfully extubated. Studies are needed to investigate more precise approaches for ventilator weaning and extubation in the target population. Multivariable models should be tested and validated to individualize management based on patient-specific clinical and physiological features. Clinical trials should evaluate the effectiveness and efficacy of different liberation strategies. These trials could be designed to integrate tracheostomy either as a treatment arm or as an outcome variable.

Timely tracheotomy represents a means of effectively weaning sedation and discontinuing mechanical ventilation in patients who require an artificial airway but are otherwise able to breathe independently. Yet studies indicate that the selection of ABI patients for tracheostomy is highly variable, often dependent on regional or institutional factors [31, 32]. Our panel recommended consideration of this procedure in mechanically ventilated ABI patients who are persistently unconscious (but with an expected acceptable quality of life) or when one or several trials of extubation have failed; however, there was no consensus on the optimal timing of tracheostomy. Carefully designed studies would be needed to validate tracheostomy decision algorithms for patients with ABI, and to determine the optimal timing of this procedure based on patient-specific factors. Trials should consider stratification by ABI etiology, severity and predicted natural history.

The management of patients with concurrent ABI and acute respiratory failure is a specific scenario which merits further discussion. In the general ICU population, there is extensive evidence supporting non-invasive strategies, such as BiPAP and high-flow nasal canula oxygen, for patients who have acute respiratory failure and an underlying cause that can be effectively treated in a relatively short time frame [33]. Randomized trials in carefully selected respiratory failure patients show that when compared to invasive ventilation, non-invasive techniques can significantly improve outcomes including survival [34]. Importantly, preserved consciousness and airway protective reflexes are generally viewed as prerequisites for the successful use of these methods. The consensus panel found very limited evidence on the use of non-invasive respiratory support in patients who have acute respiratory failure in the setting of ABI; however, it did recommend consideration of high-flow

oxygen therapy in selected patients with hypoxemia. These results are likely a reflection of clinical observations among members of the panel that high-flow nasal cannula oxygen therapy might be beneficial and is associated with a low risk of adverse effects. Studies are needed to determine the indications, safety, and efficacy of non-invasive strategies in selected ABI patients.

One additional clinical scenario which needs special consideration is that of patients who have ARDS in the setting of neurological injury. It has been reported that up to one-third of mechanically ventilated patients with ABI can develop ARDS [5]. Several interventions have been validated as effective rescue therapies to increase survivability in patients with ARDS refractory hypoxemia [5, 22]. These interventions, which include alveolar recruitment maneuvers, prone positioning, neuromuscular blocking agents, and ECMO, are increasingly used as part of a stepwise algorithm for patients in the severe ARDS stratum; however, their feasibility and safety in ABI patients with ARDS are undetermined. A significant subset of ABI patients have concurrent spinal injuries and prone positioning might be unsafe in this group. ECMO generally requires systemic anticoagulation which could have catastrophic consequences in patients with recent ABI [35, 36]. The consensus panel recommended consideration of prone positioning and neuromuscular blocking drug infusions, but it was unable to provide a recommendation on the use of alveolar recruitment or ECMO. Studies are needed to guide clinicians in selecting patients with concurrent ABI and ARDS who are most likely to benefit, and least likely to be harmed, by these therapies.

In summary, this consensus statement proposes guidance for clinicians on mechanical ventilation and respiratory support in critically ill ABI patients. As with all guidelines, the recommendations provided here must be implemented in a treatment plan that is individualized and considers not only physiological parameters but also patient co-morbidities and clinical trajectory. The panel found deficiencies in the scientific evidence across the domains studied, underscoring an urgent need for innovative and high-quality research to improve the care and outcomes in this population. Well-designed randomized controlled trials are needed to explore the role of different ventilator strategies and physiologic targets in this specific population. A promising direction is the possibility of personalizing therapy based on patient-specific clinical and physiological features, for example, data from multimodal neuromonitoring techniques.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-06283-0) contains supplementary material, which is available to authorized users.

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RS, CR: conception of the work, supervision of the consensus development, participation in literature review and interpretation, drafting the article, critical revision of the article, final approval of the version to be published. GC, KA, DP, MM: participation in the supervision of the consensus development, participation in literature review and interpretation, drafting and critical revisions of the manuscript, final approval of the version to be published. DP, MM: assisted with literature data extraction, methodological rating, and biostatistical tasks including meta-analysis and analysis of voting results. All authors: participation in literature review and appraisal, online consensus statement voting, critical review of the manuscript and approval of the final version of the manuscript.

Funding

None.

Compliance with ethical standards

Conflicts of interest
GC is Editor in Chief of ICM. MS received speaker fee and travel grant from BARD Medical (Ireland) and a research grant from GE Healthcare. JB received Speaker honoraria and travel support from Boehringer Ingelheim, Medtronic, Zoll, Sedana Medical. DS is PI of the SETPOINT2 trial on early tracheostomy in ventilated cerebrovascular ICU patients and participant in a PCORI Award for SETPOINT2. SE has support from Zoll, Siemens and Medtronic, research funding from Oridion, Diasorin, Haemonetics, participation in multicenter trials for Artisanpharma, Ely Lily, Takeda, Astra Zeneca, Eisai. The other authors have no COI to declare.

Endorsement
This project is endorsed by the Executive Committee of the European Society of Intensive Care Medicine. The content of the manuscript is affirmed by the Board of Directors of the Neurocritical Care Society for its educational value.

Publisher's Note

Received: 13 September 2020 Accepted: 5 October 2020
Published online: 11 November 2020

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