Pulmonary complications and respiratory management in neurocritical care: a narrative review

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Abstract

Neurocritical care (NCC) is not only generally guided by principles of general intensive care, but also directed by specific goals and methods. This review summarizes the common pulmonary diseases and pathophysiology affecting NCC patients and the progress made in strategies of respiratory support in NCC. This review highlights the possible interactions and pathways that have been revealed between neurological injuries and respiratory diseases, including the catecholamine pathway, systemic inflammatory reactions, adrenergic hypersensitivity, and dopaminergic signaling. Pulmonary complications of neurocritical patients include pneumonia, neurological pulmonary edema, and respiratory distress. Specific aspects of respiratory management include prioritizing the protection of the brain, and the goal of respiratory management is to avoid inappropriate blood gas composition levels and intracranial hypertension. Compared with the traditional mode of protective mechanical ventilation with low tidal volume (V_t), high positive end-expiratory pressure (PEEP), and recruitment maneuvers, low PEEP might yield a potential benefit in closing and protecting the lung tissue. Multimodal neuromonitoring can ensure the safety of respiratory maneuvers in clinical and scientific practice. Future studies are required to develop guidelines for respiratory management in NCC.

Keywords: Neurocritical care; Pneumonia; Respiratory management; Multimodel neuromonitoring; Tracheostomy; Mechanical ventilation; Positive end-expiratory pressure

Introduction

Patients in neurocritical care (NCC) compose one of the groups of patients in need of the most intensive care. NCC is not only generally guided by principles used in the general intensive care unit (ICU), but also directed by specific goals and methods for three reasons. First, neurocritical illnesses tend to be severe or emergent. These conditions necessitate the early phase of decision-making regarding the methods implemented for respiratory support. In addition, the incidence of respiratory disorders in the NCC unit is significantly higher than that in the general ICU.[1] Respiratory disturbance, however, has been shown to worsen the outcomes in NCC patients by causing conditions such as delirium and ICU-acquired weakness.[2] Respiratory support, including intubation, ventilation, and sedative choices, directly affects brain perfusion.[3] The goal of respiratory support is different in NCC patients from that in other patients, as the brain or lungs are prioritized.[4] Strategies for respiratory support and management, including artificial airways, the prone position, protective mechanical ventilation (MV), and drugs for airway management, have been summarized in previous studies.[5] Controversies still exist concerning the proper timing of a tracheostomy and levels of positive end-expiratory pressure (PEEP) in neurocritical patients. Although these topics have been widely studied in the general ICU, detailed guidelines on respiratory management in the NCC unit are not available.

We searched the electronic database PubMed and analyzed all the relevant literature. Based on the previous knowledge, this review will describe the research progress made in brain and lung interactions, pulmonary complications, and respiratory strategies in neurocritical patients and emphasize the importance and specifics of respiratory management in NCC.

Pathophysiology

Several theories regarding lung vulnerability after brain damage, including the "blast" theory, secondary inflammatory reaction, "double-hit" model, and pulmonary venule adrenergic hypersensitivity, have been studied in recent years. Inappropriate ventilation and respiratory diseases, however, can lead to secondary brain damage due to vagal signaling and high sensitivity of the brain to CO_2 and O_2 levels.

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Brain to lung pathway

Blast theory is characterized by a transient increase in catecholamine after an acute increase in intracranial pressure (ICP).[6,7] Catecholamine release has been reported to be linked to neurogenic pulmonary edema (NPE) in patients with traumatic brain injury (TBI).[8] It was first defined by Theodore and Robin[7] in 1976 as a catecholamine storm that can cause vasoconstriction of pulmonary venules, followed by a transient increase in intravascular pressure and change in the permeability of the capillary alveolar membrane, which eventually leads to protein leaking into the mesenchyme of the lung.

The emergence of the concept called pulmonary venule adrenergic hypersensitivity has challenged the blast theory. The latter includes the coexistence of high hydrostatic pressure and pulmonary endothelium injury. However, in some cases, after brain injury, despite the occurrence of NPE with direct pulmonary endothelial damage, no changes in systemic pressure have been found.[9,10] In pulmonary venule adrenergic hypersensitivity theory, NPE may result in pulmonary vasoconstriction and endothelial integrity changes following massive sympathetic discharge.[10]

After severe TBI, cerebral and systemic inflammatory reactions are triggered, and systemic inflammation is thought to play a major role in the development of pulmonary edema and alveolar damage.[6,11] The double-hit model was introduced in 2009. The first hit summarizes the effects of the catecholamine storm and systemic inflammatory reactions.[12] After the first hit, the lung is vulnerable to the second hit, which will eventually cause damage to the lung, such as a high tidal volume (V_t), inadequate PEEP during ventilation, and other further injurious events.[12] According to the double-hit model, pulmonary edema is the result of both the first hit and the second hit after brain injury.[6] Another theory is related to the endocrine system.[13,14] When the hypothalamic-pituitary-adrenal (HPA) axis is activated by TBI or surgical stressors, it releases corticotrophin-releasing hormones and arginine vasopressin.[13] These two hormones eventually stimulate the release of corticosteroids through the HPA axis. Corticosteroids mediate the anti-inflammatory response after trauma and are responsible for the hemodynamic response, which maintains blood pressure. In neurocritical patients, the persistence of an anti-inflammatory response can lead to secondary adrenal insufficiency, followed by systemic inflammatory response syndrome. This secondary adrenal insufficiency has been detected in 25% of neurocritical patients (~50% of patients after TBI or subarachnoid hemorrhage [SAH]).[1,15] Tan *et al*[16] demonstrated that intracranial hypertension and surgical stress can increase the apoptosis rate of the hypothalamus and pituitary gland in rats and rabbits.

Despite the humoral regulation pathways, TBI can also increase the risk for nosocomial pneumonia following neural circuit deficits, especially in the brain stem, including altered mental status, dysphagia, impaired gag and cough reflexes, and inability to clear secretions.[17]

Lung to brain pathway

Lung injuries and inappropriate ventilation can result in secondary brain damage in neurocritical patients, aggravating the sensitivity of the brain to acute injuries. The mechanisms of secondary brain injuries are closely related to neuroinflammation, hypoxemia, the vagal pathway, and the reactivity of cerebral blood vessels to oxygen and carbon dioxide concentrations.

In a previous study, lung injuries aggravated the sensitivity of the brain to acute injuries.[10] Indeed, lung injuries have been shown to promote the release of proinflammatory cytokines, which can spread into the systemic circulation, cause neuronal apoptosis and disrupt neural circuits.[18,19] Moreover, because hypoxemia and inflammation cause endothelial dysfunction, breakdown of the blood-brain barrier, and subsequent extravasation of erythrocytes, cerebral microbleeds will occur after lung injury, predominantly involving the brainstem, cerebellum, and juxtacortical white matter.[18,20]

González-López *et al*[21] reported that MV stimulates type 2 dopamine receptor and inactivates the prosurvival Akt/glycogen synthase kinase 3 beta pathway, which may lead to neural cell apoptosis. These authors also found that pulmonary transient receptor potential vanilloid type-4 mechanoreceptors and purinergic receptors participate in the mechanisms of ventilator-associated brain damage.[22]

Arterial carbon dioxide and oxygen levels are both related to cerebral blood flow (CBF) and ICP.[23-25] Howarth[26] demonstrated a novel role for astrocytes in mediating vasodilation in CBF responses to hypercapnia *in vivo*. They also demonstrated that ICP increases following the elevation of CBF. On the other hand, hyperventilation, which sometimes results in secondary hypocapnia, can result in cranial vasoconstriction and a decrease in CBF, and it can eventually lead to cerebral ischemia.[27] Oxygen levels in the blood and cerebral tissue are also crucial in neurocritical patients. McBryde *et al*[28] found that both carotid chemoreceptors and astrocytes can sense hypoxia and ischemia and then determine the level of sympathetic activity and arterial pressure to optimize CBF. Thus, a decrease in arterial oxygen pressure (PaO_2) during MV is related to an increase in CBF and ICP.[29,30]

Pulmonary Complications in NCC

Systemic changes secondary to neurocritical injuries can induce impairments in pulmonary function. The conditions and disorders that often occur in these patients include not only pneumonia, adult respiratory distress syndrome (ARDS), and NPE, but also several abnormal respiratory patterns and sleep-disordered breathing.[31] Lung injuries triggered by neurocritical damage can have significant effects on outcomes, such as the selection of treatment plans, disease prognosis, and mortality.

Pneumonia

Pneumonia is commonly seen in stroke patients and is associated with poor outcomes. The most frequently

cultured pathogens in NCC patients are gram-negative bacilli and gram-positive cocci, with sputum being the most commonly used sample for cultivation and detection.[32] Risk factors for pneumonia in stroke patients who have been identified in systematic reviews include the following: older age, male, MV, nasogastric tube, dysphagia, diabetes, pre-existing respiratory conditions, atrial fibrillation, and smoking.[33,34] Among the risk factors, ventilation and dysphagia have been studied more widely in recent years regarding the feasibility of an intervention. For example, the timing of tracheostomy in TBI patients[35] and the optimal ventilation strategies of NCC patients have been discussed.[25]

Ventilator-associated pneumonia (VAP) is commonly seen in NCC patients with MV. The incidence of VAP has been shown to be 21% to 60% in patients with severe TBI,[36] 20% to 48% in those with SAH, and approximately 28% in those with stroke.[1] The pathogen that is detected in most cases is *S. aureus,* followed by *H. influenzae, S. pneumoniae, E. coli,* and other types of pathogens that are found in some patients.[36-38] Apart from the risk factors mentioned above, other factors associated with the treatment process are worth noting. Esnault *et al*[36] confirmed that early-onset VAP is associated with therapeutic hypothermia, serious thoracic trauma, and gastric aspiration before intubation. Early enteral feeding, oral care, and prophylactic antibiotics have been reported to protect NCC patients from VAP.[38,39]

Another type of pneumonia associated with a neurocritical state is aspiration pneumonia. Dysphagia, which has been reported in 37% to 45% of stroke patients,[40] is associated with pneumonia and poor outcomes in these patients.[41] Feng *et al*[42] investigated the mortality rate associated with aspiration pneumonia in stroke patients, and the authors found that dysphagia is a critical factor in the development of aspiration pneumonia. Ding *et al*[43] studied dysphagia, and it has been considered a common factor in different models for predicting poststroke pneumonia.

Respiratory distress and pulmonary edema

ARDS is an alveolar condition characterized by the formation of the hyaline membrane and dysfunction of gas exchange. ARDS has a high mortality rate, and the incidence of ARDS that has been reported in different journals ranges from 19% to 35%.[1,44] Mrozek *et al*[1] summarized the incidence of ARDS to be 20% to 25% in patients with severe TBI, 20% to 38% in those with SAH,[45] and approximately 4% in those with stroke.[46] The risk factors for developing ARDS in patients with brain injury include severe primary neurological disease, hemodynamic instability, a history of chronic diseases, and other general risk factors.[1,46] ARDS patients in the NCC unit are generally treated with protective MV (pMV) and require restrictive body fluid management.[24] This year, a study in a neurological ICU stated that assisted orthostatism can be a safe auxiliary treatment for severe ARDS, as it improved the PaO_2/FiO_2 in 95.6% of the patients without causing significant hemodynamic repercussions.[47] NPE is a type of protein-rich edema of the lung. It is diagnosed with bilateral infiltrates and PaO_2/FiO_2 of < 200 mmHg in patients with severe injury of the central nervous system (CNS) and increased ICP when left atrial hypertension and other common causes of ARDS are not present. With prior participation of the neuropathway, it differs from other types of pulmonary edema and has a higher incidence in neurocritical patients. NPE secondary to neurocritical injuries has an estimated incidence ranging between 2% and 50%, and it occurs more often in patients with severe TBI than in those with SAH.[1,48] Based on the mechanism of NPE related to sympathetic nervous activity, Chen *et al*[49] examined heart function in 204 patients with SAH and found that heart rate variability can predict the occurrence of NPE.

Respiratory Support in NCC

Respiratory management in NCC follows the general rules of intensive care, but specific aspects are different from general ICU because of the higher incidence of respiratory disorders in the NCC unit.[27,50,51] Patients being treated in the NCC unit are in various states of unconsciousness and have different types of respiratory drive disorders. Thus, patients in the NCC unit are often ventilated because of unconsciousness and potential respiratory disorders or airway obstructions, not primary respiratory failure.

In addition, because various NCC patients have special needs and ventilator targets, the implementation of neuroprotective strategies, including a tailored ventilatory approach on patients with ABI, might effectively improve survival and functional outcome in these patients.[27,52] For example, choking or esophageal reflux should be avoided for patients with cerebral hemorrhage or unruptured aneurysms.[51] Protective ventilation with low tidal volumes (6–8 mL/kg of ideal body weight) could be safely applied to TBI patients.[53]

The goal of respiratory support in NCC patients is to avoid fatal secondary damage, including cerebral ischemia, hemorrhage, functional impairment, and even death,[54-56] due to factors such as inappropriate oxygen or carbon dioxide levels, aspiration, and airway obstruction, which differs from the goal in patients in the general ICU, which is to alleviate primary respiratory diseases.[57,58] The reasonable ranges of oxygen and carbon dioxide levels may differ from general ICU patients. We collected the results of different studies concerning respiratory protection maneuvers in NCC patients, and Figure 1 is a summary of the possible potential risks.

Both hypoxemia and hyperoxia should be avoided because the neurological outcomes can worsen. Hypoxemia is related to cerebral ischemia and functional impairment, while hyperoxia is related to excessive free radicals and oxidative stress, which impair cerebral autoregulation and cause damage to the lung and brain tissue.[56,59] An association between hypoxia and an increase in mortality in NCC patients has been reported,[56,60] while Fallenius *et al*[29] reported no correlation with long-term mortality in patients with spontaneous intracranial hemorrhage. Both hypercapnia and hypocapnia have a conspicuous effect on ICP. Although hypercapnia may be permissive in the general

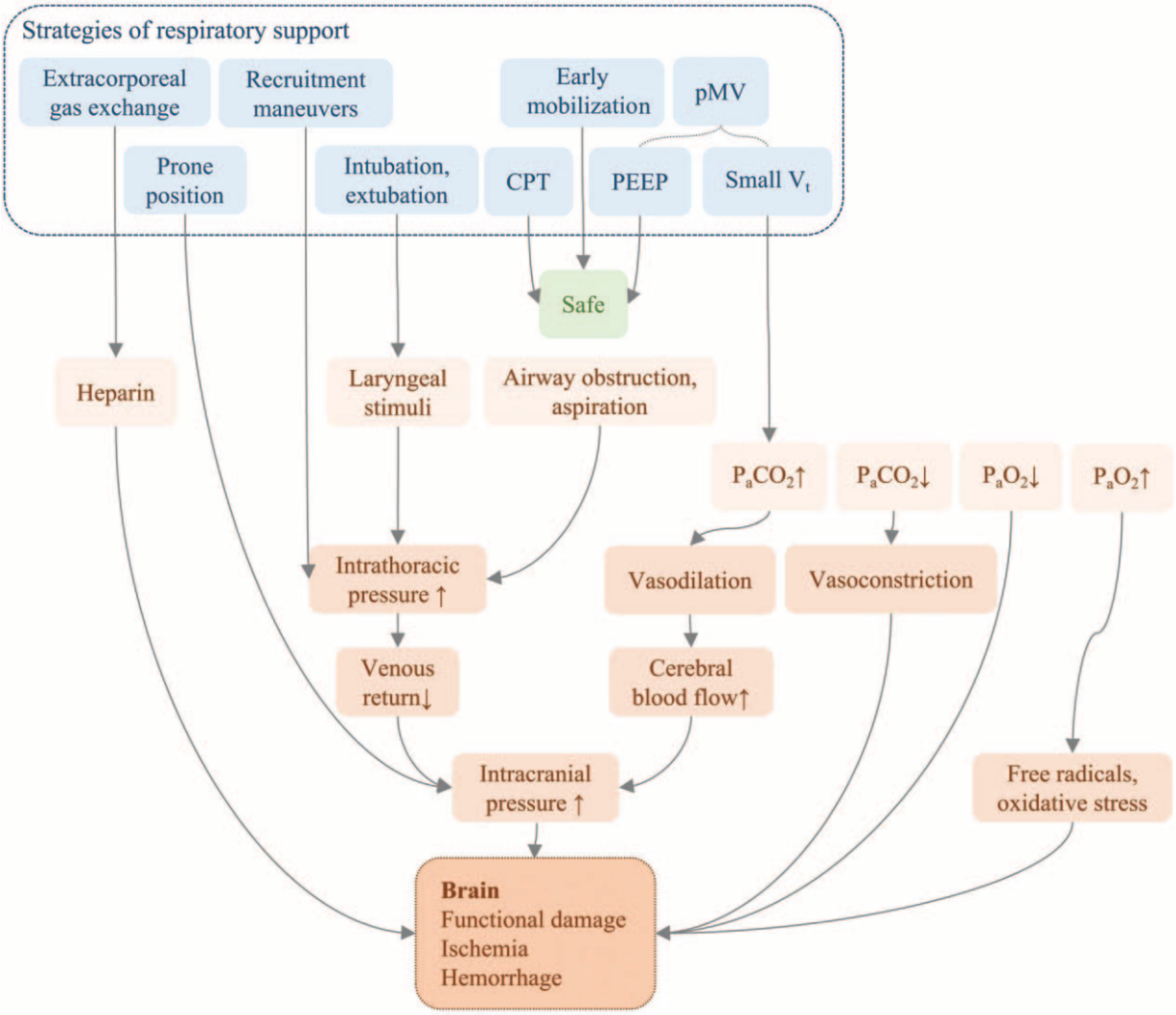

Figure 1: Potential risks of respiratory protective strategies. CPT: Chest physiotherapy; $PaCO_2$: Arterial carbon dioxide pressure; PaO_2: Arterial oxygen pressure; PEEP: Positive end-expiratory pressure; pMV: Protective mechanical ventilation; V_t: Tidal volume.

ICU, it is often prohibitive in NCC patients because of the ability to elevate ICP. However, some researchers have stated that controlled hypercapnia benefits patients with SAH and vasospasm by increasing CBF and tissue oxygenation while monitoring ICP.[58,61] Hypocapnia occurs in approximately 92% of aneurysmal SAH patients, mostly when they breathe spontaneously with minimal ventilation support.[27,58] In addition, hypocapnia is associated with a poor functional outcome in these patients.[58] Low arterial carbon dioxide levels result in a reduction in CBF and vasoconstriction, followed by brain tissue hypoxia.[23] The effects of hypercapnia and hypocapnia necessitate a moderate level of arterial carbon dioxide. Expert consensus for neurosurgical critical care in China suggests maintaining arterial carbon dioxide pressure ($PaCO_2$) at 35 to 45 mmHg, $SpO_2 > 95\%$, and $PaO_2 > 80$ mmHg.[51]

Intubation and tracheostomy

Intubation and tracheostomy are ways of creating artificial airways. In the NCC unit, intubation is indicated in patients with unconsciousness or Glasgow coma score (GCS) < 8, an abnormal blood gas composition including hypoxemia and hypercapnia, or respiratory and airway disorders, and it is indicated for treatments such as MV and the control of the ICP or seizures.[3] Tracheostomy is indicated in NCC patients who need long-term (>2 weeks) artificial airway and respiratory support, GCS < 8, and dysphagia. To reduce discomfort and sedation during intubation, better oral and tracheobronchial care that does not hinder the ability to communicate should be provided.[5,62]

The maneuvers of the intubation process and prehospital intubation have been discussed in different studies because of the potential risks of intubation in NCC patients, including an increase in the ICP resulting from laryngoscopy stimuli, hypoxemia during the operation, and aspiration, especially in difficult airways.[63,64] The LEMON approach and amendatory rating scales have been recommended in several studies for the identification of difficult airways.[3,65] These tools may be beneficial in selecting the appropriate technique (awake fiberoptic or rapid sequence induction), tools (video or direct laryngoscopy), and operator (anesthesiologist, attending, or trainee) during the intubation process.[65] In

recent years, researchers have recommended rapid sequence intubation (RSI) with sedation during the operation process to reduce the stimuli in laryngoscopy.[3,63] Although a retrospective study reported that trauma severity influenced mortality more than intubation in prehospital admissions, a large cohort-matched study noted that prehospital intubation in patients with TBI was associated with higher in-hospital mortality.[54,66]

Recent studies on tracheostomy in NCC patients mainly focus on the optimal timing and ways of performing a tracheostomy. The optimal timing is still being debated, considering the advantages and disadvantages of performing a tracheostomy earlier or later in time. Early-stage tracheostomy, defined as one with a cutoff of 7 to 8 days,[67] is associated with a reduction in the need for sedation, the incidence of nosocomial infection, and the time of MV and ICU stay compared with prolonged intubation, and it is cost effective. [67-71] Recently, some studies also found that early tracheostomy after severe brain injury is associated with a better neurological outcome, reduced in-hospital time, and reduced risk for VAP.[35,72] However, whether early tracheostomy affects the long-term mortality rate is controversial.[67,68,71] Jibaja *et al*[57] expressed the view that conducting one primary tracheostomy is advisable in patients at risk (with severe cervical spine injuries, infratentorial severe injuries, repeated failed extubation, prolonged MV, and poor neurological states). The results of tracheostomy performed later in time may exclude a certain percentage of those patients who would have undergone an early-stage tracheostomy, but postponed tracheostomy may be accompanied by a higher incidence of complications.[68] Progress has been made in improving the way tracheostomy is performed to prevent intracranial hypertension by avoiding hyperextension of the neck and shortening the duration of the procedure.[5,73] Different types of tracheostomy equipment may have similar outcomes in general patients, but percutaneous/puncture-dilated tracheostomy has been recommended in NCC patients as a safe and quick treatment, as it has the advantages of reducing the incidence of bleeding, tracheal stenosis, and infections.[73,74]

Airway management

Airway management before and after intubation or tracheostomy includes sputum drainage and drugs for RSI and spasmolysis. Sputum is a common cause of airway obstruction, and it produces an artificial airway airflow sound or whistle sound. Sputum drainage is crucial in patients with acute neurological impairment. Thus, optimal methods of achieving airway humidification and clearing in NCC patients are essential and worth discussing. Drugs for airway spasmolysis include sedatives, analgesics, muscle relaxants, and nitric oxide (NO).

Some doctors have compared different liquids for airway humidification in the lungs in patients with TBI, and they found that 0.9% sodium chloride (NaCl) with ambroxol is an ideal airway humidification liquid.[75] It was found to have anti-inflammatory and antioxidant properties, as it promoted the synthesis and secretion of pulmonary surfactants and inhibited the release of inflammatory factors and cytokines.

The inflated cuff of the endotracheal tube is designed to prevent microaspiration; thus, the cuff pressure should be at a moderate level at 20 to 30 cm of water, as air leakage or aspiration occurs when it is too low, and tracheal or subglottic stenosis occurs when it is too high.[5,76,77] In NCC patients, the cuff pressure may decline with extubation and the transition to a prone position.[78] In addition, the high incidence of pneumonia further emphasized the necessity of determining and monitoring cuff pressure. However, the palpation method performed with the operator's fingers was suggested to be inadequate to determine the cuff pressure;[77] thus, guidelines and equipment are required.

Chest physiotherapy (CPT) can mobilize respiratory secretions and increase the amount of tracheobronchial mucus that is cleared from the respiratory tree. Although CPT can increase ICP,[79] it has been indicated to be safe in NCC patients.[80-82] Tomar *et al*[81] evaluated the safety of different CPT techniques in patients with TBI, and they found that an automated or mechanical method of performing CPT can be executed without a transient rise in ICP, while the manual method might jeopardize cerebral circulatory pathophysiology. CPT is safe in patients with ICP monitoring *in situ*.[83]

Adequate sedation in neurocritical patients is paramount. Sedation can ease fear and anxiety, reduce ICP and cerebral oxygen consumption, facilitate tolerance of the endotracheal tube and MV, and reduce sympathetic nervous activity.[3] Rajajee *et al*[3] summarized the variety of sedatives available and the common sedatives used in NCC patients. Alpha-2 agonists such as dexmedetomidine have been shown to have no effect on the ICP and hemodynamic variability when they are included in standard sedation.[84] However, in several studies, they have been reported to reduce the duration of MV and ICU stays more than traditional sedatives such as propofol and remifentanil.[85,86]

Although analgesics such as fentanyl were found to be ineffective in treating episodic intracranial hypertension, analgesia is recommended before sedation in some studies.[87] Because the analgesic effect of most sedatives is unsatisfactory and sedation without pain control is a risk factor for delirium,[3] analgesia with the use of short-acting opioids is recommended. Additionally, patients in a coma with adequate pain control and airway construction do not need sedatives.

Muscle relaxants and NO also help restore respiratory function in neurocritical patients. Muscle relaxants can correct hypoxemia and prevent MV-associated lung injury.[5] Sugammadex has been used in some cases to accelerate weaning from the ventilator after prolonged MV.[88] NO inhalation is immunomodulatory and pathogen static, and it assists in the reversal of pulmonary hypertension.[4] Terpolilli *et al*[89] reported that in mice, NO inhalation can reduce secondary brain damage after TBI. Guo *et al*[90] discussed the influence of NO on cerebral autoregulation and noted that NO may assist in the regulation of CBF, which can be considered a new therapeutic target.

Parameters of MV

Regarding MV, compared with patients without neurological conditions, patients with neurological conditions have shown a longer ventilation duration, higher rates of tracheostomy, and less extracerebral organ dysfunction.[91] Considering the effect of standard MV on lung tissue damage, clinicians and researchers promote pMV in patients with respiratory disorders and intensive care. To open the lung and keep it open in the NCC unit, patients are recommended to undergo pMV with a small V_t, elevated PEEP, and recruitment maneuvers (RMs).[1] However, in recent years, controversies have been discussed in several studies on the effect of high PEEP and low PEEP.[92,93] Little progress has been made in clarifying the role and safety of high-frequency ventilation (respiratory rate > 150 breaths per minute, V_t 1–5 mL/kg[94]) in patients with neurological diseases.

PEEP is a method of keeping the alveoli open at the end of expiration. Although inducing alveolar hyperinflation has been shown to increase $PaCO_2$ and ICP in a previous study,[95] moderate PEEP (5–15 cm H_2O) is beneficial for mechanically ventilated patients with acceptable hemodynamic changes; it has been shown to be beneficial for improving oxygenation, preventing and recruiting alveolar collapse, and reducing the risk of atelectasis in patients with low V_t.[27,96] In clinical practice, in the management of neurocritical patients with ARDS, PEEP has few negative effects on the intracranial condition and can even benefit brain tissue oxygenation.[50,97,98] A study conducted by Boone *et al*[97] demonstrated that the fluctuations of the ICP and cerebral perfusion pressure (CPP) in patients with severe lung injury are more sensitive to PEEP than those in the other patients, but the application of PEEP does not appear to have a clinical effect overall. However, recent studies have suggested that instead of keeping the lungs open, the goal should be to close down the lungs and keep them closed to protect the lung tissue when low PEEP (≤3 cm H_2O) is applied in ARDS patients, but data on this topic are not available in neurocritical patients.[92,93]

pMV with low V_t and moderate PEEP is safe for patients after brain injury, but its positive effects on the outcome must be better delineated.[50,69] A small Vt is related to hypercapnia in patients with pMV. It may be permissive in the general ICU, but it deserves vigilance in the NCC unit.[12] V_t is positively associated with the incidence of ARDS and negatively associated with $PaCO_2$ and ICP in a dose-response relationship.[99] Thus, a low V_t decreases the incidence of lung injuries but is accompanied by $PaCO_2$ and ICP increases, which may affect most NCC patients. However, a randomized clinical trial involving 961 patients without ARDS in the ICU found that a low V_t was not more effective than an intermediate V_t.[92] Avoiding hypercapnia necessitates the monitoring of the cerebral hemodynamic index and carbon dioxide level, which is part of the multimodal neuro-monitoring process.[4,27] Intra-operative pMV with low tidal volumes (6–8 mL/kg) has been shown to reduce the incidence of post-operative pulmonary complications, while intraoperative high PEEP might negatively affect hemodynamics in nonobese patients.[100] Intra-operative pMV will be studied in a single-center, parallel-group randomized controlled trial to determine its efficiency and safety in neurosurgical patients undergoing a craniotomy.[101]

Recruitment maneuvers (RMs) for collapsed pulmonary alveoli can open the lung and improve oxygenation and respiratory system compliance in ARDS patients.[102,103] However, the management of ICP hinders reaeration by lung units in neurocritical patients undergoing RMs. RMs may interfere with venous blood return and increase intrathoracic pressure, which increases ICP and decreases cerebral arterial blood pressure.[104,105] Although continuous positive airway pressure (CPAP) is currently the most common RM, clinical experiments comparing different RMs in NCC patients have been conducted by several researchers, who reported that maneuvers with a lower airway pressure and longer duration are better than traditional CPAP.[27,106] RMs are safe with the strict monitoring of systemic and cerebral parameters.

Time of weaning and extubation

The extubation failure rate of NCC patients has been reported to be 17.2% to 38.0% in different studies, and ventilation discontinuation accounted for 50% of the deaths in neurovascular patients.[50,57,107] Strategies of weaning from MV and extubation have been developed from studies and protocols in patients without neurocritical conditions.[57] Patients with brain injuries were rarely described in the latest guidelines for weaning or extubation strategies.[50] Waiting for full neurological recovery is not mandatory. Prolonged MV in patients with subdural hematoma (>4 days) is associated with pulmonary complications and a longer hospital stay.[108]

Factors associated with the success of MV and extubation withdrawals have been identified and summarized in several studies.[50,57,107] Anderson *et al*[109] found that following four commands, closing the eyes, showing two fingers, wiggling the toes, and coughing, were protective factors for extubation success. A multicentric cohort study of patients with severe brain injury identified four features associated with extubation success: an age of < 40 years, visual pursuit, swallowing attempts, and a GCS of > 10.[107] Jibaja *et al*[57] expressed the view that not answering verbal commands or a low GCS does not indicate a delay or contraindication for MV or extubation withdrawal.

Studies about extubation failure in NCC patients have mentioned predictors, such as airway dysfunctions (pneumonia, atelectasis, thick secretion, no gag reflex, weak cough, and deglutition), neurological statuses (a GCS of < 7–9, inability to follow commands), and the duration of MV.[110-113] Several studies have emphasized the predictive role of fundamental state (age, fluid balance) and upper-airway functions irrespective of neurological status.[112,114] However, Mayer *et al*[113] stated that neurological status is more important than pulmonary status in deciding whether to perform extubation. Cohn *et al*[111] retrospectively reviewed the data in pediatric NCC patients and found that a weak cough reflex might be a risk factor for failed extubation.

Algorithms and criteria before extubation have been reported by researchers.[115,116] The spontaneous breathing trial (SBT) is a consensus approach used to predict extubation success. Mullaguri *et al*[115] studied an algorithm in 108 NCC patients using zero pressure support and a zero-PEEP SBT, followed by 5-cm H_2O pressure support and a 5-cm H_2O PEEP SBT, in patients who failed the zero-PEEP SBT, and the researchers found that most NCC patients who were otherwise ready to be extubated could safely be extubated after passing a zero-PEEP SBT. Tanwar *et al*[116] suggested that the airway care score can be used as a criterion for early extubation success.

Extracorporeal gas exchange

Extracorporeal decarboxylation is the normalization of the serum carbon dioxide level *in vitro* through the canalization of arteries and veins. Blood flow occurs in a pumpless arteriovenous system to create pressure gradients for the two blood vessels. As the blood flows across the device, it normalizes the carbon dioxide level, resulting in an improvement in the blood pH and a decrease in the occurrence of ventilator-induced lung injuries.[117] This approach is applied in patients with normal oxygenation and severe hypercapnia.[118] The use of this approach is restricted because of the potential intracranial hemorrhagic risk with the application of a large dose of heparin and the lack of evidence regarding improved outcomes in patients.[118,119]

Extracorporeal membrane oxygenation (ECMO) is more effective than extracorporeal decarboxylation in patients with both hypercapnia and hypoxemia. It can reduce the aggressiveness of MV and reduce the mortality rate in patients with indications for ECMO.[5] Two types of ECMO exist: venovenous ECMO (vv-ECMO), where blood is taken from the inferior vena cava and returned to the superior vena cava, and veno-arterial ECMO, where blood is returned to the aorta. Starting ECMO >7 days after the initiation of MV yields no benefits.[120] The need for relatively high doses of heparin increases the risk of these complications in NCC patients.[121] To date, only a few cases of the use of ECMO in NCC patients have been reported; because intracranial hemorrhage complications can occur after prolonged ECMO or vv-ECMO, ECMO is considered a rescue for severe hypoxemia respiratory failure in trauma patients.[120-124] The use of special biomaterials in modern ECMO without initial anti-coagulation has been considered a valid option for patients with a high risk of bleeding.[5,122]

Positioning and mobilization

Different positions and postures are suggested for NCC patients because of their pulmonary disorders and altered ICP. The proclive or reverse Trendelenburg position is a position where the level of the patient's head and chest is higher than the feet, which decreases the ICP and end-tidal carbon dioxide partial pressure.[125] It is commonly used in patients with intracranial hypertension. The supine position is the position where a patient lies down horizontally and faces upward, and this position is commonly used in patients without intracranial hypertension or difficulty in gas exchange. The prone position is the position where a patient lies down and faces downward; it facilitates venous return, as the heart and lungs are at the lowest level of the body. Because it improves pulmonary drainage and oxygenation, the prone position is commonly used in patients with severe ARDS, but to date, it has been used only in a few cases in the NCC unit. In patients without head injury or a risk of intracranial hypertension, the prone position is associated with a moderate elevation of the ICP and an increase in oxygenation.[126,127] A retrospective descriptive study suggested that the prone position is safe in patients with severe ARDS, even in patients at risk of intracranial hypertension.[128] ICP monitoring in the prone position is required in patients who are at risk of intracranial hypertension or have a history of neurosurgery.[126-128]

Early mobilization is not widely deployed in NCC patients, but recently, it has been reported to be safe, feasible, and potentially beneficial.[129,130] A multicenter study conducted in 10 patients with acute brain injury found that early mobilization appears to favor clinical and functional recovery.[130] Bahouth *et al*[129] proposed a formalized Neurocritical Care Unit mobility algorithm for adult patients with primary intracerebral hemorrhage. The study suggested that within the first week after a hemorrhagic stroke, a large percentage of patients can be mobilized without additional adverse events, and the implementation of a standardized algorithm is feasible and reduces the incidence of pulmonary embolism.[131]

Gas exchange in neuro-monitoring

An appropriate blood gas composition is crucial for neurocritical patients to avoid secondary brain damage. Pandin *et al*[132] systemically introduced the concept of multimodel neuromonitoring. Compared with other means, multimodel neuromonitoring can detect early neurological deterioration, consider individual patho-physiological variations, and allow clinicians to make individualized management decisions.[133] The process of monitoring brain and spinal cord metabolism and function can be summarized by five aspects: ICP and CPP, which represent the driving pressure of brain perfusion; trans-cranial Doppler, which shows the local and regional CBF; brain tissue oxygen pressure ($P_{bt}O_2$), which reflects the CBF and oxygen diffusion; the result of microdialysis, which is associated with CNS metabolism; and electroencephalogram monitoring, which reflects CNS function. Multimodel neuromonitoring is useful for monitoring gas exchange in brain tissues.[27,134]

Assessing pulmonary function and testing the blood gas composition are important parts of a gas exchange evaluation. Ventilator parameters, such as PEEP and V_t, and gas composition parameters, such as PaO_2 and $PaCO_2$, are indices that directly represent the gas exchange level in the lung. Corradi *et al*[104] combined the use of lung ultrasound and brain ultrasound in NCC patients with demanding MV needs in ventilation management, with the aim of tailoring the balance in intracranial hypertension-directed and lung-protective therapy.[104]

Limitations

This article has several limitations. The first is that we primarily searched a single English database. Consequently,

our search terms possibly did not capture all aspects of the topic. However, we minimized the likelihood of missed articles by applying a broad search strategy. Second, some of the included articles were case reports, method introductions, or small sample studies. Thus, the interpretation of some results may be limited.

Conclusion

Systemic changes secondary to neurocritical injuries can induce impairments in pulmonary function. Although it has been discussed for many years, the pathomechanisms remain poorly defined. With the development of brain science, brain-lung crosstalk is becoming a research hotspot. Respiratory management in NCC follows the general rules of intensive care, but in specific aspects, it is different due to the higher incidence of respiratory disorders and the prioritization of protecting the brain in NCC. Thus, strategies to protect the lungs and the brain are recommended for NCC patients. However, the optimal strategies for the management of NCC patients remain controversial, and further guidelines and criteria are urgently needed.

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Conflicts of interest

None.

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