World Journal of Critical Care Medicine

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DOI: 10.5492/wjccm.v5.i1.65

World J Crit Care Med 2016 February 4; 5(1): 65-73
ISSN 2220-3141 (online)

REVIEW

Respiratory mechanics in brain injury: A review

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Author contributions: All authors contributed to this paper; Koutsoukou A, Katsiari M, Orfanos SE and Rovina N designed the study; Koutsoukou A, Katsiari M, Kyriakopoulou M and Daganou M performed the literature review and analysis; Katsiari M, Koulouris NG and Rovina N wrote the paper; Koutsoukou A, Orfanos SE, Kotanidou A, Koulouris NG and Rovina N performed the critical revision and editing; all authors approved the final version.

Conflict-of-interest statement: No potential conflicts of interest. No financial support.

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Received: August 6, 2015
Peer-review started: August 10, 2015
First decision: September 16, 2015
Revised: October 8, 2015
Accepted: December 10, 2015
Article in press: December 11, 2015
Published online: February 4, 2016

Abstract

Several clinical and experimental studies have shown that lung injury occurs shortly after brain damage. The responsible mechanisms involve neurogenic pulmonary edema, inflammation, the harmful action of neurotransmitters, or autonomic system dysfunction. Mechanical ventilation, an essential component of life support in brain-damaged patients (BD), may be an additional traumatic factor to the already injured or susceptible to injury lungs of these patients thus worsening lung injury, in case that non lung protective ventilator settings are applied. Measurement of respiratory mechanics in BD patients, as well as assessment of their evolution during mechanical ventilation, may lead to preclinical lung injury detection early enough, allowing thus the selection of the appropriate ventilator settings to avoid ventilator-induced lung injury. The aim of this review is to explore the mechanical properties of the respiratory system in BD patients along with the underlying mechanisms, and to translate the evidence of animal and clinical studies into therapeutic implications regarding the mechanical ventilation of these critically ill patients.

Key words: Brain damage; Respiratory mechanics; Positive end-expiratory pressure; Lung injury; Ventilator-induced lung injury

Core tip: Clinical and experimental evidence supports that preclinical lung injury occurs shortly after brain damage. Brain-damaged patients exhibit altered respiratory system mechanics and hypoxemia, even in the absence of clinically evident lung injury. Measurement of respiratory mechanics in such patients may reveal brain damage related lung injury early enough, and facilitate selection of the appropriate ventilator settings to avoid ventilator induced lung injury. Lung protective ventilation, consisting of low tidal volume and moderate levels of positive end-expiratory pressure, may prevent a further deterioration of respiratory dysfunction, and could be possibly associated with improved outcome.

Koutsoukou A, Katsiari M, Orfanos SE, Kotanidou A, Daganou M, Kyriakopoulou M, Koulouris NG, Rovina N. Respiratory mechanics in brain injury: A review. *World J Crit Care Med* 2016; 5(1): 65-73 Available from: URL: http://www.wjgnet.com/2220-3141/full/v5/i1/65.htm DOI: http://dx.doi.org/10.5492/wjccm.v5.i1.65

INTRODUCTION

Brain damage (BD), either due to spontaneous hemorrhage or trauma, represents one of the most important causes of death and disability in modern societies. Although morbidity and mortality of these patients are due principally to their primary disease, medical complications are frequent, with respiratory dysfunction being the most common[1-3]. Up to one third of BD patients develop acute respiratory distress syndrome (ARDS), a complication that has been associated with poor outcome[4,5].

Several clinical and experimental studies have confirmed that lung injury occurs shortly after brain damage. Rogers *et al*[6] found a significant increase of the lung weight along with edema, congestion and hemorrhage in 50% of patients who died within 96 h after isolated brain damage.

Ultrastructural changes in type Ⅱ pneumocytes along with an inflammatory response in the lung, similar to that induced by high tidal volume ventilation, have been observed in animals within the first hours of traumatic brain injury[7]. Similarly, alterations in lung architecture, such as alveolar hemorrhage, proteinaceous debris and neutrophilic infiltration were detected by Weber *et al*[8] in experimental traumatic brain damage. In addition, decreased pulmonary tolerance to subsequent mechanical stress due to mechanical ventilation[9], as well as aggravation of preexisting lung injury[10] have been reported after massive brain damage in animals.

Although experimental as well as clinical evidence support the existence of a close interaction between the brain and lungs[11], the mechanisms by which brain damage leads to alterations in pulmonary function are unclear. They may involve neurogenic pulmonary edema, inflammation, neurotransmitter-related engagement, or adverse effects of neuroprotective therapies[12,13].

Mechanical ventilation is an essential component of life support in brain damaged patients. It is well known that, despite being lifesaving, mechanical ventilation may nonetheless cause or perpetuate lung injury if alveolar overdistention and repeated alveolar collapse and re-expansion occurs with each breath [ventilator-induced lung injury (VILI)][14]. Non lung protective mechanical ventilation could thus constitute an additional traumatic factor to the already injured or susceptible to injury lungs of such patients[9,15]. Indeed, recent research has found that a lung protective strategy is an independent predictor of favorable outcome of BD patients[16]. Furthermore, it has been shown that lung protective strategy prevented the decline of pulmonary function consequent to brain death and increased the number of lungs available for transplantation[17], a finding particularly important in the context of lung transplantation because of the scarcity of lung donors. In relation to the latter, it should be noted that preclinical lung injury may be present in BD patients with "normal" chest X-rays; thus it is of paramount importance to have a marker that could detect such an injury.

Measurement of respiratory mechanics in brain damaged patients, as well as assessment of their evolution during mechanical ventilation, may help in the detection of lung injury early enough, but also in selecting the appropriate ventilator settings to avoid VILI.

The aim of this review is to explore the mechanical properties of the respiratory system in brain damaged patients along with the underlying mechanisms, and translate the evidence of animal and clinical studies into therapeutic implications regarding the mechanical ventilation of these critically ill patients.

RESEARCH

The information in this review is based on results of a Medline and OVID search. The key words used were related to brain damage (traumatic brain injury, hemorrhagic stroke, intracranial pressure, brain death), and to acute lung injury/ARDS and mechanical ventilation (pulmonary edema, acute respiratory distress syndrome, ventilator induced lug injury, inflammation, respiratory mechanics, mechanical ventilation, tidal volume, positive end-expiratory pressure, lung transplantation). We read relevant articles in full, searched their reference lists, and chose the most relevant on the basis of findings and clinical significance. Bibliographies of identified articles, guidelines and conference proceedings of professional societies were reviewed for additional references.

FROM THE BRAIN TO THE INJURY OF THE LUNGS

Several nonexclusive mechanisms have been implicated in the brain to lungs' injury process. Pulmonary dysfunction

after brain damage has long been attributed to an increased sympathetic activity. Massive catecholamine release may lead to neurogenic pulmonary edema[18], that is the extravasation of fluid from the blood into the alveolar and interstitial space of the lungs in patients who have suffered an acute neurological event. Several theories have been proposed considering the pathophysiology of this entity. The mostly recognized is the "blast injury" theory, suggesting that the sympathetic storm which follows a sudden increase in intra-cranial pressure induces a transient increase in intravascular pressure and the consequent disruption of the alveolo-capillary membrane[18]. The development of neurogenic pulmonary edema is attributed either to hydrostatic forces, as it is supported by a low pulmonary/plasma protein ratio[19], or to high permeability mechanisms supported by increased accumulation of pulmonary extravascular protein[20]. The association between massive sympathetic discharge and neurogenic pulmonary edema is further supported by a more recent experimental study showing that pretreatment of brain-damaged rats with alpha-adrenergic antagonists prevented the hypertensive response and attenuated the subsequent lung injury[21].

In addition to the "blast injury" theory, a systemic inflammatory response seems to play a critical role in the development of lung injury after brain damage. Clinical studies in acutely brain-damaged patients have suggested an increased intracranial production[22] and release[23] of pro-inflammatory mediators into the systemic circulation along with possible activation of inflammatory cascades. Intracranial production of inflammatory cytokines probably takes place in brain microglia and astrocytes[23], while through the altered blood-brain barrier these mediators can reach peripheral organs leading to multi-organ dysfunction[22,24,25]. Indeed, Fisher *et al*[26] detected an increased concentration of proinflammatory cytokines in the bronchoalveolar lavage fluid (BALF) of patients with fatal BD. The same group later reported that increased levels of BALF interleukin-8 (IL-8) in brain dead lung donors correlated with severe early graft dysfunction and recipient mortality, pointing out to the key role of such a preclinical inflammatory process[27].

Several experimental studies have confirmed the existence of a systemic inflammatory process in BD. In animals with acute brain injury, Kalsotra *et al*[28] detected a significant migration of macrophages and neutrophils into the lungs at 24 h post injury, associated with enhanced pulmonary leukotriene B4 production. Skrabal *et al*[29] investigated the very early organ-specific inflammation responses after brain death in pigs and found an up-regulation of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), IL-1β and IL-6 in the animal lungs. All these substances are mediators that may modulate the expression of adhesion molecules and consequent activity[30]. In fact, an up-regulation of the soluble intercellular adhesion molecule-1 (ICAM-1) was found in the lungs of BD animals[29]. Similarly, Cobelens *et al*[31] found that experimental subarachnoid hemorrhage was associated with neutrophil influx into the lungs as well as increased expression of pulmonary adhesion molecules and chemokines. Adhesion molecules through activation, firm adhesion, and the chemotactic migration of leukocytes[32] may contribute to lung injury. In this respect, a strong association between increased serum levels of ICAM-1 and poor neurological outcome has been found by McKeating *et al*[33] in a cohort of BD patients. Among other molecules that have been linked with the brain to lung injury process are S-100B, E-Selectin and caspase-1[10,34]. Moreover, altered activity of pulmonary capillary endothelial angiotensin converting enzyme is present in brain dead subjects denoting preclinical pulmonary endothelial dysfunction[35]. In a similar respect, the presence of preclinical pulmonary inflammation in mechanically ventilated BD patients was revealed by markers measured in exhaled breath condensate[36].

Very recently, Nicolls *et al*[37] demonstrated that acute lung injury that followed traumatic brain injury in animals was mediated by high-mobility group box-1 (HMGB1), a nuclear protein that serves as an early mediator of inflammation[8]. The authors additionally showed that HMGB1 activates inflammatory responses through binding to receptor for advanced glycation end products (RAGE). The fact that RAGE is highly expressed on lung epithelial cells could partially explain why the lung is so sensitive to damage after brain injury.

Severe brain damage may induce lung injury through modulation of neurokinins since such substances are released in patients with BD[38,39]. Substance P and neurokinin A have been implicated in bronchoconstriction, mucosal edema, increased vascular permeability, pulmonary edema and leukocyte adhesion activation[39]. Chavolla-Calderón *et al*[40] demonstrated that the derangement of the substance P receptor protects against pulmonary inflammation.

Finally, it has been suggested that excessive lung inflammation may be the result of BD-induced impairment of the parasympathetic nervous system leading to loss of the protective cholinergic anti- inflammatory pathway[41,42]. Kox *et al*[43] have suggested that BD-associated increased intracranial pressure (ICP) may alter the immunoregulatory function of the vagus nerve, which may operate as an additional means through which the brain exerts control over cytokine expression[41]. Indeed, it has been reported that vagus nerve stimulation was followed by inhibition of TNF-α, IL-1, IL-6, IL-8 and HMGB1 release[44]. dos Santos *et al*[45] supported the protective role of the cholinergic ant-inflammatory pathway, demonstrating that vagus nerve stimulation attenuated lung injury while in contrast vagotomy exacerbated VILI.

Regardless of the responsible mechanisms, an injurious ventilatory strategy in the presence of an established inflammatory process may act as an additional stimulus that can aggravate lung damage. A "double hit" model could explain the development of organ failure associated

with acute brain injury[15]. "First hit" corresponds to the adrenergic boost and systemic production and release of inflammatory mediators that make the lungs more vulnerable to a subsequent "second hit", such as the mechanical stress induced by mechanical ventilation or the ischemia/reperfusion that may be seen in lung transplants[15].

RESPIRATORY MECHANICS AND GAS EXCHANGE

Although, as already mentioned, pulmonary dysfunction is a well-recognized complication of brain damage, it is surprising that until now very few studies have assessed respiratory mechanics in this group of patients. Moreover, although these patients usually need prolonged mechanical ventilation due to coma, few studies have assessed the impact of ventilatory settings on respiratory mechanics.

Two decades ago, Tantucci *et al*[46] studied a group of BD patients and found increased respiratory system flow resistance (Rmin,rs). Increased respiratory system resistance was also detected by Gamberoni *et al*[47] in BD patients with and, importantly, without respiratory failure. It should be noted that increased Rmin,rs was also found on the first day of mechanical ventilation in BD patients without acute lung injury[48].

Increased Rmin,rs could be attributed to bronchoconstriction, as a result of hyperventilation and consequent hypocapnia that are usually therapeutically applied in these patients. In anesthetized and paralyzed normal subjects (*i.e.*, without apparent lung pathology), D'Angelo *et al*[49] have shown that decreased partial pressure of arterial carbon dioxide ($PaCO_2$) was associated with a significant increase in Rmin,rs. However, additional factors inducing bronchoconstriction and airway mucosal edema, such as neuropeptides, cannot be excluded as potential mechanisms, since such substances appear to be released and circulate in patients with BD[38,39]. Finally, an altered control of airway caliber has been proposed as a likely explanation for the increased respiratory system resistance[47].

Increased respiratory system elastance (Est,rs) has been found in experimental[8,50] as well as in clinical BD without acute lung injury[47,48,51]. Interestingly, only one study[46] reported non increased Est,rs, but this may reflect the high tidal volumes used for ventilation in the past (15 mL/kg).

Increased extravascular lung water, a manifestation of pulmonary edema resulting from the sympathetic hypereactivity elicited by the central nervous system injury, might partially explain the aforementioned increased Est,rs. In this regard, it should be noted that, despite relatively normal chest X-rays, increased lung densities have been detected in CT scans of patients with BD[47]. In a similar respect, increased extravascular lung water along with CT scan lung densities were detected in animals soon after the induction of intracranial hypertension[10].

Finally, atelectasis, associated with anesthesia and paralysis or with impaired production/function of pulmonary surfactant as a result of brain damage, as well as alterations in chest wall mechanics, may be additional potential explanations for the increased Est,rs in this setting[7,47,48,52,53].

Gas exchange

Although hypoxemia is present in a substantial percentage of BD patients[15,47,48,54] and has been recognized as a secondary insult associated with poor neurological outcome[55-57], data on gas exchange in such patients are scarce. A moderate to severe impairment of oxygenation has been noted in patients with isolated brain injury in the absence of abnormal chest X-rays[6,58,59]. Similarly, a ratio of partial pressure of arterial of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) below the normal limit was detected on the first day of mechanical ventilation in BD patients without acute lung injury[48], while oxygenation further deteriorated after 5 d on mechanical ventilation.

Weber *et al*[8] reported that in animals with BD the degree of inflammation, as expressed by serum levels of HMGB1 were correlated with PaO_2/FiO_2. Mascia *et al*[60] found that BD patients who subsequently developed ARDS had at baseline an abnormal PaO_2/FiO_2 ratio (< 300 mmHg), and that hypoxemia was the strongest independent predictor of ARDS development. Ventilation/perfusion (V/Q) mismatch and shunt, the main pathophysiological mechanisms of hypoxemia[61] ensuing from airway closure and atelectasis due to lung surfactant depletion[7,53] and/or increased extravascular lung water[10,47] might explain oxygenation impairment.

Given that brain damage patients are usually hyperventilated for neuroprotection, data on ventilation and $PaCO_2$ disturbances are missing.

VENTILATORY STRATEGIES

Ventilatory management of brain-damaged patients presents a major challenge for physicians since the fragile lung-brain balance must be preserved. The ventilatory strategy on one hand aims at maintaining adequate oxygenation and avoiding hypercapnia in order to protect the intracranial pressure and cerebral blood flow, and thus prevent secondary brain injury; on the other hand though it should avoid VILI. In addition, it should be noted that injurious mechanical ventilation per se may cause brain activation[62] or damage to selected brain areas[63] and thus, the selection of appropriate ventilatory settings becomes of paramount importance.

According to the guidelines for the management of severe traumatic brain injury intense hypocapnia should be avoided, because it may compromise cerebral blood flow and aggravate hypoperfusion[64]. However, traditional ventilatory management of BD patients involves high tidal volumes to maintain mild hypocapnia ($PaCO_2$-30-35 mmHg) for the treatment of intracranial

hypertension accompanied by low levels of positive end-expiratory pressure (PEEP) to optimize oxygenation without impeding cerebral venous drainage[64].

Furthermore, it is well established that this ventilatory strategy can exacerbate the pulmonary and systemic inflammatory response in patients with ARDS[65]. Even in patients without ARDS, ventilation with high tidal volumes proved to have deleterious effects and to induce VILI[66]. Moreover, according to the "double hit" theory, once the lungs are primed from a severe brain injury, they may become more susceptible to the injurious effects of mechanical ventilation[15] making VILI development more probable. In this respect, it was demonstrated that apparently healthy lungs of animals subjected to massive brain-injury developed more alveolar damage under injurious mechanical ventilation[9].

In clinical settings, high tidal volume and low PEEP have been implicated in deterioration of respiratory mechanics and unfavorable outcome in BD patients. A recent clinical study reported that in patients with severe brain injury, high tidal volumes, high respiratory rates, and hypoxemia were the stronger independent predictors of ARDS development[60]. Similarly, in mechanically ventilated patients with intracerebral hemorrhage, Elmer *et al*[16] showed that high tidal volumes were among the factors associated with ARDS development. High mechanical stretch with consequent alveolar distention, alveolar epithelial and vascular endothelial disruption and inflammation[14] may have contributed to the exacerbation of lung injury and ARDS in the already primed lungs of these patients[16].

Furthermore, in BD patients without acute lung injury, application of moderate levels of PEEP for 5 d prevented lung damage, as assessed by the increased Est,rs, present in the group of patients ventilated on zero end-expiratory pressure (ZEEP)[48]. In a later study, BD patients with no apparent lung pathology ventilated with ZEEP exhibited early and sustained increases of circulating inflammatory indices as compared to patients on 8 cmH_2O of PEEP[36]. Avoiding end-expiratory collapse and maintenance of recruited alveoli by applying PEEP, may protect against "low volume" injury, that is the lung damage attributable to airway closure or heterogeneous constriction[67-72]. Atelectasis in the dependent lung zones and peripheral airway closure usually develop during general anesthesia even in normal lungs[52]. In BD patients, abnormal surfactant production due to injury of pneumocytes Ⅱ[7] or release of inflammatory mediators could enhance peripheral airway closure and atelectasis formation. Under these disorders, opening and closing of peripheral airways during tidal breathing would be possible, leading to the development of shear stresses that can damage peripheral airways[67]. In the presence of airway closure there is heterogeneous lung filling and emptying, conditions which might contribute to lung injury[73-75].

Application of PEEP in mechanically ventilated brain-injured patients has been considered controversial. Although PEEP can optimize oxygen delivery to the brain[54,76], it may result in raised mean intrathoracic pressure and therefore might increase ICP through reducing venous drainage. Additionally, the increased intrathoracic pressure could lead to a decrease in arterial pressure, which in turn may decrease cerebral blood flow in patients with impaired cerebral autoregulation[77].

Clinical studies addressing the effect of PEEP in BD patients have mainly focused on the ICP and cerebral perfusion pressure (CPP) showing conflicting results[78-80]. The Starling resistor model serves the most suitable interpretation of the PEEP effect on the ICP[81]. Luce *et al*[81] documented in an animal study that the consequences of PEEP on ICP were more evident whenever the applied PEEP was higher than ICP. Later, McGuire *et al*[82], in a clinical study, provided evidence that PEEP levels up to 15 mH_2O were not transmitted to central nervous system if baseline ICP values were higher than the applied PEEP.

Unexpected findings have been reported by Huynch *et al*[83] who have shown that increases in PEEP up to 15 cmH_2O, in 5 cmH_2O increments, correlated with reduction in ICP and augmented CPP. Nevertheless, no physiologic explanations have been provided for these findings.

Decrease in mean arterial pressure as a consequence of increased intrathoracic pressure has been implicated as a responsible mechanism of PEEP-induced decrease in CPP. An observational study involving patients with subarachnoid hemorrhage demonstrated that restoration of mean arterial pressure returned CPP to baseline, supporting a PEEP-dependent decrease of the former as the underlying mechanism of CPP reduction post PEEP application, rather than an increase in ICP[84]. In this regard, Doblar *et al*[85] showed that euvolemia, achieved with hypertonic volume expanders, averted an undesired reduction in arterial and cerebral perfusion pressure after application of various levels of PEEP.

The elastic properties of the respiratory system and its components could have an impact on the PEEP effect on ICP. In cases of low chest wall compliance or normal lung compliance, PEEP may increase intrathoracic pressure. On the contrary, reduced lung compliance could exert a protective role by minimizing airway pressure transmission[86]. However, clinical studies investigating the influence of respiratory system mechanics on the transmission of PEEP to the intracranial compartment have reported conflicting results[78,87]. Caricato *et al*[51] found that PEEP application resulted in reduction of CPP only in patients with normal respiratory system compliance, but had no effect on ICP regardless of the latter. Recently, a clinical study in patients with hemorrhagic stroke and respiratory system compliance within normal range displayed that, although PEEP up to 14 cmH_2O significantly increased ICP, arterial and cerebral perfusion pressures were not affected and thus the observed increases in ICP were not clinically meaningful[88].

Application of PEEP may affect cerebral circulation through CO_2-mediated mechanisms[89]. An increase in

$PaCO_2$ directly causes vasodilation of cerebral arteries and a consequent increase in cerebral blood volume, which might result in a rise in ICP if intracranial compliance is reduced. In patients with severe brain injury and acute lung injury, Mascia *et al*[60] studied the cerebro-pulmonary interactions during the application of low PEEP levels. In brain-damaged patients with "relatively normal" ICP, these investigators found that when the application of PEEP induced hyperinflation with consequent increase in $PaCO_2$, the ICP increased; in contrast when PEEP resulted in alveolar recruitment there were no effects on ICP and cerebral perfusion.

Despite the aforementioned clinical and experimental studies, the ideal ventilation strategy for patients with massive brain damage has not been clarified. The "open lung" approach which integrates the use of low tidal volumes with high PEEP, despite its beneficial effect on morbidity and/or mortality in ARDS patients, has not been extensively studied in brain-injured patients. Wolf *et al*[90] found that an "open lung" approach, consisting of low tidal volumes and elevated PEEP levels after performing recruiting maneuvers, improved respiratory function in neurosurgical patients with severe respiratory failure without generating negative effects on cerebral physiology. A recent animal study demonstrated that an "open lung" approach, consisting of low tidal volumes and PEEP set according to the minimal Est,rs, attenuated lung injury in rats with massive brain damage[90]; however neurological parameters and therefore the potential impact of the open lung strategy on brain damage were not evaluated in this study.

At present, it seems that the use of low tidal volume to avoid overdistention, and of moderate levels of PEEP to improve oxygenation and to avoid "low volume" injury, may be appropriate in patients with brain damage; however mean arterial pressure should be preserved and close attention to ICP and CPP alterations should be given.

CONCLUSION

Several clinical and experimental studies have confirmed that lung injury occurs shortly after brain injury. Brain-damaged patients without acute lung injury exhibit alterations of respiratory system mechanics, mainly increased respiratory system elastance and airway resistance, and hypoxemia. Ventilatory management of such patients should aim at optimizing neurologic protection, but at the same time at preventing further deterioration of respiratory dysfunction. Modifiable ventilator parameters possibly associated with improved outcome include low tidal volumes and moderate levels of PEEP. Nevertheless, more studies are needed to elucidate the potential beneficial role of an "open lung"approach in brain-damaged patients with respiratory compromise.

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P- Reviewer: Rocco P **S- Editor**: Qiu S **L- Editor**: A
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