April 17, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17038-review.docx).

Title: Brain-lung crosstalk: implications for neurocritical care patients

Author: Ségolène Mrozek, Jean-Michel Constantin, Thomas Geeraerts.

Name of Journal: *World Journal of Critical Care Medicine*

ESPS Manuscript NO: 17038

The manuscript has been improved according to the suggestions of reviewers:
1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

(1) The authors discussed the pathophysiological aspects in detail, but based on the current data the clinical management of pulmonary problems is not clearly defined. The authors need to add a subtitle for clinical management of pulmonary problems in TBI patients. Additionally an approach/managements algorithm would be beneficial for the reader.

We agree with this comment and we have added in the revised manuscript page 15-16, a subtitle 4. Clinical management of lung injuries in brain-injured patients: "*In clinical practice, there is actually no recommendation for ventilator strategy of brain-injured patients except for PaO_2 and $PaCO_2$ targets*[132].

Treatment of VAP is not specific for patients with cerebral injuries but it is important to note that prevention seems to be a key point. Treatment of VAP has to be started quickly as VAP is associated with higher mortality rate and poor neurologic outcome. It may follow the guidelines for hospital-acquired and ventilator-associated pneumonia[163]. *Risk factors of VAP in brain-injured patients are numerous and prophylactic measures have to focus on these, including oral care*[23, 104, 164]. *The high rate of VAP in brain-injured patients is, in part, explained by long duration of mechanical ventilation*[165]. *So Roquilly et al. reported in a before/after evaluation of an extubation readiness bundle, a decrease of duration of mechanical ventilation in patients with brain injury*[166]. *The bundle components were 1/ protective ventilation (Vt: 6-8 ml/kg PBW, PEEP > 3 cmH_2O) 2/ early enteral nutrition (initiation day 1 and 25 kCal/kg/d before day 3) 3/ optimization of the probabilistic antibiotherapy for VAP and 4/ a systematic approach of extubation (ventilator weaning and removal of tube if Glasgow Coma Scale ≥10 and cough). Despite a compliance with bundle elements of 21% in the intervention phase, they observed a reduction of duration of mechanical ventilation, rate of VAP and rate of unplanned extubation compared to the control observational phase. In acute stroke, the major measure is to avoid per os nutrition until swallowing is evaluated and validated*[167-169]. *No difference has been found between percutaneous gastrostomy or nasal feeding tube in terms of rate of pneumonia but percutaneous gastrostomy tube seems to be safer and more effective for feeding*[170]. *For TBI, in front of traumatic-induced adrenal insufficiency, the use of stress-dose steroids during initial management are still debated for prevention of VAP but literature doesn't allow us to provide an answer*[102].

Concerning NPE, few studies have reported specific treatment in humans. Some animal studies have focused on α-blockers treatment to limit massive sympathetic discharge after brain injuries[49, 171]. *Two cases of*

human NPE were published about use of adrenergic blocker (phentolamine or chlorpromazine) and successful treatment with improvement of hemodynamic instability and oxygenation[172, 173]. Further studies are needed to explore this way. But the key point of NPE management is to treat the underlying cerebral injuries to decrease ICP, mitigate the sympathetic discharge and improve oxygenation[42, 49].

Concerning ARDS, protective ventilation has been largely discussed in the previous section. An accurate monitoring of macrohemodynamic, respiratory and cerebral parameters are needed to optimize the management.

When a brain-injured patient presents hypoxia, all diagnoses evoked in this review could be discussed. The figure 2 summarizes different steps of management and prevention of respiratory failure in brain-injured patient. The response of the cardiopulmonary system varies widely among patients with brain injury (direct myocardial injury, non-cardiogenic mechanisms etc…). So first of all, it is important to evaluate cardiac function to adapt our management and initiate treatment of cardiogenic failure if necessary. Moreover, normalization of ICP is an important step to decrease sympathetic discharge and its consequences. Criteria of VAP, ARDS and NPE have to be researched and for some patients in which difference between NPE and ARDS could be difficult, measurement of serum catecholamines may be helpful[49]. ". Moreover, we completed the revised manuscript with an algorithm approach for pulmonary dysfunction in brain-injured patient (figure 2), page 30.

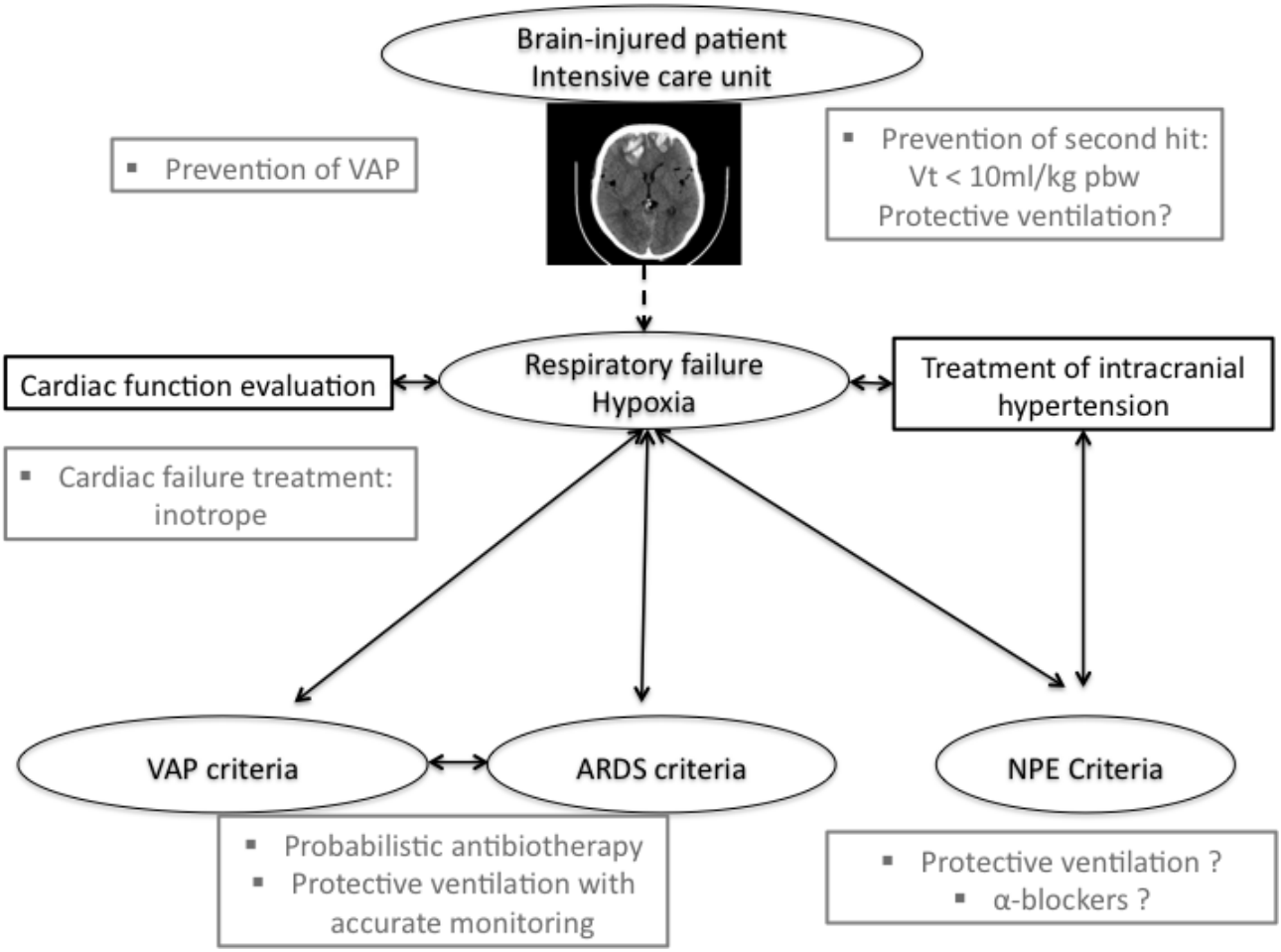


Figure 2. Algorithm approach for pulmonary dysfunction in brain-injured patient. *ARDS: acute respiratory distress syndrome. VAP: Ventilator-associated pneumonia. Vt: tidal volume. pbw: predictive body weight. NPE: neurogenic pulmonary edema.*

(2) In recent years pituitary dysfunction has been reported in substantial percentage of the TBI patients. In the acute phase of TBI around 25-50 % of the neurocritical care patients were reported to develop ACTH deficiency (secondary adrenal failure) due to head trauma. The HPA axis (hypothalamo-pituitary adrenal axis, which the cortisol is the end hormone) has important effects on stress response and systemic inflammatory response. The authors need to add experimental and/or clinical data regarding the possible relation between HPA axis dysregulation and pulmonary response after TBI.

We have added in the revised manuscript, page 9-10, in section **2. Pathophysiology of brain-lung crosstalk, Brain to lung pathway**, a paragraph about possible relation between HPA axis and lung dysfunction in patients with brain injuries:

"*Hypothalamo-pituitary adrenal axis (HPA axis)*

Since several years, HPA axis in brain injury has been explored in experimental and clinical studies and it could participate to lung dysfunction. Indeed, it has major effects on stress and systemic inflammatory response after trauma[81, 82]. In the initial phase of trauma, inflammation mediators, such as IL-6, activate massively HAP axis to induce an initial hypercortisolism, main effector of compensatory anti-inflammatory response syndrome (CARS)[81, 83, 84]. This hypercortisolism allow decreasing deleterious effects of inflammatory response, as its spread in organism and protect also other organs[82, 85]. Moreover, endogenous glucocorticoids stimulate anti-infectious immunity[86] and HAP axis has major role in hemodynamic response and maintain of blood pressure[87, 88].

After traumatic brain injury, 25-50% of patients present an acute secondary adrenal insufficiency[89-92]. These patients had worse outcomes and neurologic prognostic, lower arterial pressure, greater vasopressor use and higher mortality rate[89, 90, 93, 94]. Moreover, trauma-induced adrenal insufficiency is correlated with systemic inflammatory response syndrome[95]. Patients with adrenal insufficiency have longer high plasma IL-6 levels than patients with normal adrenal response to stress[90, 96]. In multiple-injured patients, persistence of high IL-6 plasma level at day 7 is associated with higher mortality rate and incidence of pneumonia[97]. Persistence of systemic inflammatory response syndrome seems to be predictive of nosocomial infection in trauma patients[98, 99]. The principal theory is that secondary adrenal insufficiency exposes patients to deleterious effects of uncontrolled systemic inflammation with immunodepression, nosocomial infections, especially VAP and overwhelming inflammatory response [91, 99, 100]. So this HAP axis dysfunction could participate to weaken the lung after TBI.

A multicenter, randomized trial reported in 150 intubated patients with severe trauma and corticosteroid insufficiency, a decrease risk of hospital-acquired pneumonia with stress-dose of hydrocortisone, particularly in the sub-group of patients with severe TBI[101]. However, this result was not confirmed with recent trial in patients with severe TBI[102]. Stroke-induced immunodepression has been described with HAP axis-related abnormalities following acute ischemic stroke[103] and is probably implicated in high incidence of pneumonia[104].".

(3) Please check the incidence of acute respiratory distress syndrome in patients with ischemic stroke carefully in the second paragraph of acute respiratory distress syndrome section regarding reference #4. Please check how the severity of the initial brain injury is revealed with Glasgow Coma Scale score in the third paragraph of Acute respiratory syndrome section regarding reference #31, 35, and 36.

We have checked the incidence of ARDS in patients with ischemic stroke according to the reference 4. This is the prevalence of ARDS in admissions of patients with stroke and the authors concluded that ARDS is rare in stroke. We have specified in the revised manuscript that this is the incidence of admissions with a diagnosis of stroke and ARDS: "*A recent retrospective study conducted from 1994 to 2008 in the United States of America reported an incidence of ARDS in admissions of patients with acute ischemic stroke of 4%*" and we added another reference: "*Aspiration-related ARDS was diagnosed in 3.6% patients in another recent retrospective cohort study on 1495 patients with acute stroke[34]*."

We have checked the reference 31, 35 and 36 for the severity of the initial brain injury. The reference 31 has

also been removed because it was not relevant. Contant *et al.* (ref 35) reported significant effects (final exact logistic regression model) of presence of midline shift on CT scan for the development of ARDS. Moreover, patients who developed ARDS had higher ICP and more refractory intracranial hypertensions. Bratton *et al.* (ref 36) observed that lower Glasgow Coma Scale scores, periods of increased ICP and worse global CT findings on the initial scan were more frequent in patients who developed ALI. On Day 1, 60% patients with ALI presented GCS of 3-4 vs. 41%patients without ALI ($p< 0.03$). So we complete in the revised manuscript the following sentence: "*First, the severity of the initial brain injury revealed by low Glasgow coma score (GCS 3-4) and initial cerebral computed tomography (CT) scan abnormalities (midline shift and global CT findings)* [36, 37]".

(4) Please check the reference citations in the manuscript carefully.

We have checked carefully the reference citations in the revised manuscript.

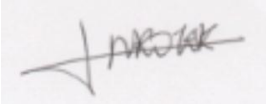
(5) Please check the reference number in Table carefully.

We have checked the reference numbers in Table and corrected according to the novel references.

3. References and type setting were corrected

Thank you again for publishing our manuscript in the *World Journal of Critical Care Medicine.*

Sincerely yours,



Ségolène MROZEK, MD
Anesthesiology and Critical Care Department
Equipe d'accueil "Modélisation de l'agression tissulaire et nociceptive"
University Hospital of Toulouse
Toulouse, France.
Tel: +33 5 61 77 21 67
Fax: +33 5 61 77 21 70
E-mail: mrozek.s@chu-toulouse.fr