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## **Crosstalk between brain, lung and heart in critical care**

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## **Crosstalk between brain, lung and heart in critical care**

### **Abstract**

Extracerebral complications, especially pulmonary and cardiovascular, are frequent in brain-injured patients and are major determinants of the outcome. Two major pathways have been described: brain-lung and brain-heart interactions. Lung injuries after acute brain damages include ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS) and neurogenic pulmonary oedema (NPE), whereas heart injuries can range from cardiac enzymes release, ECG abnormalities to left ventricle dysfunction or cardiogenic shock. The pathophysiologies of these brain-lung and brain-heart crosstalk are complex and sometimes interconnected. This review aims to describe the epidemiology and pathophysiology of lung and heart injuries in brain-injured patients with the different pathways implicated and the clinical implications for critical care physicians.

### **Keywords:**

Acute respiratory distress syndrome; brain injury; brain-lung crosstalk; brain-heart crosstalk; cardiomyopathy; neurogenic pulmonary oedema

## **Introduction**

Extracerebral complications, especially pulmonary and cardiovascular, are frequent in brain-injured patients and are major determinants of the outcome [1,2]. Two major pathways have been described: brain-lung and brain-heart interactions. The lung appears to be more “vulnerable” to aggression in case of brain injury. Lung injuries after acute brain damages include ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS) and neurogenic pulmonary oedema (NPE), whereas heart injuries can range from cardiac enzymes release, ECG abnormalities to left ventricle dysfunction or cardiogenic shock. These extracerebral complications can occur after traumatic brain injuries (TBI), subarachnoid haemorrhage (SAH), acute ischemic stroke (AIS), intracerebral haemorrhage (ICH), epileptic seizures or central nervous system infections. The pathophysiologies of these brain-lung and brain-heart crosstalk are complex and sometimes interconnected. This review aims to describe the epidemiology and pathophysiology of lung and heart injuries in brain-injured patients with the different pathways implicated and the clinical implications for critical care physicians.

### **1. Lung and heart injuries after acute brain damages**

#### **1.1 Lung injuries**

The main pulmonary complications in brain-injured patients are ventilator-associated pneumonia (VAP), acute respiratory distress syndrome (ARDS) and neurogenic pulmonary oedema (NPO). Two observational studies conducted in patients with severe TBI described the incidence of various extra-cerebral damages [1,2]. Eighty-one percent of patients developed respiratory dysfunction ( $\text{PaO}_2/\text{FiO}_2 = 226\text{-}300$ ), with a  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 150$  in 23% of patients in 209 patients with severe TBI [1]. Another study on 154 severe TBI reported respiratory complications as the most common with 61% of patients[2]. These non-neurological organ failures, in particular in intensive care unit (ICU), seem to be more common in brain-injured patients, even if they are younger, with less comorbidities highlighting specific pathophysiology.

### **Ventilator-associated pneumonia (VAP)**

Pneumonia and VAP are commonly found in brain-injured patients due to the alteration of the level of consciousness and inhalations or even micro-inhalations. Risk factors for VAP in brain-injured patients have been identified such as the use of barbiturates, nasal carriage of *staphylococcus aureus*, gastric aspiration before intubation, therapeutic hypothermia and severe thoracic lesions [3,4]. In addition, the use of mechanical ventilation, sedation and curare, a previous administration of antibiotics and the lack of head-up position during mechanical ventilation increase the risk of VAP [5]. Brain injury-induced immunosuppression contributes to the development of infectious diseases [6].

The incidence of VAP in patients with severe TBI varies between 21 and 60% [2,4,7]. Methicillin-sensitive *staphylococcus aureus* (MSSA) is the bacterial pathogen the most commonly found in VAP in patients with TBI. Early enteral nutrition and oral care would reduce the incidence of VAP in neurological ICU [7,8]. Pelosi et al. have reported higher rates of VAP in patients with TBI compared to patients with AIS or SAH and to patients without neurological involvement [9]. Cinotti et al. have described an incidence of VAP of 49% in a retrospective analysis of 193 patients with SAH who were mechanically ventilated and MSSA was the most common pathogen [10]. Kasuya et al. have reported an incidence of VAP of 28% in 111 mechanically ventilated patients with stroke. The presence of a chronic pulmonary disease, high severity score at admission, and the presence of haemorrhagic transformation were independent risk factors for the occurrence of VAP. The most commonly identified pathogens were MSSA and methicillin-resistant *Staphylococcus aureus* (MRSA) in this cohort [11].

### **Acute respiratory distress syndrome (ARDS)**

The incidence of ARDS is high in brain-injured patients. The criteria used to define ARDS in most studies are those of the European-American Consensus Conference. A prospective study conducted in 192 patients with neurological involvement (SAH, subdural haematoma (SDH), TBI and AIS) has reported a 35% incidence of ARDS [12]. Other studies have found an incidence ranging between 19 and 35% in patients with a Glasgow score < 9 [12–14]. About 20-25% of patients with isolated TBI [15,16] and 20-38% of patients with SAH [17–19] will develop ARDS. A recent retrospective US study conducted over the 1994-2008 period has reported an incidence of ARDS of 4% in patients with AIS [20].

Risk factors for the development of ARDS have been clearly identified in these brain-injured patients: First, the severity of the initial brain damage represented by a low Glasgow score and severe initial lesions on Computed Tomography (CT) scans. Second, the presence of induced hypertension, vasoactive drug administration and a history of drug abuse have been identified as independent risk factors for ARDS in patients with TBI [21]. Lastly, more general risk factors have been reported such as young age, male gender, some ethnicities, a history of chronic hypertension, diabetes, chronic obstructive pulmonary disease (COPD), the occurrence of sepsis, the presence of cardiovascular, kidney and haematological dysfunction [16,20]. Mascia et al. have studied the ventilatory management of 82 patients with TBI in a multicentric, prospective, observational study. Twenty-two percent of patients developed ARDS and their initial tidal volume (Vt) was greater than that of patients who did not develop ARDS. The proportion of ARDS increased in a dose-dependent manner with Vt adjustment. Seventy-two percent of patients who developed ARDS had within the previous days a Vt  $\geq$  10 mL/kg of ideal predictive bodyweight (IPB) [14]. The ventilatory management of brain-injured patients seems to be a key point in the development of ARDS and is part of the "double hit" concept where the lung, weakened by an inflammatory environment, is vulnerable to any other aggression such as a too high Vt. Indeed, clinicians are often tempted to set high Vt to achieve the objectives of PaCO<sub>2</sub>, major determinant of secondary brain injuries. The objectives of PaCO<sub>2</sub> should not be reached by an increase in Vt but rather by an increase of respiratory rate (RR).

The temporal distribution of the occurrence of ARDS is bimodal with an early peak on day 2-3 after the implementation of mechanical ventilation and a second later peak on day 7-8 [22], often associated with the occurrence of pneumonia [4].

### **Neurogenic pulmonary oedema (NPE)**

NPE was described more than a century ago and is defined as a clinical entity associating an acute onset of protein-rich pulmonary oedema after significant central nervous system damage such as TBI, SAH, AIS, spinal cord injury, status epilepticus, meningitis or SDH in the absence of other possible causes [23].

In a review of the literature reporting NPE cases from 1990 to 2003, the most common associated neurological involvement was SAH (42.9%) with symptom onset less than 4 hours after brain injury in 71% of patients. The mortality of NPE patients was high

(about 10%) but in patients who survived, symptoms improved rapidly (in less than 72 hours for 52.4% of patients) [24]. Rogers et al. have published a large series of autopsies of brain-injured patients who died immediately or within 96 hours after brain injury. The diagnosis of NPE was based on the presence of pulmonary oedema, congestions and haemorrhages associated with an increase in lung weight. In patients with isolated TBI who died immediately, the incidence of NPE was 32%. It reached 50% in patients who died within 96 hours. An inverse correlation between the cerebral perfusion pressure (CPP) and the PaO<sub>2</sub>/FiO<sub>2</sub> ratio was observed even when the chest X-ray was considered normal [25]. In patients with SAH due to ruptured aneurysm, the incidence of NPE varies between 2 and 25% according to studies [18,26–28]. It seems to be higher in fatal SAH [29]. For patients with AIS, a retrospective analysis of 210 patients with AIS or transient ischemic attack reported around 18% of pulmonary oedema independently of cardiac abnormalities [30]. The true incidence of NPE is difficult to evaluate, as definition criteria are variable according to study, and cardiac implication has to be remote that is not easy in retrospective study. Risk factors such as older age, time to surgery, vertebral artery surgery and initial clinical and radiological score (Hunt-Hess and Fisher score) severity have been identified [27,31].

The distinction between NPE and ARDS is sometimes difficult. Based on the consensus definition of ARDS, NPE may be considered as a form of ARDS. Thus, some authors have proposed to use the following diagnostic criteria for NPE: 1. Radiological bilateral infiltrates; 2. PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 200; 3. Absence of evidence of left heart failure; 4. Presence of severe central nervous system involvement leading to increased intracranial pressure (ICP); 5. Absence of other causes of ARDS (such as inhalation, massive blood transfusion or sepsis) [32].

### **Prognosis and lung impairment**

Pulmonary involvement is therefore common and may lead to significant consequences in these brain-injured patients by directly affecting their prognosis. Respiratory failure and mechanical ventilation are indeed independent risk factors for increased mortality, worsening of neurological outcome in brain-injured patients [19,33,34] and are associated with an increased length of stay in ICU and in hospital [20,35]. In a multicentric, prospective, observational study, Pelosi et al. have assessed the prognosis of intubated and mechanically ventilated patients with various cerebral damages (362 patients

with AIS or ICH and 190 patients with TBI) by comparing them to neurologically unaffected patients [9]. Respiratory involvement was the most common non-neurological organ dysfunction. In addition, brain-injured patients requiring mechanical ventilation showed a longer length of stay in ICU and increased mechanical ventilation duration with a more common use of tracheostomy, a higher incidence of VAP and a higher mortality than "non-neurological" patients. In patients with severe AIS, a 3-fold increase in mortality rate is reported when VAP occurs [36]. In all cases, the occurrence of ARDS increased morbidity and mortality in brain-injured patients [14,15,18–22,27,33,37]. Occurrence of ARDS after TBI leads to a 3-fold increase in hospital mortality [16]. The occurrence of NPE after SAH is associated with increased cardiac Troponin I (cTnI) plasma levels [38] and mortality [27,28]. However, multivariate analyses evoke that NPE may not be an independent factor of worse clinical outcome [18,26].

## **1.2 Cardiac injuries**

Cardiac impairments represent common extracerebral complications in brain-injured patients and range from simple electrocardiographic (ECG) modifications to left ventricular wall motion abnormalities with cardiogenic shock [39]. A particular entity, after acute brain injuries, defined with transient left ventricular dysfunction, ECG changes and elevation in cardiac enzymes is commonly referred in literature such as "neurogenic stunned myocardium" or "neurogenic stress cardiomyopathy (NSC)" [40]. However, tremendous heterogeneity of criteria definition exists [40]. NSC has presentation similarities with stress cardiomyopathy (SCM) occurring in a stressful event. Whether SCM and NSC are different presentations of a common pathophysiologic pathway or represent two different clinical entities remains unclear, and some authors consider them as one single entity [41], but others highlight significant differences [42].

### **ECG abnormalities**

A wide variety of ECG abnormalities is reported such as Q–T interval prolongation, long Q-T syndrome, U-wave, S-T segment depression, T-wave inversion or ischemic-like ECG changes. Moreover, ventricular and supraventricular (atrial fibrillation, atrial flutter) arrhythmias, sinus bradycardia, sinus tachycardia and *torsade de pointes* are frequently described in acute brain injuries. ECG abnormalities are most often seen in the anterolateral



and inferolateral leads. So confusion with subendocardial infarction or anterolateral ischemia is frequent [43]. However, risk factors are common for artery coronary disease and ischemic stroke and coexistence of these two pathologies are not excluded. These abnormalities are more frequent in SAH and ICH [43,44] and 40% to 85% of these patients have at least one ECG abnormalities [45–47]. Sinus bradycardia and tachycardia are the most frequent arrhythmias in SAH; atrial fibrillation, atrial flutter and supraventricular tachycardia are others described arrhythmias. When cTnI is increased in patient with SAH, ventricular arrhythmias are more frequent and is associated with increased mortality [48]. For AIS, incidence of ECG abnormalities is around 15% to 65% [42]. For TBI, only few studies reported ECG abnormalities with an incidence from 60% to 100% [49,50].

### **Cardiac Biomarkers**

Cardiac involvement after acute brain injuries can be expressed by myocardial necrosis enzyme (cardiac troponin: cTn) release and increased B-type natriuretic peptide (BNP). For SAH, the incidence of cardiac biomarkers release varies from 10 to 70% with a mean frequency at 35% according to different studies and meta-analysis [48,51]. cTn is the most sensitive and specific biomarker of myocardial injuries among others biomarkers for SAH. The troponins I and T (protein subunits, cTnI and cTnT) are specific cardiac isoforms and so are widely used for identification of cardiac damages after SAH [52]. BNP biomarker is a vasoactive hormone with natriuretic, diuretic and vasodilator activity. It reflects left cardiac dysfunction, wall stress or hypertrophy. It is mainly expressed in the ventricles in response to cardiac overload and results from myocyte stretch [51]. However, BNP is not heart specific and can be produced in brain tissue especially in the hypothalamus [53]. High sensitive troponin and N-terminal BNP (Nt-proBNP) are currently used with high specificity for myocardial injuries in patients with SAH [51]. Increase in these biomarkers is correlated with clinical and radiologic severity of SAH, regional wall motion abnormalities (RWMAs) and arrhythmias incidence. Plasma cTnT levels reach their peak rapidly on admission whereas NT-proBNP levels peak at day 2-day 4 [54].

For AIS, levels of troponin and cTnT are increased in 5 to 34% of patients and are especially correlated with stroke severity on admission and insular cortex injuries [55,56]. The release can be due to concomitant coronary and heart diseases, neutrally mediated myocytic damages or non-cardiac comorbidities [57,58]. BNP and Nt-proBNP levels are

frequently increased in patients with AIS and higher in patients with cardioembolic stroke. Their levels are correlated with severity of AIS (clinical severity score, as the National Institute for Health Severity Score (NIHSS), and volume infarct size) at admission [59].

For ICH, few studies have been reported about cardiac biomarkers. Troponin levels are increased in 27 to 41% of patients with ICH in a recent studies [60,61]. Their levels are correlated with clinical severity on admission [61]. NT-proBNP levels are correlated with haematoma size and amount of intraventricular blood [62].

For TBI, several studies have reported elevated levels of troponin with an incidence around 30% [63]. Higher values are correlated with lower Glasgow coma scale (GCS) and higher injury severity score (ISS) and head Abbreviated Injury Scale (AIS) values [49]. NT-proBNP levels peak on the third day and are correlated with severity of TBI. Levels are higher in patients with intracranial pressure (ICP) > 15 mmHg and with large intra-axial lesions. Levels of NT-proBNP can increase when haemorrhage and oedema increase [64].

### **Regional wall motion abnormalities (RWMA) and echocardiographic changes**

Cardiac impairment after acute brain injuries can result in left ventricular regional wall motion abnormalities (RWMA), global hypokinesia, diastolic dysfunction or NSC, including Takotsubo cardiomyopathy, a particular form of myocardial dysfunction. The early systolic dysfunction in this context is most often reversible with a recovery rate from 66% to 100% within 1 or 2 weeks after acute brain injuries [42,65].

Incidence of these cardiac impairments is variable according to severity of SAH. For RWMA, incidence varies from 2% to 28% [42,48] and for diastolic dysfunction from 70% to 85%, but few studies have reported this last dysfunction [42]. A recent meta-analysis reported RWMA in 9 to 71% of patients with a mean at 22% (17 studies) [51]. Global hypokinesia, defined as left ventricular ejection fraction (LVEF) < 50%, occurred in 10% to 15% [48,66,67] in patients with SAH. Incidence increases when LVEF cut-off increases with 20% when LVEF < 55% [68] and 63% when LVEF < 60% [69]. Takotsubo cardiomyopathy has been reported after acute brain injuries and is a particular form of myocardial dysfunction with RWMA. The typical form is an apical ballooning syndrome with acute transient apical and circumferential mid-ventricular hypokinesia and basal hypercontractility associated with electrical changes and minimal myocardial enzymatic release [70,71]. This typical form has been frequently reported in non-neurogenic Takotsubo cardiomyopathy. Conversely,

particularly in patients with NSC or pheochromocytoma, inverted Takotsubo or basal variant has been reported with circumferential basal hypokinesia and apical hypercontractility [71]. Cardiogenic shock might be present in patients with NSC as a result of severe left ventricular dysfunction but can be aggravated by concomitant mitral regurgitation due to acute papillary muscle dysfunction or by systolic anterior motion and left ventricular outflow tract obstruction promoted by hyperdynamic myocardial function [72]. For AIS, systolic dysfunction and RWMA have been reported on echography with an incidence from 10 to 30% [42,73]. Patients with higher NIHSS have lower LVEF and more mitral regurgitation compared to those with lower NIHSS [74]. Porto et al. reported systematic review of transient regional left ventricular dysfunction triggered by neurological disorders. Among 124 patients reported in 81 selected papers, 42% presented SAH and 19% presented AIS/transient ischemic attack so AIS was the second most frequently brain injury leading to transient left ventricular dysfunction [75]. For ICH, few data have been reported about left ventricular dysfunction or RWMA. Putaala et al. noted among 948 patients with ICH, 3,8% of acute heart failure [76]. For TBI, several cases report (around 20) have described Takotsubo cardiomyopathy [42]. Two prospective studies in severe TBI reported neither RWMA nor global hypokinesia at admission [77,78]. However, Prathep et al. showed in retrospective study of 139 patients with TBI 12% of patients with reduced LVEF and 17% with RWMA (majority of TTE was performed between D1 and D3) [79]. Two other recent prospective studies about moderate-to severe TBI found an incidence of 13% (LVEF < 55% or RWMA) [80] and 22% (fractional shortening < 25%) [65] of cardiac dysfunction. In the last study, all patients recovered their cardiac function within a week after TBI. Hasanin et al. reported 28% of abnormal echocardiography in 50 patients with severe TBI (prospective study) [81].

Recently, two-dimensional speckle tracking images or 2D strain with echocardiography, usually used for patients with chronic cardiac impairment, has been developed and used even in intensive care unit. Some authors reported evaluation of systolic function with global longitudinal strain (GLS) in patients with acute brain injuries. Cinotti et al. found up to 37% of severe SAH with severe GLS impairment (GLS > -16%) that improves promptly within a week whereas only 10% had altered LVEF (< 50%) [82]. However, Dalla et al. compared different parameters to evaluate cardiac dysfunction in patients with SAH. In patients with myocardial injury defined with an increase of troponin levels, 13% had altered LVEF (< 50%) and 17% had altered GLS (> -15%). Authors concluded that diagnostic performance of GLS by strain

imaging is not superior to standard echocardiography for the detection of myocardial injury in SAH [66]. In patients with TBI, few studies reported contradictory results. Cuisinier et al. found no altered GLS in 20 patients with severe TBI [78], whereas Krishnamoorthy et al. reported 38% of systolic dysfunction using LVEF (< 50%) and 38% using GLS (> -16) in 15 patients with moderate-severe TBI. Regional myocardial impairment was primarily in the basal and mid-ventricular segments [83].

### **Prognosis and cardiac impairment**

Cardiac abnormalities are heterogeneous (ECG, cardiac biomarkers, RWMA or altered LVEF) and the impact on prognosis mainly depends on neurologic injuries: SAH, TBI, ICH or AIS. Cardiac abnormalities are associated with death and poor outcomes [42,48,49]. For patients with SAH, ventricular arrhythmias and increased of cTnI are associated with increased mortality [48]. ECG changes and biomarkers of myocardial impairment (cTn, BNP) are independently associated with poor neurologic outcome [48,84]. However, no correlation has been reported between QTc prolongation and ST-T changes and increased intracranial pressure, delayed cerebral ischemia (DCI) or mortality [85]. A recent meta-analysis concluded to an increased risk of DCI, poor outcome and death after SAH in case of RWMA, increase in cTn, BNP and NT-pro-BNP [51]. For patients with TBI, a high cTnI level is associated with higher mortality and higher multiple organ dysfunction syndrome [81]. An abnormal echocardiographic finding (reduced LVEF or RWMA) is an independent predictor of in-hospital mortality [79,81]. For patients with AIS, high cTnT level is associated with poor clinical outcome and higher mortality but the role of concomitant heart disease is still unclear for elevated troponin level [42,55,86]. For patients with ICH, cardiac complications are related with early mortality and poor outcome [87]. Thus, biomarker interpretation in patients with brain injuries must be done with caution because cardiac biomarkers are correlated to the severity of brain lesion and with outcomes but are not reliable surrogate markers of clinical cardiac dysfunction.

Table 1 summarises incidences of main pulmonary and cardiac complications according to the different acute brain injuries.

## **2. Pathophysiology of brain-lung and brain-heart interactions**

### **2.1 From the brain to the lung and the heart**

The pathophysiology of pulmonary and heart injuries after acute brain injury is still debated and several theories have been proposed, including the recent "double hit" model [88]. The response of the sympathetic system to increased ICP plays an important role in lung and cardiac impairment. Some authors explain part of NPE genesis by neuro-cardiac and neuro-haemodynamic paradigms [32]. It has been clearly demonstrated that direct myocardial lesions within the context of NSC could be involved in NPE and will be described later. The neuro-haemodynamic theory is defined by indirect ventricular compliance disorders due to a rapid increase in systemic and pulmonary pressures. Indeed, the rapid and massive blood flow transfer from the systemic circulation with high resistance to the pulmonary circulation with low resistance could lead to a hydrostatic form of pulmonary oedema. Animal models have shown increased pulmonary, systemic and left atrial pressures at the onset of NPE [89]. Although changes in hydrostatic pressure and impaired cardiac function probably play a role in the genesis of NPE, these theories do not explain the presence of red blood cells and proteins in the bronchoalveolar lavage fluid.

#### **From the brain to the lung**

##### ***From the blast theory to pulmonary venule adrenergic hypersensitivity***

Theodore and Robin have defined for the first time the blast theory in the context of NPE as an impaired vascular permeability [90]. The transient increase in intravascular pressure, resulting from the sudden increase in ICP, would damage the alveolar-capillary membrane. Thus, a damaged pulmonary endothelium would result in protein-rich plasma leakage. This theory includes the coexistence of a high hydrostatic pressure and a damaged pulmonary endothelium. Some degree of capillary hypertension seems necessary for the occurrence of this pulmonary oedema, and a pressure-dependent increase in permeability could be the common feature of NPE [91]. After this initial hemodynamic instability and massive sympathetic response, the systemic and pulmonary pressures would return to normal while the damage to the alveolar-capillary membrane would persist [90]. Some

authors have not observed any change in systemic blood pressure when NPE occurred with underlying direct pulmonary endothelial damage in brain-injured patients [92]. This concept has led to the pulmonary venule adrenergic hypersensitivity theory. Some case reports, in which patients received a continuous haemodynamic monitoring, have allowed reporting the occurrence of NPE in the absence of haemodynamic instability [92]. Thus, NPE could partly result from selective pulmonary venoconstriction after massive sympathetic discharge during acute brain injury. Indeed, the pulmonary vessels express  $\alpha$  and  $\beta$ -adrenergic receptors ( $\beta$ -ARs) which, when activated, can lead to changes in endothelial integrity [93]. Peterson et al. have administered  $\alpha$ -adrenergic blockers to anaesthetised sheep in which the ICP was progressively increased. They have reported the prevention of pulmonary oedema formation with minor effects on systemic blood pressure reinforcing the concept of a direct adrenergic action on the pulmonary vascular bed [94].

### ***Double hit model***

The inflammatory systemic response involved in the occurrence of acute brain injury seems to play a major role in the development of lung injuries [88]. In brain-injured patients, a cerebral inflammatory response is rapidly implemented with local production of proinflammatory cytokines (interleukin 1 (IL-1), interleukin 6 (IL-6), tumour necrosis factor (TNF), interleukin 8 (IL-8)) by the injured brain tissue [95]. The microglia and astrocytes are the main sources of inflammatory mediators. The alteration of the blood-brain barrier (BBB) then allows their passage into the systemic circulation through a transcranial gradient. In addition, numerous studies have shown the role of hepatic chemokines in inducing and amplifying the acute systemic response after brain injury [96]. The activation of sympathetic nerve endings after brain injury could be partly the cause of inflammation in extracerebral organs. These different phenomena could therefore lead to their dysfunctions [97]. Thus, this systemic invasion by inflammatory mediators forms an inflammatory environment or "the first hit" for the other organs. They become more susceptible to a subsequent event or "the second hit" such as mechanical ventilation, surgery, or sepsis [88] without major consequences under normal conditions. Lopez-Aguilar et al. have randomised rabbits into a control group or a brain-injured group, ventilated for 120 min with the same respirator settings followed by more aggressive mechanical ventilation. The lungs were more significantly impaired in terms of ultrafiltration coefficient, weight increase and alveolar

haemorrhage in the group of brain-injured rabbits while they were subjected to the same respiratory mechanical constraints [98]. In an experimental model of intracerebral haemorrhage, the brain and lungs have been shown to express increased levels of intracellular adhesion molecule-1 (ICAM-1) and tissue factor. The progressive recruitment of neutrophils and morphological pulmonary lesions such as altered bronchoalveolar structures were then highlighted [99]. Kalsotra et al. have also reported a significant migration of macrophages and neutrophils in the airways and alveolar spaces after brain injury in rats with increased lung production of leukotriene B4 [100]. In addition, organ donor patients in a state of brain death show a higher IL-8 concentration in the bronchoalveolar lavage fluid than healthy subjects or mechanically ventilated patients who are not in a state of brain death. The lung infiltration by neutrophils was correlated with IL-8 concentrations [101]. Recently, Heuer et al. have studied pigs with intracranial hypertension (ICHT). They have reported higher scores of inflammation, oedema and necrosis in the lungs and other organs compared to control pigs without ICHT and in the absence of hypoperfusion or hypoxemia [102]. The same team had previously compared four groups of pigs: control, with ICHT, with ARDS and with ICHT+ARDS. They had analysed the lung CT-scans of each group. The presence of ICHT alone led to an increase in lung density and exacerbated it in the ARDS group. In addition, the pulmonary gas-to-tissue ratio was decreased by ICHT in healthy and injured lungs with an increase in poorly ventilated and atelectatic areas. This pulmonary damage was exacerbated by the presence of ICHT [103].

Thus, the catecholaminergic release, along with the cerebral and systemic inflammatory reaction (first hit), creates an inflammatory environment leading to an increase in lung susceptibility to any other harmful event (second hit). This pathway is probably the bed of pulmonary damage after acute brain injury.

### ***Hypothalamic-pituitary-adrenal (HPA) axis***

For many years, the hypothalamic-pituitary-adrenal (HPA) axis has been explored in acute brain injuries in experimental and clinical studies. The HPA axis could be involved in pulmonary dysfunction due to its major effects on stress and the systemic inflammatory response after trauma [104]. During the initial phase of trauma, inflammatory mediators such as IL-6 strongly activate the HPA axis, which induces hypercorticism, the main effector of the compensatory anti-inflammatory response syndrome (CARS) [105]. Hypercorticism

alleviates the deleterious effects of the inflammatory response by spreading throughout the body and protecting the other organs [104]. In addition, endogenous glucocorticoids stimulate the anti-infectious immunity, and the HPA axis plays a key role in the haemodynamic response and in maintaining blood pressure [106].

After TBI, 25-50% of patients experience acute secondary adrenal insufficiency [107]. In addition, trauma-induced adrenal insufficiency is correlated with inflammatory systemic response syndrome [108]. Patients have higher and sustained plasma concentrations of IL-6 compared to patients with normal adrenergic stress response [109]. A persistent systemic inflammatory response also appears to be predictive of the occurrence of nosocomial infection in trauma patients [110]. In patients with acute secondary adrenal insufficiency, the main assumption is a greater exposure to the deleterious effects of uncontrolled systemic inflammation with immunosuppression and the occurrence of nosocomial infections, in particular VAP [109,110]. Thus, the dysfunction of the HPA axis could participate in the weakening of the lungs after TBI.

A multicentric randomised study conducted in 150 patients intubated after multiple trauma and with adrenal insufficiency has reported a reduced risk of developing VAP with hydrocortisone administration, especially in the subgroup of patients with cranial trauma [111]. However, these results have not been confirmed in a recent study of patients with TBI [112]. Immunosuppression has also been reported after AIS with alteration of the HPA axis [113]. It is likely involved in the high incidence of pneumonia [114].

### **From the brain to the heart**

Brain-heart interaction has been reported for decades with the Cushing reflex. The cerebral and cardiovascular systems are highly connected and the brain-heart network has been studied. However, pathophysiology of NSC is not completely understood. Different axes implicated in this complex brain-heart crosstalk will be described. Cardiac abnormalities are often more present in patients with cardiovascular comorbidities, especially for patients with AIS for which risk factors are the same. This is why prospective cohorts that include patients with cardiovascular comorbidities have often confounding factors in terms of cardiac dysfunction [57].



### ***Catecholamine hypothesis***

The term of NSC implies the pathophysiology of myocardial dysfunction due to the stress of catecholamine excess, triggered by an acute neurological injury. Several theories have been advanced: transient multiple coronary arteries spasm; microvascular dysfunction; aborted myocardial infarction with spontaneous coronary thrombolysis [115] and the catecholamine hypothesis [40]. However, only the catecholamine hypothesis, reflecting catecholamine-mediated direct myocardial injury is widely accepted [116]. Indeed, the increase sympathetic activity could explain several mechanisms, probably intricate such as diffuse coronary microvascular dysfunction, multiple epicardial arteries spasm, the transient dynamic LV outflow tract obstruction and, maybe, the presence of coronary clots with spontaneous lysis [117]. Acute brain injuries and sudden increase of intracranial pressure lead to a sympathetic storm with increase in cardiac tissue and plasma catecholamine levels [118]. Experimental studies reported immediate major local release of norepinephrine from myocardial sympathetic nerve endings [119] and hypersensitivity to norepinephrine infusion [120]. In baboon models of brain death, cardiac abnormalities were blocked by cardiac sympathectomy or denervation but not after bilateral adrenalectomy. Thus, cardiac injuries after acute brain damages result from massive endogenous release of catecholamines from myocardial sympathetic nerve terminals rather than plasmatic catecholamines [121]. These high levels of catecholamine lead to myocyte calcium overload, free radical production and adenosine triphosphate depletion resulting in ECG changes, myocardial contractility dysfunction and cell death [116]. In case of massive sympathetic release, a specific lesion, “myocardial contraction band necrosis”, has been described with hypercontraction of sarcomeric myofibrils, eosinophilic transvers band and interstitial mononuclear infiltration [122]. In NSC, cell death results in hypercontraction with appearance of contraction bands, early onset of calcification and myofibrillar injuries near cardiac innervation, whereas cell death with ischemia results in cell relaxation, necrosis and polymorphonuclear response in the compromised vascular territory [123].

There is a natural apical-basal gradient in left ventricle of  $\beta$ -adrenoreceptors ( $\beta$ -AR) and sympathetic innervation. The apex presents highest  $\beta$ -AR and lower sympathetic nerve density. Moreover, the apex is structurally more vulnerable to catecholamines than the basal regions because of larger proportion of  $\beta_2$ - than  $\beta_1$ -ARs and greater  $\beta_2$ -ARs-induced sensitivity than in basal myocytes [124]. This apical-basal gradient of  $\beta$ -ARs could explain left

ventricle kinetic abnormalities involving apical region as in Takotsubo syndrome. Conversely, some authors reported more frequent “inverted Takotsubo” or “basal variant” or “apex sparing” in patients with neurologic disorders explaining by paucity of sympathetic nerve terminals in the apex [71]. Evaluation of in-vivo myocardial sympathetic innervation with scintigraphy, left ventricle systolic function and myocardial perfusion was performed in patients with SAH. Twenty-nine percent of the patients presented sympathetic functional denervation whereas none had perfusion decrease. Moreover, authors reported a correlation between RWMA and decrease of myocardial sympathetic innervation [125].

$\beta$ -ARs morphologies can play a role in cardiac abnormalities in brain-injured patients. In physiologic levels of epinephrine,  $\beta$ 2-ARs stimulus leads to positive inotropic response by activation of the Gs stimulating protein adenylyl cyclase/Protein Kinase A pathway. However, at supraphysiologic levels of catecholamine, a negative inotropic effect has also been reported [126]. This different effect is due to a shift in  $\beta$ 2-ARs coupling (“stimulus trafficking”) with G stimulating protein signalling switch to G inhibiting protein signalling [126]. Considering apical-basal sympathetic nerve endings gradient, a differential contractile response is noted between the basal and the apical regions exposed to high catecholamines levels. And to finish, genetic polymorphism of the  $\beta$ 2-ARs can affect cardiac responsiveness to catecholamines. Zaroff et al. reported correlation between specific  $\alpha$ - and  $\beta$ -ARs polymorphisms and increased sensitivity to catecholamines in patients with SAH. Single adrenoceptor polymorphisms were associated with 3- to 5-fold increase in cardiac abnormalities whereas combinations of two of these polymorphisms had 10- to 15-fold increased risk [127]. A correlation has been described with a polymorphism of G protein-coupled receptor kinase 5, involved in post-receptor signal transduction and left ventricle apical ballooning syndrome [128]. But these correlations were not reported in other studies [129].

This question about inotropic support in case of NSC and circulatory failure or cardiogenic shock remains unsolved [71]. Indeed, activation of catecholamine receptors or their downstream pathways might worsen myocardial stunning, haemodynamic status and the prognosis [124]. The expert consensus therefore states that “the use of inotropes should be generally regarded as contraindicated in Takotsubo syndrome...” with evidence for a paradoxical negative effect of sympathomimetic drug in these patients which appears to be dose-dependent [70]. Some authors recommend favouring inotropic agents without

catecholamine toxicity such as milrinone, an inhibitor of type III phosphodiesterase that prevents the degradation of cyclic adenosine monophosphate (cAMP) within the cell, leading to increased intracellular calcium and thereby myocardial contractility independently of  $\beta$ -receptor stimulation [130]. However, even if milrinone acts independently of adrenergic receptors, it leads to modulation of calcium flux, as adrenergic pathway. Levosimendan, a calcium sensitizer that improves interaction between actin and myosin filaments, might thus be preferred, as its action is independent of calcium flux. Low-dose infusion of levosimendan may also be used rather than other inotropes [70,131]. It was successfully used in patients with TBI and cardiac dysfunction [132].

### ***The insula cortex and cardiovascular system***

The cardiovascular system is regulated via several cardio-regulatory sympathetic pathways, which are implicated in pathophysiology of the brain-heart crosstalk and so cardiac abnormalities in brain-injured patients. The insula cortex, the anterior cingulate gyrus and the amygdala are a corner stone of the brain-heart axis [133]. Cardiovascular functions are lateralised with sympathetic tone predominantly regulated in the right insular region, whereas parasympathetic effects are situated in the left insular region. In experimental and clinical studies, cardiovascular changes depended on the side of cortex stimulation: bradycardia or decrease of diastolic arterial pressure was more frequent with left insular stimulation, whereas tachycardia or increase of arterial pressure was more frequent with right insula stimulation [133]. However, recent study in 47 epileptic patients reported spatial distribution of insular stimulation with tachycardia responses predominated in the posterior insula, whereas bradycardia sites were more anterior in the median part of the insula. These findings seemed to indicate a posterior predominance of sympathetic control in the insula, whichever the side; whereas the parasympathetic control seemed more anterior [134].

In clinical practice, insular cortex injuries are associated with ECG changes, arrhythmias, cardiac dysfunction and poor outcomes [133,135]. Patients with AIS with ischemia of the right insular cortex had higher arterial pressure and norepinephrine levels [136], whereas left insular cortex injury was associated with cardiac dysfunction and RWMA [137]. The NSC may result from disinhibiting of the right insular cortex with increasing of sympathetic tone [138]. The autonomic balance can shift to sympathetic predominance and

thus lead to decrease of cardiac contractility in patients with left insular AIS [133,137]. Mazzeo et al. reported the main centres involved in the neural regulation of the cardiovascular system, which could be implicated in cardiac abnormalities in brain-injured patients such as hypothalamus, locus coeruleus, nucleus tractus solitarii, rostral ventral lateral medulla, caudal ventrolateral medulla, and periaqueductal gray [116].

The autonomic nervous system (ANS) plays therefore a major role in cardiac abnormalities after acute brain injuries. The balance of the ANS can be appreciated by heart-rate variability (HRV), low frequency (LF), high frequency (HF) and baroreflex sensitivity. These parameters have been reported in patients with SAH, AIS (involving right insula) and TBI with impairment of ANS balance [139–141].

### ***Place of inflammation***

Inflammation could participate to pathophysiology of myocardial injury in NSC. Indeed, acetylcholine inhibits the release of pro-inflammatory cytokines and so parasympathetic dysfunction may facilitate unchecked inflammation leading to myocardial damages and cell death [142]. Patients with SAH have increase of platelet activating factor, inflammatory cytokines and coagulation factors in CSF and serum that may contributing to myocyte damages [143]. In a recent study in 32 moderate-severe TBI, early systemic inflammatory response syndrome (SIRS) was frequent and the presence of SIRS criteria was associated with systolic cardiac dysfunction [144].

## **2.2 From the lung and the heart to the brain**

An extremely complex pathway involving the autonomic, neuroinflammatory, neuroendocrine and immunological systems has been described. This pathway is involved in a normal physiological state in the maintenance of homeostasis but it could contribute to the occurrence of adverse effects [145]. Two elements involved in this pathway from the lung to the brain must be distinguished: pulmonary lesions themselves such as ARDS, and mechanical ventilation.

Pulmonary lesions resulting from inadequate respirator adjustment would lead to an inflammatory response initially localised to the lung parenchyma, but may extend into the systemic circulation and other organs, including the brain. A true multi-organ failure may

then occur, resulting from these pulmonary injuries. In patients with ARDS, the leading cause of mortality is organ failure and not hypoxemia or lung failure [146]. It has clearly been shown that ARDS survivors experience cognitive deterioration including memory, language and cognitive impairments [147], and that patients with long-term mechanical ventilation experience neurological impairment with memory and cognitive impairment [148]. However, ARDS may lead to lesions in the hippocampus with memory impairment, regardless of the degree of hypoxia [149]. ARDS, like septic shock, induces neuronal damage [150]. In an animal model of ARDS (washing model), the plasma concentration of protein S-100 $\beta$  was significantly higher in pigs with washing-induced hypoxemia (ARDS) than in hypoxemia induced by decreased oxygen-inspired fraction [151]. In addition, histopathological changes were only observed in the hippocampus of pigs with hypoxemia in ARDS. The authors have concluded that cerebral lesions could only be observed in ARDS regardless of hypoxemia. Increased protein S-100 $\beta$  and NSE levels could reflect cerebral lesions and impaired BBB in patients with ARDS [150]. BBB and pulmonary barrier permeability may be impaired by these pathophysiological situations and thus allow a communication between the brain and the lung [152].

It should be noted that the presence of pulmonary injuries may worsen brain sensitivity to any new aggression. Indeed, in their previous study, Heuer et al. have reported brain damages in pigs with ARDS alone, but also a reciprocal synergistic effect between the lung and the brain with worsening of brain lesions in the ARDS+ICHT group [103]. Brain oxygen pressure (PtiO<sub>2</sub>) and brain tissue density (reflecting cerebral oedema) were decreased in all animals (ICHT, ARDS, and ARDS+ICHT) compared to control animals. The plasma concentrations of protein S-100 $\beta$  and NSE were also increased in all animals compared to the control group but more significantly in the ARDS group, as well as IL-1 $\beta$  and IL-6 concentrations. Thus, ARDS may exacerbate brain lesions in ICHT. Lung inflammation may thus reach the nervous system via humoral, cellular and neuronal pathways [152].

In addition to these pulmonary lesions, the mechanical ventilation strategy, applied daily in ICU, could alter regional cerebral blood flow and cerebral oxygenation. Bickenbach et al. have assessed PtiO<sub>2</sub> and brain metabolism in a porcine model of ARDS for 8h. Pigs were randomised into 2 groups: low Vt (6 mL/kg) and high Vt (12 mL/kg) [153]. There was no difference between both groups in terms of PaO<sub>2</sub>, PaCO<sub>2</sub> and pH. The development of ARDS led to a significant decrease in PtiO<sub>2</sub> in both groups but it increased significantly at 4h and

8h in the low Vt group compared to the high Vt group. Brain lactate levels were higher in the high Vt group at 2, 4 and 8 hours. After 2 hours, the plasma concentrations of proteins S-100 $\beta$  decreased in the low Vt group, while the plasma concentrations of IL-6 increased in the high Vt group. Ventilation with low Vt therefore improves brain tissue oxygenation compared to high Vt application in ARDS. The respirator settings may directly affect the brain, mainly through inflammatory mediators. These data stress the importance of the ventilatory management, especially in brain-injured patients.

The axis from the heart to the brain seems to be less specific in brain-injured patients in contrast of the brain-lung axis. Indeed, as we reported in previous section, cardiac abnormalities are related to death and poor outcomes with higher mortality and mortality [42,48,49] in brain-injured patients, but the causal relationship between cardiac impairment and outcomes is not understood. We can only note that cardiac impairment with bradycardia, arrhythmia, RWMA or LV hypokinesia can lead to systemic haemodynamic dysfunction or even cardiogenic shock and so worsening cerebral perfusion pressure (CPP) [154]. In the same way, sympathetic hyperactivation or autonomic nervous system balance impairment can result in arterial hypertension, tachycardia and sometimes high CPP in patient with alteration of autoregulation [154]. This high CPP leads to high cerebral blood flow and capillary hydrostatic pressure, causing cerebral oedema and intracranial hypertension.

The figure 1 represents involvement of pulmonary and cardiac complications in secondary brain damages.

### **3. In clinical practice**

We can propose a care bundle in clinical practice to prevent severe respiratory and cardiac dysfunction.

First, the use of low tidal volume decreases systemic and pulmonary inflammatory responses in patients with ARDS [155], but also in patients with inflammatory processes such as aspiration, sepsis, pneumonia or trauma. This is why Vt should be considered at admission of brain-injured patients to prevent pulmonary injuries. PEEP is necessary to prevent collapse and/or recruit collapsed alveoli and thereby reduce atelectasis, especially when low

Vt is used. Its application is also a key point of protective ventilation. PEEP could be safely used and must probably be used in brain-injured patients if the optimal PEEP is searched and adapted individually, as for patients with ARDS and a healthy brain. The use of PEEP appears to be safe, if arterial blood pressure is maintained. Euvolaemia is probably a condition that can minimise the effect of PEEP on arterial blood pressure [156]. Moreover, some authors recommend to optimise elevation of the head to enhance cerebro-venous drainage through the vertebral venous system, not subjected to intrathoracic pressure and to maintain PEEP lower than ICP to limit interference with venous outflow [156]. In parallel, recommendations about healthcare associated pneumonias in intensive care unit have to be applied to decrease incidence of pneumonia [157]. A multicentric randomised study is in progress about interest of antibioprophylaxis for brain-injured patients during 12h after intubation to prevent pneumonia [158].

The association between poor outcome, higher mortality and cardiac impairment does not imply a causal relationship. Two main questions remain unresolved: 1/Is it relevant to detect and monitor cardiac impairment? 2/Is there a specific treatment for cardiac dysfunction in patients with acute brain injuries? Few studies have compared outcomes with cardiac function monitoring or not. Mutoh et al. reported decrease in transcranial Doppler vasospasm, DCI and cardio-pulmonary complications when cardiac output was monitored using transpulmonary thermodilution and goal-directed haemodynamic management compared with standard therapy in patients with SAH [159]. However, functional outcomes at 3 months were similar between groups. The Neurocritical Care Society (NCS) Consensus Conference on the SAH advises to evaluate cardiac function with serial enzymes, ECG and echocardiography mostly for poor grade SAH. Yoneda et al. reported in 138 patients with poor grade SAH higher extravascular lung water index, pulmonary vascular permeability index and systemic vascular resistance index with lower cardiac index compared to good-grade SAH. Lower global end-diastolic volume index was present in patients who developed DCI [160]. For patients with AIS, impaired left ventricular systolic function or diastolic functions are identified as a strong predictor for poor neurologic outcomes or increased future vascular events [161]. Non-cerebrovascular complications are the main contributors to long-term morbidity and mortality in patients with AIS. Moreover, lower LVEF is a useful parameter for predictive of poor prognosis outcome in setting of AIS [74]. The question of early evaluation and maintain of LVEF in patients with AIS thus emerges progressively [74].

Effective prevention and treatment of cardiac injuries have to be shown in brain-injured patients. For TBI, beta-adrenergic blocker seems to have a protective role in this setting [49]. Indeed, several large observational studies have reported significantly improved survival after TBI for patients treated with beta-blockers compared to those who were not [162,163], especially in patients with an elevated TnI [164]. The benefit of beta-blockers was also observed when beta-blockers were introduced after TBI [165]. Significant decrease of the incidence of supraventricular tachycardia and ECG ST-T wave changes and significantly reduced catecholamine-induced stress necrosis at necropsy in 114 patients with TBI was reported in a randomised, double-blind study with administration of atenolol [166]. El-Menyar et al. proposed therapeutic strategy using beta-blockers therapy for the management of patients with moderate-to-severe TBI according to troponin level and echocardiography findings [49]. However, clinical randomised controlled studies are needed to confirm this benefit.

## **Conclusion**

Brain, heart and lungs interact in a very complex manner. In ICU, severe brain injury can induce severe heart and lung dysfunction. In brain-injured patients, the lungs are particularly vulnerable to aggression like mechanical ventilation or infection. Heart and lung dysfunction can affect brain physiology inducing genuine secondary insults to the brain. These strong interactions should be taken into consideration in ICU for brain-injured patients, by applying strategies to protect the lungs, the heart and the brain.

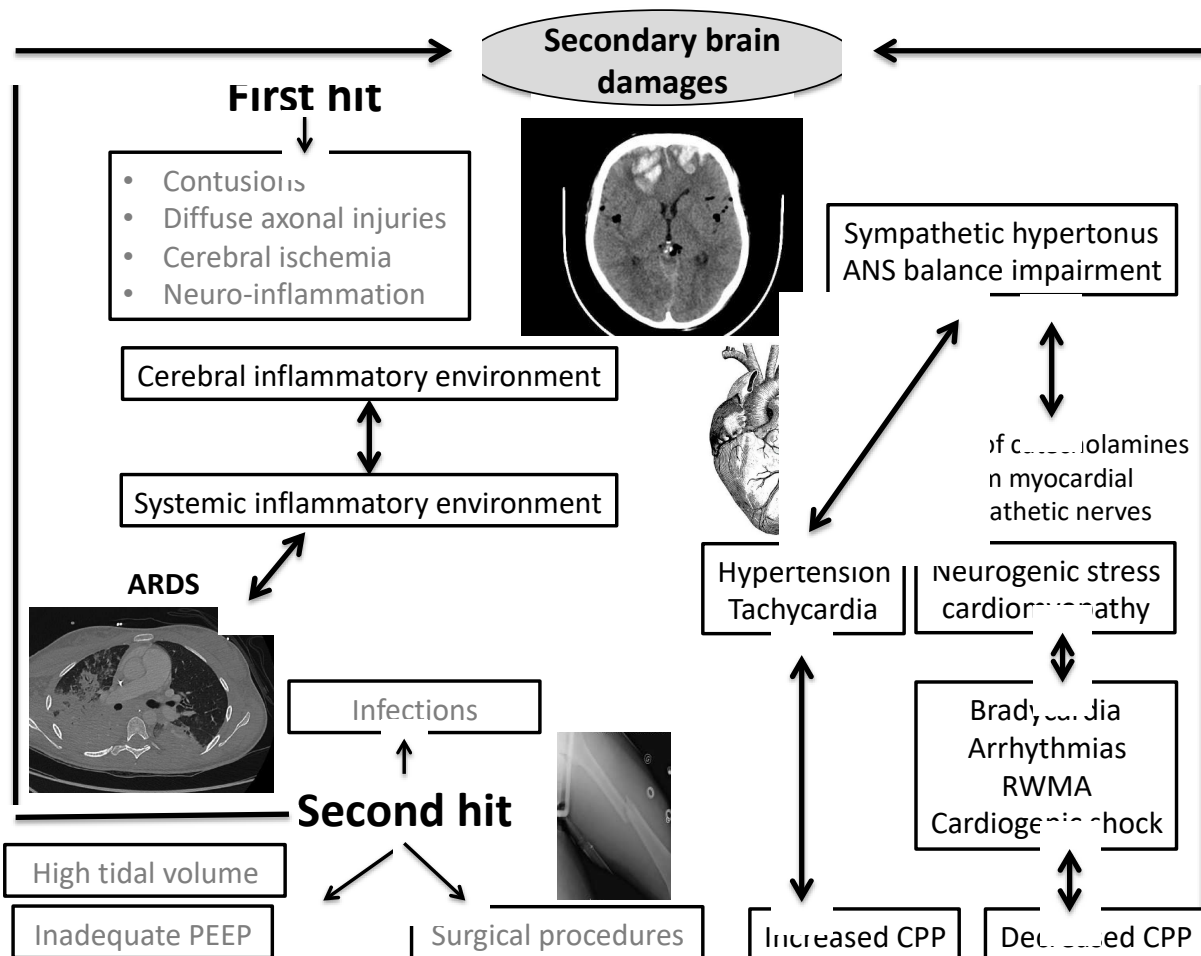


	Ventilator-associated pneumonia	Acute Respiratory Distress Syndrome	Neurogenic Pulmonary Œdema	ECG abnormalities	Cardiac biomarkers (cTn, BNP)	RWMA and echocardiographic changes
<b>TBI</b>	21-60%	20-25%	32 to 50% of fatal TBI	60-100%	Aprox 30%	0-28%
<b>SAH</b>	49%	20-38%	2-25%	40-85%	35% (10-70%)	22% (9-71%)
<b>AIS</b>	28%	4%	18%	15-65%	5-34% (for cTn)	10-30%
<b>ICH</b>	*	*	*	40-85%	27-41%	3.8% (acute heart failure)

**Table 1: Incidences of main pulmonary and cardiac complications according to acute brain injuries: Traumatic Brain Injury (TBI), Subarachnoid Haemorrhage (SAH), Acute Ischemic stroke (AIS) and Intracerebral Haemorrhage (ICH).**

*Abbreviations: RWMA: Regional Wall Motion Abnormalities, ECG: Electrocardiogram, cTn: Cardiac Troponin, BNP: Brain Natriuretic Peptid*

*\*: too few data.*



**Figure 1: Involvement of pulmonary and cardiac complications after acute brain injuries in secondary brain damages.** ANS: autonomic nervous system. CPP: cerebral perfusion pressure. ARDS: acute respiratory distress syndrome, RWMA: Regional Wall Motion Abnormalities, PEEP: Positive End Expiratory Pressure.

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