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Pathophysiology and Management of Neurogenic Pulmonary Edema in Patients with Acute Severe Brain Injury

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Abstract

Purpose: This article will provide a narrative review of evidence regarding proposed mechanisms, diagnosis, and treatment of neurogenic pulmonary edema (NPE) in the critical care setting.

Methods: PubMed and Ovid databases were searched for observational or prospective studies relevant to the diagnosis and treatment of NPE.

Results: While the specific mechanisms responsible for NPE remain uncertain, putative mechanisms include catecholamine release with resultant pulmonary vasoconstriction termed the "blast injury theory", increased vagal tone, and increased capillary permeability. Diagnosis involves identifying signs of pulmonary edema in the setting of a brain injury, and treatment modalities appear to work best when balanced towards maintaining a normal physiologic state.

Conclusion: Acute Brain Injury (ABI) consists of any acquired insult to the brain and is a significant cause of morbidity and mortality worldwide. Approximately 20–30% of patients with ABI develop lung injury. Neurogenic Pulmonary Edema (NPE) is an often underdiagnosed, but an important sequela of ABI, which may result in additional long-term morbidity. It is therefore an important for providers to recognize and tailor their clinical approach towards.

Keywords: Acute respiratory distress syndrome; Control of ventilation; Catecholamine; Neurology; Pulmonary edema; Acute brain injury

Abbreviation: ABI: Acute Brain Injury; ARDS: Acute Respiratory Distress Syndrome; CBF: Cerebral Blood Flow; CNS: Central Nervous System CPP: Cerebral Perfusion Pressure; CVP: Central Venous Pressure; DVT: Deep Vein Thrombosis; FRC: Functional Residual Capacity; ICH: Intra-Cerebral Haemorrhage; ICP: Intra-Cranial Pressure; INO: Inhaled Nitrous Oxide; IPH: Intra-Parenchymal Haemorrhage; LV: Left Ventricle; MAP: Mean Arterial Pressure; NPE: Neurogenic Pulmonary Edema; PE: Pulmonary Embolism; PEEP: Positive End Expiratory Pressure; SAH: Sub-Arachnoid Haemorrhage; SDH: Sub-Dural Haemorrhage; SSP: Sagittal Sinus Pressure; TCD: Transcranial Doppler

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Introduction

Trauma is a frequent cause of Acute Brain Injury (ABI) worldwide and although less frequent, Subdural Hemorrhage (SDH), Subarachnoid Hemorrhage (SAH), Intra-Parenchymal Hemorrhage (IPH), meningitis, stroke, status epilepticus and others have also been attributed to brain injury [1]. An often under-recognized unique complication of ABI is Neurogenic Pulmonary Edema (NPE). Overall, the incidence of NPE is estimated to be around 20-30% of patients with ABI [2-9]. Approximately 15% of patients with either Hunt and Hess grade III-V or Fisher grade III-IV Subarachnoid Hemorrhage (SAH) develop neurogenic pulmonary edema [10,11].

This review aims to describe the proposed pathophysiologic mechanisms with an additional focus on the management of pulmonary complications in patients with NPE.

Methodology

Pathophysiology

Although the exact cause is unknown, several theories have been proposed to explain the pathophysiology of pulmonary edema in the setting of ABI. We will discuss the proposed mechanisms involving multiple cascading events that concomitantly occur during the development of NPE.

Catecholamine induced peripheral vasoconstriction: A wealth of knowledge was gained from the early observations in animal experiments using noxious stimulation of the Central Nervous System (CNS) to study its effects on the cardio-pulmonary system. It was observed that lesions of the CNS produced in this way resulted in an elevation of pulmonary and systemic arterial pressures [13-15]. Moreover, bilateral upper thoracic sympathetectomy or even total lung denervation did not prevent the elevation of these pressures [13]. It was thus concluded that severe peripheral vasoconstriction induced by catecholamines released as a consequence of CNS injury results in severe systemic hypertension causing strain on the Left Ventricle (LV), similarly seen in Takotsubo cardiomyopathy [16]. This leads to secondary LV dysfunction causing elevation of left atrial and pulmonary venous pressures, and subsequently pulmonary edema. Pulmonary edema has been seen as the sole presentation in patients with pheochromocytoma, presumably from the catecholamine surge [17].

Pulmonary venoconstriction: Maron MB and Dawson CA [18] showed that in an experimental model with increased cerebrospinal fluid pressure in dogs caused catecholamine induced pulmonary venoconstriction in a denervated lobe of the lung. Indirect observations in humans using initial alveolar edema fluid to plasma protein concentration ratio in patients without heart failure or volume overload points towards a hydrostatic mechanism for the development of NPE. Smith WS and Matthay MA [19] concluded either pulmonary venoconstriction or transient elevation in left-sided cardiovascular pressures as the contributing causes to the development of human neurogenic pulmonary edema.

In addition to the catecholamine mediated pulmonary venoconstriction, centrally mediated reflex neural mechanisms have also been proposed. Moss G, et al. [20] demonstrated that changes of ARDS can occur following cerebral hypoxemia without any increase in systemic blood pressure. They proposed a centrally mediated pulmonary venous spasm triggered by hypothalamic hypoxia resulting into pulmonary hypertension and ARDS, suggesting an alternative reflex neural mechanism independent of systemic hypertension. Other studies demonstrated by Gamble JE and Patton HD [21] and Maire FW and Patton HD [22], that selective bilateral lesions of the preoptic regions of the hypothalamus resulted into hemorrhagic pulmonary edema in rats. However, the effects of these lesions on the cardiovascular system were not studied in these experiments. Schraufnagel DE and Patel KR [23] studied the effects on neural stimulation after a blunt force to the brain in a rat model. They found that pulmonary veins have sphincters that are strategically placed to influence blood flow which respond to neural stimuli initiated by a sharp head blow and could potentiate the degree of neurogenic pulmonary edema.

Blast injury theory: Direct vasoconstriction on the pulmonary vascular bed endothelium is difficult to consider as a sole cause of NPE. Administration of vasoconstrictors into heart-lung preparations has shown no significant effect on lung weight [24]. This suggests a synergistic process and the formation of what has come to be called the “blast injury theory”, first introduced by Theodore J and Robin ED [25]. Similar to the neuro-hemodynamic models, the "blast injury theory" posits that the severe abrupt increases in systemic and pulmonary pressures following the catecholamine surge result in a net shift of blood volume from the systemic circulation to the low resistance pulmonary circulation [7,26]. This increase in pulmonary venous pressure leads to the development of transudative pulmonary edema [26]. However, in an experimental model of intracranial hypertension, the acute rise in capillary pressure also induces a degree of barotrauma capable of damaging the capillary-alveolar membrane, which ultimately leads to vascular leak and persistent protein-rich pulmonary edema [25,27]. This additive effect of a high-pressure hydrostatic insult coupled with direct pulmonary endothelial membrane injury subsequently gives rise to the degree of edema formation described as the “blast injury theory” [26,28].

Vagal tone: A series of 11 patients who developed acute pulmonary edema within 2 hours of acute increase in ICP from various causes (SDH, status epilepticus, epidural hemorrhage, intraventricular hemorrhage and SAH) was conducted. All but 1 patient died, and autopsy showed non-cellular foamy diffuse pulmonary edema [29]. Whether bradycardia caused by increased vagal tone following increased ICP produces pulmonary congestion by reducing cardiac output is unclear, but animal experiments do suggest an association [14,15,30].

Direct increase in pulmonary capillary permeability: Data in observational studies have suggested that in addition to the hemodynamic effects, catecholamines also induce pulmonary edema by increased inflammatory stimulus evidenced by pro-inflammatory cytokine expression and cellular recruitment [31,32].

In summary, pulmonary edema in the setting of acute lung injury appears to be multifactorial in etiology and is characterized in the following **Figure 1.**

Diagnosis

The ability to identify patients at a greater risk of NPE allows clinicians to monitor patients with greater vigilance and subsequently take earlier measures to minimize the impact and its progression to other forms of lung injury in ABI including ARDS. Diagnosis of NPE is clinical and relies on symptoms and physical exam findings consistent with pulmonary edema, such as dyspnea, tachypnea, and crackles, plus radiographic changes (bibasilar opacities, air bronchograms) in the setting of a neurologic insult. The resolution of symptoms within 72 hours is also a strong indicator of NPE. Some potential markers of disease

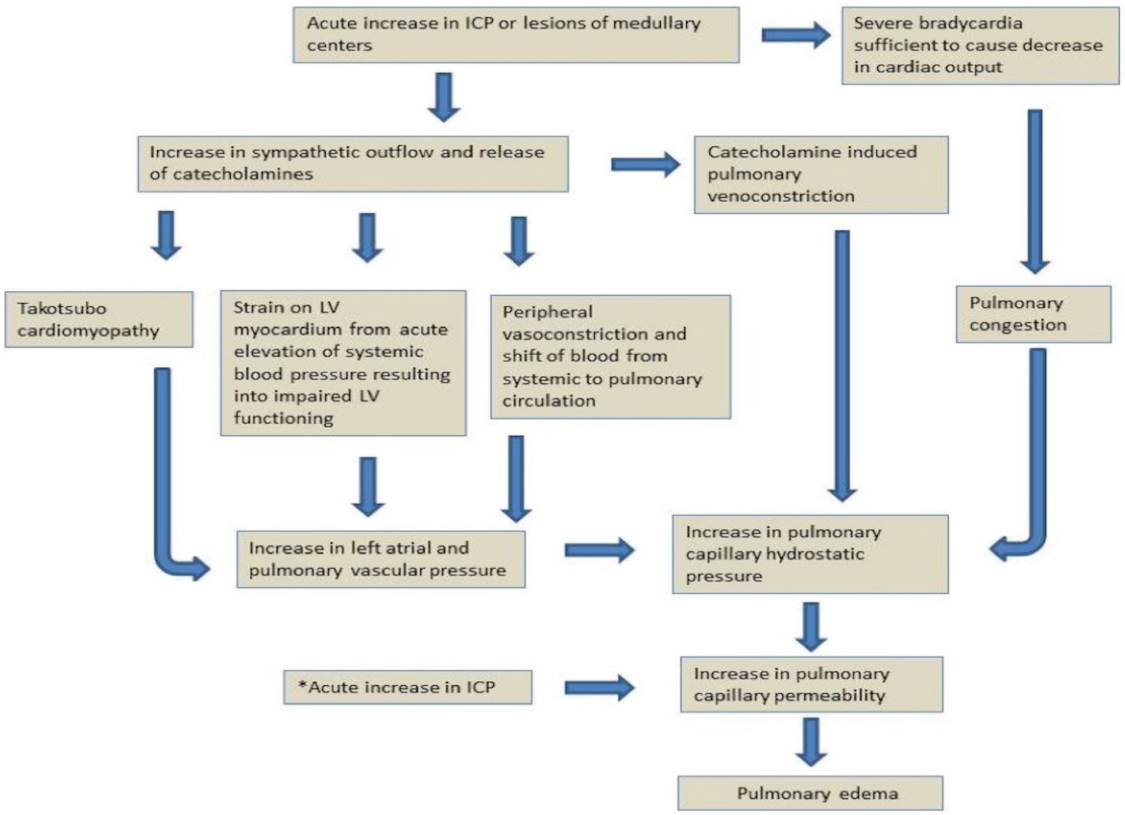

Figure 1 Cascade of additive mechanisms after initial increase in intracranial pressure eventually leading to pulmonary edema. ICP: Intracranial Pressure; LV- Left Ventricle. **Note:** There is evidence that increase in ICP may be responsible for increase in pulmonary capillary permeability independent of change in pulmonary hemodynamics.

include elevated Troponin I, APACHE II score >20, leukocytosis, and IL-6 >40 pg/mL [33-35]. However, these need further rigorous testing to confirm their predictive accuracy in patients with ABI before they can be widely utilized. Because there is no definitive test for NPE, exclusion of other more common disease processes including infectious, cardiogenic, and noncardiogenic causes of pulmonary edema is necessary.

Results and Discussion

Management

NPE can present very similarly to ARDS. Therefore, the basis of treatment modalities begins with those found to be helpful in ARDS, with some modifications to account for management of the accompanying neurologic injury. Treatment must take into consideration the balance of consequences that lung treatment has on the brain and that brain treatment has on the lung. Furthermore, it is important to recognize that even in patients who develop NPE, the instigating neurologic insult is more likely to determine the outcome than the NPE itself. However, those who develop NPE tend to have worse outcomes overall. This being said, treatment must focus primarily on neurologic preservation and insult reversal, with supportive care provided to manage the associated pulmonary edema. Specific strategies are outlined below.

Ventilator management of lung injury in ABI: Positive pressure ventilation and intracranial pressure/hemodynamics are inter-related, and achieving a balance of adequate oxygenation with PEEP, non-injurious ventilation with low tidal volumes, while maintaining ICP in a desired range can be challenging. PEEP improves oxygenation by alveolar recruitment and increasing Functional Residual Capacity (FRC). However, in theory, PEEP can also reduce Mean Arterial Pressure (MAP) and increase Central Venous Pressure (CVP), thus impeding venous return from the brain resulting in increased ICP, which may individually and collectively reduce Cerebral Perfusion Pressure (CPP). Studies evaluating the effect of PEEP on ICP and CPP are contradictory some suggesting that PEEP can have a deleterious effect on ICP, especially in patients with baseline elevated ICP, while others indicate no significant impact on ICP [36-41]. The relationship of ICP and PEEP is influenced by several factors, which includes the level of PEEP applied, baseline ICP, compliance of the lungs, MAP, cardiac output, and intracranial compliance. These conflicting results are, at least in part, reflective of differences in both lung compliance and intracranial compliance in the populations studied [42]. Permutt and colleagues demonstrated that the rise in ICP is greater in subjects with normal ICP than in those with baseline increased ICP, a phenomenon explained by the starling resister concept which describes the flow of fluid in collapsible tubes, also described as the “vascular waterfall” [43]. Although

Sagittal Sinus Pressure (SSP) increases with therapeutic levels of PEEP, the collapse of the veins connecting cortical veins to the superior sagittal sinus prevents transmission of the pressure to the cortical veins and results in a significant rise in cortical veins which collapse easily [44-46].

If there is strong clinical suspicion for a low intracranial compliance at baseline, then ICP monitoring should be considered especially if patients are expected to need higher levels of PEEP. PEEP adjustments can then be guided by the effect on ICP and CPP. If ICP or other cerebral monitoring (e.g. brain tissue oxygenation) devices are not in place, then the minimum PEEP necessary to maintain oxygenation should be used in order to minimize the detrimental effects elevated ICP can have in ABI.

Hypoxemia and hyperoxia: Hyperoxia has been studied in patients with ABI suggesting that hyperoxygenation should improve or prevent cerebral hypoxia and limit secondary injury [47-49]. Increasing fraction of inspired oxygen (FIO_2) to 1.0 has been shown to improve brain tissue oxygenation and lower cerebral lactate levels when measured by microdialysis.

Cerebral vasodilation consequent to hypoxemia can increase ICP and reduce CPP especially in patients with intracranial hypertension who may already be on the steep portion of the ICP/volume curve [50]. A Transcranial Doppler (TCD) ultrasound study in healthy human volunteers found that the hypoxic vasodilatory threshold of PaO2 is 58 mmHg and SpO2 of 90% [51]. While brain injury may alter these thresholds, it is reasonable to target PaO2 and SpO2 above these levels to minimize the risk of hypoxemia induced cerebral vasodilation and elevations of ICP.

Hypercapnia and hypocapnia: Studies on cerebral vasomotor reactivity using TCD and cerebral angiography have shown cerebral vessels reacting to changes in pCO_2 [52,53]. Hypocapnia causes vasoconstriction and potentially decreasing ICP, while hypercapnia causes vasodilation with the potential to increase ICP. However, the appropriate target PaCO2 and the appropriate tool to measure the impact of changes in PaCO2 remain controversial. Prolonged prophylactic hyperventilation is associated with worse clinical outcomes [54,55] and is not recommended by the Brain Trauma Foundation (BTF) [56].

It appears reasonable to target a PaCO2 of 35-38 mm Hg in patients with NPE. This may be problematic while attempting to minimize ventilator-induced lung injury by employing low tidal volume ventilation. Low tidal volume ventilation results in decreased mortality and increased number of ventilator free days not only in medical patients with lung injury, but also in patients with ABI [57-59]. Low tidal volume ventilation, however, commonly results in PaCO2 levels that are elevated (40-44 +/- 10-12 mm Hg in the ARDSNet trial). Thus, a balance may need to be struck between tidal volume, minute ventilation and PaCO2. One suggestion may include the use of slightly higher tidal volume targets than the ARDS Net trial – perhaps as high as 7-8 mL/kg ideal body weight if needed to maintain eucapnia [57]. Alternatively, it may be helpful to offset the elevated PaCO2 by increasing the respiratory rate while being mindful of plateau pressures.

Glucocorticoids: The use of steroids in the treatment of NPE is of unclear benefit. Brain trauma foundation guidelines advocate avoiding steroids in patients with ABI. The effects of steroids in lung injury such as NPE, is suggested by studies focusing on ARDS. However, conclusions from these are inconsistent and contradictory. Early studies have shown benefit of using methylprednisolone for the treatment of ARDS [60]. However, this was again examined in a randomized controlled study, showing that methylprednisolone did not alter 60 day or 180 day mortality when started after 7 days of persistent ARDS. Although it did improve cardiopulmonary physiology when started early, increased mortality was noted when glucocorticoids were initiated beyond 14 days of ARDS onset [61]. One meta-analysis by Tang and colleagues showed improved mortality with the use of corticosteroids, while another one showed a trend towards reduced mortality and increased ventilator free days [62,63].

A randomized placebo-controlled trial (MRC CRASH) studying 10,008 patients with ABI and using high doses of methylprednisolone for 48 hours starting within 8 hours after the injury, demonstrated increased 2-week mortality in the corticosteroid group [64]. A recent phase 3 randomized clinical trial examining the safety and efficacy of progesterone in a large sample of patients with severe traumatic brain injury, failed to demonstrate any difference in favorable outcome or mortality compared to placebo [65]. Though corticosteroids may have some beneficial effect in lung injury, with data suggesting lack of efficacy and increased mortality in patients with ABI, routine use of steroids cannot be recommended.

Non-conventional strategies to improve oxygenation

Patient positioning: Head of bed elevation to 15 to 30 degrees should be considered, as that can have additional beneficial effect of ICP reduction [66].

Prone positioning improves oxygenation and as such is an attractive option for patients with hypoxemia [67]. However, there remains a concern regarding its effect on intracranial pressure. One small study of 11 patients suggested that prone position does not increase ICP in patients with reduced intracranial compliance, while a randomized controlled study of 51 patients showed significant increase of ICP with prone positioning [68,69]. Other than the concern regarding increased ICP, prone positioning can pose technical challenges of turning patients with ICP monitoring devices, and some with on-going multimodality monitoring due to the risk of accidental removal and thus safe use of these devices. Reinprecht A, et al. [69] studied prone positioning in SAH patients with ARDS and while ICP increased, and CPP decreased, there was improvement in brain tissue oxygenation and PaO2. However, currently there is no compelling evidence that isolated improvement in brain tissue oxygenation results in improved outcome. Therefore, prone positioning should probably be reserved as rescue therapy in patients with refractory severe hypoxemia despite the use of conventional measures, while carefully monitoring the ICP.

Fluid management: Careful fluid balance is essential in the management of critically ill patients. Hypervolemia is common among patients with ABI through various mechanisms of LV strain, Takotsubo cardiomyopathy, shifts of blood volume from peripheral

circulation to pulmonary circuit, pulmonary venoconstriction, etc. [16]. This fluid imbalance concern can lead to acute pulmonary hypertension resulting in worsening pulmonary edema and poor outcomes in patients with ABI. Because of this, hypervolemia is no longer recommended in the management of acute brain injuries. It has been demonstrated that even small doses of fluids in the presence of acute pulmonary hypertension can either precipitate or worsen pulmonary edema [70]. Maintenance of euvolemia is of particular importance when applying PEEP, as MAP can drop if intravascular volume is low, which can affect CPP [36,37].

Conclusion

NPE is a frequent cause of lung injury in patients with ABI and should be considered along with other common causes, including but not limited to, aspiration pneumonia, pulmonary trauma, and pulmonary embolism. Development of NPE is associated with increased mortality and worse neurologic outcomes. Catecholamine surge during an acute CNS insult is a central common pathway which leads to a cascade of downstream events including NPE via different mechanisms such as left ventricular strain, Takotsubo cardiomyopathy, shifts of blood volume from periphery to pulmonary circuit and pulmonary venoconstriction. Diagnosis relies on the presence of respiratory symptoms and corresponding imaging findings in the setting of a neurologic insult. Management strategies should focus on maintenance of euvolemia, normocapnia, and normoxemia. Effect of PEEP on ICP requires balancing between effective oxygenation and improving intracranial compliance. Early institution of ICP monitoring may be considered in the appropriate patient. Clinicians should recognize NPE associated lung injury as unique and requires early recognition and specific treatment approaches that may reduce further injury.

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