Neurogenic Pulmonary Edema

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Objective: Neurogenic pulmonary edema is an underrecognized and underdiagnosed form of pulmonary compromise that complicates acute neurologic illness and is not explained by cardiovascular or pulmonary pathology. This review aims to provide a concise overview on pathophysiology, epidemiology, clinical characteristics, impact on outcome and treatment of neurogenic pulmonary edema, and considerations for organ donation.

Data Sources: Database searches and a review of the relevant medical literature.

Study Selection: Selected studies included English-language articles concerning neurogenic pulmonary edema using the search terms "neurogenic" with "pulmonary oedema" or "pulmonary edema," "experimental neurogenic pulmonary edema," "donor brain death," and "donor lung injury."

Data Extraction: Selected studies were reviewed by both authors, and data extracted based on author consensus regarding relevance for this review.

Data Synthesis: Existing evidence is organized to address: 1) pathophysiology, 2) epidemiology and association with different neurologic diseases, 3) clinical presentation, 4) impact on outcome, 5) treatment, and 6) implications for organ donation after brain death.

Conclusions: Neurogenic pulmonary edema occurs as a complication of acute neurologic illness and may mimic acute lung injury of other etiology. Its presence is important to recognize in patients due to its impact on clinical course, prognosis, and treatment strategies. (*Crit Care Med* 2015; XX:00–00)

Key Words: experimental neurogenic pulmonary edema; neurogenic; pulmonary edema

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Pulmonary compromise during an acute neurologic illness is a recognized complication of neurologic injury and is termed "neurogenic pulmonary edema" (NPE) if not explained by cardiovascular or pulmonary factors or pathology (1, 2). However, preexisting cardiac or pulmonary dysfunction or an effect of neurologic damage on cardiac function may be present and can cause confusion about the occurrence of NPE (1). According to the 2012 Berlin definition of acute respiratory distress syndrome (ARDS) (3), NPE can be considered a form of ARDS with the caveat of different pathophysiology (see below).

Early description of NPE dates back to victims of gunshot wounds to the head that developed severe pulmonary edema soon after the injury (4, 5). Subsequently, NPE has been described in many different neurologic diseases, including subarachnoid hemorrhage (SAH) (6–10), intracranial hemorrhage (ICH) (7, 11), traumatic brain injury (7, 12, 13), stroke (14, 15), acute hydrocephalus (16, 17), seizures and status epilepticus (18–22), meningitis, subdural hemorrhage, cervical medulla injury, cerebral thrombosis, cerebral gas embolism, medication overdose, multiple sclerosis, and arteriovenous malformation (1, 2, 23).

PATHOPHYSIOLOGY

Despite many experimental studies in animals, the exact mechanisms responsible for the development of NPE are not entirely understood, however distinctly different from ARDS despite similar clinical and radiographic features. Work of different groups support the concept that an increase in extravascular lung water and impairment of oxygenation are elicited by CNS injury and are not dependent on cardiac dysfunction (24–27). A central sympathetic discharge, specifically, a massive increase in α-adrenergic discharge, is considered to be the major initial factor (4, 5, 28, 29). Animal studies have shown that elevated pulmonary artery pressure but not increased systemic arterial blood pressure is an essential component to the development of NPE (30). The importance of the sympathetic, rather than the parasympathetic, nervous system is supported by experiments, showing that stellate gangliotomy, but not bilateral vagotomy, results in prevention of pulmonary edema (31). Furthermore, intact innervation of the lung is required—experiments with interruption of neural pathways revealed that a denervated lung is protected from the development of NPE (32).

Several mechanisms have been proposed for the further steps of generation of NPE: a hemodynamic theory and a theory of increased pulmonary permeability independent of

hemodynamics. The hemodynamic theory is based on systemic and pulmonary vasoconstriction following the sudden increase in circulating catecholamines. This vasoconstriction and hypertension may cause increased pulmonary blood volume through a shift of blood from the systemic to the pulmonary circulation, as well as displacement of pulmonary blood into low pressure areas, leading to an increase in the pulmonary hydrostatic pressure, which subsequently results in increased pulmonary capillary permeability by damage through high intravascular pressure (28, 29). In support of this theory, high intravascular pressures have been shown to damage pulmonary capillaries (27, 33), and such high pressures can develop in animals during experimental NPE (34, 35). In the largest single series of patients with NPE and pulmonary fluid analysis, the primary mechanism was hydrostatic, supporting either transient left heart failure or neurally induced pulmonary vasoconstriction as possible mechanisms for the development of NPE in humans (36). Elevated pulmonary artery occlusion pressures, as observed in different studies, similarly would support a mechanism of increased left ventricular filling pressures (25, 37).

However, increased pulmonary capillary permeability has also been observed to develop in the setting of normal systemic pressures but under the influence of elevated intracranial pressure (ICP), suggesting a neurally mediated mechanism for the development of NPE (10, 35, 38). Oxygenation studies in patients with SAH and pulmonary edema suggested that the principal cause of impaired oxygenation was neither cardiac failure nor hydrostatic fluid overload, but rather another process by which ventilation and perfusion are mismatched (25): direct damage to the lungs by the massive sympathetic discharge in the setting of elevated ICP (39). Another mechanism that has been proposed (and may coexist) postulates that cytokines which are released due to the brain injury increase the permeability of pulmonary capillaries, also leading to an increase of lung capillary permeability (40).

Where in the brain is the process triggered? The trigger common for many of the neurologic diseases associated with NPE is a sudden elevation in ICP, leading either to a global decrease in cerebral blood flow (CBF) or to localized ischemia in so-called NPE trigger zones. These trigger zones, which lead to the overactivation of the sympathetic nervous system with a surge of catecholamine output, are mainly found in the hypothalamus and medulla oblongata (41). Pathways thought to be involved include the caudal medulla, area postrema, and the nucleus tractus solitarius (1). These areas are involved in the sympathetic connections between the medulla and the hypothalamus and are important sites of integration for CNS control of cardiopulmonary function. The activation of a trigger zone results in increased pulmonary vascular pressure, pulmonary venoconstriction, and vascular congestion and hydrostatic injury to the capillary endothelium (28, 41, 42), leading to extravasation of protein-rich fluid into the alveolar space and intra-alveolar hemorrhage (28, 42). The increase in pulmonary pressures during massive sympathetic discharge is caused mainly by systemic vasoconstriction that results in shift of blood volume to the pulmonary circulation (43). The sympathetic surge can also directly injure the myocardium and change cardiopulmonary hemodynamics, resulting in pulmonary edema (44).

These theories have been supported by several studies in both animal models and humans. Pulmonary venous sphincters develop increased constriction in head-injured rats, with resultant increase in pulmonary capillary pressure, reduced pulmonary blood flow, and interstitial proteinaceous pulmonary edema leading to the development of NPE (45).

EPIDEMIOLOGY

NPE has long been considered a rare event; however, it may occur more frequently than originally assumed based on recent studies, mostly in patients with SAH (25). The overall reported prevalence of NPE remains relatively low (2–8%) (46, 47). Pulmonary edema in general is quite frequent after neurologic disease, and distinction of NPE from other forms of pulmonary edema is not always made, because it is difficult to retrospectively differentiate pulmonary edema secondary to cardiopulmonary failure from NPE. Furthermore, the lack of etiologic-specific diagnostic markers may contribute to poor recognition and diagnosis. Therefore, the true prevalence of NPE is difficult to assess.

Most data on NPE originate from studies on experimental or human SAH (25, 47–49), and the reported prevalences for NPE and pulmonary edema are highly variable in the literature. In a study of patients with fatal aneurysmal SAH, the prevalence of clinically apparent pulmonary edema was 31%, with autopsy showing pulmonary edema in 78% of patients (26). In a retrospective study in patients with SAH, the prevalence of acute lung injury (defined as $Pa_{O_2}/F_{I_{O_2}}$ ratio < 300) was 27% (25). A study on patients with SAH indicated that 20% of patients had fulminant NPE, 20% had pneumonia, and 40% had early oxygenation difficulties manifested as diminished $Pa_{O_2}/F_{I_{O_2}}$ ratios at the time of admission (50). In a different series, 80% of patients with SAH were found to have impaired oxygenation during the first week of illness, with the majority of patients (> 90% of these) presenting to the emergency department with oxygenation abnormalities (25). A review of 686 deaths from head injury or spontaneous CNS hemorrhage demonstrated the prevalence of pulmonary edema in approximately 75% (51). In brain-dead organ donors, the reported prevalence of pulmonary edema is 13–18% (52), a large proportion of which presumably reflects NPE, in accordance with the overall reported prevalence of NPE.

CLINICAL PRESENTATION

The clinical presentation consists of signs of oxygenation failure, such as dyspnea, tachypnea, tachycardia, cyanosis, pink frothy sputum, and crackles and rales on auscultation. Hypoxia is reflected by low Pa_{O_2} and a $Pa_{O_2}/F_{I_{O_2}}$ ratio below 200. Chest radiograph (CXR) usually shows features of pulmonary edema with bilateral diffuse alveolar infiltrates. Two distinct clinical forms of NPE have been described: an early form that develops

within minutes to hours—in most cases, between 30 and 60 minutes—following neurologic injury (53) and a delayed form that develops 12–24 hours after the CNS insult (54). Symptoms usually resolve within 48–72 hours after onset (55), but may subside as rapidly as they developed, so that some patients may not display symptoms when examined in the hospital.

One study defined the fulminant form of NPE with hypoxemia with an A-a do_2 more than 100, extensive pulmonary edema on CXR, occurring with preserved cardiac output of more than 4.0 L/min, lack of ischemic changes on electrocardiogram, and a net fluid balance of +0.5 L or less from time of admission to the time of worst A-a do_2 measurement (25). Taking into account the limitations of using cardiac output as marker of cardiac function, and the A-a do_2 gradient as marker for the severity of hypoxemia, this may set NPE apart from cardiac pulmonary edema or cryptogenic pulmonary edema or pneumonia (25). However, NPE often occurs in the setting of concurrent neurogenic cardiac disturbances so that cardiac pulmonary edema and NPE may overlap and determine the overall clinical state of the patient.

Cardiogenic pulmonary edema is not only the most important differential diagnosis but may also coincide with NPE. Aspiration pneumonia is also common among patients with CNS disease and must be considered in the differential diagnosis. Other common causes of acute respiratory failure such as transfusion-related lung injury or sepsis must also be excluded. Furthermore, postairway obstruction edema, ventilator-associated pneumonia, and ventilation-induced lung injury must be considered and excluded in mechanically ventilated patients (1, 2, 23, 56).

IMPACT ON OUTCOME

Data on how NPE may affect outcome are sparse and mainly available for SAH. Pulmonary dysfunction in patients with aneurysmal SAH has been reported to adversely affect outcome (48). Pulmonary edema in patients with SAH has been associated with high-grade SAH (47), increased mortality (47, 48, 57), and high troponin blood levels (58). In a study on implications of pulmonary infiltrates for patients with SAH, only pulmonary infiltrates that occurred after 3 days were associated with poor outcome, while early infiltrates, which included most cases of NPE, did not affect mortality (59). Other analyses suggest that pulmonary edema may not be an independent factor of worse clinical outcome (46, 49). For patients with SAH and neurogenic pulmonary complications in specific, there was a significant effect of oxygenation abnormalities on prolonging hospital length of stay from a mean of 7 to 19 days (25).

In general, mortality in NPE is said to be high, with rates over 50% in some series, and even higher for the fulminant form of NPE, between 60% and 100% (60). The fulminant NPE has been reported to be rapidly fatal, as in a recent case report of a 34-year-old woman with a spontaneous cerebellar hemorrhage and subsequent NPE, who failed to survive hypoxemia despite aggressive supportive measures (61). However, mortality may be related to the neurologic disease and not the respiratory failure; therefore, the exact impact on mortality is unknown (36).

TREATMENT OF NPE

The two mainstays of therapy are treatment of the underlying neurologic condition focused on reduction of ICP in order to halt the sympathetic discharge that is presumed to be the culprit for the lung injury and supportive treatment for pulmonary edema. Few studies have identified specific treatment modalities.

One main focus of supportive treatment relies on volume management (62), including vasoactive drugs, diuretics, and fluid supplements (1, 2, 23, 56). The challenge is that while adequate volumes may be necessary for brain resuscitation, management of NPE may require effective volume reduction. Hemodynamic instability, with subsequent organ hypoperfusion, metabolic acidosis, and the progress of inflammation, can be avoided by use of vasoactive drugs (1). Real-time sonography of the lung targeted to detection of B-lines provides an accurate noninvasive bedside assessment of respiratory failure, as well as quantification and monitoring of pulmonary interstitial fluid, and may guide the intensivist with regard to volume management (61). Another tool that may assist the intensivist is the recently introduced transpulmonary thermodilution indicator technique. This technique, based on the injection of a cold saline bolus into the central venous circulation with subsequent measurement of change in blood temperature and establishment of a thermodilution curve that allows calculating hemodynamic variables such as the cardiac index and the extravascular lung water index (63), can be helpful to distinguish between hydrostatic NPE and NPE due to increased permeability and may be of help in management of NPE (61).

Ventilation strategies, the other mainstay of supportive therapy, are geared toward establishing a therapeutic regimen enabling a combination of protective ventilation with prevention of hypoxemia and hypercapnia. This may be challenging due the different goals of carbon dioxide control in brain injury and acute lung injury. $Paco_2$ plays a major role in the regulation of CBF, and derangements in $Paco_2$ have been found to worsen clinical outcomes after brain injury (64). Low tidal volume ventilation (LTVV), as standard per ARDS Network recommendations (65), on the contrary, often requires permissive hypercapnia. However, given that for NPE, a role of LTVV has not been established, adherence to the recommendation of maintaining normocapnia (35–40 mm Hg) (66) is probably the most common approach. Hyperventilation with a $Paco_2$ goal of 32–34 mm Hg can be used as temporizing measure to reverse an increase in ICP, however is not recommended as a sustained intervention (66, 67).

Optimal oxygenation, that is, avoidance of hypoxia (Pao_2 < 60 mm Hg or oxygen saturation < 90%) (68) usually can be achieved by using an adequate Fio_2 and by application of appropriate positive end-expiratory pressure (PEEP). Although an increase of PEEP can positively influence not only oxygenation in the lung but also brain tissue oxygen pressure, the concern with PEEP values too high is that it can lead to an increase in ICP and affect cerebral perfusion pressure (CPP) by induction of vasodilation and lowering of the mean arterial pressure (MAP) (69). However, an increase of PEEP up to

15 cm H_2O without impeding CPP has been reported in several studies (1, 52, 70). Furthermore, maintenance of PEEP below the patient's ICP (69) and supporting the MAP to remain at normal levels with either volume or vasoactive drugs may counterbalance the effect of PEEP on ICP and CPP (71, 72).

More specific therapies have been described only in case reports and series and in experimental studies. α-adrenergic blockade with IV phentolamine was effective in improving the clinical condition in a patient with ICH and NPE that had documented high serum catecholamine levels (2). Another study investigated the use of phentolamine in treatment of donor lungs from brain-dead rats and found that phentolamine achieved good hemodynamic control and prevented hydrostatic injury to the lung, but did not completely prevent the nonhydrostatic increase in permeability (73). Other studies also found that phentolamine only partly protects the lung from NPE and suggested that other mediators released during the sympathetic surge, such as neuropeptide Y, may play a role in increasing lung permeability (74, 75). Interferon-β has been reported to significantly reduce lung inflammation after experimental SAH and may therefore be an effective drug to prevent SAH-mediated lung injury (76). Quite recently, use of brilliant blue G, a selective P2X purinoceptor 7 antagonist, has been reported in a rat model with SAH-related NPE. It attenuated lung inflammation and prevented lung-blood barrier disruption and, thus, may have therapeutic potential for NPE (77).

Corticosteroids may have a role in certain neurologic conditions (e.g., brain tumors and multiple sclerosis), however are not beneficial or even harmful in others (such as traumatic brain injury) (78). Therefore, use of steroids should only be considered on an individual basis. The use of inhaled nitric oxide (NO) and extracorporeal membrane oxygenation (ECMO) for NPE has mostly been described for brain-dead organ donors with NPE and is discussed below.

CONSIDERATIONS OF ORGAN DONATION

Brain death can lead to significant multisystem physiologic instability. It may also result in the development of a systemic inflammatory response in the donor, which can damage all organs with deleterious impact on their function after transplantation (79–83). Poor management of a brain-dead patient scheduled for organ donation can cause further deterioration of the organ functions prior to retrieval, which may make the organ transplantation not viable (52). Furthermore, the donor inflammatory response is progressive and can be amplified by neurogenic hypotension (40, 84). In addition, pulmonary edema in the brain-dead patient may be caused in a similar manner to the pathophysiology of NPE in the patient with acute brain insult (52, 70), and particularly, the lung can sustain neurogenic injury during the sympathetic storm and hypertensive crisis that accompany the brain death process (43).

Among common physiologic abnormalities in brain-dead organ donors, the prevalence of pulmonary edema has been found to be between 13% and 18% (52). NPE causes severe hypoxia and can threaten organ preservation of the potential organ donor (85). The donor with NPE is also at risk of aspiration, infection, and injury from mechanical ventilation. For these reasons, it has been suggested that organs should be retrieved as early as possible to avoid further injury (86). In the United States, 80% of donors are rejected for lung transplantation, with poor quality being the main reason (87). However, there is accumulating, yet mostly retrospective and single-case-based, evidence that suboptimal lung donors could improve with time and aggressive management and provide excellent transplant results (88), and that donors with NPE should not be abandoned but should be given time to recover (73).

The protective ventilatory strategy for brain-dead organ donors with NPE is similar to the ventilatory management of patients with ARDS (1). Lung units are retained by applying a PEEP of 5 cm H_2O while limiting the tidal volume to 4–8 mL/kg predicted body weight and the plateau pressure to 30 cm H_2O with a focus on recruitment. Re-recruitment is important especially after tracheal suction or after an apnea test and can be achieved by increasing the PEEP as needed.

Hemodynamic lability with hypertension and hypotension, that oftentimes occurs in the process of severe brain injury, negatively impact lung function. A hypertensive crisis can cause rupture of the capillary-alveolar membrane, as shown in an animal model (40). The massive sympathetic discharge also leads to hemodynamic injury of the donor lung that can result in increased reperfusion injury after lung transplantation (73). On the other hand, neurogenic hypotension can amplify the inflammatory response significantly and therefore should be corrected (40).

Animal studies have demonstrated amelioration of NPE with steroid treatment (89, 90). Donor steroid treatment has also been shown to increase lung recovery in a clinical retrospective study (91).

NO gas inhalation is a noninvasive, easily, and rapidly performed strategy to enhance pulmonary perfusion. NO results in preferential pulmonary vasodilatation without affecting the systemic blood pressure, reduces pulmonary vascular resistance, augments hypoxic pulmonary vasoconstriction, and improves oxygenation and ventilation-perfusion matching (92). Two case reports describe use of NO for brain-dead organ donors. In the management of a brain-dead patient in the ICU, NO inhalation over 18 hours improved NPE-caused hypoxia, and after stopping NO inhalation, anesthesia for organ retrieval was started (85). Another recent case report describes a successful trial of NO gas inhalation in a brain-dead organ donor who was already in the operating room for organ procurement and whose level of PEEP and plateau pressure were increased to maximum recommended level with fear that further pressure increase would raise ICP and central venous pressure, decrease venous perfusion and cardiac output, and cause ventilator-induced lung injury. NO inhalation at 20 ppm was used during anesthesia and successful in this case, resulting in significant improvement in oxygenation within 20 minutes (92).

Other strategies to improve perfusion include use of ECMO to overcome severe NPE after transplantation in a case of a donor who died of a gunshot wound to the head (93). Ex vivo lung perfusion, a strategy previously deemed unsuitable for

transplantation (94), was also successfully used in a donor lung with NPE, leading to donor lung salvage and short postoperative mechanical ventilation and duration of hospital stay (94).

CONCLUSION

NPE occurs as a complication of acute neurologic illness and may mimic acute lung injury of other etiology. However, its pathophysiology is distinctly different from respiratory failure of cardiopulmonary origin, with a central sympathetic discharge playing a major role. Treatment strategies are mainly supportive and must target both the neurologic condition and NPE. The presence of NPE is important to recognize due to its impact on clinical course, prognosis, and, if applicable, management of donor lungs.

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