

Neurogenic pulmonary edema

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Neurogenic pulmonary edema (NPE) is usually defined as an acute pulmonary edema occurring shortly after a central neurologic insult. It has been reported regularly for a long time in numerous and various injuries of the central nervous system in both adults and children, but remains poorly understood because of the complexity of its pathophysiologic mechanisms involving hemodynamic and inflammatory aspects.

NPE seems to be under-diagnosed in acute neurologic injuries, partly because the prevention and detection of non-neurologic complications of acute cerebral insults are not at the forefront of the strategy of physicians. The presence of NPE should be high on the list of diagnoses when patients with central neurologic injury suddenly become dyspneic or present with a decreased P_aO_2/F_iO_2 ratio. The associated mortality rate is high, but recovery is usually rapid with early and appropriate management.

The treatment of NPE should aim to meet the oxygenation needs without impairing cerebral hemodynamics, to avoid pulmonary worsening and to treat possible associated myocardial dysfunction.

During brain death, NPE may worsen myocardial dysfunction, preventing heart harvesting.

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SINCE the beginning of the 20th century, pulmonary edema correlated with central neurologic insult has been reported regularly (1), initially after a war gunshot wound to the head (2–4). Since that time, however, there has been little development in our understanding of the condition or its treatment, partly because of the complexity of the pathophysiologic mechanisms involved.

Neurogenic pulmonary edema (NPE) is usually defined as an acute pulmonary edema occurring shortly after a central neurologic insult. It often presents without pre-existing cardiovascular or pulmonary pathology – pathology that could explain the edema. However, this definition does not exclude a coexisting effect of neurologic insult on myocardial function, especially in a setting of pre-existing myocardial dysfunction, which is a cause of confusion in the reported incidence of NPE.

NPE has been reported in numerous and various pathologies of the central nervous system in both adults and children (5, 6).

Epidemiology

Any acute cerebral or even cervical spinal cord insult can lead to NPE. Cases have been reported in

aneurysmal subarachnoid hemorrhage (SAH), traumatic brain injuries, cervical medulla injuries, cerebral thrombosis, cerebral gas embolism, intracerebral hemorrhage, intracranial tumors (7), epilepsy, post-operative intracranial surgery, enterovirus encephalitis (hand, foot, mouth disease) (5), meningitis (8) and multiple sclerosis (9). Brambrink and Dick (10) estimated that 71% of all NPE cases occur after cerebral hemorrhage, 2% after seizure activity and only 1% after cerebral trauma.

Acute subarachnoid hemorrhage

Several authors have reported acute SAH as the main cause of NPE. After SAH, pulmonary edema may occur in 23% of patients, 6% with severe forms (11). The associated hypoxia can have devastating effects, being lethal in up to 10% of patients (12). In approximately 90% of sudden deaths from spontaneous SAH, acute pulmonary edema has been documented (13). In 305 consecutive patients suffering from SAH, Friedman et al. (14) found pulmonary complications in 22% of cases: NPE in 2%, nosocomial pneumonia in 9%, congestive heart failure in 8% and aspiration pneumonia in 6%. However, the true incidence of NPE remains unclear

because of the lack of hemodynamic measurements in many studies. The wide variation of NPE incidence in the literature could be explained by the disparity in the severity of SAH and in the patient populations, and by the very frequent lack of specific hemodynamic evaluation.

NPE arises more often between D1 and D7 after SAH, associated with primary or secondary cerebral insults.

In clinical practice, the most important risk factors for NPE are the clinical and radiologic severity of SAH (Hunt–Hess and Fischer grades) and vertebral artery origin (15). There is also a positive correlation with age, delay to surgery and intentional hypervolemia (11). Early detection and treatment of NPE are necessary in order to minimize the mortality associated with SAH (11).

Head injury

NPE has been reported in up to 20% of cases of severe head injury (Glasgow Coma Scale < 8) (16). In a large autopsy database (17), the incidence of NPE in isolated patients with head injury dying at the scene was 32%, and 50% in victims dying within 96 h. A reversed relation has been noted between the initial cerebral perfusion pressure and the P_{aO_2}/F_{iO_2} ratio, despite the normal appearance of the chest X-ray film (17). The importance of pulmonary lesions during elevated intracranial pressure (ICP) has been particularly well described in brain death cases. In these patients, NPE and infection are the two main causes of a contra-indication to lung harvesting. Thus, only 20% of multiorgan donors have suitable lungs for transplantation (18).

Status epilepticus

According to some series, up to one-third of patients suffering from status epilepticus may present with NPE symptoms (19). According to some authors, status epilepticus is the major cause of NPE (20, 21), particularly in children (22). NPE occurs mainly during the post-ictal period and can be recurrent (23).

Pathophysiology

Two different mechanisms seem to coexist, triggered by a sudden increase in ICP (and global decrease in brain perfusion) or localized ischemic insult in suspected brain trigger zones (vasomotor centers, pulmonary input and output locations: medulla oblongata, area postrema, caudal medulla, solitarius tractus nuclei) (19).

1. Hemodynamic mechanism: an intense pulmonary vasoconstriction, which is mainly the effect of the adrenergic response to the cerebral insult, results in an increase in pulmonary hydrostatic pressure, followed by an increase in the permeability of pulmonary capillaries.
2. An ‘inflammatory’ mechanism also induces an increase in the permeability of pulmonary capillaries.

From an anatomical standpoint, the cerebral sites regarded as NPE trigger zones are mainly found in the hypothalamus and medulla oblongata, and include: (i) two regions of the medulla oblongata – the ventral medulla including the A1 catecholaminergic group neurons, and the dorsal medulla comprising the medial reticulated nucleus, the dorsal motor vagus nucleus and the solitarius tractus nuclei (24, 25); (ii) the posterior hypothalamus, where ischemia and hemorrhage could be the two local triggers of major sympathetic activation.

Hemodynamic mechanism

The hemodynamic mechanism is usually referred to as the ‘blast injury’ theory. A sudden increase in ICP induces an α -adrenergic catecholaminergic response, which, in turn, causes transient but dramatic increases in both pulmonary and systemic vasoconstriction in the veins or arteries. The resultant striking increase in pulmonary vascular pressure causes an alteration of the Starling forces in the lungs, with a subsequent shift of fluid into the pulmonary alveoli and the interstitial spaces. Durable mechanical stress lesions caused by an increase in capillary pressure can also occur (26). Hydrostatic edema occurs when the transmural pressure exceeds 40 mmHg, initially causing injury to the pulmonary capillary endothelium, followed by injury to the basement membrane of the alveolar capillaries and, finally, injury to the alveolar epithelium, resulting in the leakage of red blood cells and proteins into the alveolar spaces (27).

This alteration in pulmonary circulation is frequently associated with a simultaneous cardiac insult. An increased cardiac workload, followed rapidly by a severe myocardial depression and even stunned myocardium, confirmed by invasive monitoring (28), is classically described. Alteration of the left ventricular contractility explains the hemodynamic instability, which is often associated with fluid loading (29). Indeed, a poor functional myocardial reserve increases the risk of pulmonary edema. Conversely, it is likely that patients with hypertensive cardiomyopathies are less sensitive to the effect of catecholamines (either endogenous or exogenous), and

this may provide them with some protection against the acute effects (30). Severe cardiac arrhythmias (31–34) and even cardiac arrest (35, 36) have also been reported.

Several mediators have been implicated in the genesis of NPE, the ensuing sympathetic activation and the resulting endothelial injury (37, 38).

Norepinephrine and neuropeptide Y, which are co-located in large dense vesicles in the sympathetic nerve endings, are secreted locally in large quantities in response to a sympathetic storm (38, 39). They may play an important role in the development of NPE by their vasoconstrictive action and by increasing pulmonary vascular permeability (40, 41).

Vascular endothelial pressure-related insults cause the local release of endothelin-1, which is one of the most potent vasoconstrictors in mammals, and has also been suspected to be involved in different experimental models. It has been shown that there is a time-dependent increase in endothelin-1 in broncho-alveolar lavage fluid in rats with NPE following the induction of an epileptic attack by the administration of a γ -aminobutyric acid (GABA) antagonist. Pre-treatment with an inhibitor of endothelin-converting enzyme has a protective effect, with a decrease in the quantity of endothelin-1 in broncho-alveolar lavage fluid (42). In another study involving rat models, intrathecal injection of endothelin-1 caused a 22-fold increase in the pulmonary vascular permeability, resulting in pulmonary edema. Conversely, intravenous injection does not lead to pulmonary edema. Pre-emptive injection of a selective antagonist of endothelin receptors or of phenolamine prevents this increased permeability and consequent increased pulmonary edema. Sympathectomy has the same effect (43). These results suggest that the increase in pulmonary vascular permeability may be the result of an intense pulmonary vasoconstriction, mediated by the stimulation of α -adrenergic receptors by norepinephrine released in response to the activation of medullary endothelin receptors on injection of intrathecal endothelin-1.

Nitric oxide has also been implicated. It has been shown that the injection of a nitric oxide synthase inhibitor in rats with cerebral trauma increases mortality, as a result of an alteration in endothelial-mediated vasodilatation (44).

Inflammatory mechanisms

A systemic inflammatory response might take part simultaneously in the generation or the perennialization of NPE. Brain cytokines and chemokines have been implicated, but the central or peripheral origin

of cytokine and chemotactic factors produced following an acute cerebral insult remains controversial. The activation of pro-inflammatory genes in somatic organs is one of the consequences of brain death (45).

A major cerebral insult causes a local inflammatory reaction, with the cytokines tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and IL-6 (46) being produced by astrocytes and microglial cells (47). These can gain access to the systemic circulation after disruption of the blood–brain barrier, and can cause the stimulation of target cells in the blood and peripheral organs (48). Marked release of IL-1 β can be detected by cerebral microdialysis within less than 60 min after brain injury (49). The level of cerebral cytokines is related to the progression towards cerebral death (50). Experimentally induced cerebral insult can also cause the expression of the neuropeptides substance P and neurokinin A in the frontal cortex (51); these have been proposed to cause bronchoconstriction and edema of the bronchial mucosa, as well as an increase in pulmonary capillary permeability, pulmonary edema and leukocyte activation (52).

Severe biologic insults and their visceral complications may also result in a systemic inflammatory response in peripheral organs and in the lung itself, much like that observed in brain death, inducing the direct expression of pro-inflammatory cytokines in some peripheral organs (53). Indeed, supra-physiologic doses of catecholamines can lead to an increase in IL-6 expression (54). American and European guidelines recommend the maintenance of the cerebral perfusion pressure above 60 mmHg by means of volume expansion and norepinephrine use (55, 56). However, the potential pro-inflammatory effect of exogenous catecholamines (57–59) is a double-edged sword, which limits their benefit, and is one of the rationales behind the Lund therapeutic strategy which aims to avoid the needless use of vasopressors (60).

The sympathetic storm resulting from a cerebral insult may also initiate the stimulation of cytokine expression and an inflammatory process in the lungs, caused by the severe change in pressure, a process which can be aggravated by hypotension occurring at the possible phase of decompensation. The resulting increased levels of IL-1 β and IL-6 seem to affect all peripheral organs, whereas TNF- α augmentation seems to affect only the lungs (61, 62). In the same way, the genetic expression of certain cytokine-dependent downstream molecules of the inflammatory cascade is also increased in some tissues: (i) RNAm of monocyte chemoattractant protein-1, a chemotactic factor that facilitates the infiltration of T lymphocytes and basophils into the area of injury, and

RNA of transforming growth factor- β are increased in the heart and lungs; (ii) RNA of intercellular adhesion molecule-1, the main ligand of polynuclear neutrophils and monocytes expressed in the endothelial and epithelial cells, is increased in the lungs (63). Using electronic microscopy, ultrastructural damage in type II pneumocytes is obvious 2 h after brain injury and worsens with time, concurrently with lipid peroxidation levels (64).

The existence of an inflammatory component in the genesis of pulmonary lesions may offer novel therapeutic approaches, such as the prescription of drugs that inhibit specific mediators in this biochemical cascade. This might explain the efficiency of small doses of inhaled corticosteroids during the treatment of NPE in animal studies (65) and of intravenous methylprednisolone (66, 67). The links that exist between the sympathetic activation and this inflammatory process may also be a potential target, as the central blockade of the sympathetic nervous system (68) or the use of α -blockers seems to be able to modulate and limit this inflammatory response (69).

Diagnosis

Clinical presentation

There is no specific clinical presentation of NPE. It usually starts in conjunction with the initial central neurologic insult, but can also occur at any worsening phase. Clinical signs are those of acute pulmonary edema, but usually the signs of left ventricular failure are missing in the pure form of NPE. Tachypnea, tachycardia, basal pulmonary crackles, respiratory failure and a lack of cardiac gallop are more often reported. Leakage of blood into or around the brain or the medulla can cause fever. Unilateral NPE seems to be possible (70).

Neurogenic pulmonary shunting. Pure ventilation-perfusion mismatch without pulmonary edema has been reported occasionally. The hypothalamus, which is intimately involved in matching pulmonary ventilation to perfusion, may be implicated in these cases (71).

Complementary investigations

Chest X-ray demonstrates bilateral pulmonary infiltrates (Fig. 1). In the pure form of NPE, echocardiography, transesophageal Doppler and central venous pressure values are normal. The electrocardiogram (ECG) is unchanged.

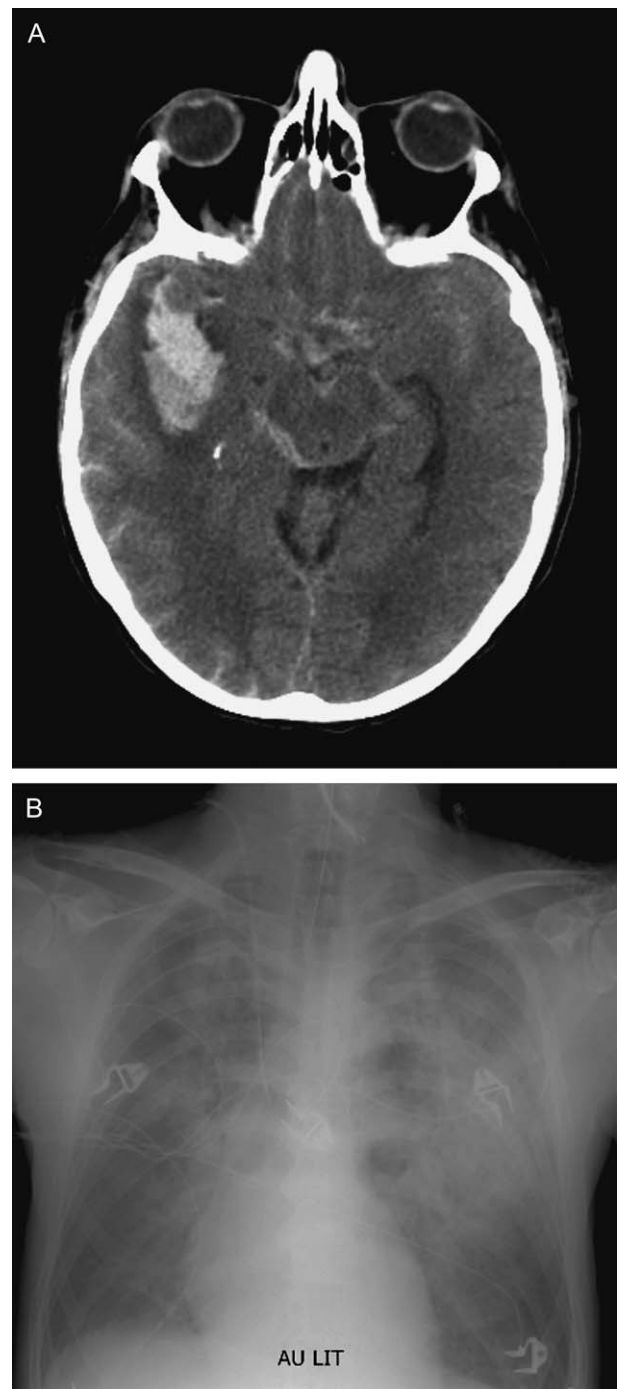


Fig. 1. (A) Man aged 53 years with subarachnoid and intracerebral hemorrhage caused by rupture of mid-cerebral artery aneurysm. (B) Neurogenic pulmonary edema on H + 8 chest X-ray.

The transient but constant and important increase in the pulmonary artery occlusion pressure (PAOP), classically described (26, 29), is most often not found in clinical practice, because of its very early occurrence and very short duration and the delay in measurement. Moreover, after the increase in PAOP

and subsequent capillary injury, the relationship between PAOP and pulmonary edema is definitively altered, and PAOP cannot then be substituted for the hydrostatic pressure in pulmonary capillaries. Thus, measurements using the Swan-Ganz catheter are most often within the normal range (72).

There is no specific biologic marker of NPE. Troponin Ic and brain natriuretic peptide (BNP) elevations are quite frequent during aneurysmal SAH, but their causes are uncertain and may be related to catecholamine over-secretion (73) or to the severity of SAH-related myocardial insult (74). Blood C-reactive protein and IL-6 levels can also be increased (75).

Differential diagnosis

The differential diagnoses include aspiration pneumonia, ventilator-associated pneumonia and ventilation-induced lung injury.

Aspiration pneumonia and ventilator-associated pneumonia

Aspiration pneumonia (Table 1), ventilator-associated pneumonia and other types of pneumonia are frequent complications of acute neurologic pathologies associated with the impairment of consciousness. The blood level of pro-calcitonin may provide evidence of invasive bacterial infection (76, 77). The absence of suspicion of aspiration during tracheal intubation and the appearance of tracheal secretions can be helpful clues.

Ventilation-induced lung injury

Major cerebral insult is a predisposing factor to lung injury through the pro-inflammatory cytokines, the decreased tolerance to alveolar membrane stretching or over-inflation injuries and increased susceptibility to reperfusion injury (78), which are also held to be responsible for early pulmonary graft dysfunction (79).

Treatment/management of NPE

Depending on the severity of the primary insult, NPE may resolve in 48–72 h with the appropriate treatment, and patient prognosis is then dependent on the neurologic injury. However, the possibility of serious and life-threatening deterioration warrants systematic review (80).

Two opposing situations need to be described: (i) central nervous injury with a favorable prognosis; (ii) brain death with the eventuality of multiorgan harvesting.

Acute neurologic insult

The management of NPE is first based on the control of the triggering central nervous system insult, and it is critical to treat the underlying cause as rapidly as possible (decrease ICP, evacuate hematoma, treat convulsions, etc.). Treatment is also based on classical pulmonary edema therapies, but restricted by the requirements of cerebral management and the lack of specific etiologic treatment.

Ventilation. The physician should aim for appropriate gas exchange using a type of ventilation that meets the oxygenation needs and cerebral hemodynamic constraints and avoids pulmonary worsening. The choice between invasive and non-invasive ventilation should be determined by the severity of NPE and the patient's level of consciousness. Some patients with moderate signs may be handled using non-invasive ventilation, but patients with serious NPE must be intubated early, sedated and properly ventilated with positive end-expiratory pressure (PEEP). PEEP values lower than 15 cmH₂O have been shown not to impede the cerebral perfusion pressure (81–83). Classical use of permissive hypercapnia is relatively inadvisable because of its potential impact on ICP, and should only be considered in the worst situations and with respect to neurologic priority. Permissive hypercapnia and prone positioning should only be allowed if ICP monitoring is

Table 1

Differential diagnosis: neurogenic pulmonary edema (NPE) vs. aspiration pneumonia (AP).

	Onset	Fever	P_{aO_2}/F_{iO_2}	Chest X-ray anomalies	Leukocytes	CRP	PCT	Evolution duration
NPE	Hours	Yes/no	Decreased	Bilateral	Normal or hyper	Normal or elevated	Normal	1–3 days
AP	24 h	Yes	Normal or decreased	Uni/bilateral	Hyper	Elevated	Elevated or normal	1–3 weeks

CRP, C-reactive protein; F_{iO_2} , inspiratory fraction of oxygen; P_{aO_2} , arterial partial pressure of oxygen; PCT, procalcitonin.

available, as maintaining ICP within the normal range remains the first objective (84–86). Direct tracheal oxygen insufflation has been described (87), but remains a rescue treatment. Inhaled nitric oxide use may impair platelet function, which can be detrimental in acute neurologic pathology, and the risk to benefit ratio should be correctly assessed, remembering its disappointing effects on mortality rates in acute respiratory distress syndrome.

Hemodynamic function. In the presence of myocardial impairment, treatment should attempt to minimize the cardiogenic aspect of respiratory failure. Treatment should aim to reduce pre- and afterload and to increase myocardial contractility. If a decrease in blood pressure is required, only drugs without cerebral vasodilatory effects should be used (i.e. urapidil or clonidine). β -Blockers should be avoided in the case of associated post-adrenergic surge heart failure, because of their effect on myocardial function. Dobutamine has beneficial effects on NPE (cardiac index, left ventricular stroke work index, pulmonary pressure, P_{aO_2}/F_{iO_2} ratio) and does not compromise cerebral oxygenation (28). Epinephrine and norepinephrine do not seem to worsen NPE and, in particular, do not increase the pulmonary vascular permeability despite increasing the pulmonary capillary pressure (88). Conversely, there may be a β -adrenoreceptor-related increase in the clearance of fluid from the pulmonary alveoli by increased sodium transport (89). The adrenergic improvement in peripheral perfusion may also limit systemic inflammation. Diuretic drugs can be used if the circulating blood volume and cerebral perfusion pressure can be maintained.

Neurologic care. Decreasing high ICP, whilst optimizing the cerebral perfusion pressure, is the first goal. In this setting, mannitol or hypertonic saline, which are usually used, may also be of interest for the lungs. Indeed, a hyperosmolar state seems to increase the off-loading of pulmonary interstitial fluid (90). The exact mechanism of this pulmonary water outflow remains unclear, but is probably related to the diuretic effect of mannitol and the up-regulation of pulmonary aquaporins (91).

When NPE occurs in a patient with acute SAH, hemodynamic, respiratory and neurologic resuscitation take priority over angiography, but should not delay aneurysm treatment for more than 12–24 h.

Brain death

There is a worrying shortage of pulmonary grafts (18) and there are calls for an active policy to improve

potential pulmonary graft quality (92). Graft quality can be affected by even mild forms of NPE (93) and, as such, prevention strategies should be initiated with commencement of treatment. Keeping in mind the possibility of protective ventilation strategies with permissive hypercapnia, inhaled nitric oxide to optimize the V_A/Q ratio and to decrease the pulmonary vascular pressure (94) may be used when the progression towards brain death is certain (92). In addition, hemodynamic instability leads to peripheral organ hypoperfusion, which, in turn, will worsen metabolic acidosis, worsen the inflammatory process and increase the occurrence of multiorgan failure. In this context, vasoactive drugs, whilst improving local perfusion, may also lessen the inflammatory process. In addition, adrenergic drugs used during organ donor resuscitation are no longer an impediment to pulmonary graft harvesting (92).

Finally, in experimental models of brain death, the use of α - and/or β -blockers seems to limit the visceral consequences of a catecholaminergic storm (95–98). Recently, β -blockers have been shown to be efficient in improving graft quality in human brain death-related autonomic storm (99). However, these promising results require further confirmation by a large prospective randomized trial.

Conclusion

NPE has been widely described, but remains poorly understood, and seems to be under-diagnosed in acute neurologic injuries, partly because the prevention and detection of non-neurologic complications of acute cerebral insults are not at the forefront of the strategy of physicians.

The presence of NPE should be high on the list of diagnoses when patients with central neurologic injury suddenly become dyspneic or present with a decreased P_{aO_2}/F_{iO_2} ratio. The associated mortality rate is high, but recovery is usually rapid with appropriate management. Severe forms require early and adequate intervention for a favorable outcome.

Early and appropriate treatment of the underlying neurologic cause is the cornerstone of NPE management. Most patients should be intubated, sedated, appropriately ventilated with PEEP and maintained with normal hemodynamic stability. NPE in the setting of brain death is a major cause of graft dysfunction and even of transplantation failure.

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