

Respiratory Failure in the Neurological Patient: The Diagnosis of Neurogenic Pulmonary Edema

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Abstract: Neurogenic pulmonary edema (NPE) is a potential complication of a central nervous system (CNS) insult such as intracranial hemorrhage, uncontrolled generalized seizures, head trauma, tumors, and neurosurgical procedures. The proposed etiology is massive sympathetic discharge following a CNS event. The pathogenesis is not completely understood. However, there are two theories on how NPE occurs: the blast theory and the permeability defect theory. There is evidence for both theories, and NPE is probably the result of a combination of the two. The treatment is mainly supportive with the use of mechanical ventilation and alpha-adrenergic blocking agents while managing increased intracranial pressure. A thorough understanding of the pathophysiological mechanisms behind the development of NPE aids in the management of these patients to prevent further complications.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema (NPE) is a condition commonly associated with serious central nervous system (CNS) insults such as head injury and intracranial hemorrhage, but it also can occur with a variety of intracranial pathologies, including uncontrolled generalized seizures, tumor, hydrocephalus, and neurosurgical procedures.^{5,9} In contrast to other forms of pulmonary edema, NPE occurs in the absence of underlying heart or lung dysfunction.⁸ Its pathogenesis is not completely understood. However, two main theories have evolved. It is generally agreed that the common mediator appears to be massive sympathetic discharge following CNS insult or acute elevation of intracranial pressure.⁸ This leads to peripheral vasoconstriction with elevation of blood pressure (BP) and shifts of blood to the central circulation.⁵ NPE may occur within minutes to hours of the CNS event, or it may have a delayed onset, occurring days later. It may have a fulminant picture or remain subclinical.⁹ Diagnosing NPE is often difficult. Other causes of noncardiogenic pulmonary edema should be excluded before the diagnosis is made. Prompt diagnosis

and treatment of NPE are essential to avoid secondary brain injury from hypoxia.

This article reviews the pathophysiology of NPE and addresses the therapeutic modalities used in the care of these patients in order to minimize subsequent complications. Existing and experimental treatment strategies and their implications for nursing practice also are discussed.

Pathophysiology

To understand the two main theories on the pathophysiological mechanisms of NPE, one must first look to the pressure gradients that normally exist within the pulmonary circulation, the Starling forces.¹¹ The transcapillary fluid migration is governed by capillary hydrostatic pressure and interstitial tissue colloid osmotic pressure, which tend to favor movement of water out of the capillary, whereas plasma colloid osmotic pressure and interstitial tissue hydrostatic pressure tend to favor movement of water into the capillary.¹¹ Under normal conditions, a state of near equilibrium exists between these pressures. As a result, the amount of fluid filtered out through the arterial capillaries is equal to the amount of fluid reabsorbed at the venous ends. A small amount that is not reabsorbed is drained into the vascular system by means of the lymphatic system. The relationship of the four pressures is demonstrated by the Starling equation:

$$Q = K (P_c - P_i) - O (\pi_c - \pi_i)$$

where

Q = net filtration

K = fluid filtration coefficient

P_c = capillary hydrostatic pressure

P_i = interstitial tissue hydrostatic pressure

O = protein reflection coefficient

π_c = plasma colloid osmotic pressure

π_i = interstitial colloid osmotic pressure.

Normally, plasma colloid osmotic pressure is maintained by endothelial tight junctions that inhibit the movement of solute from the pulmonary capillary into the interstitial space. The capillary hydrostatic pressure is regulated by the smooth muscle tone in the precapillary arterioles and the postcapillary venules.¹¹ Fluid may move into the interstitial tissue space, thereby producing interstitial pulmonary edema, when capillary hydrostatic pressure rises and plasma colloid osmotic pressure falls. The fluid is normally drained by the lymphatics.¹¹

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When the amount of fluid in the interstitial tissue space exceeds the lymphatic drainage, fluid accumulates in the air spaces, producing pulmonary edema.

In NPE, the pathogenesis is not quite as clear. Studies have determined two possible mechanisms: the blast theory or the permeability defect theory. Clinical evidence exists for both mechanisms, and NPE is probably a product of some combination of the two.⁹ For both mechanisms, the initiating factor appears to be centrally mediated sympathetic discharge known as a catecholamine storm. The catecholamine release has been shown to cause systemic arterial hypertension, peripheral vasoconstriction, increased pulmonary artery pressure, pulmonary microvascular vasoconstriction, and failure of left ventricular relaxation.³ This has a significant effect on the pulmonary vasculature because these vessels have an extensive distribution of sympathetic nerves.³

The blast theory postulates that the initial CNS insult results in a massive sympathetic discharge with resultant severe systemic and pulmonary hypertension and increased venous return.¹⁰ This transient systemic and pulmonary hypertension leads to an increase in pulmonary capillary pressure. The systemic vasoconstriction redirects the blood from the systemic to the pulmonary circuit, thus causing a marked increase in pulmonary blood volume and pulmonary vascular pressures, favoring development of edema.¹⁰ The blast effect or elevated intravascular pressure damages the pulmonary endothelium and a permeability defect persists even after restoration of normal pulmonary pressures.¹⁰ Pulmonary edema occurs as proteins leak into the interstitial space, even in the absence of increased pressure.

The permeability defect theory proposes that NPE is caused by a neurally induced increase in capillary permeability without a precipitant increase in microvascular pressure.¹⁰ It is suggested that stimulation of the sympathetic nerves to the lung could directly affect vascular permeability by altering the number and dimensions of the endothelial pores,¹⁰ thus allowing fluid to enter the interstitial space.

NPE presents either as an acute process occurring within minutes to hours of the CNS event or as a delayed process over a period of days after the initial CNS insult. The nature of the precipitating CNS event does not determine the clinical expression of the NPE, because the same type of insult can cause either of the two forms.³ In the early form of NPE, severe systemic hypertension and increases in pulmonary capillary wedge pressure occur transiently just before pulmonary edema develops, so that the high microvascular pressure precipitates edema formation.³ The pulmonary edema fluid has been noted to have a high protein content, indicating a permeability defect as well.

The late form of NPE is characterized by entirely normal hemodynamics and a high protein content, which is

consistent with increased permeability pulmonary edema.³ So both hydrostatic and permeability abnormalities are involved in the pathogenesis of NPE.

Diagnosis

Diagnosis is based on clinical presentation and should be considered in any patient with CNS injury. It is most often associated with severe head injury or intracranial hemorrhage.⁹ It is often a diagnosis of exclusion and occurs in the absence of underlying heart or lung dysfunction. NPE can occur within minutes or days of the CNS event, and the type and extent of CNS injury are not indicators of early or late formation. With both forms, symptoms usually resolve within 24–48 hours.^{2,5} If symptoms continue, alternative diagnoses should be considered.

Diagnosis of NPE is based on clinical presentation and should be considered in any patient with CNS injury.

The physical examination reveals tachypnea, tachycardia, cough, and diffuse crackles; right-sided heart failure signs are notably absent. The patient also may complain of chest pain. However, this complaint is usually not noted because the majority of the patients at risk are comatose. Usually, patients with NPE demonstrate acute respiratory decompensation, mild leukocytosis, arterial desaturation, and diffuse bilateral alveolar infiltrates on chest radiograph.⁵ If NPE is not recognized and promptly treated, severe hypoxemia, cyanosis, and acute respiratory failure develop, resulting in death.⁵

Management

Clinical management of NPE requires not only recognition of the pulmonary edema, but also differentiation from other causes of diffuse pulmonary infiltrates with profound hypoxemia.² Treatment of NPE is mainly supportive. However, management must take into consideration the cause of the NPE, the CNS insult. In a patient with reversible brain injury, poorly planned care may result in irreversible damage, because lung function ultimately contributes to systemic oxygen transport.⁵ Treatments to normalize intracranial pressure such as ventricular drainage, osmotic diuretics, and appropriate positioning are utilized while mechanical ventilation is instituted to avoid the detrimental effects of hypoxemia.

Primary treatment strategies for NPE involve mechanical ventilation and alpha-adrenergic agents. Mechanical ventilation may be necessary for the patient with hypoxemia in the absence of hypercapnia to increase lung volume during the inspiratory phase of the respiratory cycle.⁵ If hypoxemia is unresponsive to increasing levels of oxygen, positive end-expiratory pressure (PEEP) may be instituted. PEEP is commonly used

and is effective in the management of hypoxia secondary to alveolar capillary leak and ventilation perfusion mismatch by increasing intrathoracic pressure and improving arterial oxygenation.⁹ However, there is much controversy regarding the effect of PEEP on intracranial pressure (ICP) in patients with CNS injury. PEEP increases intrathoracic pressure, which leads to impedance of venous return, which can increase ICP and decrease cerebral perfusion pressure (CPP), cerebral oxygenation, and cardiac output.⁵ If PEEP must be instituted to manage hypoxemia, it should be used in small increments with careful monitoring of ICP, CPP, and cardiovascular status. PEEP should be reduced if increased ICP and neurological changes occur. Other measures, such as adjusting the flow rate, lowering the tidal volume, or increasing respiratory rate to maintain minute ventilation, also could be instituted to decrease mean airway pressure.⁵

Nursing care of patients with CNS injury and NPE should focus on maintaining pulmonary function while preventing increases in ICP.

Alpha-adrenergic blockade is an experimental treatment in the management of NPE. Clinical trials to support the use of these agents have not been conducted. The theory behind the use of alpha-adrenergic blockade is to counteract the alpha-adrenergic effects of increased vascular resistance from the massive sympathetic discharge that follows CNS injury. However, because the sympathetic discharge and its effects are transient, this treatment modality would need to be instituted shortly after the CNS insult occurs and before the pressure injury capillary leak occurs. Agents such as sodium nitropruside (Nipride), phentolamine mesylate (Regitine), and phenoxybenzamine hydrochloride (Dibenzylin) have been recommended to counteract sympathetic reflex activity.⁹ Nitropruside, however, should be used with caution in this population, because its effect of reducing blood pressure may also result in decreased cerebral perfusion pressure.

There have been studies of the use of chlorpromazine hydrochloride (Thorazine) and labetalol hydrochloride (Normodyne) in the treatment of NPE in patients without a history of prior pulmonary or cardiac dysfunction. Both of these drugs demonstrated an increase in pulmonary shunting after administration.^{4,12} This was the result of dilation of the pulmonary vasculature leading to increased blood flow to the dependent areas of the lung,⁴ and a subsequent decrease in PaO₂ and an increase in PaCO₂. As a result of increased blood flow through the pulmonary shunt, hypoxic pulmonary vasoconstriction was impaired.⁷

The resultant hypoxemia in patients with CNS injury is detrimental to outcome. As a result, shorter acting

alpha-adrenergic blocking agents have been recommended. Although both of these studies provide important clinical information, further investigations into pulmonary physiology are required to delineate the mechanisms of PaO₂ and PaCO₂ changes in NPE.

Dobutamine hydrochloride (Dobutrex) is another experimental treatment in the management of NPE that has demonstrated beneficial effects. Dobutamine hydrochloride is a synthetic catecholamine that stimulates alpha-1 and beta-2 receptors at therapeutic doses of 2–20 mcg/kg/min.⁷ The positive inotropic effect of dobutamine hydrochloride results in an increase in cardiac output and subsequent reflex withdrawal of sympathetic tone and decrease in the total peripheral vascular resistance.⁸ These effects counteract the response of increased cardiac afterload from the massive sympathetic discharge.

Amrinone lactate (Incor) and milrinone (Primacor) also are being studied for treatment of NPE. These drugs are nonglycoside, noncatecholamine inhibitors of phosphodiesterase III and they increase intracellular cyclic adenosine monophosphate. They have both inotropic and vasodilating actions on venous capacitance and arterial conductance vessels, and therefore they increase cardiac output and lower pulmonary vascular resistance, systemic vascular resistance, and pulmonary capillary wedge pressure.⁷ As with dobutamine hydrochloride, their effectiveness is probably limited, unless administration occurs shortly after the CNS event. More clinical trials need to be conducted to demonstrate the effectiveness of these drugs in the treatment of NPE.

Osmotic diuretics that are utilized in CNS injury to normalize ICP also are beneficial in the treatment of NPE. Osmotic diuretics extract water from the intracellular and interstitial compartments by increasing the osmolarity of the vascular space and drawing water into the vascular space.⁵

Nursing Implications

The key factor in the management of a patient with NPE is recognition of the syndrome, with the awareness that there is an early and late form. Because there are no specific clinical markers, all patients presenting with severe CNS insult should be considered at risk for NPE. It is important, however, to exclude other more common disease processes that could cause hypoxemia and chest radiographic abnormalities, such as aspiration, pneumonia, and congestive heart failure.³ A thorough history and physical examination with a careful assessment of cardiopulmonary status should lead to the correct diagnosis.

Nursing care of patients with CNS injury and NPE should focus on maintaining pulmonary function while preventing increases in ICP. Therefore, activities associated with patients diagnosed with pulmonary edema, such

as frequent suctioning and turning, should be done with caution, monitoring the patient's response to prevent further neurological deterioration with increased ICP.⁵ With ICP monitoring instituted, care can be adjusted according to the changes in ICP. However, if ICP monitoring is not in place, the possibility of increased ICP with patient activity should be considered.⁵

Respiratory care should be supportive to maintain adequate oxygenation. Often, mechanical ventilation will be instituted with PEEP. Respiratory status should be continuously evaluated by pulse oximetry or arterial blood gas analysis to assess the adequacy of ventilation and oxygenation.¹ If the patient resists the ventilator, neuromuscular blocking agents (pancuronium or vecuronium) with mild sedation may be required to prevent increases in ICP.¹ As stated earlier, suctioning should be done with caution to prevent increases in ICP. Lidocaine may be given either intravenously (2%, 1.5 mg/kg) or via endotracheal tube (4%, 2 ml) prior to suctioning to block the cough reflex, which is often stimulated during endotracheal suctioning, leading to increases in ICP.¹ Nurses therefore can have a significant role in preventing increases in ICP and further neurological deterioration.

Areas for Research

The main focus for research should be the role of alpha-adrenergic blocking agents, and their administration shortly after the onset of the CNS event, to determine whether they could prevent the formation of NPE. Other research could focus on the use of agents to reduce pulmonary capillary permeability and provide membrane stabilization, such as corticosteroids, oxygen free-radical scavengers, and cyclo-oxygenase inhibitors.

Case Study

- Patient profile: 64-year-old white female
- Past medical history: peripheral vascular disease; multiple deep venous thromboses—most recent episode 1 year ago
- Past surgical history: right femoral-popliteal bypass; bilateral carotid endarterectomy
- Current medications: warfarin
- Allergies: cephalosporin
- Social history: nonsmoker, nondrinker
- Chief complaint: left-sided weakness; decreased mental status.

History of Current Illness

On October 15, the patient woke up with new onset of left-sided weakness.

She was taken to the emergency department, and a computed tomography (CT) scan of the head was completed. The CT scan demonstrated a large right frontal intracerebral hemorrhage. The patient's International Normalized Ratio (INR) on admission to the emergency

department was 6.5. The patient was treated with fresh frozen plasma and intubated for airway management due to decreased mental status.

Her physical examination on admission revealed the following:

- Vital signs (VS): BP 140/70, HR 72, RR 12, temp 99.8° F
- HEENT: trachea midline; neck supple; no JVD; + left bruit
- Neuro: pupils equal and reactive to light; does not follow commands; localizes left < right; purposeful movement noted on the right; Glasgow Coma Scale (GCS) score = 8
- Respiration: lungs clear and equal bilaterally
- CV: S1, S2; ECG—normal sinus rhythm
- GI: abdomen soft; decreased bowel sounds
- GU: clear yellow urine in urinary drainage system
- PV: increased warmth right lower extremity
- Heme: INR 6.5.

The management plan was to reverse the coagulopathy with fresh frozen plasma and vitamin K. After the coagulopathy was reversed, the patient was taken to the operating room for a craniotomy to remove the clot. Postoperatively, the patient was admitted to the neurological intensive care unit for monitoring. The patient remained intubated and ventilated on the following settings: assist control (AC) 12 breaths per minute (bpm), tidal volume (TV) 500 ml, FiO₂ of 50%, and PEEP of +5 cm H₂O. The arterial blood gas results: pH 7.45, pCO₂ 38 mm Hg, pO₂ 145 mm Hg, HCO₃ 27 mEq/l. The operating room total fluids were reported as intake 1,500 ml, output 3,000 ml, for a negative balance of 1,500 cc. The estimated blood loss was 100 ml.

Postoperative Course

On postoperative day 1 the patient's physical examination revealed the following:

- VS: BP 136/73, HR 80, RR 16, temp 100.3° F
- Neuro: left hemiparesis; following commands on the right side; pupils equal and reactive to light
- Respiration: remains intubated and ventilated: AC 12 bpm, TV 500 ml, FiO₂ 40%, PEEP +5 cm H₂O; lungs with rhonchi bilaterally
- CV: normal sinus rhythm; no ectopy
- Ext: no edema or swelling
- Meds: mannitol, phenytoin, cimetidine, ceftriaxone, clindamycin
- Labs: hemoglobin 8.2 g/dl, hematocrit 23%—transfused with 2 units packed red blood cells; prothrombin time 12.3 sec, INR 1.15, partial thromboplastin time 24 sec
- I/O: 4,135 ml/3,780 ml (+355)
- Studies: duplex ultrasound bilateral lower extremities and upper extremities showed no deep venous thrombosis (DVT) in femoral-popliteal system bilaterally, no DVT in jugular, innominate or

subclavian veins bilaterally; chest radiograph showed clear lung fields.

In the late evening the patient had an acute desaturation, with an SpO₂ of 90%. Arterial blood gas revealed pH 7.39, PCO₂ 46 mm Hg, PO₂ 67 mm Hg, HCO₃ 28 mEq/l. Physical examination demonstrated lungs with rales bilaterally and frothy white secretions. A chest radiograph revealed interstitial prominence of Kerley B lines suggestive of pulmonary edema. The patient was treated with furosemide 40 mg and a left subclavian triple lumen catheter was placed, which revealed a central venous pressure of 10 mm Hg. Ventilator settings were adjusted to AC 12 bpm, TV 500 ml, FiO₂ 50%, PEEP +7.5 cm H₂O. Arterial blood gas results on the adjusted ventilator settings were pH 7.52, pCO₂ 34 mm Hg, pO₂ 123 mm Hg, HCO₃ 27 mEq/l, oxygen saturation 99%.

Postoperative day 2 revealed vital signs to be stable and neurological status to be unchanged. Respiratory evaluation demonstrated decreased breath sound in all lung fields. Ventilation was adjusted to decrease the

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assist control to 10 bpm. Later in the day the patient had an acute desaturation with an SpO₂ of 88% and breath sound with rales. Arterial blood gas sampling revealed pH 7.52, pCO₂ 34 mm Hg, pO₂ 68 mm Hg, HCO₃ 27 mEq/l on AC 8 bpm, TV 500 ml, FiO₂ 40%, PEEP +7.5 cm H₂O. A chest radiograph revealed pulmonary edema localized to upper lobes, which raised the question of NPE. A ventilation/perfusion scan was performed, which demonstrated normal lung perfusion—no defects. The patient was treated with furosemide 40 mg and ventilation was adjusted to AC 10 bpm, TV 500 ml, FiO₂ 50%, PEEP +7.5 cm H₂O. Arterial blood gas results were recorded as pH 7.49, pCO₂ 34 mm Hg, pO₂ 85 mm Hg, HCO₃ 26 mEq/l, oxygen saturation 97%.

Postoperative day 3 revealed vital signs to be stable. Neurological status was unchanged. Respiratory status revealed decreased breath sounds bilaterally. A chest radiograph revealed clearing pulmonary edema and the patient was placed on pressure support ventilation.

On postoperative day 4, the patient's lungs were clear by physical examination and also on chest radiograph evaluation. The patient continued on pressure support ventilation. On postoperative day 5, the patient underwent a tracheotomy for airway protection due to a poor neurological status. The patient remained on pressure support ventilation. A chest radiograph revealed clear lung fields.

The treatment and management strategies for this patient involved the diagnosis of NPE, which was treated with mechanical ventilation and diuretics (furosemide and mannitol). The patient was not treated with alpha-adrenergic blocking agents, because they must be administered shortly after the CNS event has taken place. The neurogenic edema in this case was delayed in onset, taking place 1 day after the cerebral hemorrhage.

Summary

NPE is a significant complication of CNS insult. The etiology is thought to be due to massive sympathetic discharge following a CNS event, but the exact pathophysiology is not completely understood. It appears that both hydrostatic and permeability mechanisms have roles in the development of NPE. The diagnosis is based on a clinical presentation and should be considered in any patient diagnosed with a CNS injury. Recognition and prompt treatment in patients with reversible neurologic injury are key to preventing further damage to the CNS from hypoxemia that can develop with NPE. Treatment is mainly supportive with mechanical ventilation and management of ICP. There is a possible role for alpha-adrenergic blocking agents, provided that they are administered immediately after the occurrence of the CNS event to counteract the massive sympathetic discharge. Their effectiveness still needs to be evaluated through formal clinical trials.

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