Neurogenic pulmonary oedema

Ronan O'Leary FRCA PhD
Justin McKinlay MA(Oxon) BM BCh FRCA

Revalidation FOR ANAESTHETISTS
RCA Revalidation matrix
Matrix reference 1A01, 2C04, 3C00

Key points

Pulmonary oedema which arises due to increased pulmonary capillary pressure, in the absence of left ventricular failure, is hydrostatic pulmonary oedema.

Neurogenic pulmonary oedema (NPO) is the most frequent manifestation of hydrostatic pulmonary oedema and develops after a severe neurological insult.

NPO forms due to a combination of increased pulmonary capillary pressure and stress fracture disruption of the pulmonary capillary basement membrane.

Treatment is by definitive management of the underlying neuropathology, respiratory support with protective lung ventilation, and optimization of cardiac output.

Similar pathophysiological processes include negative pressure pulmonary oedema, high-altitude pulmonary oedema, and pulmonary oedema in hypertensive crises.

Ronan O'Leary FRCA PhD
Registrar in Anaesthesia and Intensive Care Medicine
Department of Anaesthesia
The General Infirmary at Leeds
Great George Street
Leeds LS1 3EX
UK

Justin McKinlay MA(Oxon) BM BCh FRCA
Consultant in Neuroanaesthesia and Neurosciences Intensive Care Medicine
Department of Anaesthesia
The General Infirmary at Leeds
Great George Street
Leeds LS1 3EX
UK
Tel: +44 113 3926672
Fax: +44 113 3922645
E-mail: justin.mckinlay@leedsth.nhs.uk (for correspondence)

Hydrostatic pulmonary oedema

At the end of the 18th century, the French physician and inventor of the stethoscope, Rene Laennec described 'an infiltration of serum into the pulmonary tissue carried to a degree such that it significantly diminishes its permeability to air'. One hundred years later, Ernest Starling explained the relationship between osmotic and hydrostatic pressure and maintenance of extravascular fluid homeostasis which when disrupted leads to the development of pulmonary oedema and respiratory embarrassment.

Pulmonary oedema

Pulmonary oedema is the accumulation of fluid within the interstitium and air spaces of the lung. It may form due to intrinsic lung pathology or systemic dysfunction. Traditionally, pulmonary oedema has been divided into cardiogenic (left ventricular) and non-cardiogenic causes.

The non-cardiogenic causes include a wide range of diseases, for example, pulmonary oedema caused by the acute lung injury–adult respiratory distress syndrome (ALI–ARDS) spectrum of pathology, and pulmonary oedema arising from increased pulmonary capillary pressure (hydrostatic pulmonary oedema).

Trying to classify the causes of pulmonary oedema, however, understates the degree of interaction between the various components involved and it is probable that pulmonary oedema results from the interactions of dysfunction affecting the left ventricle, the pulmonary capillary endothelium, intravascular osmotic and oncotic pressures, and right side of the heart. In any case, the term hydrostatic pulmonary oedema is reserved for oedema developing due to, for example, brain injury, airway obstruction, and high altitude, and refers to oedema forming because of increased transcapillary pressure within the pulmonary vasculature.

Neurogenic pulmonary oedema (NPO) is the most frequently encountered manifestation of hydrostatic pulmonary within critical care environments and is often fatal. Where it does not cause death, it may exacerbate secondary brain injury. This article will outline the physiology regulating extravascular lung water and the pathological processes which disrupt this before discussing NPO and other causes of hydrostatic pulmonary oedema.

Physiology

Pulmonary capillary structure

Pulmonary oedema forms at the pulmonary capillary network, a branching vascular tree arising from the pulmonary artery which goes through 16–18 branches before the formation of the capillaries which then feed into the pulmonary venous network. The surface area of the capillary network is 125 m^2, around 85% of the alveolar surface area. Each capillary is approximately the thickness of an erythrocyte and the network can be thought of as a large sheet of blood interspersed with posts of capillary wall giving an extremely thin film of blood with both sides exposed to alveolar air. The wall of the capillary is intermeshed with the cells and the extracellular matrix of the alveolus to form the blood–gas barrier and is extraordinarily thin, around 0.2–0.4 μm.[1]

The vessels of the pulmonary circulation have poor ability to direct flow and regulate or resist high pressures. This reflects the typically low pressures within the pulmonary circulation. A low mean pressure of around 15 mm Hg (and low resistance) is sufficient to perfuse the pulmonary circulation with the entire cardiac output, and furthermore, unlike the systemic circulation, there is no facility for the more proximal vessels in the pulmonary circulation to resist high pressures. Consequently, high pulmonary pressures are damaging to the blood–gas interface.

Starling's forces: fluid movement across capillary membranes

Regulation of fluid across the blood–gas interface may be described in terms of Starling's forces (Fig. 1).

doi:10.1093/bjaceaccp/mkr006 Advance Access publication 11 April, 2011

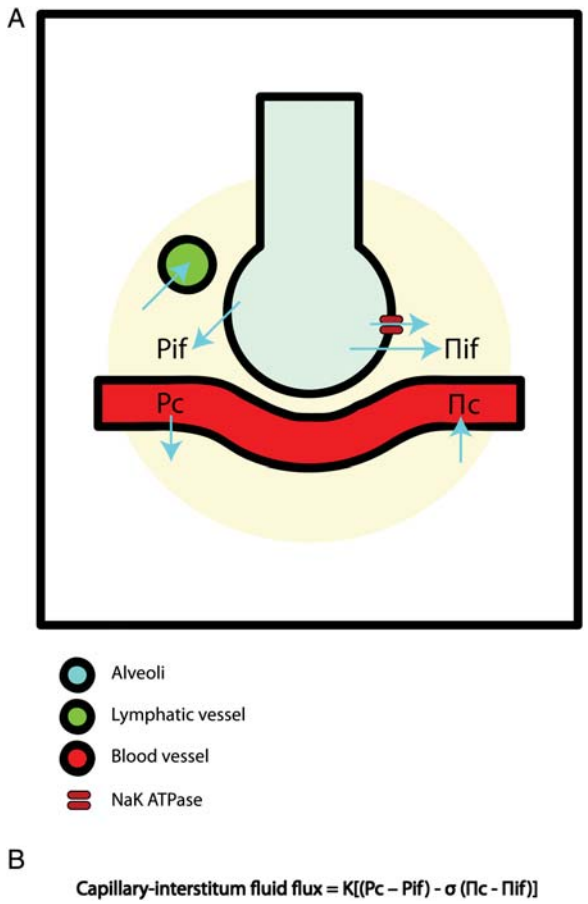

Fig 1 Fluid regulation in the lung. Pulmonary oedema develops when net fluid movement out of the pulmonary vasculature is greater than the net re-absorbative capacity. The important site of fluid extravasation is the pulmonary capillary. (A) Capillary hydrostatic pressure (Pc 8–12 mm Hg) drives fluid out of the capillary into the lung, capillary oncotic pressure (Πc 25 mm Hg) retains fluid in the capillary. Interstitial oncotic pressure (Πif 12–15 mm Hg) retains fluid within the interstitium (the net lymphatic pressure must be slightly below the interstitial pressure to aid fluid removal via the lymphatics). The interstitial hydrostatic pressure (Pif −5–0 mm Hg) is negative or zero in health but when positive, i.e. during the development of oedema, acts to drive fluid into the alveolus. The alveolar sodium–potassium ATPase acts to remove water from the alveolar space. The arrows indicate the direction of fluid movement in health. (B) The net movement out of the capillary is described as Pc–Pif and the net force pulling water into the capillary is Πc–Πif. The movement of fluid is also subject to correction factors; first, the membrane reflection coefficient (σ) which is an expression of the permeability of the endothelium to solutes. A value of 1 indicates total reflection corresponding to zero concentration of solute in the interstitial fluid. A value of zero indicates free passage of the solute across the membrane. Secondly, a filtration coefficient constant (K) is a product of the capillary surface area and the capillary hydraulic conductance (i.e. flow rate of solvent per unit pressure gradient across the endothelium).

The hydrostatic pressure (i.e. arterial pressure) in the capillaries acts to force fluid, electrolytes, and proteins through the capillary pores into the interstitial space. This is balanced by the colloid oncotic and electrolyte osmotic pressures in plasma which draw fluid from the interstitial spaces into the blood. Under normal circumstances, the colloid and osmotic pressure prevents significant fluid loss from the capillary into the interstitial and alveolar spaces.

Further processes act to decrease the accumulation of fluid within the alveolus. The negative hydrostatic pressure in the perivascular space (−5–8 mm Hg) acts as a sump where fluid may accumulate rather than enter the alveolus and the oncotic pressure of the interstitial proteins (10–15 mm Hg) draws fluid from the alveolar space to the interstitium. Fluid may also leave the interstitial space via the lymphatics which, under normal conditions, have a low flow rate of around 10 ml h^{-1} which can greatly increase when fluid flow into the interstitial spaces rises.

During the development of oedema, larger volumes of fluid leave the capillaries, lymphatic uptake is exceeded, and interstitial fluid surrounds the alveoli. Increases in the hydrostatic pressure of the interstitial fluid then produce alveolar flooding as the hydrostatic pressure in the interstitium exceeds the surface tension of each alveolus. Initially, this fluid may be pumped out by transmembrane Na–K ATPases; however, these are overwhelmed by increasing volumes and frank pulmonary oedema results.

An important detail is the transalveolar pressure. This is often not included in discussions on the formation of oedema, but it is significant in the development of negative pressure pulmonary oedema (NPPO), discussed below, and is crucial in the treatment of oedema by the application of positive airway pressure. It is not clear whether the important site of action of positive airway pressure is the alveolar lumen effectively increasing the hydrostatic pressure of fluid within the alveoli, therefore causing fluid to move into the interstitial spaces, or whether it acts on the capillary membrane to counter the hydrostatic forces within the capillary, or even whether it increases movement and drainage into the lymphatic network. In reality, it is probably a combination of all three.

Neurogenic pulmonary oedema

Pathophysiology

NPO is characterized by sudden onset respiratory failure after an injury to the central nervous system (CNS) and typically associated with raised intracranial pressure (ICP). Subarachnoid haemorrhage (SAH) is the most frequently associated neurological insult.[2] In patients suffering an SAH, NPO occurs more frequently in those with posterior circulation aneurysms, poor clinical grade SAH, and those under 30 yr of age. It may also be associated with traumatic brain injury, epileptic seizures, embolic stroke, neurological endovascular procedures, and raised ICP due to blocked VP shunts.[3]

High-quality observational and experimental data on the pathophysiology of NPO are scarce. There are thought to be two interacting processes: first, a centrally mediated profound sympathetic discharge leading to precipitous loss of vasomotor homeostasis, intense pulmonary vascoconstriction, and increased cardiac rate and contractility; secondly, an inflammatory mediator-related increase in vascular permeability.

Increased pulmonary vascular pressure

The CNS discharge increases sympathetic nervous system tone and circulating catecholamine release. The anatomical location where the centrally mediated vasoconstriction arises from is uncertain. Animal data suggest that the presence of blood, thrombus, and inflammatory mediators in the hypothalamus, medulla oblongata, and surrounding tissues is pivotal, particularly when associated with ischaemia. The structures are thought to include the A_1 catecholaminergic neurones in the caudal ventrolateral medulla, the dorsal motor vagus nucleus, the tractus solitarius, and the posterior hypothalamus.

This results in a dramatic increase in pulmonary and systemic vascular resistance (PVR, SVR), cardiac contractility (until cardiac dysfunction supervenes, see below), and tachycardia. The increased pulmonary vascular pressure alters the Starling's forces and shifts the balance towards extravasation of fluid into the lung interstitium.

There is a concomitant mechanical stress injury to the pulmonary capillary basement membrane which occurs at pressures as low as 24 mm Hg.[4] This exacerbates the flow of fluid out of the capillary and as the endothelium is progressively damaged, fluid is followed by plasma proteins, red blood cells, and inflammatory cells. The disruption of the basement membrane underlies the change in the characteristics of pulmonary fluid obtained at bronchoscopy. It is initially a protein and cell poor transudate, but it progresses to contain abundant plasma proteins and cells.

The combination of increased SVR and PVR causes increased demands on the myocardium to maintain output and when associated with tachycardia, there is a critical impairment of myocardial oxygen delivery due to increased transmural pressure and decreased diastolic time. This can result in reversible myocardial stunning or overt myocardial injury and may be associated with a spectrum of pathology ranging from simple ECG changes, to troponin rises, infarction,[5] and structural changes such as Tako-subo cardiomyopathy.[6]

The myocardial dysfunction developing after the sympathetic discharge can be considered to be, effectively, cardiogenic shock in the presence of acute, severe neuropathology and while these changes are frequently thought to reflect a reversible stunning, there is evidence of long-lasting changes to the heart.[5] It is impossible, in the acute phase, to differentiate between a stunned myocardium that retains the capacity to recover and irreversible injury. The impaired cardiac function may exacerbate pulmonary oedema (i.e. superadded cardiogenic oedema) and can contribute to worsening cerebral ischaemia in the presence of cerebral arterial spasm and may be fatal in its own right.

Cytokine-mediated capillary permeability

The second proposed component in the development of NPO is increased vascular permeability mediated by inflammatory cytokines. There are thought to be two sources of these signalling molecules: first, the injury to the brain results in the expression and release of a number of pro-inflammatory molecules within the brain. These move into the systemic circulation by disruption of the blood–brain barrier and initiate physiological changes in lung endothelial cells which drives the recruitment and extravasation of inflammatory cells and permits the translocation of fluid. Secondly, the lung increases the expression and release of cytokines in response to the mechanical insult caused by increased pulmonary capillary pressure which is exacerbated by the barotrauma of mechanical ventilation.

Management of NPO

Diagnosis

The diagnosis of NPO is one of exclusion and the management supportive. There is no specific test and the variable presentation and associated pathology makes the development of straightforward diagnostic criteria difficult.

NPO typically arises in the presence of associated neuropathology which may be traumatic, vascular, or due to another cause. It is possible that neurological pathology may be unknown, for example, the development of NPO in a patient who has had a seizure before presentation at hospital. The diagnostic investigations are outlined in Box 1 and the differential diagnoses are shown in Table 1.

Management

The initial step in management is identification and definitive treatment of the precipitating cause. Clearly, the management of acute neurological pathology will entail measures which may aid management of NPO such as mechanical ventilation; however, aspects of stabilization may also involve steps which are detrimental to NPO such as inter-hospital transfer. This should not influence definitive management of the underlying pathology.

The strategy for treatment of NPO is to reverse the pathophysiological disturbance while supporting organ function. Extrapolation from other areas of critical illness suggests that a goal-directed approach may be of benefit and candidate goals could include cardiac index, SVR, mean pulmonary arterial pressure, pulmonary capillary wedge pressure (PCWP), and plasma partial pressure of oxygen. Our guidance for management (Box 2) assumes that definitive (i.e. neurological) care has been established.

The majority of cases will resolve within 24–48 h with appropriate treatment; however, some cases may require intensive care for many days. Some cases go on to develop severe ALI–ARDS independently, in part due to the inflammatory cascade triggered in the aetiology of NPO, and also due to the protein-rich nature of the fluid within the alveolus after damage to the alveolar–blood interface.

The mortality in this patient group is high and many patients will progress to being candidates for organ donation. Severe NPO will clearly compromise suitability for organ harvest and treatment (i.e. an organ donor management protocol) should continue after brain stem death has been established.

Box 1 Clinical investigations

Chest X-ray

It typically shows bilateral pulmonary infiltrates and increased vascular shadowing. It should also be inspected for the presence of other causes of respiratory failure such as pneumonia or the consequences of trauma. NPO and a second pathology, for example, traumatic lung contusions, can co-exist.

ECG

An isolated process of NPO may exhibit a normal ECG; however, neurological injury such as SAH and traumatic brain injury can cause ECG changes such as T-wave inversion, ST segment changes, and arrhythmias. Elevated plasma troponin levels are frequently observed.

Transthoracic echocardiography

Transthoracic echocardiography (TTE) may show myocardial stunning, reduced ejection fraction (as low as 20–30%), impaired contraction, and wall motion abnormalities, but may also be normal.

Central venous pressure

It may be normal or reduced reflecting a relative hypovolaemic state, see below.

Cardiac output monitoring

There are few studies using advanced cardiac output monitoring during the progression of NPO reflecting its emergent nature where priorities lie elsewhere. Pulmonary artery catheter studies show a reduced cardiac index ($<$2.5 litre min m^2), with increased mean pulmonary arterial pressure and SVR. PCWP may be elevated ($>$20 mm Hg) or normal. However, established or nascent left ventricular impairment may co-exist with NPO which would give rise to elevated PCWP. Equally, the PCWP may be normal in the presence of ARDS or pulmonary contusions.

Clinically related conditions

Negative pressure pulmonary oedema

NPPO is associated with upper airway obstruction in a spontaneously breathing patient. It occurs in 0.05–0.1% of all general anaesthetic cases and laryngospasm has been reported as being the cause in 50% of cases.[7] The clinical course is most frequently observed on emergence from anaesthesia where incomplete recovery from general anaesthesia increases the likelihood of the development of laryngospasm, but it has also been reported after airway obstruction with a foreign body and blockage and biting of tracheal tubes, hanging, and strangulation. Pulmonary oedema is typically described as developing within 2 min of the obstruction.

Once the airway is occluded, the spontaneously breathing patient will continue to generate negative intrathoracic pressure which will increase substantially as respiratory distress develops. There is an associated increase in sympathetic tone due to the stress of hypoxia and airway obstruction which increases SVR and elevates pulmonary artery pressure. This is further exacerbated by hypoxic pulmonary vasoconstriction. The combination of these processes creates a pressure gradient across the capillary–alveolar membrane which favours the movement of fluid into the lung parenchyma.

Table 1 NPO differential diagnoses. The diagnosis of NPO is difficult and relies largely on the history of severe neurological insult. This table shows that there are frequently few features which differentiate NPO from LVF and ARDS and it is possible that more than one of the above conditions affects a patient with NPO. In comparison with the conditions in the table, NPO would generally be associated with a history of neurological insult and very rapid progression of respiratory failure, over 0–6 h. The CXR seen in NPO may have a more homogenous distribution of oedema compared with the typical bat wing appearance of LVF

Condition	Differentiating features from NPO
Aspiration pneumonitis	Evidence of vomiting or oropharyngeal contamination on intubation
	Food particles on tracheal suctioning
	Unliateral changes on CXR
	Later changes include pyrexia, raised inflammatory markers
Community-acquired pneumonia	History of worsening symptoms over 2–3 days
	Characteristic signs on auscultation
	Focal CXR signs which include air bronchograms absent from NPO
	Pus or purulent sputum on suctioning
	Raised inflammatory markers and pyrexia
	Positive microscopy and culture of sputum
Left ventricular failure	Absence of history of neurological insult
	History of ischaemic cardiac disease
	Ischaemic ECG changes and elevated plasma troponins (which may be present with NPO)
	Raised JVP, CVP, or PCWP ($>$15 mm Hg)
	Rapid progression of respiratory failure in the acute setting
Pulmonary contusions	History of trauma
	Associated injuries such as rib fractures
	Frank haemoptysis or blood on suctioning
	Respiratory failure progresses over 24–36 h
	Focal but widespread changes on CXR

It is most common in younger patients, presumably because they are able to generate higher negative inspiratory pressures and, arguably, have a higher sympathetic tone and better cardiac function. The condition may resolve rapidly after definitive management of the airway obstruction, but in some cases, copious pulmonary oedema may form and it can be associated with pulmonary haemorrhage suggesting capillary membrane damage.

After recognition of the cause of obstruction, the treatment required ranges from relatively modest support such as brief periods of CPAP for 2 h to positive pressure ventilation over a period of 24 h.

High-altitude pulmonary oedema and exercise-induced pulmonary oedema

High-altitude pulmonary oedema (HAPE) is characterized by the onset of breathlessness or loss of exercise capacity on the second or third day after assent to, or above, 2500 m. The clinical findings are of interstitial oedema causing a cough and dyspnoea which can progress to alveolar oedema and respiratory failure. Hypoxic

Box 2 Management of NPO

Airway

The patient's neurological state should be the primary determinant of whether tracheal intubation is required. Subsequently, if the level of respiratory support indicates that intubation and mechanical ventilation is required, it should be performed using a technique which will avoid increases in either ICP or systemic arterial pressure yet maintain cerebral perfusion.

Breathing

NPO necessitates a protective lung ventilation strategy. Ventilation should prevent hypoxaemia and avoid iatrogenic lung injury. Initial tidal volumes should be 6–7 ml kg^{-1} utilising PEEP to aid clearance of the oedema and maintain alveolar recruitment. Care should be taken, however, that high PEEP does not impair cardiac function.

Any patient with raised ICP should be ventilated according to neuroprotective parameters which may conflict with optimal ventilation for NPO. Permissive hypercapnia should not be used in the presence of raised ICP or only permitted if ICP monitoring is in place.

High-frequency oscillation ventilation may aid the treatment of refractory hypoxaemia. Prone positioning has been used successfully in the treatment of NPO;[10] however, the presence of cervical spine injury may be a relative contraindication.

Circulation

The haemodynamic management of NPO is challenging and there is no robust evidence on which to base recommendations. However, our suggestion is to use a combination of inotropic cardiac support and peripheral vasodilation as first-line treatment and we suggest that established NPO is an indication for pulmonary artery catheterization. With correct interpretation, this may allow modulation of haemodynamic parameters to increase cardiac output, reduce PVR and SVR, and optimize mean arterial pressure and hence cerebral perfusion pressure.

The precise choice of drugs will depend on the patient, any associated injuries, and pre-existing pathology. The aim of therapy should be to maintain cardiac index at >2.5 litre min^{-1} M^{-2} while avoiding tachycardia and maintain SVR below 1000 dyn s cm^{-5}. These figures are only a guide and the unwanted consequence of inodilator therapy—tachycardia and arrhythmias—is clearly worrying. Changes in PCWP may be used to give an indication of improving forward flow from the left side of the heart while pulmonary artery pressure can be useful to monitor the progress of treatment, even so, oxygen saturations change rapidly as treatment becomes effective. Clearly, all of these parameters vary in an interdependent manner and treatment is best titrated by small changes and observing the response at the bedside.

Dobutamine has been suggested as a first-line drug in the treatment of severe NPO; other authorities suggest phosphodiesterase inhibitors, β1 agonists alone, or in combination with a vasodilator such as glyceryl tri-nitrate, and α-antagonists.[11,12] It is essential that cerebral perfusion is maintained and therefore meticulous attention should be paid to intravascular volume and cerebral perfusion. Clearly, this will be further complicated by the use of vasodilators to treat spasm after SAH. The duration of vasoactive drug therapy is usually brief, 3–4 days, but may be required for much longer.

Other issues

It is likely that many of the patients encountered with NPO will be fluid deplete due to a combination of the diuretic effects of neuropathology, increased renal perfusion, and fluid loss through the lung and third spaces due to the raised systemic capillary pressure. Fluid is initially redistributed from the peripheral vessels to the central structures and, following pharmacological vasodilation, a redistributative hypovolaemia occurs. Patients should be assessed for volume status and fluid responsiveness and i.v. fluids should be used judiciously. Relative hypovolaemia means that diuretic therapy may be contraindicated, emphasizing the importance of distinguishing NPO from cardiogenic pulmonary oedema, Additionally, diuretics should be avoided where possible in patients with SAH due to potentially deleterious effects on cerebral vasospasm.

pulmonary vasoconstriction is likely to be the central physiological process leading to HAPE.[8] Studies have shown that calcium channel antagonists and phosphodiesterase inhibitors reduce pulmonary vascular pressures, while steroids reduce the inflammatory damage to the lung epithelium. However, the most effective treatment is descent, by at least 1000 m or by simulating descent by using a mobile pressure (Gamow) chamber.

Exercise-induced pulmonary oedema has been reported in humans after strenuous exercise, it is not entirely certain whether it is hydrostatic or left ventricular in origin;[9] however, there are a number of case reports of pulmonary oedema in the presence of normal electrophysiology and echocardiography after a variety of exercise activities.

Hypertensive crisis and pre-eclampsia

There is a broad spectrum of hypertensive disease which can present with pulmonary oedema. Clearly, in certain cases, the pulmonary oedema will reflect fluid overload, left ventricular failure, or both; however, a hydrostatic mechanism of damage to the pulmonary capillary vasculature seems likely to be part of the pathophysiology.

In common with all the other pathological processes discussed here, little is known about the development of pulmonary oedema in hypertensive crisis and, particularly, pre-eclampsia. The oedema

forming during pre-eclampsia has been suggested to be a result of endothelial cell dysfunction, pulmonary hypertension, and over-aggressive fluid resuscitation; however, it is tempting to speculate that there may be a centrally mediated component.

Conclusions

Increased pulmonary capillary pressure both alters the balance of forces across the capillary–alveolar membrane and forces fluid out of the capillary and ultimately into the alveolar lumen. Further increases in pressure can cause stress fractures of the basement membrane of the capillary endothelium. NPO is, in anaesthetic and critical care practice, the most frequently encountered consequence of hydrostatic pulmonary oedema. The management of NPO is difficult and there is little in the way of evidence-based guidelines to aid therapy. Treatment is supportive and should follow the principles of reversing the underlying pathophysiology.

Conflict of interest

None declared.

References

1. West JB. *Respiratory Physiology: The Essentials*, 8th Edn. New York: Lippincott Williams & Wilkins, 2008
2. Adams JP. Non-neurological complications of brain injury. In: Adams JP, Bell MDD, McKinlay J, eds. *Neurocritical Care: A Guide to Practical Management*. London: Springer, 2010; 77–88
3. Macmillan CSA, Grant IS, Andrews PJD. Pulmonary and cardiac sequelae of subarachnoid haemorrhage: time for active management? *Intensive Care Med* 2002; **28**: 1012–23
4. West JB. Pulmonary capillary stress failure. *J Appl Physiol* 2000; **89**: 2483–9
5. Bahloul M, Chaari AN, Kallel H *et al.* Neurogenic pulmonary oedema due to traumatic brain injury: evidence of cardiac dysfunction. *Am J Crit Care* 2006; **15**: 462–70
6. Lee VH, Connolly HM, Fulgham JR *et al.* Tako-tsubo cardiomyopathy in aneurysmal subarachnoid hemorrhage: an underappreciated ventricular dysfunction. *J Neurosurg* 2006; **105**: 246–70
7. Papaioannou V, Terzi I, Dragoumanis C *et al.* Negative pressure acute tracheobronchial hemorrhage and pulmonary edema. *J Anesth* 2009; **23**: 417–20
8. Hopkins SR. Stress failure and high-altitude pulmonary oedema: mechanistic insights from physiology. *Eur Respir J* 2010; **35**: 470–2
9. Ghio AJ, Ghio C, Bassett M. Exercise induced pulmonary hemorrhage after running a marathon. *Lung* 2006; **6**: 331–3
10. Fletcher SJ, Atkinson JD. Use of prone ventilation in neurogenic pulmonary oedema. *Br J Anaesth* 2003; **90**: 238–40
11. Deehan SC, Grant IS. Haemodynamic changes in neurogenic pulmonary oedema: effect of dobutamine. *Intensive Care Med* 1996; **22**: 672–6
12. Jain R, Deveikis J, Thompson BG. Management of patients with stunned myocardium associated with subarachnoid hemorrhage. *Am J Neuroradiol* 2004; **25**: 126–9

Please see multiple choice questions 8–11.