CHEST

Negative-Pressure Pulmonary Edema

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Negative-pressure pulmonary edema (NPPE) or postobstructive pulmonary edema is a well-described cause of acute respiratory failure that occurs after intense inspiratory effort against an obstructed airway, usually from upper airway infection, tumor, or laryngospasm. Patients with NPPE generate very negative airway pressures, which augment transvascular fluid filtration and precipitate interstitial and alveolar edema. Pulmonary edema fluid collected from most patients with NPPE has a low protein concentration, suggesting hydrostatic forces as the primary mechanism for the pathogenesis of NPPE. Supportive care should be directed at relieving the upper airway obstruction by endotracheal intubation or cricothyroidotomy, institution of lung-protective positive-pressure ventilation, and diuresis unless the patient is in shock. Resolution of the pulmonary edema is usually rapid, in part because alveolar fluid clearance mechanisms are intact. In this review, we discuss the clinical presentation, pathophysiology, and management of negative-pressure or postobstructive pulmonary edema.

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Negative-pressure pulmonary edema (NPPE) develops in patients with spontaneous respiratory effort who have upper airway obstruction and generate very negative intrathoracic pressures leading to severe hypoxemia and pulmonary edema. Multiple case series have described patients with NPPE, also known as postobstructive pulmonary edema. Reexpansion pulmonary edema, another uncommon form of pulmonary edema, is a separate clinical entity and is beyond the scope of our discussion.[1] In this review, we report a representative patient with NPPE, describe NPPE in the characteristic clinical setting, consider the mechanisms of pulmonary edema formation in these patients, and discuss appropriate treatment.

Illustrative Case of NPPE

A 25-year-old man was admitted to hospital for facial fractures sustained in a high-speed motor vehicle accident.[2] He was taken to the operating room on hospital day 3 for repair of zygomatic arch and maxillary fractures. Preoperatively, his chest examination results were normal and a chest radiograph indicated clear lung fields. The operative course was notable for an estimated 1.5 L of blood loss requiring 7.3 L of crystalloid and 1.5 L of blood products for an overall positive fluid balance of 5.6 L. Intraoperative oxygenation and lung mechanics were normal, with a ratio of Pa_{O_2} to fraction of inspired oxygen (Pa_{O_2}/F_{IO_2}) of 470 mm Hg and a quasi-static respiratory system compliance of 47 mL/cm H_2O.

ABBREVIATIONS: NPPE = negative-pressure pulmonary edema

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Postoperatively, the patient arrived at the recovery room breathing spontaneously on a T-piece with an F_{IO_2} of 0.40. Shortly thereafter, he became agitated, biting down on the endotracheal tube, with two consecutive periods of total airway occlusion and negative inspiratory effort lasting several minutes, associated with systemic hypertension (205/95 mm Hg), tachycardia (131 beats/min), and oxygen desaturation to 85%. The patient was given midazolam, morphine sulfate, droperidol, and succinylcholine to produce sedation and paralysis, at which point control of ventilation was achieved in a volume-cycled mode with an F_{IO_2} of 1.0. Immediately thereafter, copious frothy secretions projected from the endotracheal tube, and the P_{AO_2}/F_{IO_2} ratio was 74 mm Hg. A 3-mL sample of the undiluted pulmonary edema fluid was collected with a 14-gauge standard suction catheter. A plasma sample was also obtained. The edema fluid protein concentration was 3.0 g/100 mL, and the plasma protein concentration was 6.8 g/100 mL, yielding a ratio (0.44) consistent with hydrostatic pulmonary edema (see the Pathophysiology of Edema Formation section). The chest radiograph revealed bilateral lower lobe alveolar infiltrates, and the patient was admitted to ICU and ventilated and sedated. The hypoxemia resolved over a period of 17 h with positive-pressure ventilation and diuresis, and the patient was extubated and transferred out of the ICU shortly thereafter. He was discharged from the hospital 4 days later.

Etiology and Clinical Presentation

This case description illustrates the most salient aspect of NPPE: the rapid onset of pulmonary edema after efforts at inspiration against an obstructed airway. Since 1973, when the first clinical report of NPPE was published,[3] multiple case reports and series have appeared in the literature, and several clinical causes of NPPE have been identified.[4-6] Most of the reported cases in children have been caused by glottic or subglottic obstruction due to acute infectious croup or epiglottitis.[7,8] In these cases, patients present with an acute upper respiratory illness and ventilatory failure due to glottic or supraglottic obstruction with prolonged stridor. Pulmonary edema is often detected after initiation of mechanical ventilation. Regarding incidence, one retrospective study of two ICUs identified 167 children who were admitted with acute airway obstruction due to either croup or epiglottitis and required either intubation or tracheostomy.[9] Among these 167 children, there were 12 patients aged 18 months to 5 years who developed NPPE (7%). In the same study, nine children were also identified with chronic airway obstruction requiring endotracheal intubation, and in this subgroup four patients developed NPPE. The causes of chronic obstruction were hypertrophic redundant uvula, choanal stenosis, and tonsillar/adenoid hypertrophy.

In adults, airway obstruction leading to NPPE is most often reported in the context of postextubation laryngospasm following surgery.[6] The incidence of NPPE following laryngospasm is difficult to compute from case series data, although one study derived from the Australian Incident Monitoring Study (AIMS) reported 189 cases of laryngospasm in 4,000 anesthesia adverse events.[10] There were five cases of NPPE, an incidence of 3% of those with laryngospasm. This statistic may overestimate the true incidence of NPPE, as reporting of cases in AIMS is voluntary and likely favors severe presentations over milder episodes of laryngospasm. Indeed, other estimates of the incidence of NPPE have ranged as low as 0.1% of laryngospasm cases.[11] Of note, one study reported a higher incidence of NPPE among men (80% of NPPE cases) following laryngospasm, and in patients categorized as ASA (American Society of Anesthesiologists) status I or II (73% of NPPE cases). The authors postulate that this finding may relate to higher negative thoracic pressures achieved by healthy male patients.[11]

The most common causes of NPPE—upper airway infection, tumor, and laryngospasm—lead to cases presenting in the postanesthesia care unit, ED, and pediatric intensive care settings. In the medical ICU, NPPE is uncommon but can be encountered, and it should be considered in the differential diagnosis for unexplained pulmonary edema. One particularly instructive report described five cases of NPPE over a 4-year period in the medical ICU at a 1,500-bed tertiary care hospital: the clinical causes were acute epiglottitis, post-stenting for bronchial stenosis, strangulation, goitrous obstruction, and obstruction from prolonged biting of the endotracheal tube.[12] Indeed, as we have noted in a previous review,[13] the case series literature on NPPE reveals nearly as much diversity in the causes of NPPE as potential causes of upper airway obstruction: foreign-body aspiration, hypothyroidism, inspissated tracheal secretions, hiccups, thyroid goiter, temporomandibular joint arthroscopy, difficult intubation, hematoma, upper airway tumor, oropharyngeal surgery, Ludwig angina, acromegaly, mediastinal tumor, biting of the endotracheal tube or

laryngeal mask, and severe patient-ventilator asynchrony.[14-22] OSA has been reported as a cause of NPPE, although heart failure and pulmonary edema are frequently comorbid with OSA, and thus distinguishing the contributions of hypoxemia, obesity, diastolic dysfunction, and airway obstruction is challenging. However, it is worth noting that in cases of unexplained postoperative pulmonary edema in patients without a history of laryngospasm, undiagnosed OSA should be considered.[23,24]

Pathophysiology of Edema Formation

The pathophysiology of NPPE stems from the markedly negative thoracic pressure induced by inspiratory effort against an obstructed glottis, known as the Müller maneuver. Healthy adults can generate as much as –140 cm H_2O negative inspiratory pressure.[25] However, early reports were conflicting as to whether high negative inspiratory pressures result in high-permeability or hydrostatic edema formation. The primary determinants of the rate of pulmonary edema formation, or fluid flux, from the capillary to the alveolar interstitium are transvascular hydrostatic and protein osmotic pressure gradients and vascular permeability, as modeled by the Starling equation for transcapillary fluid flux:

$$Qf = K[(Pmv - Pi) - \sigma(\pi mv - \pi i)]$$

where Qf is net fluid flux from the capillary lumen to the alveolar interstitium; K is the coefficient of capillary permeability; Pmv is the capillary lumen hydrostatic pressure; Pi is the alveolar interstitial hydrostatic pressure; σ is the reflection coefficient (the effectiveness of the vascular barrier in preventing diffusion of protein); πmv is the microvascular protein osmotic pressure; and πi is the interstitial protein osmotic pressure.[26]

The normal hydrostatic difference between the intravascular and extravascular compartments in the lung favors steady state fluid filtration from the capillaries into the interstitium; this filtrate is cleared by the lung lymphatics. If a positive balance develops from increases in either the hydrostatic or the protein osmotic gradient, lung lymphatic flow rises. When the rate of interstitial fluid accumulation outpaces the capacity for lymphatic drainage, edema fluid accumulates in the interstitium and floods the alveolus, becoming clinically detectable either by arterial oxygen desaturation, new opacities on chest radiographs, the appearance of edema fluid in the endotracheal tube, or expectoration by the nonintubated patient.

Several studies have analyzed the pulmonary edema fluid in patients with NPPE.[13,22,27] In the largest of these studies, 341 patients requiring mechanical ventilation between 1982 and 2002 at the University of California, San Francisco were retrospectively screened for NPPE.[13] There were 10 patients with "postobstructive pulmonary edema" as the diagnosis. Of these 10 patients, eight had postoperative laryngospasm, one had a foreign body aspiration, and one had severe ventilator asynchrony with inspiratory attempts against a closed inspiratory valve. Pulmonary edema fluid, which had been collected by suctioning through the endotracheal tube, and simultaneous plasma samples were analyzed for total protein concentration. The average ratio of edema fluid protein to plasma protein was 0.54 ± 0.15, a value below the standard cutoff of 0.65 for hydrostatic versus high-permeability edema and favoring hydrostatic physiology as an explanation for the accumulation of pulmonary edema in NPPE (Table 1).[28-30] However, it is worth noting that three of the 10 patients had values above this cutoff (0.66, 0.69, 0.80), suggesting increased microvascular permeability in some cases. Indeed, the occasional report of blood-tinged secretions in NPPE[31,32] could be consistent with pressure-induced stress fracture of capillaries in those cases, potentially providing a mechanism for high-permeability edema. Alternatively, in some cases, a relative delay in edema fluid collection could result in samples with higher protein concentration because of alveolar clearance of water and ions but not protein.

To model the hemodynamics and edema formation in an experimental system, Loyd et al[33] applied inspiratory resistance loading while measuring lymph flow and lymph-to-plasma protein concentration ratios in awake sheep. Mean airway pressures of between –10 and –15 cm H_2O were achieved continuously. After initiation of inspiratory resistance loading, lymph flow increased, and the lung lymph-to-plasma protein concentration ratio declined from 0.56 to 0.51, with a nadir of 0.47 after 1 h. These data are consistent with a low-protein, hydrostatic physiology of edema of formation (Fig 1). Interestingly, lung lymph-to-plasma protein concentrations rose at the end of the period of resistance loading, possibly suggesting removal of solute and water to the interstitial space by alveolar fluid clearance.[34]

Of note, during the experiment, pulmonary artery pressures remained unchanged. This finding is not

TABLE 1] Laboratory Measurements in 10 Patients With Negative-Pressure Pulmonary Edema

Patient	Edema Fluid Protein (g/dL)	Plasma Protein (g/dL)	Edema Fluid-to-Plasma Protein Ratio	Alveolar Fluid Clearance (% Clearance/h)
1	1.17	3.87	0.30	7.3
2	2.38	5.53	0.43	57.1
3	3.00	6.88	0.44	2.7
4	1.53	3.43	0.45	21.0
5	2.06	4.41	0.47	27.3
6	3.18	6.14	0.52	7.0
7	3.62	5.71	0.63	1.6
8	4.62	6.06	0.66	9.3
9	2.72	3.94	0.69	4.3
10	4.72	5.89	0.80	2.4

Reproduced with permission from Fremont et al.[13]

unexpected since the pulmonary artery is buffered against pressure decrease by systemic venous return. Given that interstitial pressures become negative in the setting of negative airway and pleural pressures, the hydrostatic pressure gradient was increased, leading to transcapillary flux according to the Starling equation. One caveat to interpreting the study by Loyd et al in a clinical context is that the negative interstitial pressures achieved were small (–10 to –15 cm H_2O), whereas patients attempting to breathe across an obstructed glottis generate much more negative pressures. Negative pleural pressure from respiratory effort is transmitted to the pericardium and thus increases transmural pressures across the cardiac chambers, raising myocardial wall stress and afterload by the Laplace principle. Furthermore, as in the clinical case, agitation leads to a hyperadrenergic state and systemic hypertension, serving to further increase ventricular afterload. Thus, while pulmonary arterial pressures were reported as unchanged in the Loyd study, pulmonary pressures may, in fact, be elevated in clinical cases of NPPE because of impaired left ventricular performance or elevated left atrial pressure, further increasing the hydrostatic gradient in the lung microvasculature.

Demonstrating this effect of the Müller maneuver on left ventricular function, Scharf et al[35] reported that ejection fraction measured by left ventricular contrast angiography decreased with inspiratory effort against a closed glottis in patients with angina. Thus, NPPE is likely to be more pronounced in patients with structural heart disease. Moreover, given that negative pressures in patients with NPPE are likely much higher than the modest maneuver used by Sharf et al (20-30 cm H_2O), the effects on afterload may depress left ventricular performance in many if not all patients with NPPE, even in the absence of heart disease. Figure 2 illustrates these possible mechanisms of hydrostatic transvascular gradient formation.

Resolution of Pulmonary Edema

Most cases of NPPE resolve rapidly, within 24 to 48 h, probably because of the absence of persistent hydrostatic stress. Moreover, patients who are endotracheally

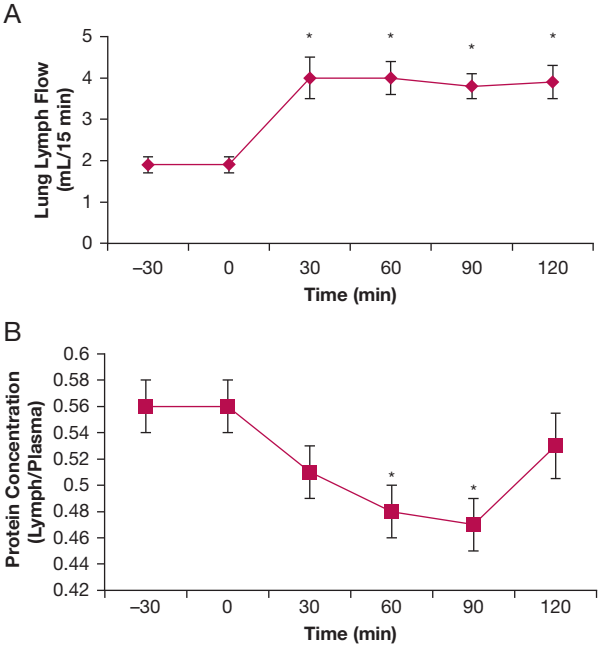

Figure 1 – *Negative-pressure pulmonary edema in a sheep model. Sheep were intubated and mechanically ventilated. At time 0, an inspiratory resistive load of –20 cm H_2O was applied to the airway circuit, with measurement of lung lymphatic flow (A) and lung lymph and plasma protein concentrations (B) (n = 7). (Reproduced and adapted with permission from Loyd et al.[33])*

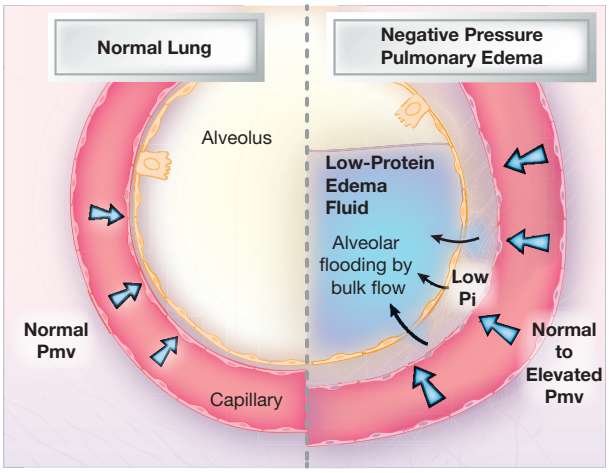

Figure 2 – *The alveolocapillary unit. In health (left), the alveolus remains fluid-free, because liquid filtered by Starling transcapillary forces is cleared by interstitial lymphatics. In negative-pressure pulmonary edema (right), negative interstitial pressure results in an increased hydrostatic gradient and alveolar flooding. The afterload-increasing effect of the Müller maneuver increases this gradient because of elevated left ventricular, left atrial, and thus pulmonary capillary pressures. Pi = interstitial pressure; Pmv = microvascular pressure.*

intubated with positive-pressure ventilation are relieved of their inspiratory resistive load as long as the ventilator-set inspiratory flow rate exceeds patient demand and they do not occlude the tube by biting.[36] The resolution of pulmonary edema has been well studied and is driven by vectorial ion transport.[37] Sodium is taken up by apical sodium channels on alveolar epithelial type 1 and 2 cells, while the basolateral sodium-potassium ATPase drives transport of the sodium from the epithelial cells into the lung interstitium. This creates an osmotic gradient for reabsorption of water from the alveoli into the interstitium, where lung lymphatics remove the fluid from the lung. The net rate of alveolar fluid clearance can be quantified by measurement of protein concentrations in serial samples of pulmonary edema fluid. Because alveolar protein clearance occurs at a much slower rate compared with alveolar fluid or liquid clearance, an increase in the edema fluid protein concentration normally indicates net alveolar fluid clearance.[37] In patients with hydrostatic pulmonary edema, such as left heart failure, the normal rate of alveolar fluid clearance (10%-20%/h) is preserved, whereas in patients with a high-permeability edema such as in acute lung injury, the rate of clearance is impaired.[29,38] In the pulmonary edema fluid samples analyzed by Fremont et al,[13] the average rate of alveolar fluid clearance in 10 patients with NPPE was 14% ± 17%/h. While some patients had lower values (Table 1), this average is well within the range of alveolar fluid clearance reported in patients with hydrostatic pulmonary edema.[29]

By comparison, most patients with pulmonary edema in the setting of acute lung injury (a high-permeability edema) have impaired alveolar fluid clearance (0%-3%/h).[38] In NPPE, it is possible that the rate of alveolar fluid clearance is enhanced during the acute phase, when patients may have markedly elevated levels of plasma epinephrine associated with the severe hypoxemia and also hypercapnia that occurs with upper airway obstruction.[37] Elevated endogenous catecholamines accelerate the rate of alveolar fluid clearance by stimulating sodium absorption from the alveolus into the interstitium.[37,39]

Treatment

Endotracheal intubation and positive-pressure ventilation with supplemental oxygen are usually required for NPPE, because patients present with upper airway obstruction. In some cases, as discussed previously, patients develop NPPE while already intubated after prolonged biting or obstruction of the endotracheal tube. In these patients, sedation and paralysis are paramount. Another major challenge in the acute clinical setting is how to institute positive-pressure ventilation if upper airway obstruction makes endotracheal intubation difficult. In the postoperative setting of glottic or subglottic edema, endotracheal reintubation is usually not difficult. However, in patients who present with acute epiglottitis, endotracheal intubation may be challenging. In these circumstances, clinicians need to be prepared to obtain adequate airway access rapidly by cricothyroidotomy or tracheotomy.[40,41]

Once the airway is secured, the inciting cause of NPPE, negative airway pressure, is alleviated by positive-pressure mechanical ventilation. In most cases, NPPE resolves within 24 to 48 h.[13] However, clinicians may occasionally be confronted with severe hypoxemia due to massive pulmonary edema and resulting shunt. Several general therapies for acute pulmonary edema could be considered in this setting:

1) Diuretics are the standard of care in heart failure-associated pulmonary edema and are useful in patients with ARDS to achieve a fluid conservative strategy when the patient is not in shock.[42] In NPPE, vascular pressures can be elevated, as discussed previously; diuresis is unlikely to be harmful, volume status and renal function permitting, and may hasten the resolution of pulmonary edema. Point-of-care

measures such as cardiac and inferior vena cava ultrasound, as well as determination of central venous pressures, can be useful guides to diuretic therapy in addition to monitoring of oxygenation saturation and chest radiographic changes.

2) Low tidal volume ventilation, while as yet unstudied in NPPE, is recommended unless there is a specific contraindication. This recommendation is based on evidence that lung-protective ventilation may prevent the development of ventilator-associated lung injury even in patients without ARDS. In one study, for example, patients at risk for pulmonary complications were randomized during upper abdominal surgery to either low tidal volume ventilation or ventilation with higher volumes reflecting the pre-lung-protective ventilation era; those randomized to the low tidal volume strategy had a lower incidence of major pulmonary and extrapulmonary complications as well as a lower average length of stay in hospital.[43] A meta-analysis of 20 studies of more than 2,800 patients without ARDS found benefit in low tidal volume regarding both development of lung injury and mortality.[44]
3) β-Agonists, while they have not been studied specifically in NPPE, have been shown in preclinical models to improve alveolar fluid clearance by augmentation of vectorial ion transport and, clinically, to have prophylactic benefit in high-altitude pulmonary edema.[45,46] While a large randomized controlled trial showed no benefit in ARDS,[47] alveolar fluid clearance mechanisms remain intact in NPPE compared with ARDS.[13] In other words, in NPPE, given relatively intact alveolar epithelial physiology, there may be an opportunity for augmentation of vectorial ion transport with β-agonists.
4) Rescue therapies for severe and refractory hypoxemia should be considered early, if appropriate, including neuromuscular blockade, proning, and extracorporeal membrane oxygenation.

Conclusions

NPPE develops most commonly in adults in the setting of laryngospasm after anesthesia for surgical procedures, whereas in children NPPE is more commonly associated with upper respiratory infections, such as epiglottitis, that cause upper airway obstruction and inspiratory stridor. Patients with NPPE usually require endotracheal intubation or a tracheotomy to bypass the upper airway obstruction and then positive-pressure ventilation with supplemental oxygen. Once the airway obstruction has been relieved, the resolution of pulmonary edema and respiratory failure usually occurs within 48 h. Therapy should include lung-protective ventilation with a tidal volume of 6 mL/kg predicted body weight and a plateau airway pressure less than 30 cm H_2O. Diuresis may also hasten the resolution of pulmonary edema by reducing lung vascular pressures. The pulmonary edema fluid in most cases has a low protein concentration, supporting a hydrostatic mechanism for edema formation in NPPE.

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