Malcolm Lemyze
Jihad Mallat

Understanding negative pressure pulmonary edema

M. Lemyze and J. Mallat contributed
equally to this work.

M. Lemyze (✉) · J. Mallat
Department of Respiratory and Critical Care
Medicine, Schaffner Hospital, 99 route de la
Bassée, 62300 Lens, France
e-mail: malcolmlemyze@yahoo.fr

J. Mallat
Department of Anesthesiology, Schaffner
Hospital, Lens, France

Abbreviations

NPPE	Negative pressure pulmonary edema
PE	Pulmonary edema
UAO	Upper airway obstruction
ICU	Intensive care unit
ARDS	Acute respiratory distress syndrome
NIV	Noninvasive positive pressure ventilation

Negative pressure pulmonary edema (NPPE) is a form of noncardiogenic pulmonary edema (PE) that results from the generation of high negative intrathoracic pressure (NIP) needed to overcome upper airway obstruction (UAO). NPPE is a potentially life-threatening complication that develops rapidly after UAO in otherwise healthy young persons who are capable of producing large markedly NIPs. The incidence of NPPE, in patients developing acute UAO, has been estimated to be up to 12 % [1]. The true incidence, however, is not known and may be higher than has been suggested, since many cases may have been misdiagnosed because of a lack of familiarity with the syndrome. All causes of obstructed upper airway may lead to NPPE [2]. However, the most commonly reported etiology of NPPE in adults is laryngospasm during intubation or in the postoperative period after anesthesia (50 % of cases of NPPE) [3]. Nevertheless, NPPE may be more common in ICU patients than is thought; For instance, ventilation with low tidal volume during the acute phase of ARDS in patients with increased respiratory drive can lead to patient–ventilator asynchrony that causes increased breathing effort and the generation of high NIPs that will further worsen PE. Also, strong inspiratory efforts in the presence of increased resistive work of breathing will lead to negative alveolar pressures mimicking the cardiothoracic relationships present during NPPE, and may contribute to extubation failure in some patients.

Understanding the pulmonary fluid homeostasis is crucial to comprehend the mechanisms responsible for pulmonary edema formation. In the normal lung, the net fluid transfer across the pulmonary capillaries depends on the net difference between hydrostatic and colloid osmotic pressures, as well as on the permeability of the capillary membrane (Starling's law). Under normal conditions, most of this filtered fluid is removed from the interstitium through the lymphatic system to return to the systemic circulation [4]. The alveolar epithelium, because of its tight intercellular junctions, acts as an effective barrier limiting water intrusion into alveolar spaces. However, when the hydrostatic pressure in the pulmonary capillary bed increases and/or the lung interstitial pressure decreases, the rate of transvascular fluid filtration rises, causing edema in the perimicrovascular interstitial spaces,
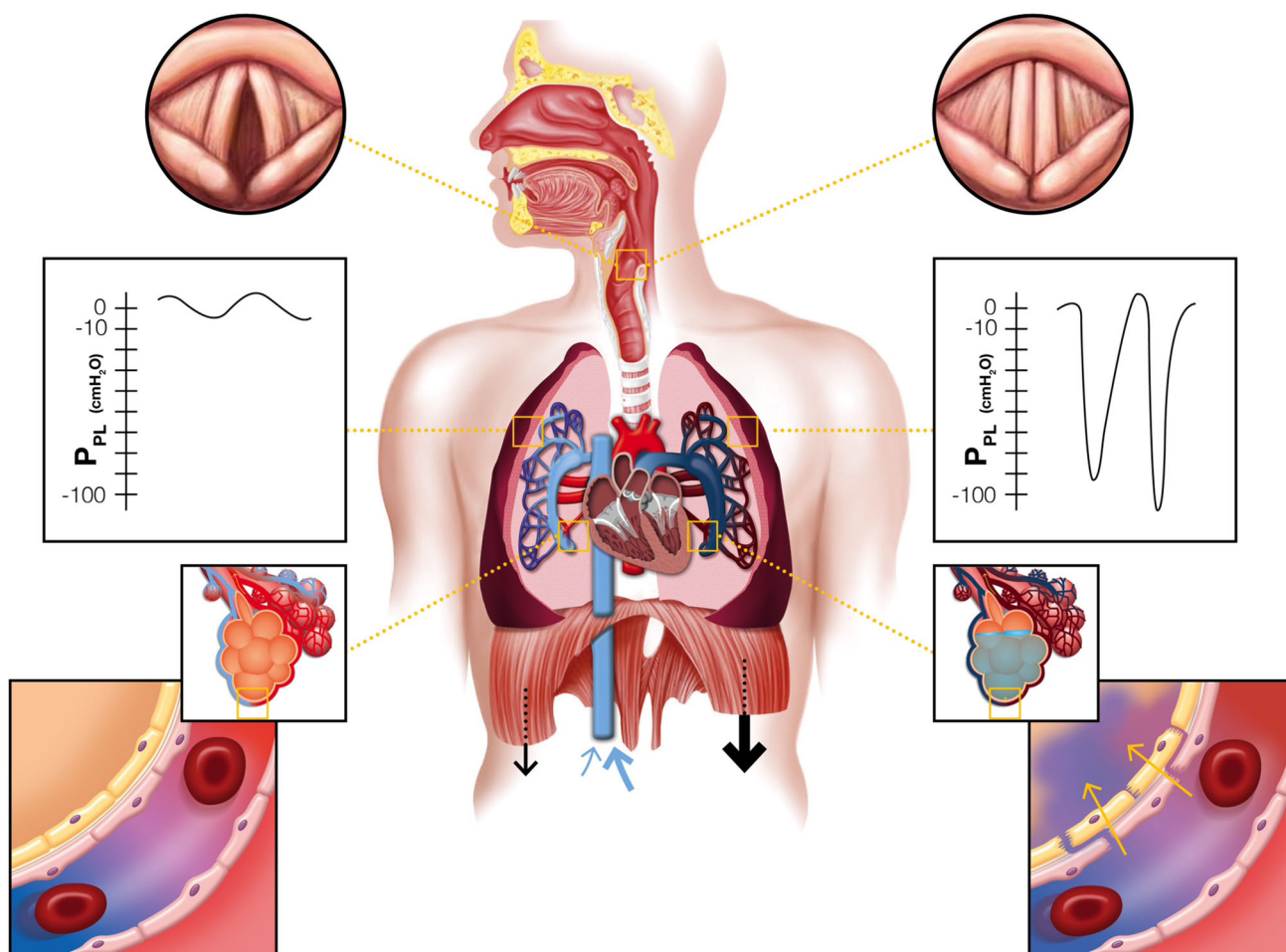
Fig. 1 As shown in the *left part* of the illustration, breathing through the normally open upper airway requires minimal diaphragmatic efforts (*thin black arrow*) that generate small levels (-2 to -8 cmH$_2$O) of negative pleural pressure (P_{PL}) during inspiration. In normal conditions, the alveolar–capillary pressure gradient is small, and when hydrostatic pressures slightly increase in the pulmonary capillary bed, the fluid overload may be offset by increased lymphatic drainage. Conversely, inspiration against an obstructed upper airway—as represented by closed vocal cords in the *right side* of the illustration—requires forceful diaphragmatic efforts (*large black arrow*) generating high levels (-50 to -140 cmH$_2$O) of negative P_{PL} that increase venous return to the right side of the heart (*large blue arrow*). This may result in higher hydrostatic pressures in the pulmonary capillaries and a sudden drop of pressures in the alveolar spaces, creating a huge pressure gradient across the pulmonary capillary wall and disruption of the alveolar–capillary membrane, leading to alveolar flooding and pulmonary edema (*yellow arrows*)

and maybe alveolar flooding if a critical quantity of edema fluid in the interstitial space has been reached [4, 5].

What is the pathophysiology of NPPE? Two different mechanisms have been suggested to explain the pathogenesis of PE during UAO. One belief is that NPPE is developed by substantial fluid shifts due to swings in intrathoracic pressure [6]. Markedly NIP is generated by deep inspiratory efforts against an occluded airway or a closed glottis (modified Müller maneuver). Young healthy subjects can generate very high levels of negative inspiratory pressure with a maximum of -140 cmH$_2$O [7]. This NIP is transmitted by the same amount to the intrapleural spaces, resulting in augmentation of venous return to the right side of the heart, and pulmonary venous pressures, while decreasing perivascular interstitial hydrostatic pressure, which favors movement of fluid from the pulmonary capillaries into the interstitium and alveolar spaces [8] (Fig. 1). Also, the hyperadrenergic state associated with catastrophic UAO can cause peripheral vasoconstriction and an increase in venous return, which could further increase pulmonary blood flow, contributing to edema. Furthermore, the NIP increases left ventricular afterload by increasing the transmural left ventricular pressure, thus raising ventricular wall tension [9]. The increase in afterload depresses left ventricular ejection. In addition, the resulting hypoxemia decreases myocardial contractility and increases

pulmonary arterial resistance. The fall in left ventricular ejection fraction augments in succession end-diastolic pressure, left atrial pressure, and pulmonary venous pressure, further increasing the pulmonary capillary hydrostatic pressures that promote the formation of PE [9]. Therefore, the combination of increased preload and afterload associated with a decrease in pulmonary interstitial pressure cause a high increase in the hydrostatic pulmonary pressure gradient (disturbance of the Starling equilibrium), allowing transudation of fluid out of the pulmonary capillary into the lung interstitium, resulting in PE. This mechanism of NPPE is similar to hydrostatic PE as observed in patients suffering from congestive heart failure or volume overload states.

The second suggested mechanism is that the mechanical stress developed from respiration against an obstructed upper airway may induce breaks in the alveolar epithelial and pulmonary microvascular membranes, resulting in increased pulmonary capillary permeability and protein-rich PE [7, 10]. This theory is based on the concept of wall stress failure developed more than 20 years ago by West et al. [11], in which increasing transmural pulmonary capillary pressures cause disruption of the alveolar–capillary membrane with resultant high-permeability PE. In animals, when pulmonary capillaries are subjected to increased transmural pressure, ultrastructural damage of the walls of the capillaries and alveolar epithelium is observed under scanning electron microscope [12]. Stress failure of pulmonary capillaries has been suggested to be involved in several conditions causing PE and hemorrhage, including neurogenic and high-altitude PE [13], and following intense exercise in elite human athletes [14]. This indicates that acute

increases in transmural pulmonary capillary pressures as observed in NPPE may lead to high-permeability PE [15]. However, Fremont et al. [2], in 10 NPPE patients, found a low PE fluid-to-serum protein ratio with normal alveolar fluid clearance, further supporting a hydrostatic mechanism for edema fluid formation. Nevertheless, we believe that the pathogenesis of NPPE is probably multifactorial, ranging from transudative to high-permeability edema when a very high transmural pulmonary capillary pressure has been produced.

Treatment of NPPE generally includes maintaining a patent airway, and oxygen supplementation with addition of positive end-expiratory pressure or noninvasive positive pressure ventilation (NIV) as guided by physical examination and arterial blood gas analysis. Mechanical ventilation should be reserved for severe patients who do not respond to NIV. Diuretics are often used; however, there is no evidence of their utility, and they may exacerbate hypovolemia and hypoperfusion. Ultimately, NPPE usually has a rapidly resolving clinical course in 12–48 h when recognized early and treated immediately.

Understanding the pathophysiological mechanisms contributing to PE can help in distinguishing NPPE from other causes of noncardiogenic PE, thus preventing use of inappropriate and dangerous treatment for patients with NPPE.

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