

## Reviews

## Non-Cardiogenic Pulmonary Edema

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The barrier between pulmonary capillaries and alveolar gas consists of a series of three anatomical layers with distinct structural characteristics. The cytoplasmic projections of the capillary endothelial cells represent the first layer of this barrier and overlap to form a continuous cytoplasmic tube. At the overlapping junctions of these cytoplasmic projections are clefts of varying sizes (averaging approximately 4 nm in width), which provide communication between pulmonary capillaries and the interstitial space (*loose junctions*). The interstitial space represents the second layer and contains connective tissue, fibroblasts, macrophages, small arteries, veins and lymphatic channels. The third layer is the alveolar wall which is continuous with the bronchial epithelium and is composed of large squamous cells with thin cytoplasmic projections. These projections overlap in a similar way to the projections of capillary endothelium. In contrast to the endothelial junctions, which allow for variable continuity between capillaries and interstitial space, the alveolar epithelial clefts are obliterated by complete fusion of the membranes of the adjacent cells, so as to demand greater forces for their disruption (*tight junctions*). The tightness of these junctions helps to forestall alveolar flooding, which represents the final stage of pulmonary edema.

In other tissues there is normally a continuous exchange of liquid and colloids

between the vascular bed and the interstitium. The lymphatics serve to continuously remove colloids and fluid from the interstitial space to the systemic venous circulation, so as to ensure that the volume of interstitial space remains constant.

Pulmonary edema develops when the movement of liquid from the blood vessels to the interstitial space and in some instances to the alveoli exceeds the return of liquid to the blood by way of the lymphatics. Whether initiated by an imbalance of Starling forces or by primary damage to the various components of the alveolar-capillary membrane, the sequence of liquid exchange and accumulation in the lungs is the same and can be represented as three separate stages<sup>1</sup>.

In stage 1, there is an increase in transfer of liquid from blood capillaries to the interstitial space. The pulmonary capillary endothelial junctions are widened by an increase in filtrative forces or by toxic damage of the membrane. Despite the increased filtration, there is no increase in interstitial volume because there is an equal increase in lymphatic drainage. When the filtered load from the pulmonary capillaries to the interstitial space is increased beyond a limit, the lymphatics cannot follow this rapid rhythm and liquid and colloid begin to accumulate in the more compliant interstitial compartment surrounding bronchioles, arterioles and venules (stage 2).

With further increase in filtered load, the volume limits of the more compliant

spaces of the interstitial space are exceeded and the liquid begins to accumulate in the less compliant compartments of the interstitial space. The alveolar-capillary membrane is very thin and disrupts immediately, so that alveolar flooding occurs (stage 3). This flooding decreases pulmonary oxygenation which results in deterioration of left ventricular function. This mechanism leads to further increase of pressure in the pulmonary capillaries and further deterioration of pulmonary edema<sup>2</sup>.

### Classification of pulmonary edema

The two most common forms of pulmonary edema are those initiated by an imbalance of Starling forces (Hydrostatic Pulmonary edema) and those initiated by disruption of alveolar-capillary membrane (NCPE). Less often, lymphatic insufficiency can be involved as a predisposing factor (post lung transplant, lymphangitic carcinomatosis, fibrosin lymphangitis). Irrespective of the initiating event, the stage of alveolar flooding is characterized to some degree by disruption of alveolar-capillary membrane<sup>1</sup>.

### Cardiogenic pulmonary edema

Hydrostatic pulmonary edema is usually cardiogenic. The usual causes of systolic and diastolic left ventricular dysfunction (coronary artery disease, myocarditis, cardiomyopathy, hypertension, congenital heart diseases etc.) are responsible for the development of acute pulmonary edema. Usual triggering factors are acute ischemia, myocardial infarction, rhythm or conduction abnormalities, high blood pressure, infection, omission of drug intake, dietary abuse, physical or psychological stress.

The normal pulmonary capillary pressure is about 8 mmHg. Due to the effect of gravity, hydrostatic pressure is greater from apex to base and this explains the non-homogeneous blood perfusion to the lungs. Deviation from this gravity-dependant pattern has been called vascular redistribution. Redistribution is due to increased pulmonary venous pressure and is demonstrated by greater perfusion to the apex than to the base of the lungs. This kind of redistribution is seen after an acute attack of alveolar pulmonary edema or in chronic situations with high left atrial pressure as happens in mitral stenosis and congestive heart failure<sup>2</sup>.

Pulmonary edema will occur only when the pulmonary capillary pressure rises to values exceeding the plasma colloid osmotic pressure, which is

approximately 28 mmHg in humans. Although pulmonary capillary pressure must be abnormally high for the development of pulmonary edema, this pressure may not correlate with the severity of pulmonary edema. The rate of increase in lung liquid at any given elevation of capillary pressure is related to the functional capacity of lymphatics and to variations in interstitial and pulmonary pressures<sup>1</sup>.

In patients with chronic heart failure lymphatics are hypertrophied and lymph flow may exceed up to twenty times the normal rate. This creates a safety margin for compensation of increased hydrostatic pressure and increased filtration. That is why patients with heart failure may have pulmonary artery wedge pressure to 45 mmHg without being in pulmonary edema<sup>1,2</sup>. Experimental work showed that the resection of over half the pulmonary capillary bed has been required to produce pulmonary edema<sup>2</sup>.

### Non-cardiogenic pulmonary edema

NCPE continues to represent an important cause of morbidity and mortality with a large human and financial cost. Because of the resemblance of the clinical picture to that seen with respiratory distress of the neonate, NCPE has been referred to as the Adult Respiratory Distress Syndrome (ARDS). In spite of the great improvement in supportive therapy, mortality continues to exceed 50%. Early diagnosis is important for the management of this syndrome.

Many conditions are associated with pulmonary edema that appears to be due to diffuse damage and increased permeability of alveolar-capillary membrane. These conditions include infectious (bacterial, viral, parasitic) septicemia, trauma and disseminated intravascular coagulation. Also, shock lung in association with non-thoracic trauma, acute hemorrhagic pancreatitis, inhalation of toxic gases (smoke, ozone, cadmium, phosgene, chlorine, nitrogen dioxide), circulating foreign substances (snake venom, alloxan, alpha-naphthyl thiourea) and endogenous vasoactive substances (histamine, kinins). Burn, aspiration of gastric contents, inhalation of foreign body, acute radiation pneumonitis and drowning have been also implicated in the development of pulmonary edema.

### Special forms of non-cardiogenic pulmonary edema

Conditions considered as initiating mechanisms for the development of NCPE are listed in the table that follows.

**Table 1.** Special forms of non-cardiogenic pulmonary edema.

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<b>Pharmaceutical</b>
Narcotic overdose
Chemotherapy
Salicylate intoxication
Calcium antagonist overdose
Hydrochlorothiazide
Contrast fluids
<b>High-altitude</b>
<b>Neurogenic</b>
<b>Pulmonary embolism</b>
<b>Eclampsia</b>
<b>Post cardioversion</b>
<b>Post anaesthesia</b>
<b>Post cardiopulmonary bypass</b>

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**Pharmaceutical*****Narcotic overdose***

Pulmonary edema is usually a complication of pharmaceutical intoxication with antidepressants, opiates. It is a well-recognized complication of heroin overdose and represents the most important cardiopulmonary toxic effect of opiates overdosing. It is usually a standard pathologic finding in fatal cases and may be the result of intravenous, oral or administration of the narcotic drug by inhalation. The pathophysiologic feature of the syndrome is increased permeability of pulmonary capillaries and the normal or even low left atrial pressure. The mechanisms which are responsible for the endothelial damage remain unclear.

In spite of the fact that pulmonary edema usually appears shortly after heroin injection, it may appear late, even 6 hours later<sup>3</sup>. Mechanical ventilation with positive airway pressures (PEEP) offers great support to patients<sup>2,4</sup>.

***Chemotherapy***

NCPE is a rare pulmonotoxic complication of anti-cancer therapy. It is less well recognizable than pneumonitis and fibrosis. Chemotherapeutic agents clearly associated with NCPE are cytarabine, gemcitabine, interleukin 2, as well as all-trans retinoid acid in acute promyelocytic leukemia. The pathophysiology of lung injury in drug-induced NCPE, remains unclear. There are indications suggesting that both a direct cytotoxic insult to the lung epithelial cells and induction of a cytokine-triggered inflammatory response may be involved in its pa-

thogenesis. By distinction to drug-induced pulmonary pneumonitis that may lead to permanent pulmonary fibrosis, NCPE is not fatal. It can be reversed upon prompt recognition, immediate discontinuation of the offensive drug and intensive supportive treatment with intravenous corticosteroids<sup>5</sup>.

***Salicylate intoxication***

Salicylate intoxication is frequently overlooked as a cause of NCPE and altered mental status in adult patients. Non-early diagnosis and treatment leads to high morbidity and mortality. A high index of suspicion is necessary for early recognition and successful treatment with hemodialysis and urinary alkalization<sup>6,7</sup>.

***Calcium antagonist overdose***

NCPE has been reported after an overdose of diltiazem, nifedipine and verapamil. Multiple cellular mechanisms appear to be responsible for the development of NCPE after overdoses of calcium channel blockers. First, prostaglandins have been shown to play an important role in maintaining cellular integrity, especially during lung inflation. The protective role of prostaglandins in cellular integrity is lost with excessive concentrations of calcium channel blockers (inhibition of prostacyclin release). This leads to a "leaky capillary syndrome". Secondly, calcium channel blockers, cause systemic precapillary vasodilation and peripheral edema due to their effect on vascular smooth muscle. Finally, it has been shown that the pulmonary vasodilatory effect of calcium antagonists may lead to perfusion-ventilation mismatch and hypoxemia. Management of these patients includes infusion of calcium and catecholamines and correction of hyperglycemia<sup>8,9,10</sup>.

***Hydrochlorothiazide use***

Less than 40 cases of NCPE have been reported to be associated with use of hydrochlorothiazide. Even a single dose (50mg) may induce the syndrome, the etiology of which remains unknown. It is suggested that a possible involvement of an immunologic mechanism is responsible for this adverse reaction. The reaction is associated with granulocytic infiltration into the lungs and IgG deposition in alveolar membranes. It is reported good response to dopamine and steroids<sup>11</sup>.

### **Radiopaque media**

Fulminant NCPE has been reported several minutes after intravenous administration of radiocontrast media. The low pulmonary–capillary wedge pressure and the high protein concentration in pulmonary edema fluid indicated a NCPE related to increased lung vascular permeability. The response is considered as allergic reaction and the possibility of its occurrence is increased in patients with known immunologic abnormality<sup>12</sup>.

### **High-altitude**

This uncommon type of NCPE occurs in young people who have quickly ascended to altitudes above 2700m and who then engage in strenuous physical exercise at that altitude, before they have become acclimatized. The incidence of this illness is about 6.5 cases per 100 exposures in persons less than 21 years of age.

Although most patients have pulmonary hypertension, the pulmonary capillary wedge pressure is normal. The direct effect of alveolar hypoxia on increasing alveolar-capillary membrane permeability is considered possible mechanism for the pathogenesis of NCPE<sup>13</sup>. Transient intravascular coagulation has also been implicated. Gradual ascent, allowing time for acclimatization and limiting physical exertion for 2-3 days in high altitudes are thought to be preventive<sup>14</sup>.

Reversal of this syndrome is rapid (in less than 48 hours) and certain by returning the patient to a lower altitude and by administering a high inspiratory concentration of oxygen. When this is not available, treatment with nifedipine is recommended until descent is possible<sup>14</sup>.

### **Neurogenic**

It is suggested from experimental studies that sympathetic overactivity plays a key role in the pathogenesis of this disorder<sup>15</sup>. Central nervous system disorders ranging from head trauma to grand mal seizures can be associated with acute pulmonary edema, without detectable left ventricular disease. Neurogenic pulmonary edema is often associated with increased intracranial pressure and can be the initial manifestation of hyponatremic encephalopathy with nausea and vomiting as it happens in otherwise healthy Marathon runners<sup>16</sup>. In a study of Marathon runners who collapsed after competing in

a Marathon and had pulmonary edema, the mean plasma sodium level was  $121 \pm 3$  mmol/l and oxygen saturation was less than 70%. Electrocardiograms and echocardiograms were normal and chest radiographs showed pulmonary edema with a normal heart. Cardiac enzymes and pulmonary artery wedge pressure were not elevated. Scanning of the brain showed cerebral edema. Treatment includes intubation and mechanical ventilation with intravenous administration of hypertonic sodium chloride (NaCl) with such a rate of continuous infusion as to increase plasma sodium levels by 10mmol/l in 12 hours. Pulmonary and cerebral edema resolve as the sodium level increases<sup>15,16</sup>.

### **Pulmonary embolism**

Pulmonary edema can occur after massive or multiple smaller pulmonary embolisms and is most often attributed to concomitant left ventricular dysfunction due to hypoxemia and displacement of the interventricular septum to the left ventricular cavity by right ventricular dilatation. There are data to suggest that an increase in permeability of the alveolar-capillary membrane also occurs. Thrombin generated by the clotting process in association with the embolus causes aggregation of platelets, complement activation and leukostasis. The radiographic findings are relevant to the severity of pulmonary edema and in 20% of the cases there is a coexistent pneumonia<sup>17,18</sup>.

### **Eclampsia**

Multiple factors such as cerebral dysfunction with massive sympathetic discharge, hypervolemia, hypoalbuminemia and disseminated intravascular coagulation probably play a role in the pathogenesis<sup>19</sup>.

### **Post Cardioversion**

The mechanism of pulmonary edema which occasionally occurs after cardioversion of tachyarrhythmias, remains unknown. Ineffective left atrial function after cardioversion, left ventricular dysfunction and neurogenic mechanisms have all been suggested as contributing factors<sup>20</sup>.

### **Post anaesthesia**

In previously healthy subjects, pulmonary edema has been found in the early post anaesthesia period with-

out a clear relationship to fluid overload or any evidence of left ventricular dysfunction. The mechanism of this disorder is unknown but some cases have been connected to the administration of naloxone. Upper airway obstruction due to laryngospasm is considered the most possible mechanism causing rapid changes in intrathoracic, alveolar and interstitial pressures, which recover within 48 hours after proper intervention. Early diagnosis and management is lifesaving for the patient<sup>21,22</sup>.

### Post cardiopulmonary bypass

NCPE is a rare adverse event that occurs in 0.2% of cardiopulmonary bypass patients, with mortality rates approaching 30%. Although all patients who undergo cardiopulmonary bypass, have significant heart disease, the development of edema has been associated with normal left atrial pressures.

Alterations in surfactant due to prolonged collapse of the lung, with subsequent need to apply high negative intrapleural pressures for reexpansion, hypotension, hemorrhagic shock, transfusion of fresh frozen plasma and packed red blood cells and possibly drugs (amiodarone) may be responsible for the pathogenesis.

Complement activation or direct pharmacologic release of histamine by high concentrations of protamine (given for reversal of heparin anticoagulation), is the suspected cause. Cautious administration and accurate calculation of protamine doses may prevent such an event<sup>22,24,25</sup>. Treatment is supportive.

### Differential diagnosis

The differentiation between hydrostatic (cardiogenic) and increased permeability edema (NCPE), can usually be made through assessment of the clinical context in which it occurs and by means of clinical and laboratory data. This approach may be difficult as there is overlapping of pathogenetic mechanisms in the two forms. For example, the primary hemodynamic event of cardiogenic pulmonary edema, that is increase in intravascular pressure, may disrupt the capillary and alveolar membranes producing a NCPE. The basic differences between the two forms of pulmonary edema are provided by history, clinical examination and laboratory tests.

In NCPE, there is neither history of acute cardiac event nor underlying cardiac disease. In car-

diogenic pulmonary edema, clinical examination reveals low flow state (cool periphery), S3 gallop, cardiomegaly, jugular venous distention and wet crackles.

NCPE is usually high flow state (warm periphery), with bounding pulses, no gallop, no jugular venous distention and with dry crackles.

Concerning laboratory tests, in cardiogenic pulmonary edema, we may have ECG signs of ischemia or infarction, raised cardiac enzymes and perihilar distribution of congestion in chest x-ray. Pulmonary capillary wedge pressure exceeds 18mmHg and the ratio of pulmonary edema fluid protein to plasma protein concentration is less than 0.5. On the contrary in NCPE, ECG and cardiac enzymes are usually normal, on chest x-ray there is peripheral distribution of edema, pulmonary capillary wedge pressure is less than 18mmHg and the ratio of pulmonary edema fluid protein to plasma protein concentration is 0.7 or above.

Chest x-ray findings usually appear late, at least 12 hours after the onset of cardiopulmonary symptoms. It is stated that the value of chest radiography is limited in the differentiation of the two types of pulmonary edema in severe cases. However, recent studies have suggested that chest radiography can be used to distinguish these types of pulmonary edema, if careful attention is given to certain radiographic features. In some studies, independent investigators (thoracic radiologists), managed to distinguish NCPE from cardiogenic with an accuracy of 91%. The distinguishing radiographic criteria of the two types of pulmonary edema are listed below<sup>26-28</sup>:

1. In NCPE, the initial site of fluid accumulation is the pulmonary interstitium including peribronchial cuffs and septal lines. This type of edema appears predominantly as alveolar filling, since the altered (disrupted) alveolar-capillary membrane allows for the direct accumulation in the air spaces of fluid that is too proteinaceous to be cleared via the interstitium. In contrast, in cardiogenic pulmonary edema filling of air spaces (alveolar flooding) occurs when the interstitial space is finally overwhelmed.
2. Kerley lines are never seen in increased permeability edema whereas they are a common finding in cardiogenic. The appearance of Kerley lines in NCPE, indicates the coexistence of cardiogenic pulmonary edema.
3. Patchy or peripheral pattern of edema is relatively specific for NCPE. Air bronchograms are frequently seen in patients with NCPE.

4. In cardiogenic pulmonary edema the distribution of edema is central and pleural effusion usually coexists.
5. In NCPE, cardiac size, vascular pedicle width and pulmonary blood volume are usually normal. On the contrary, in cardiogenic pulmonary edema cardiac size is increased, vascular pedicle width is enlarged and there is inverted distribution of blood flow.

In the study of Milne et al<sup>27</sup> in which radiography was useful in distinguishing the type of pulmonary edema, patients were not very ill and underwent radiography while positioned upright. In more severe cases the distinguishing radiographic features are neither sensitive nor specific and differentiation between the two types of edemas is more difficult<sup>28</sup>.

### Management of non-cardiogenic pulmonary edema

At the time of initial injury and several hours thereafter, the patient may be free of respiratory symptoms or signs. The earliest sign is an increase in respiratory frequency followed shortly by dyspnea. Whatever the underlying cause of pulmonary edema, analysis of arterial blood to assess the type and degree of gas exchange abnormality is necessary, followed by institution of appropriate inhalation therapeutic measures. Arterial blood gas measurement in the earlier period will disclose a depressed  $PO_2$  and decreased  $PCO_2$ . At this point, oxygen given by mask or nasal prongs, results in a significant increase in the arterial  $PO_2$ .

Physical examination may be unremarkable, although a few fine inspiratory rales may be audible. With progression, the patient becomes cyanotic and increasingly dyspneic and tachypneic. Rales are more prominent and easily heard throughout both lung fields along with regions of tubular breath sounds. At this stage, hypoxemia cannot be corrected by the simple administration of oxygen, and mechanical ventilatory assistance must be initiated to provide adequate oxygenation of arterial blood. Should this treatment be delayed, the combination of increasing tachypnea and smaller tidal volume, results in a rising  $PCO_2$  and further fall in  $PO_2$  to fatal levels<sup>1</sup>.

When there is hypoxemia ( $PO_2 < 60$  mm Hg) without hypercapnia, enrichment of the inspired gas may suffice and can be given either by nasal prongs or Venturi mask with reservoir, depending upon the degree of oxygen enrichment required to elevate the

$PO_2$  sufficiently. If  $PO_2$  cannot be maintained at or near 60 mmHg despite inhalation of 100%  $O_2$  at 20 liters per minute, or if there is progressive hypercapnia, mechanical ventilation is necessary<sup>29</sup>.

### Mechanical ventilation

Mechanical ventilation is particularly useful in the treatment of patients with NCPE. If hypoxemia is not corrected by mechanical ventilation or if toxic concentrations of oxygen are necessary for prolonged periods, further improvements in arterial oxygenation at the same inspired oxygen concentration or equivalent levels of arterial oxygenation at lower concentrations of oxygen can be achieved by increasing end-expiratory lung volumes by the addition of positive end-expiratory pressure (PEEP)<sup>1</sup>.

In these conditions we usually apply PEEP at 5-20 cm  $H_2O$ . The role of PEEP is to avoid collapse of alveoli and to maintain their inflation throughout the respiratory cycle. This actually increases FRC and avoids the risk for further pulmonary injury<sup>29</sup>.

Although application of PEEP is effective improving oxygenation in the majority of patients, it might pose a risk for complications particularly when mechanical support is applied in an injured lung like in NCPE.

Application of PEEP at very high pressures may cause deterioration of alveolar edema, decrease cardiac output and diminish pressure and renal blood supply. An additional contribution may come from greater pulmonary vascular resistance due to increased lung volume. The result of increased right ventricular afterload is a displacement of the interventricular septum to the left, which impedes left ventricular diastolic filling<sup>30</sup>. Another complication of PEEP is barotrauma, the incidence of which is between 5-15% and it is presented as pneumomediastinum, pneumothorax and subcutaneous emphysema<sup>31</sup>.

### Conclusion

Pulmonary edema is a generalized descriptive term for the accumulation of fluid within the interstitial and/or the alveolar spaces of the lungs. This accumulation of fluid has a cause that may be termed cardiogenic or non-cardiogenic. Pulmonary edema of cardiogenic origin is usually due to failure of the left side of the heart. Non-cardiogenic pulmonary edema is a clinical syndrome characterized by simultaneous

presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiograph and no evidence of left atrial hypertension/congestive heart failure.

Prompt recognition of pulmonary edema is important to avoid life-threatening complications. The aim of this review is to alert cardiologists, that besides known factors for the development of cardiogenic pulmonary edema, there are other significant mechanisms that cause NCPE. The reader of this article should be able to identify the differences between cardiogenic pulmonary edema and NCPE, to identify the most common causes of NCPE and state the actions that are indicated in the care of patients with NCPE.

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