Clinical and Radiologic Features of Pulmonary Edema

Pulmonary edema may be classified as increased hydrostatic pressure edema, permeability edema with diffuse alveolar damage (DAD), permeability edema without DAD, or mixed edema. Pulmonary edema has variable manifestations. Postobstructive pulmonary edema typically manifests radiologically as septal lines, peribronchial cuffing, and, in more severe cases, central alveolar edema. Pulmonary edema with chronic pulmonary embolism manifests as sharply demarcated areas of increased ground-glass attenuation. Pulmonary edema with veno-occlusive disease manifests as large pulmonary arteries, diffuse interstitial edema with numerous Kerley lines, peribronchial cuffing, and a dilated right ventricle. Stage 1 near drowning pulmonary edema manifests as Kerley lines, peribronchial cuffing, and patchy, perihilar alveolar areas of airspace consolidation; stage 2 and 3 lesions are radiologically nonspecific. Pulmonary edema following administration of cytokines demonstrates bilateral, symmetric interstitial edema with thickened septal lines. High-altitude pulmonary edema usually manifests as central interstitial edema associated with peribronchial cuffing, ill-defined vessels, and patchy airspace consolidation. Neurogenic pulmonary edema manifests as bilateral, rather homogeneous airspace consolidations that predominate at the apices in about 50% of cases. Reperfusion pulmonary edema usually demonstrates heterogeneous airspace consolidations that predominate in the areas distal to the recanalized vessels. Postreduction pulmonary edema manifests as mild airspace consolidation involving the ipsilateral lung, whereas pulmonary edema due to air embolism initially demonstrates interstitial edema followed by bilateral, peripheral alveolar areas of increased opacity that predominate at the lung bases. Familiarity with the spectrum of radiologic findings in pulmonary edema from various causes will often help narrow the differential diagnosis.
INTRODUCTION

Pulmonary edema is defined as an abnormal accumulation of fluid in the extravascular compartments of the lung. The relative amounts of intravascular and extravascular fluid in the lung are mostly controlled by the permeability of the capillary membrane as well as the oncotic pressure. This relation is described by the Starling equation, which is used to determine the theoretical amount of fluid $F_{filt}$ filtered per unit area per unit of time:

$$F_{filt} = K_{filt}(HP_i - HP_e) - t(OP_i - OP_e).$$

In this equation, $HP_i$ and $HP_e$ represent the intravascular and extravascular hydrostatic pressure, respectively, and $OP_i$ and $OP_e$ represent the intravascular and extravascular oncotic pressure, respectively. $K_{filt}$ represents the conductance of the capillary wall and expresses the water resistance created by the capillary endothelial cell junctions with changes in $HP_i$ and $HP_e$. $t$ represents the oncotic reflection coefficient and expresses the permeability of the capillary membrane to macromolecules. The greater this reflection coefficient is, the more the passage of macromolecules will be restricted, thus decreasing overall fluid filtration. The net flow $F_{net}$ is defined as $Q_{filt} - Q_{lymph}$, where $Q_{filt}$ represents fluid transudation or exudation and $Q_{lymph}$ represents lymphatic absorption. Pulmonary edema develops when the equilibrium between fluid transudation or exudation $Q_{filt}$ and lymphatic absorption $Q_{lymph}$ is disturbed. Thus, although under normal conditions the endothelial cells are relatively impermeable to protein but remain permeable to water and solutes, the tight intercellular junctions of the alveolar epithelium remain nearly impermeable to water and solutes, thus constituting an effective barrier that is a major factor in preventing the development of pulmonary edema. Lymphatic drainage $Q_{lymph}$ represents another way of eliminating excess lung water. A manifold increase in lymphatic flow has been observed with chronically increased hydrostatic pressure. This increase in lymphatic flow is very efficient in eliminating excess water, especially when there is diminished oncotic pressure due to hypoalbuminemia. However, its impact requires time; thus, it may not be as effective in acute settings.

Pulmonary edema can be divided into four main categories on the basis of pathophysiology: (a) increased hydrostatic pressure edema, (b) permeability edema with diffuse alveolar damage (DAD), (c) permeability edema without DAD, and (d) mixed edema due to simultaneous increased hydrostatic pressure and permeability changes. This classification scheme is helpful because pulmonary edema is often seen in the clinical setting, especially in the intensive care unit and emergency department. The clinical and radiologic manifestations of acute pulmonary edema are generally well established. However, pulmonary edema may also demonstrate unusual findings.

In this article, we describe the clinical and radiologic features of pulmonary edema in a series of 80 patients who were seen over a 10-year period in the intensive care units and emergency department at our institution. Pulmonary edema in these patients was categorized according to the classification scheme described earlier. Atypical pulmonary edema is defined as lung edema with an unusual radiologic appearance but with clinical findings that are usually associated with well-known causes of pulmonary edema. Unusual forms of pulmonary edema are defined as lung edema from unusual causes (ie, rare diseases or rare manifestations of common diseases).

INCREASED HYDROSTATIC PRESSURE EDEMA

Two pathophysiologic and radiologic phases are recognized in the development of pressure edema: interstitial edema and alveolar flooding or edema. These phases are virtually identical for left-sided heart failure and fluid overload, the two most frequently observed causes of pressure edema in intensive care and emergency patients. The intensity and duration of both phases are clearly related to the degree of increased pressure, which is determined by the hydrostatic-oncotic pressure ratio.

Interstitial edema occurs with an increase of 15–25 mm Hg in mean transmural arterial pressure and results in the early loss of definition of subsegmental and segmental vessels, mild enlargement of the peribronchovascular spaces, the appearance of Kerley lines, and subpleural effusions. If the quantity of extravascular fluid continues to increase, the edema will migrate centrally with progressive blurring of vessels, first at the lobar level and later at the level
Figure 1. Increased hydrostatic pressure edema in a 33-year-old man with acute myelocytic leukemia who was admitted for fluid overload with renal and cardiac failure. Successive chest radiographs demonstrate progressive lobar vessel enlargement, peribronchial cuffing (arrows in b), bilateral Kerley lines (arrowheads in c), and late alveolar edema with nodular areas of increased opacity. The fluid overload is confirmed by the increasing size of the azygos vein.

of the hilum. At this point, lung radiolucency decreases markedly, making identification of small peripheral vessels difficult. Peribronchial cuffing becomes apparent, particularly in the perihilar areas (4,7). With increases in transmural pressure greater than 25 mm Hg, fluid drainage from the extravascular compartment is at maximum capacity and the second phase (alveolar flooding) commences, leading to a sudden extension of edema into the alveolar spaces and thus creating tiny nodular or acinar areas of increased opacity that coalesce into frank consolidations (Fig 1). Some investigators have observed that, with such pressure increases, the onset of alveolar edema may also be associated with direct pressure-induced damage to the alveolar epithelium (8).

Pulmonary artery catheters are frequently used to assess hydrostatic pressure in intensive care patients. Pulmonary capillary wedge pressure has been shown to reflect left atrial pressure and correlates well with the radiologic features of congestive heart failure and pulmonary venous hypertension (Table) (4,9). However, in
acute heart failure, a time lag is often observed between the increased pulmonary capillary wedge pressure and the radiologic manifestation of pulmonary edema due to the relatively slow movement of water through the widened capillary endothelial cell junctions (10). Similarly, as pulmonary edema resolves, the radiologic findings will persist with decreasing or even normal pulmonary capillary wedge pressure (Fig 2).

**Bat Wing Edema**

Bat wing edema refers to a central, nongravitational distribution of alveolar edema. It is seen in less than 10% of cases of pulmonary edema (4) and generally occurs with rapidly developing severe cardiac failure as seen in acute mitral insufficiency (associated with papillary muscle rupture, massive myocardial infarct, and valve leaflet destruction due to septic endocarditis) or renal failure (Figs 3, 4). In bat wing edema, the lung cortex is free of alveolar or interstitial fluid. This pathologic condition develops so rapidly that it is initially observed as an alveolar infiltrate, and the preceding interstitial phase that is typically seen in pulmonary edema goes undetected radiologically.

Several theories have been proposed to explain the pathophysiology of bat wing edema. One such theory involves an increase in hydraulic conductivity. Mucopolysaccharides fill the spaces in the perivascular cytoskeleton and, under normal conditions, inhibit the flow of liquid. However, with increased tissue hydration, this extracellular matrix allows water to easily flow centrally (4). Other investigators have suggested a pumping effect of the respiratory cycle, which is more pronounced in the lung cortex (10) and causes overall fluid flow toward the hilum. Another probable contributing factor is the contractile property of alveolar septa, which allows them to expel interstitial edema toward the hilum (4).

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<th>Correlation between Pulmonary Capillary Wedge Pressure and Radiologic Findings</th>
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<td>Pulmonary Capillary Wedge Pressure (mm Hg)</td>
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Source.—Reference 4.
Figures 3, 4. (3) Bat wing edema in a 71-year-old woman with fluid overload and cardiac failure. Chest radiograph (a) and high-resolution CT scan (b) demonstrate bat wing alveolar edema with a central distribution and sparing of the lung cortex. The infiltrates resolved within 32 hours. (4) Bat wing edema in a 66-year-old woman with fluid overload of renal origin who was undergoing hemodialysis for hypertensive nephroangiosclerosis. The patient was found unconscious after lying on her right side for several hours. Chest radiograph shows unusual recumbent bat wing pulmonary edema with associated right-sided pleural effusion.

3a.  4.

3b.

- **Asymmetric Distribution of Increased Pressure Edema**
  The most frequent cause of asymmetric distribution of pressure edema is morphologic changes in the lung parenchyma in chronic obstructive pulmonary disease. In cardiac failure, extensive lung emphysema of the apices (seen in heavy smokers) or marked destruction and fibrosis of the upper and middle portions of the lungs (seen in end-stage tuberculosis, sarcoidosis, or asbestosis) will result in pulmonary edema that predominates in the regions that are less affected by these disease processes (Figs 5, 6).
Hemodynamic factors can also cause asymmetric distribution of pulmonary edema. Edema associated with mitral regurgitation has been shown to predominate in the right upper lobe as a result of flow impairment caused by the reflux stream that is directed toward the right upper pulmonary vein (Fig 7) (11,12). Such asymmetric distribution occurs in 9% of adults and 22% of children with grade 3 or 4 mitral regurgitation (13,14).

Finally, the position of the patient also influences intra- and extravascular fluid distribution (Fig 8). In supine patients, axial CT usually demonstrates an anteroposterior gradient, whereas more asymmetric distribution of edema secondary to prolonged surgery or immobilization is frequently observed in the lung fields in recumbent patients. This distribution is typically seen in congestive heart failure but is also observed in overhydration.

- **Pulmonary Edema with Acute Asthma**

Pulmonary edema with acute asthma is a rare pathologic condition because the associated trapped air tends to maintain a positive intralveolar pressure, thus decreasing the hydrostatic pressure gradient. Its pathogenesis can be asso-
On the other hand, the lowered pleural pressure results in decreased interstitial pressure, whereas intravascular pressures are only minimally influenced. The airway obstruction in acute asthma is not uniform throughout the lungs, resulting in heterogeneous extravascular fluid accumulation. During the past 5 years, pulmonary edema with acute asthma was documented radiologically only once at our institution. In that case, chest radiography demonstrated Kerley lines, peribronchial cuffing, ill-defined vessels, enlarged and ill-defined hila, and alveolar areas of increased opacity.

Associated with the severity of the Müller maneuver (ie, forced inspiration as the patient struggles to inhale). Pulmonary edema with acute asthma has been reported in one series of eight children (15). During tidal inspiration, children with episodes of acute asthma have been shown to have very high negative peak inspiratory pressures (mean, $-29$ cm of water) compared with those in healthy subjects (mean, $-7$ cm). Furthermore, it has been demonstrated that the mean pleural pressure is markedly decreased over the entire tidal respiration, reaching $-25.5$ cm of water compared with $-5$ cm in healthy subjects (15). This high negative pleural pressure during acute asthmatic episodes helps maintain the patency of the narrowed airways.
These radiologic findings could not be differentiated from those in other causes of cardiogenic edema.

- **Postobstructive Pulmonary Edema**

  Postobstructive pulmonary edema occurs after relief from an upper airway obstruction and represents a pure form of hydrostatic edema (3,4). It is most frequently caused by an impacted foreign body, laryngospasm, epiglottitis, or strangulation.

  If the obstruction occurs primarily with forced inspiration as the patient struggles to inhale (Müller maneuver), it causes a high negative intrathoracic pressure that increases venous return. The resulting edema is caused by a sudden, marked decrease in the negative pleural pressure, which leads to a high hydrostatic pressure gradient between the intravascular and extravascular compartments (16,17). An obstruction that prevents both inspiration and expiration may create a high positive intrathoracic pressure that impairs the development of edema initially. Later, edema develops as the obstruction is relieved and the intrathoracic pressure suddenly drops.

  At chest radiography and CT, postobstructive pulmonary edema typically manifests as septal lines, peribronchial cuffing, and, in more severe cases, central alveolar edema (Fig 10). These findings are similar to those in pressure edema. Cardiac size is usually normal, indicating a pressure edema that is not related to overhydration. Resolution of clinical symptoms and radiologic findings is rapid and usually occurs within 2–3 days.

- **Edema with Acute and Chronic Pulmonary Embolism**

  For many years, pulmonary edema has been seen occasionally at chest radiography in acute pulmonary embolism (18). Even with the generalized use of helical CT for the assessment of acute pulmonary embolism, pulmonary edema is seen in less than 10% of cases (19,20). Pulmonary edema usually appears at CT as heterogeneous areas of increased ground-glass attenuation localized in the territories of the patent segmental or subsegmental arteries. However, some authors have suggested that in chronic pulmonary embolism these areas of increased attenuation may also represent relatively normal lung parenchyma with no underlying pulmonary edema (with the area of increased attenuation being evident only when compared with the adjacent hypoperfused lung). Thus, some authors have suggested that this is the reason why other high-resolution CT features of pulmonary edema (eg, septal thickening) are not seen in these high-attenuation areas (ie, because they do not actually represent territorial increases in extravascular fluid) (21). If this is true, then pulmonary edema (when present) may be due primarily to hydrostatic causes superimposed on the underlying embolic disease.

  On the other hand, it is believed that the mechanism of pulmonary edema in massive acute pulmonary embolism is directly related to pulmonary hypertension (18,22). This hypertension is caused by the occlusion of more than 50% of the pulmonary arterial bed. Because the right-sided cardiac output is then directed through a reduced arterial network, the capillary hydrostatic pressure increases markedly. The resulting increased perfusion of the areas not involved by the vascular thrombosis leads to edema (23).
In our experience, pulmonary edema is seen in many patients with chronic pulmonary embolism, a finding that has also been described by many other investigators (22,24–26). In this setting, pulmonary edema manifests as areas of increased ground-glass attenuation that are sharply demarcated from areas of regional transparency distal to the occluded arteries and thus deprived of blood flow (Fig 11a) (27). Areas of ground-glass attenuation are closely associated with dilated pulmonary arteries in more than 70% of cases of chronic pulmonary embolism (Fig 11b) (28–30). Therefore, these areas are probably of mixed origin and are associated with both simple overperfusion or hyperemia and a component of extravascular fluid accumulation within the perfused regions. The pathogenesis of these focal areas of pulmonary edema has been demonstrated with single-photon emission CT and scintigraphy of the lung (28). Juxtaposition of areas of increased ground-glass attenuation with areas of hypoperfusion produces a familiar mosaic pattern known as mosaic oligemia.

**Edema with Pulmonary Veno-occlusive Disease**

Pulmonary veno-occlusive disease is a lethal condition associated with the narrowing or occlusion of small pulmonary veins and venules by organized thrombi (30–32). This disease process demonstrates widespread involvement of the lungs but does not involve the large pulmonary veins. Pulmonary veno-occlusive disease has no sex or age predilection and causes a type of hydrostatic edema due to the increased hydrostatic pressure that is directly associated with the resulting increase in peripheral resistance. Its pathogenesis remains unclear, although striking similarities with veno-occlusive disease of the liver have been reported (31–33). The use of oral contraceptives may play a role in both pulmonary and hepatic veno-occlusive disease because they have been found to dramatically reduce the endothelial cell production and metabolism of prostaglandin and prostacyclin, both of which are strong inhibitors of coagulation (34). Patients present with rapidly progressive dyspnea, orthopnea, and acute pulmonary edema with or without hemoptysis. The main diagnostic features include a normal or low pulmonary capillary wedge pressure reflecting the patency of the large pulmonary veins, pulmonary arterial hypertension, and edema. Chest radiography and CT reveal enlarged pulmonary arteries, diffuse interstitial edema with numerous Kerley lines, peribronchial cuffing, and a dilated right ventricle (Fig 12) (31).
Near Drowning Pulmonary Edema
Near drowning is defined as asphyxiation due to water inhalation followed by survival for a minimum of 24 hours (35). Three stages of near drowning are currently recognized (35,36). Stage 1 manifests as acute laryngospasm that occurs after inhalation of a small amount of water. In patients in whom the laryngospasm persists, thereby preventing outright flooding of the lungs, one observes “dry drowning.” As in postobstructive pulmonary edema, the resulting lesions are due to negative pressure edema arising from a prolonged episode of the Müller maneuver (35). Kerley lines, peribronchial cuffing, and patchy, perihilar alveolar areas of airspace consolidation are the most important radiologic findings (Fig 13a). These findings disappear completely within 24-48 hours following appropriate therapy (Fig 13b, 13c). In stage 2, the victim still usually presents with laryngospasm but may begin to swallow water into the stomach. In stage 3, 10%-15% of patients still present with dry drowning caused by persistence of the associated laryngospasm; in the remaining 85%--
90% of patients, the laryngospasm relaxes secondary to hypoxia and large amounts of water are aspirated (35). In such cases, the lung lesions are no longer associated with pressure edema but mainly with hypoxia, which leads to cytokine release and subsequent permeability edema (36–38). In addition to causing hypoxia, inhaled water has a deleterious effect on the capillary endothelium, alveolar pneumocytes, and surfactant production. This in turn leads to permeability edema with DAD, atelectasis, and shunting, thereby causing adult respiratory distress syndrome (ARDS). This situation is often worsened by the aspiration of gastric fluid and by infections due to fresh-water saprophytic bacteria, which may cause further alveolar damage. Stage 2 and 3 lesions are radiologically nonspecific, varying from tiny, ill-defined lesions to large, lobar airspace consolidations. Lesion size depends on the volume of inhaled water, the duration of the ensuing hypoxia, and on whether fresh or salt water is involved (35,37,38). Clearing of the lungs begins slowly and continues at a rate that depends on the severity of capillary and alveolar damage. This process occurs several days after the incident if the situation remains uncomplicated by gastric aspiration, infection, or other causes of additional alveolar damage (37,38).

**Figure 13.** Pulmonary edema in a 5-year-old boy who was admitted 1 hour after nearly drowning in chlorinated water. (a) Chest radiograph obtained at the time of admission reveals cardiac enlargement, diffuse confluent alveolar patterns of pulmonary edema, and peribronchial cuffing. (b, c) Chest radiograph (b) and high-resolution CT scan (c) obtained 3 hours later demonstrate a marked decrease in pulmonary edema, although it still predominates in the dependent portions of the lungs. The cortical lung is remarkably free of interstitial edema, a finding that may suggest either direct alveolar damage from the inhaled water or edema following laryngospasm rather than secondary damage from the associated hypoxia. The laryngospasm was probably the major component given the rapid clearing of the areas of increased opacity.
PERMEABILITY EDEMA WITH DAD

ARDS is the term used for various acute or subacute, diffuse pulmonary lesions that cause severe hypoxemia. These lesions are associated with a variety of precipitating factors and are not caused or influenced by concurrent cardiac insufficiency. Therefore, ARDS occurs without an increase in pulmonary capillary pressure.

ARDS represents the most severe form of permeability edema associated with DAD (2). DAD may be the direct result of a local precipitating factor or may occur secondary to some systemic condition. Primary or direct injuries to the alveolar and vascular endothelium of the lung usually result from the exposure of these cells to chemical agents, infectious pathogens, gastric fluid, or toxic gas, which destroy or severely damage the cells. Secondary damage is due to a systemic biochemical cascade creating oxidating agents, inflammatory mediators, and enzymes, which also harm these endothelial cells during sepsis, pancreatitis, severe trauma, or blood transfusion. On the basis of these etiologic differences, two major pathophysiologic mechanisms in the development of ARDS have been described: 

1. ARDS due to an underlying pulmonary disease, which is associated with pulmonary consolidation, and
2. ARDS secondary to extrapulmonary disease, which manifests as interstitial edema and alveolar collapse (39).

These mechanisms are based on physiologic ventilation mechanics, and, although they have not yet been pathologically proved, they do have distinct implications for the treatment of affected patients.

ARDS encompasses three often overlapping stages. The first (exudative) stage is characterized by interstitial edema with a high protein content that rapidly fills the alveolar spaces and is associated with hemorrhage and ensuing hyaline membrane formation. The rapid extension of edema into the alveolar spaces probably explains why findings that are typically seen in interstitial edema (eg, Kerley lines) are not prominent in ARDS. The second (proliferative) stage manifests as organization of the fibrinous exudate. Following this organization, one observes the regeneration of the alveolar lining and thickening of the alveolar septa. The third (fibrotic) stage is characterized by varying degrees of scarring and formation of subpleural and intrapulmonary cysts.

Initially, most patients present with few if any clinical symptoms. Soon, however, they develop rapidly progressive dyspnea, tachypnea, and cyanosis. Hypoxemia is present and remains unresponsive to oxygen therapy mainly due to the presence of arteriovenous shunting. Mechanical ventilatory assistance with positive end-expiratory pressure is often necessary to adequately expand the lung parenchyma and increase oxygen diffusion.

The early exudative stage demonstrates few radiologic findings. Initially, interstitial edema is observed, followed rapidly by perihilar areas of increased opacity. The progression from interstitial edema to the filling of alveolar spaces corresponds to the appearance of widespread alveolar consolidation on air bronchograms. Compared with hydrostatic edema, the alveolar edema in ARDS usually has a more peripheral or cortical distribution. Radiologic signs that are typically seen in cardiogenic edema (eg, cardiomegaly, apical vascular redistribution, Kerley lines) are absent. Despite the presence of diffuse, homogeneous DAD, ARDS usually displays a gravitational gradient that is easily visualized at CT and can be modified by changing the patient’s position (Fig 14) (40). This suggests that atelectasis is also an important factor in the inhomogeneous regional distribution of ARDS. Furthermore, this gravitational pattern can help exclude concomitant infectious processes because such dependent atelectasis is more common in patients with early ARDS without pneumonia (41).

With progression of the disease into the proliferative stage, an inhomogeneous pattern of ground-glass areas of increased opacity is seen, along with early modifications due to fibrosis. During the fibrotic stage, subpleural and intrapulmonary cystic lesions may be observed and may be the direct cause of pneumothoraces (2,42). Recurrent exudative episodes can still occur in the proliferative and fibrotic stages of ARDS, resulting in mixed radiologic findings that demonstrate parts of all three stages simultaneously.

Atypical ARDS, which is characterized by a predominance of anterior airspace consolidations in supine patients, was observed in about 5% of patients who underwent CT during the exudative stage (Fig 15). The pathophysiologic explanation for this finding remains unclear but may involve regional differences in mechanically assisted ventilation pressures.
Figure 14. ARDS associated with DAD in a 20-year-old man involved in a motor vehicle accident who underwent massive bronchoaspiration during tracheal intubation. (a–c) Chest radiograph (a) and supine unenhanced CT scans (10-mm section thickness) (b, c) (c obtained caudad to b) reveal characteristic bilateral diffuse airspace consolidations with a marked anteroposterior gradient. In addition, bilateral peripheral areas of hyperlucency representing trapped air are seen. Kerley lines are notably absent, and pleural effusions are minor compared with the extent of the airspace lesions. (d, e) High-resolution CT scans (e obtained caudad to d) obtained 1 day later after the patient had been maintained in a prone position for 12 hours demonstrate markedly decreased posterior airspace consolidations with small, posterior pleural effusions. Note the residual inter- and intralobular septal thickening. A posteroanterior gradient is now present, clearly demonstrating the importance of dependent atelectasis in ARDS. Note also the presence of numerous dilated small bronchi and bronchioles.
PERMEABILITY EDEMA WITHOUT DAD

As the name implies, permeability edema without DAD refers to pulmonary edema in which permeability changes are not primarily associated with DAD. The absence of cellular damage is often not proved pathologically but may be inferred from the clinical and radiologic course of the disease because rapid regression is often observed, with ventilatory improvements occurring within a short period of time. Although some degree of DAD may occur, damage remains minor and usually only partially affects patient outcome.

- **Heroin-induced Pulmonary Edema**

Pulmonary edema directly associated with an overdose of opiates occurs almost exclusively with heroin but is also rarely encountered with the use of cocaine and "crack." Heroin-induced pulmonary edema is seen in about 15% of cases of heroin overdose with an overall mortality rate.

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**Figure 15.** Atypical ARDS secondary to septic shock in a 47-year-old man who had undergone endoscopic sclerotherapy for esophageal varices. Supine high-resolution CT scans (b obtained caudal to a) demonstrate bilateral airspace consolidations that predominate anteriorly. This distribution is of unknown origin because the patient was never placed in the prone position during the course of the disease.

**Figure 16.** Heroin-induced pulmonary edema in a 19-year-old male addict with ARDS. (a) Chest radiograph reveals massive diffuse pulmonary edema. (b) Chest radiograph obtained 27 hours later reveals substantial resolution of the pulmonary edema, which is only possible in the absence of DAD. Intubation and positive pressure ventilation may have partially influenced the edematous change.
Interleukin (IL)-2 is an endogenous glycoprotein that enhances the in vivo and in vitro tumoricidal activity of natural killer cells. It is used in patients with metastatic melanoma and metastatic renal cell adenocarcinoma. Another cytokine known as tumor necrosis factor may be administered by intraarterial infusion and subsequently increases the production and release of IL-2 via cytokine cascades with intermediary products such as IL-8. Both IL-2 and tumor necrosis factor may cause permeability disruptions without DAD and lead to pulmonary edema. They predominantly affect the capillary endothelial cells, although the precise underlying pathophysiologic process has yet to be established (2,48,49). Most patients undergoing therapy with IL-2 and tumor necrosis factor demonstrate a mild increase in pulmonary capillary wedge pressure due to the direct toxic effect of these cytokines on the myocardial cells and on the heart’s conduction system. Although this toxic effect may lead to arrhythmia and a decreased ejection fraction, it is not sufficient to explain the onset of pulmonary edema from pressure gradients: Two studies have demonstrated that pulmonary capillary wedge pressure increases by only about 12 mm Hg (50,51).

Heroin overdose is believed to directly cause depression of the medullary respiratory center and lead to hypoxia and acidosis, both of which cause permeability edema without DAD (46). This absence of DAD can be directly inferred from the rapid resolution of the disorder observed in all cases that are not complicated by aspiration of gastric contents or by infection. Unlike cocaine, heroin has no direct deleterious effect on myocardial function (47).

Often, a patient who overdoses on heroin may lie motionless in a given position for hours or even days. These recumbent positions give rise to a markedly asymmetric distribution of edema associated with gravity dependency and may lead to extensive crush injuries with associated muscle damage and ensuing renal insufficiency. At radiology, heroin-induced pulmonary edema is indistinguishable from other types of edema without DAD. It manifests as widespread, patchy, bilateral airspace consolidations, ill-defined vessels, and peribronchial cuffing and is frequently complicated by edema due to fluid overload associated with renal insufficiency (Fig 16). When heroin-induced pulmonary edema is not associated with renal insufficiency or other complications such as aspiration of gastric contents, rapid resolution of the infiltrates is observed within 1 or 2 days with no parenchymal sequelae (Fig 17).
About 75% of patients undergoing intravenous IL-2 therapy and about 15%-20% of those treated with intraarterial tumor necrosis factor infusions will demonstrate radiologic signs of pulmonary edema (3,49). In contrast, only 25% of patients treated with recombinant IL-2 will develop clinical signs and symptoms of pulmonary disease (eg, cough, dyspnea, tachypnea, fever). Approximately 5%-7% of this subgroup will require respiratory assistance (3). Radiologic signs are usually seen at conventional chest radiography 1–5 days after the start of cytokine therapy (Fig 18) and include bilateral, symmetric interstitial edema with thickened septal lines. Peribronchial cuffing is observed in 75% of cases (3,49). No alveolar edema is observed unless there is associated cardiac insufficiency. Interstitial edema is associated with small pleural effusions in about 40% of cases and, like other types of permeability edema without DAD, regresses rapidly.

- **High-Altitude Pulmonary Edema**

High-altitude pulmonary edema is a potentially fatal condition that occurs in a previously healthy individual. It is caused by prolonged exposure to an environment with a lower partial oxygen atmospheric pressure. High-altitude pulmonary edema occurs most frequently in young males 24–48 hours after they have made a rapid ascent to heights greater than 3,000 meters and have remained in that environment (52-54). Numerous cases of high-altitude pulmonary edema have been described in the literature, often demonstrating individual susceptibility (54). High-altitude pulmonary edema usually follows acute mountain sickness, which actually represents a milder form of the disease and can act as an indicator of impending high-altitude pulmonary edema (2). Clinical manifestations include dyspnea at rest, cough with frothy pink sputum production, and neurologic disturbances associated with concomitant brain edema. Arterial oxygen saturation levels correspond directly to the severity of the disorder and may be as low as 38% (52).

The pathophysiology of high-altitude pulmonary edema remains controversial. However, there is general agreement that this condition results from acute, persistent hypoxia, which induces heterogeneous vasoconstriction leading to marked pulmonary hypertension (52). This in turn induces endothelial leakage, which results in interstitial and alveolar edema without DAD. This vascular leakage creates edema with a high protein content, which explains the frothy appearance of the sputum (2,52,55). The clinical manifestations of high-altitude pulmonary edema will resolve rapidly if the patient quickly descends to a low altitude and undergoes adequate therapy with oxygen and pulmonary vasodilators (56).

The radiologic features of high-altitude pulmonary edema vary with the degree of hypoxemia that is present. Usually, this condition manifests as central interstitial edema associ-
involves a combination of factors associated with hydrostatic edema and factors associated with permeability edema without DAD. The cellular mechanisms that cause capillary leakage are also not well understood. Modifications in neurovegetative pathways are probably the cause of sudden, significant increases in microvascular pressure in the lungs, particularly in the pulmonary venules. This leads to reduced venous outflow, which in turn causes pulmonary capillary and arterial hypertension (59). In addition, there are probably direct effects of various mediators that cause leakage of vascular endothelial cells and cell junctions.

Patients may present with varying degrees of dyspnea, tachypnea, and cyanosis shortly after suffering the brain insult. These signs and symptoms decrease and disappear rapidly in most cases. Conventional chest radiography demonstrates the presence of bilateral, rather homogeneous airspace consolidations, which predominate at the apices in about 50% of cases (Fig 20).

**MIXED EDEMA**

- **Neurogenic Pulmonary Edema**
  Neurogenic pulmonary edema is seen in up to 50% of patients who have suffered a severe brain insult such as trauma, subarachnoid hemorrhage, stroke, or status epilepticus (58). Differentiation of neurogenic pulmonary edema from simple fluid overload or postextubation edema may be difficult if not impossible in trauma patients or immediately following surgery. Therefore, the diagnosis of neurogenic pulmonary edema is obtained by exclusion. Its cause remains controversial but probably involves a combination of factors associated with hydrostatic edema and factors associated with permeability edema without DAD. The cellular mechanisms that cause capillary leakage are also not well understood. Modifications in neurovegetative pathways are probably the cause of sudden, significant increases in microvascular pressure in the lungs, particularly in the pulmonary venules. This leads to reduced venous outflow, which in turn causes pulmonary capillary and arterial hypertension (59). In addition, there are probably direct effects of various mediators that cause leakage of vascular endothelial cells and cell junctions.

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More recently, some authors have observed the predominance of diffuse pulmonary edema that is rather inhomogeneous in distribution (58). Radiologic findings in neurogenic pulmonary edema also disappear within 1–2 days, thereby confirming the absence of any associated DAD (59).

Reperfusion Pulmonary Edema
Reperfusion pulmonary edema is an acute, mixed, noncardiogenic edema that is observed in up to 90%–100% of patients who have undergone pulmonary thromboendarterectomy for massive pulmonary embolism or for webs and segmental stenoses associated with chronic pulmonary embolism (60). The main pathophysiologic mechanism of this disorder is directly associated with the rapid increase in blood flow and blood pressure in the areas distal to the recanalized pulmonary arteries. Other mechanisms such as mechanical stress due to surgical intervention and biochemical phenomena (eg, release of oxygen radicals by neutrophils, alterations in surfactant production) must also be considered (60).

Patients develop dyspnea, tachypnea, and cough during the first 24–48 hours after the reperfusion event. They will almost always require oxygen therapy and will sometimes also need mechanically assisted ventilatory support. Radiologic findings of pulmonary edema appear within the first 2 days following surgery (Fig 21). Findings at conventional chest radiography usually consist of heterogeneous airspace consolidations that predominate in the areas distal to the recanalized vessels (61). Recently, however, investigators have also found a random distribution of pulmonary edema in up to 50% of cases (62). These authors hypothesize that the reperfusion pulmonary edema may also be due to systemic factors that have not yet been identified.
Pulmonary edema following lung transplantation is a noncardiogenic form of edema that is observed in up to 97% of patients during the first 3 days following surgery (63). The most important causal factors are probably those related to the tissue hypoxia that primarily involves the graft but also the host organs during the procedure, which is performed with extracorporeal circulation. Other factors such as the disruption of pulmonary lymphatic drainage and lung denervation with ensuing microvascular changes are also likely to contribute to the process. Pulmonary edema following lung transplantation is not due to left ventricular failure, fluid overload, acute rejection, atelectasis, or infection, although these conditions can coexist and thus complicate the clinical picture.

The manifestation of this disease entity is variable. A mixed hydrostatic and permeability edema is seen at radiology during the first 2 days following surgery. The infiltrates progress and are most pronounced on day 5 (Fig 22) (63–67).
These signs disappear 2 weeks after surgery without any sequelae, indicating that if DAD is present, it is mild and has little or no significance (67).

- **Reexpansion Pulmonary Edema**

Reexpansion pulmonary edema is an uncommon iatrogenic complication that occurs after the rapid reexpansion of a collapsed lung following drainage or evacuation of pleural disease such as pneumothorax, hydrothorax, or hemothorax. In 64% of cases, reexpansion pulmonary edema appears suddenly within 1 hour after lung reexpansion. The process usually involves the entire reexpanded lung (68), although on rare occasions only a single lobe or segment may be involved (69). In most cases, reexpansion pulmonary edema increases in severity for 24–48 hours and then slowly resolves over the next 5–7 days, indicating that the pathophysiologic process is not purely hydrostatic (2). A prolonged local hypoxic event, the abrupt restoration of pulmonary blood flow, and the sudden, marked increase in negative intrapleural pressure are probably all significant factors in the development of pulmonary edema (70). However, the presence of proteins and red blood cells in the alveolar fluid as well as the persistence of the clinical symptoms and radiologic findings indicate the presence of a certain degree of DAD. The presence of DAD is also indicated by the inefficiency of the reexpanded lung in terms of gas exchange, which leads to a shunt effect that persists for some time (70).

Patients may be asymptomatic despite findings of pulmonary edema at chest radiography. On the other hand, they may present with severe symptoms associated with frank respiratory insufficiency. Sometimes, there is little correlation between the extent of the infiltrates at radiology and clinical findings. In most cases, patients present with cough, dyspnea, tachypnea, and tachycardia, although in rare instances large amounts of frothy pink sputum may be seen (70). Early recognition of reexpansion pulmonary edema is important because the disease proves fatal in up to 20% of cases (Fig 23) (68). Although reexpansion pulmonary edema manifests unilaterally in the reexpanded lung, its radiologic appearance is usually indistinguishable from that of other forms of mixed pulmonary edema.
Postpneumonectomy Pulmonary Edema

Postpneumonectomy pulmonary edema is a life-threatening complication that occurs early in the postoperative period following pneumonectomy. It affects the remaining lung and is usually diagnosed by exclusion. The prevalence of postpneumonectomy pulmonary edema is generally reported to range between 2.5% and 5% with a very high associated mortality rate in all series (71–73). On the other hand, minor postpneumonectomy pulmonary edema has been described in up to 20% of patients (74). Risk factors for postpneumonectomy pulmonary edema have classically included excessive administration of fluid during surgery, transfusion of fresh frozen plasma, arrhythmia, marked postsurgical diuresis, and low serum colloidal osmotic pressure (71,74,75). Recently, however, some authors no longer consider perioperative fluid overload to be a major contributing factor (71,72). Postpneumonectomy pulmonary edema following administration of fresh frozen plasma may also represent a variant of transfusion-related acute lung injury from a leukoagglutinin reaction, which is probably another cause of permeability edema with limited DAD. Patients who undergo right pneumonectomy are considered to be at higher risk for postpneumonectomy pulmonary edema than are those who undergo left pneumonectomy, probably because of the smaller volume of the remaining lung (74).

The precise cause and pathophysiology of postpneumonectomy pulmonary edema remain controversial and largely unknown. Increased capillary hydrostatic pressure and altered capillary permeability are both probable contributing factors in the development of postpneumonectomy pulmonary edema (72,73). They follow concomitant but separate pathways and may potentiate each other in the development of alveolar edema. Because the remaining lung is subject to increased pulmonary blood flow due to the redistribution of cardiac output, an increase in mean pulmonary arterial blood pressure is observed. On the other hand, it has been postulated that the transient hypoxia seen perioperatively and immediately following surgery may induce reflex pulmonary vasoconstriction, leading to the release of catecholamines (75). These catecholamines cause sudden additional increases in pulmonary capillary pressure that may prompt edema formation due to hydrostatic pressure gradients (“stress failure” of the alveolar wall) (55). In addition, these changes in pressure and oxygen level may lead to the formation of lesions of the pulmonary capillary endothelium, resulting in alveolar wall damage and subsequent passage of fluid and proteins into the alveolar lumina. The latter is suspected due to the high protein content of the airspace fluid seen with postpneumonectomy pulmonary edema (72,73,75).

Patients with postpneumonectomy pulmonary edema experience marked dyspnea during the first 2–3 days following surgery. At conventional chest radiography, severe postpneumonectomy pulmonary edema manifests as infiltrates with an appearance identical to that of ARDS. In our experience, the most frequently seen radiologic findings in milder forms of postpneumonectomy pulmonary edema are similar to those in hydrostatic pulmonary edema without DAD and include Kerley lines, peribronchial cuffing, and ill-defined vessels. These findings have a tendency to disappear within a few days, which strongly indicates that lesions of the capillary endothelial cells, if present, are mild in this form of the disorder. Pulmonary edema following lobectomy has also been described in some reports but with an overall prevalence of less than 1% (72,75).
Postreduction Pulmonary Edema

In an as yet unpublished series of 21 patients who underwent lung reduction for severe emphysema, we found three cases of postreduction pulmonary edema that, in our opinion, resulted from a pathophysiologic process similar to that which causes postpneumonectomy pulmonary edema. At our institution, lung reductions are performed with video-assisted thoracoscopy with a totally collapsed ipsilateral lung; thus, reexpansion pulmonary edema could be an additional cause of this disorder. Postreduction pulmonary edema is usually clinically silent. Chest radiography reveals mild airspace consolidations involving the ipsilateral lung that appear rapidly within 24 hours after surgical intervention and disappear within 48 hours (Fig 24). Once again, the diagnosis is reached by means of exclusion.

Pulmonary Edema due to Air Embolism

In an as yet unpublished series of 21 patients who underwent lung reduction for severe emphysema, we found three cases of postreduction pulmonary edema that, in our opinion, resulted from a pathophysiologic process similar to that which causes postpneumonectomy pulmonary edema. At our institution, lung reductions are performed with video-assisted thoracoscopy with a totally collapsed ipsilateral lung; thus, reexpansion pulmonary edema could be an additional cause of this disorder. Postreduction pulmonary edema is usually clinically silent. Chest radiography reveals mild airspace consolidations involving the ipsilateral lung that appear rapidly within 24 hours after surgical intervention and disappear within 48 hours (Fig 24). Once again, the diagnosis is reached by means of exclusion.

Figure 24. Postreduction pulmonary edema in a 64-year-old woman who had undergone bilateral lung reduction for emphysema. (a) Chest radiograph obtained 18 hours after surgery demonstrates the appearance of pulmonary edema that was observed in 14% of affected patients. Kerley lines are the most prominent finding. The heart and vascular structures are normal. (b) High-resolution CT scan obtained 2½ hours later demonstrates numerous thickened interlobular septa, predominantly in the right lung field (arrows). Areas of ground-glass attenuation are observed bilaterally, predominantly in the lung cortex. These findings were not present preoperatively and disappeared within 48 hours.

The pathophysiologic mechanism of pulmonary edema due to air embolism is quite simple. The embolized air bubbles cause mechanical obstruction of the pulmonary microvasculature due to the relatively low absorption coefficient of air (76,77). These collections of air create turbulent flow, which favors platelet aggregation, fibrin formation, and vasoconstriction, thus increasing the pressure exerted on the vessel wall. Other, nonmechanical factors (eg, liberation of oxygen radicals from neutrophils) also contribute to the disruption of the capillary endothelium. Macromolecules, proteins, and blood cells may then enter the interstitial and alveolar spaces (77). This creates a variable pathologic picture that ranges from mild interstitial edema to hemorrhagic airspace consolidations.

Sudden onset of chest pain, tachypnea, dyspnea, and hypotension are observed at clinical examination. During intraoperative transesoph-
ageal echocardiography, the indwelling air may be observed within the right-sided cardiac chambers (Fig 25a). Conventional chest radiography initially demonstrates interstitial edema followed by bilateral, peripheral alveolar areas of increased opacity that are predominantly found in the lung bases (Fig 25b). There is no associated cardiac enlargement, and the lesions disappear rapidly in patients who survive the acute event.

**CONCLUSIONS**

In this article, we have demonstrated various conventional radiographic and lung CT patterns of pulmonary edema associated with different clinical disorders. Pulmonary edema can be divided into four main categories on the basis of pathophysiology and will often have clinical and radiologic characteristics that are specific to a given category. Pulmonary edema is often encountered in the clinical setting; therefore, we believe that recognition and understanding of the spectrum of findings in this disease are necessary and will help narrow the differential diagnosis.

**REFERENCES**


![Figure 25. Pulmonary edema due to air embolism in a 72-year-old woman immediately following coronary artery bypass graft surgery. One liter of air was inadvertently injected during flushing of the extracorporeal circulation device.](image-url)


43. Frazer RG, Paré JAP, Paré PD, Frazer RS, Generieux GP. Drug and poison induced pulmonary disease. In: Frazer RG, Paré JAP, Paré PD, Frazer RS,


