Other Pulmonary Disorders

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Objectives:

1. To discuss the pathogenesis, clinical features and treatment of pulmonary disorders that occur in patients with sickle cell hemoglobinopathies.
2. To review the pathogenesis, clinical features, and treatment of lung disease in patients with liver disease.
3. To review the pathogenesis and clinical features of pulmonary oxygen toxicity.
4. To discuss pulmonary injury caused by radiation therapy of malignancy.
5. To outline the pulmonary disorders that occur after thermal injury and smoke inhalation.

Key words: acute chest syndrome; oxygen toxicity; pulmonary radiation injury; smoke inhalation

Pulmonary Disorders in Persons With Sickle-Cell Hemoglobinopathies

The sickle cell hemoglobinopathies are characterized by a predominance of hemoglobin S. The most common is sickle cell anemia (hemoglobin SS), which affects about one in 650 African-Americans. Other disorders occur when hemoglobin S is associated with another abnormal hemoglobin. In the United States, sickle cell disease occurs predominantly in African-Americans, and Hispanics from the Caribbean, Central America and South America.

Pathogenesis

When deoxygenated hemoglobin SS polymerizes, the RBCs assume a rigid configuration and occlude the microvasculature, leading to ischemia or infarction of tissues. Compared with hemoglobin AA, hemoglobin SS has reduced affinity for oxygen, facilitating polymerization. SS-red cells also interact with vascular endothelium, and increased adherence of these cells to endothelial surfaces is a feature of vasoocclusive crises. Sickle cell disease is also associated with a hypercoagulable state due to thrombocytosis and the procoagulant effects of RBC membrane lipids, but the incidence of venous thromboembolism does not appear to be increased in these patients. Three overlapping pulmonary syndromes are described in patients with sickle-cell hemoglobinopathies: acute chest syndrome (ACS), fat embolism syndrome, and chronic restrictive lung disease with pulmonary hypertension.

Acute Chest Syndrome

Patients with sickle cell disease frequently present with a syndrome of chest pain, fever, and cough, usually shortly after the onset of a painful crisis. In adults, the radiograph typically shows multilobe or lower lobe pulmonary opacities; pleural effusion is present in around 15% of cases. ACS is the leading cause of death in patients with sickle cell disease, most commonly due to respiratory failure or thrombotic neurologic complications. The pathogenesis of ACS is probably multifactorial, and it is usually impossible to demonstrate one specific cause for an episode. Disorders leading to ACS include fat embolism from infarcted bone marrow, pulmonary microvascular occlusion, and *in situ* thrombosis and pneumonia. The most common pathogens implicated in ACS are *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and respiratory viruses. Other bacteria are less common causes of ACS but include *Streptococcus pneumoniae*, *Haemophilius influenzae*, and *Staphylococcus aureus*. Thoracic bone infarction occurs commonly during an acute painful crisis and may lead to atelectasis and pneumonia by causing splinting from pain.

Since the pathogenesis of ACS is multifactorial, each treatment is of uncertain benefit in any patient. Patients are almost always treated with analgesics, hydration to prevent hemoconcentration, and oxygen supplementation to reduce sickling. Most patients receive antibiotics empirically, since it is usually impossible to determine whether or not they have pneumonia. Antibiotics should be directed against both "typical" and "atypical" pathogens. In severe cases, packed RBC transfusions may improve ACS rapidly. Incentive spirometry was shown to prevent atelectasis and pulmonary infiltrates in patients with sickle cell disease hospitalized with acute chest pain.

Fat Embolization Syndrome

Besides being a common cause of ACS, fat embolization may cause a systemic disorder with neurologic changes, renal failure, petechiae, and multilobe opacities or ARDS. The syndrome usually occurs during an active painful crisis; circulation of free fatty acids from necrotic bone marrow is implicated in the pathogenesis of diffuse vascular injury that may lead to ARDS and multiorgan failure. Fat globules may be detected in sputum and urine, and bone scans are usually positive. The systemic fat embolization syndrome appears to be especially common in patients with hemoglobin SC and in the postpartum period. Treatment is supportive.

Chronic Lung Disease

Patients with sickle cell disease, and especially those with recurrent ACS, may develop progressive, irreversible, and profound lung disease. Undoubtedly, recurrent fat embolization, infarction, and infection all contribute to this syndrome. As the disease progresses, patients develop increasing hypoxemia, radiographic evidence of pulmonary fibrosis, and a predominantly restrictive functional impairment, which may lead to pulmonary hypertension and cor pulmonale. With improved treatment of early sickle cell disease, end-stage pulmonary disease may become less common in the future.

Liver-Lung Syndromes

Since venous blood flows from the liver to the lungs, these organs are in many ways interdependent. Pulmonary hypertension may cause hepatic congestion and ascites. Conversely, decreased hepatic synthetic and metabolic function may lead to deranged production and metabolism of vasoactive substances and other mediators that profoundly affect the lung. The major pulmonary complications of liver disease are the so-called "hepatopulmonary syndrome," portopulmonary hypertension, α_1-antitrypsin deficiency, and hepatic hydrothorax.

Hepatopulmonary Syndrome

This term refers to a syndrome of liver disease, hypoxemia, and pulmonary vascular abnormalities referred to as "intrapulmonary vascular dilatations," the hallmark of the syndrome. Hepatopulmonary syndrome usually presents in the setting of chronic liver disease, especially cirrhosis. The vascular abnormalities include precapillary and capillary dilatation and arteriovenous anastamoses. Vascular dilatations probably cause hypoxemia by "diffusion-perfusion" impairment, where oxygen may not diffuse to the center of a dilated pulmonary capillary. Intrapulmonary vascular dilatations may be the consequence of abnormal vasoactive mediators leaving the liver and entering the lungs, causing remodeling of the pulmonary vessels. Arteriovenous shunts are the most important determinant of hypoxemia in severe hepatopulmonary syndrome. Nitric oxide (NO) is also implicated in the pathogenesis of this disorder: the lungs of patients with cirrhosis generate excessive NO, which in turn activates intracellular guanylate cyclase, increases cyclic guanosine monophosphate, and causes vasodilation.

Pulmonary vascular dilatations can be diagnosed by contrast-enhanced echocardiography or perfusion scanning with technetium-labeled macroaggregated albumin. Pulmonary angiography may also be used but is rarely necessary. The most effective treatment is liver transplantation. Pharmacologic approaches have been disappointing, but methylene blue administration shows some promise. This agent blocks NO-induced vasodilation by inhibiting stimulation of guanylate cyclase by NO, and its administration improves hypoxemia and the hyperdynamic circulatory state associated with the hepatopulmonary syndrome.

Portopulmonary Hypertension

In contrast with the vasodilation characteristic of hepatopulmonary syndrome, 1 to 2% of patients with cirrhosis develop pulmonary vasoconstriction and pathologic changes indistinguishable from primary pulmonary hypertension (PPH). The diagnostic and treatment approaches are also the same as for PPH. Unfortunately, and for unknown reasons, portopulmonary hypertension does not usually improve following liver transplantation.

α_1-Antitrypsin Deficiency

The pulmonary manifestations of this genetic defect are actually the result of a primary hepatic abnormality. With a gene mutation, abnormal α_1-protein accumulates in hepatocytes and is not released from the liver. The resulting low circulating concentration

of this protective protease inhibitor leads to excessive neutrophil elastase activity in the lungs and destruction of pulmonary elastic tissue. Dr. Braman's chapter on COPD discusses this disorder in detail.

Hepatic Hydrothorax

Some patients have congenital anatomic defects in the diaphragm. If ascites develops, the positive infradiaphragmatic pressure moves fluid through these defects into the negative-pressure pleural space, causing accumulation of pleural fluid with the same characteristics as the ascites. This condition is referred to as hepatic hydrothorax. Pleural fluid is typically a transudate and more often on the right side than the left. Spontaneous bacterial empyema may occur with or without spontaneous bacterial peritonitis. The initial treatment is directed at reducing the volume of ascites with salt restriction and diuretics. Thoracentesis may be helpful to relieve dyspnea and hypoxemia acutely, but the fluid usually reaccumulates. Chest tube drainage is often hazardous, as ascitic fluid translocates rapidly into the pleural space, leading to volume depletion and electrolyte abnormalities. Pleurodesis is generally unsuccessful because the fluid usually reaccumulates too rapidly for the pleural surfaces to come together and adhere. Surgical repair of diaphragmatic defects by videothoracoscopy can be attempted, but few centers are experienced in the procedure. Peritoneovenous shunts are usually not successful in patients with hepatic hydrothorax because the pleural space has a lower pressure than the venous system, and fluid moves preferentially to the pleural space. Transjugular intrahepatic portosystemic shunt (TIPS) is an option in patients who have recurrent hydrothorax despite diuretic therapy and repeated thoracenteses. The best treatment of refractory hepatic hydrothorax is liver transplantation.

Oxygen Toxicity

Oxygen is necessary for life, but it also has the potential to be toxic through the generation of free-radical intermediates. A balance of oxidative and antioxidant processes maintains life while maintaining organ function. Our knowledge of oxygen toxicity is largely inferred from experimental data in other mammalian species and clinical observations.

Mechanisms of Oxygen-Induced Injury

The stepwise reduction of oxygen to water produces free radicals that in turn are injurious to tissues. These include the superoxide anion ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), and hydroxyl radical species ($\cdot OH^-$). The latter is among the most reactive biological molecules known, capable of damaging almost any component of living cells. Oxygen radicals have a beneficial role, since they are used by neutrophils during phagocytosis and killing of bacteria and may be important mediators of vascular tone by interacting with NO. However, unopposed hyperoxia promotes the excessive production of these molecules, leading to damage to cellular and lysosomal membranes, in turn increasing cell permeability, releasing lysosomal proteolytic enzymes, inactivating cellular enzymes, and damaging DNA. These effects are augmented by recruitment of neutrophils into the lung, which cause further injury by releasing free radicals when activated.

Oxidant injury is opposed by antioxidant mechanisms. Intracellular enzymes that reduce oxidant activity include superoxide dismutase (eliminates superoxide anion), catalase (metabolizes H_2O_2), and glutathione peroxidases (reduces H_2O_2 and lipid peroxides). Vitamin E inhibits lipid peroxidation in membranes, and deficiencies of vitamin E result in increased susceptibility of cells to oxidant injury.

The lung and capillary endothelium are the only tissues that can be exposed to high concentrations of oxygen, since other tissues consume more oxygen than is dissolved in the blood. Thus, lung cells may be exposed to a $Po_2 > 600$ mm Hg in a pure oxygen atmosphere under normobaric conditions, but other tissues are rarely exposed to oxygen tensions more than 10 mm Hg above normal because dissolved O_2 accounts for less than 10% of total O_2 content.

Other factors may influence the degree of injury on exposure to O_2. Prior exposure stimulates the production of antioxidant enzymes, conferring protection at the next exposure. In experimental models, endotoxin also induces antioxidant enzyme activity and increases tolerance to high concentrations of O_2. Conversely, drugs and toxins enhance lung injury due to oxygen. Hyperoxia and bleomycin exert synergistic toxic effects on the lung, probably because bleomycin increases the gen-

eration of free O_2 radicals. Amiodarone, nitrofurantoin, mitomycin, and paraquat also potentiate hyperoxic injury. Nitric oxide combines with O_2 - to form the peroxynitrite anion (ONOO-) that is potentially extremely toxic.

Clinical Manifestations

Patients may complain of retrosternal pain after inhaling pure oxygen for a few hours, and tracheobronchitis is found on biopsy. Mucociliary velocity is impaired, possibly due to damage to ciliated airway epithelium. It is difficult to diagnose parenchymal oxygen toxicity in humans because the clinical picture is always obscured by the disease that prompted the oxygen therapy. In experimental models, damage to type I pneumocytes increases permeability and leads to recruitment of inflammatory cells into capillaries and alveolar septae. The alveolar epithelium may undergo extensive necrosis with hyaline membrane formation and be replaced with proliferating type II cells. With ongoing injury, fibrosis ensues. These changes are morphologically indistinguishable from ARDS due to other causes.

What Is a "Safe" Concentration of Oxygen?

There is no treatment for oxygen-induced lung injury, so the best strategy should be to prevent it by minimizing exposure. However, no "safe" threshold has been established in humans. The question is in some ways misguided, since any concentration is potentially harmful in the absence of adequate antioxidant defenses. In experimental lung injury, even 50% O_2 enhances lung damage, and that concentration is the threshold at which replication of human pulmonary epithelial cell replication is inhibited. In patients who received bleomycin, *any* supplemental O_2 is deemed hazardous. For general clinical management, most clinicians assume that an $F_{IO_2} \leq 0.5$ is safe, even for prolonged periods, but this has not been established convincingly.

Pulmonary Radiation Injury

Radiation is intentionally given to the lung in the treatment of lung cancer and cannot be avoided in radiation therapy of cancers of the esophagus and breast. The lungs are exposed in mantle radiation of the mediastinum for lymphoma, and the lungs are the dose-limiting tissue for whole-body irradiation in preparation for bone marrow transplantation. Killing tumor cells is accompanied by destruction of surrounding normal lung tissue, leading to two clinical syndromes: radiation pneumonitis and radiation fibrosis. Although many patients who receive radiotherapy show radiographic changes, the incidence of symptomatic disease is approximately 7%, and with advances in combined chemotherapy and radiation therapy for cancers, this disorder should become even less common.

Pathogenesis

Radiation causes death of cells in mitosis. Type II pneumocytes and capillary endothelial cells have the highest turnover rates and are, therefore, the most susceptible to radiation injury. Histopathologic changes include edema and increased permeability of small vessels and capillaries, followed by obstruction by platelets, fibrin, and collagen. Damage to type II pneumocytes lead to hyaline membranes, followed by hyperplasia and interstitial fibrosis. Tissue injury also causes a cytokine response that recruits immune cells to perpetuate the inflammatory response, and subsequent reparative fibrosing process.

Predisposing Factors

The magnitude of lung injury depends on several factors:

1. Irradiated volume of lung tissue. The risk of pneumonitis increases with the volume of exposed lung.
2. Total dose. The total dose of radiation predicts the development of radiation fibrosis better than pneumonitis. There is a steep dose-response relationship; < 30 Gy is usually well tolerated, > 40 Gy almost always cause radiographic changes, and > 50 Gy almost always causes symptomatic lung injury.
3. Fraction size. Dividing the total dose over time reduces the risk of lung injury.
4. Prior irradiation increases the risk.
5. Chemotherapy may potentiate radiation damage. The classic example is bleomycin.
6. Withdrawal of corticosteroids may lead to overt pneumonitis when subclinical lung injury becomes overt.

Radiation Pneumonitis

After a latent period of up to 6 months, patients may develop dyspnea (the most common symptom), dry cough, pleuritic chest pain, and fever. The physical examination is usually normal. A progression of chest radiographic findings is typical, from a hazy area of opacity that may coalesce to form a sharply demarcated opacity corresponding to the field of radiation. Radiographic changes may occur outside the radiation field, perhaps due to a lymphocyte-mediated hypersensitivity reaction. Pleural effusions are seen occasionally. CT scans and nuclear imaging may be helpful in the diagnosis of early disease with a normal radiograph.

Radiation Fibrosis

When lung injury is chronic, fibrosis may occur. This is usually not apparent until at least 6 months after exposure, may take up to 2 years to evolve, and generally remains stable after that. The symptoms depend on the extent and severity of fibrosis, ranging from no symptoms to severe dyspnea, hypoxemia, and death. Mediastinal fibrosis may cause superior vena cava syndrome or constrictive pericarditis. Severe fibrosis may occur in the absence of clinically apparent pneumonitis. The chest radiograph typically shows volume loss in the affected areas. Bronchiectasis and pleural thickening are common findings on CT scans. At times, confluent fibrosis may be difficult to distinguish from recurrent tumor.

Treatment

Most cases of radiation pneumonitis are asymptomatic or mild and require no therapy. Although controlled studies in humans are lacking, animal data and clinical experience indicates that corticosteroids are effective in most patients. The optimal dose is unknown; prednisone, around 60 mg daily, is recommended, followed by a gradual taper. The disease may flare during a steroid taper. There is no effective treatment for radiation-induced fibrosis.

Smoke Inhalation

Smoke generated in a fire is a suspension of particles and toxic gases in hot air. Fire victims may suffer a variety of inhalation injuries, including thermal injury to the airways and the effects of inhaling carbon monoxide and other products of combustion.

Thermal and Toxic Injury

The same high temperatures that burn the skin may injure the upper airways, and inhalation injury is an important predictor of mortality in burn victims. The peripheral airways and alveoli are not burned unless steam is inhaled, because the heat is dissipated centrally. Along with hot air, soot and toxic gases are also inhaled. Upper airway obstruction due to laryngeal edema or spasm may be severe, especially in patients with facial burns. Smoke inhalation is associated with bronchospasm, impaired mucociliary function, mucus hypersecretion, inflammation, and edema. Expectoration of soot with sputum reflects smoke inhalation but not necessarily airway injury. The chest radiograph is usually normal at the time of presentation. Therefore, fiberoptic laryngoscopy and bronchoscopy should be done to assess the degree and extent of airway damage in patients with suspected airway injury. Even if the airway is not grossly compromised at the time of the initial examination, inflammation and edema usually progresses over the first 24 to 48 h. The presence of edema and blistering should prompt intubation, but if the airway appears uninjured, then the patient should be observed closely. In the absence of a significant airway burn, intubated patients can usually be extubated safely after a few days, when the edema subsides. Corticosteroid administration does not attenuate the course of pulmonary injury and increases the risk of infection and death.

With improvements in burn wound management, pneumonia is now the most common cause of infection in burn units and a very common cause of death. Pathogens associated with nosocomial pneumonia, especially *Pseudomonas aeruginosa*, are also common in burn patients. Herpes simplex tracheobronchitis is common, perhaps due to direct extension from an oral source in patients who are immunocompromised due to severe burn injury.

Carbon Monoxide Poisoning

Inhalation of carbon monoxide (CO) is the most common cause of unintentional poisoning death in the United States. CO is produced by the

incomplete combustion of carbonaceous materials in the presence of a decrease in ambient oxygen. Fires, automobile exhaust, and unvented coal, kerosene, and wood-burning stoves and fireplaces are the commonest causes of carbon monoxide poisoning.

CO competes with O_2 for hemoglobin binding sites. Its affinity is more than 200 times greater than that of O_2, and CO shifts of the oxyhemoglobin binding curve to the left. The result is decreased O_2 content of arterial blood and decreased O_2 release to the tissues, leading to tissue hypoxia. PaO_2 may be normal, and pulse oximetry overestimates arterial oxygen saturation, as most devices do not reliably distinguish oxyhemoglobin from carboxyhemoglobin. However, direct measurement of arterial oxygen saturation and content are reduced. The major signs of CO poisoning are CNS and cardiac disturbances, and patients with severe CO poisoning (>40%) may have severe lactic acidosis.

CO measurements may be used to guide treatment, but they do not necessarily correlate with clinical abnormalities, especially when measured hours after exposure. In asymptomatic persons, levels up to 20% usually require no treatment. Patients with higher levels, or with symptoms suggestive of CO poisoning, should be treated with supplemental O_2; 100% oxygen reduces the half-life of CO in the blood from around 5 hours to 80 min. Most experts recommend hyperbaric oxygen in severe cases (CO > 40%, coma or other CNS dysfunction, arrhythmia, or cardiac ischemia). Hyperbaric oxygen treatment hastens the resolution of symptoms, but it is still unresolved whether it prevents delayed neuropsychiatric dysfunction.

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Notes

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