2 Pathophysiology of Acute Respiratory Distress

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Considering the complex series of cardiorespiratory changes that occurs at birth, it is not surprising that the transition to extrauterine life does not always proceed smoothly. Neonatal respiratory disorders account for the majority of admissions to intensive care units and result in significant morbidity and mortality.

Once the infant shows signs of respiratory distress, prompt diagnosis is essential. Respiratory distress may be related to structural problems such as poor lung development or defects of the chest wall or diaphragm. Biochemical and physical immaturity may exist. Abnormalities in the central nervous system may cause alterations in the respiratory regulatory apparatus. Perfusion abnormalities may impair gas exchange. Aspiration and infection can also occur.

Not all infants with respiratory distress have a respiratory disease (Figure 2-1). In some cases, congenital heart disease may be difficult to distinguish from primary lung disease. Labored breathing may also result from a metabolic problem. The coexistence of other factors, such as cold stress and polycythemia, may compound respiratory distress. Most neonatal respiratory problems are treated medically, but a number of conditions that present with respiratory distress may require surgical intervention. Institution of appropriate therapy requires an accurate diagnosis. Knowledge of the pathophysiology of neonatal pulmonary diseases is essential to ensure comprehensive management. This chapter discusses the pathophysiology of the most common pulmonary disorders that present as acute respiratory distress in the newborn period.

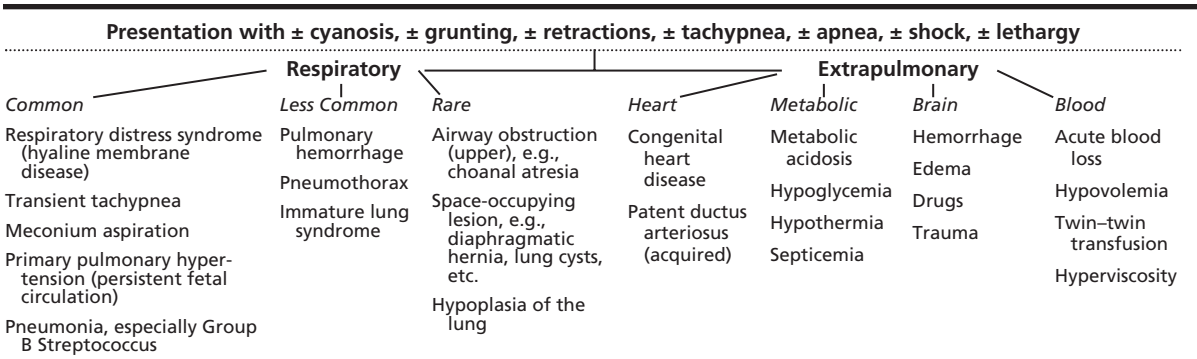
Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), also known as hyaline membrane disease and surfactant deficiency syndrome, is the major pulmonary problem occurring in the neonate. This syndrome affects approximately 40,000 infants annually in the U.S. Nearly 65 percent of these infants are born at gestational ages of 30 weeks or less.[1] Infants of 37–40 weeks gestational age rarely develop RDS. The prematurity rate is the main reason RDS remains a major neonatal problem. The frequency of RDS, which primarily affects preterm infants less than 35 weeks gestational age, increases inversely with gestational age. However, susceptibility to RDS depends more on the neonate's stage of lung maturity than on precise gestational age. Table 2-1 lists risk factors known to predispose the neonate to developing RDS.

Despite significant advances in understanding the pathophysiology of the disease, RDS ranks eighth among the top ten causes of neonatal deaths. Extreme prematurity; congenital anomalies; chromosomal abnormalities; bacterial sepsis; maternal complications of pregnancy; and complications of the placenta, cord, and fetal membranes currently outrank RDS as causes of neonatal mortality.[2] A sizable reduction in infant mortality from RDS has been linked to the introduction of exogenous surfactant therapy. However, the largest reduction in mortality from RDS in the U.S. occurred during the 15-year period before surfactant replacement therapy was introduced.[3] Regionalized neonatal care, improvements in mechanical ventilation, antenatal corticosteroid therapy, and surfactant replacement therapy have had a cumulative effect on reducing mortality from RDS.

RDS is often the most acute problem of the very immature infant. Numerous complications associated with

FIGURE 2-1
Differential diagnosis of respiratory distress in the newborn period.



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shortened gestation and preterm birth can prolong hospitalization and add enormous costs. Most infants with RDS do not die from primary lung disease but from complications directly associated with RDS, such as air leak syndrome, intraventricular hemorrhage, pulmonary hemorrhage, or chronic lung disease, or from extreme prematurity itself. Chronic lung disease in infants with birth weights of less than 1,000 g has been identified as a significant predictor of later neurodevelopmental impairment.[4] Efforts aimed at preventing RDS can be expected to improve morbidity and mortality, leading to significant cost savings and improved health for low birth weight infants.

Maternal antenatal steroid therapy reduces neonatal mortality and the incidence of RDS in preterm infants. Additional short-term benefits of this type of therapy include a decreased incidence of intraventricular hemorrhage, lower oxygen and ventilatory support requirements, and improved circulatory stability.[5] A single course of antenatal steroids is currently recommended for women at risk of delivery between the 24th and 34th week of gestation. Initiation of maternal treatment at least 24 hours before delivery produces the greatest benefit for the infant. Treated infants born at 24–28 weeks gestation experience less severe RDS than untreated infants, and disease incidence and mortality are reduced in treated infants born at 29–34 weeks gestation. The benefits of antenatal corticosteroids are additive to those gained from surfactant therapy. Risk and benefit data are insufficient to support the use of higher or repeat doses of antenatal corticosteroids, however.[6,7]

Other factors thought to produce a "sparing effect"—that is, to lessen the severity of RDS in the at-risk population—include maternal toxemia, heroin addiction, prolonged rupture of membranes, and chronic intrauterine stress leading to fetal growth restriction. Chronic fetal stress increases production of endogenous corticosteroids and results in accelerated lung maturity because the effect on surfactant production is similar to that seen with antenatal steroid therapy.

Etiology and Pathophysiology

Normal postnatal pulmonary adaptation requires the presence of adequate amounts of surface-active material to line the air spaces. In the normal lung, surfactant is continually formed, oxidized during breathing, and replenished. Surfactant provides alveolar stability by decreasing the forces of surface tension and preventing alveolar collapse at expiration. This allows more complete gas exchange between the air space and the capillary blood. Additional advantages of surfactant include increased lung compliance, decreased work of breathing, decreased opening pressure, and enhanced alveolar fluid clearance. (More detailed discussions of surfactant can be found in Chapters 1 and 11.)

The development of RDS is thought to begin with surfactant deficiency (Figure 2-2). This deficiency results from insufficient surfactant quantity, abnormal surfactant composition and function, or disruption of surfactant production. A combination of these factors may be present. The phospholipid composition of surfactant changes with gestational age.

Inability to maintain a residual volume of air in the alveoli on expiration results in extensive atelectasis. The reduced volume at the end of expiration requires the generation of high pressures to re-expand the lung with each breath (Figure 2-3).

TABLE 2-1
Risk Factors for Development of RDS

Prematurity
Male sex
Maternal diabetes
Perinatal asphyxia
Second-born twin
Familial predisposition
Cesarean section without labor

Infants with RDS have abnormal ventilation-perfusion relationships. Hypoxia results from right-to-left shunting of blood through the foramen ovale, causing significant venous admixture of arterial blood. The ductus arteriosus relaxes in response to hypoxia, allowing left-to-right shunting of blood. In addition, intrapulmonary shunting occurs as blood is directed away from areas of the lung that are ventilated, resulting in hypercarbia. Acidemia, hypercapnia, and hypoxia increase pulmonary vasoconstriction.

The presence of large amounts of fetal lung fluid in preterm infants contributes to early alveolar flooding. The development of alveolar edema adds to the compromised lung function as protein-rich interstitial fluid fills the alveolar air spaces. When ventilation is initiated, distal lung units tend to remain fluid filled and undistended while more proximal airways dilate to accommodate the ventilatory volume. With expiration, the fluid moves to the proximal airways as the lung collapses. The cyclic movement of fluids erodes the bronchiolar epithelium. Within hours of birth, hyaline membranes are formed from serum proteins such as fibrinogen and albumin, and cell debris is created from bronchiolar and epithelial damage.[1]

Clinical Presentation

Infants with RDS develop typical signs of respiratory distress immediately after birth or within the first six hours of life. The usual presentation includes a combination of grunting, intercostal retractions, cyanosis, nasal flaring, and tachypnea. In the very small infant, the disease usually manifests itself as respiratory failure at birth. The presence of apnea in the early stage of the disease is an ominous sign: It usually indicates hypoxemia and respiratory failure; it may also reflect thermal instability or sepsis.

The clinical course is variable in terms of severity. There is usually a pattern of increasing oxygen dependence and poor lung function in which surfactant

FIGURE 2-2
Pathophysiology of respiratory distress syndrome.

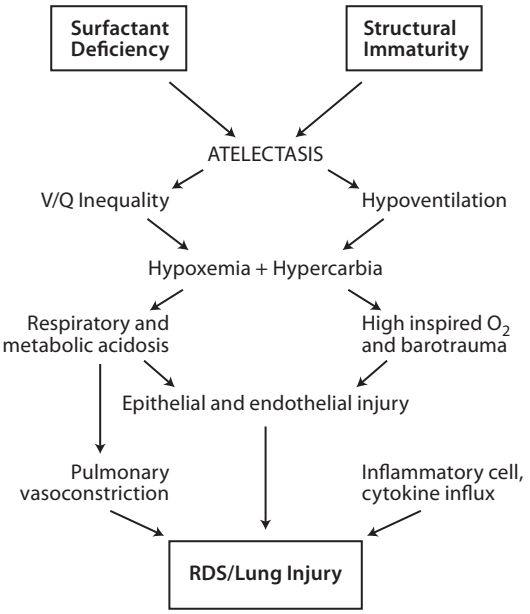

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FIGURE 2-3
Pressure-volume curves of normal newborn lung and RDS lung.

Comparison of the pressure-volume curve of a normal infant *(solid line)* with that of a newborn with respiratory distress syndrome *(dotted line).* Note that very little hysteresis (i.e., the difference between the inspiratory and expiratory limbs) is observed in the respiratory distress syndrome curve because of the lack of surfactant for stabilization of the alveoli after inflation. The wide hysteresis of the normal infant's lung curve reflects changes (reduction) in surface tension once the alveoli are opened and stabilized.

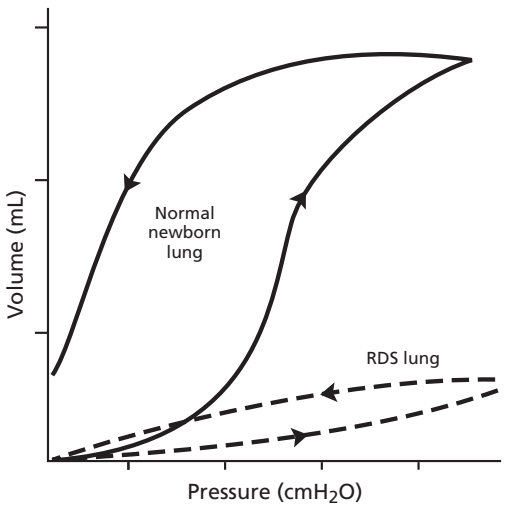

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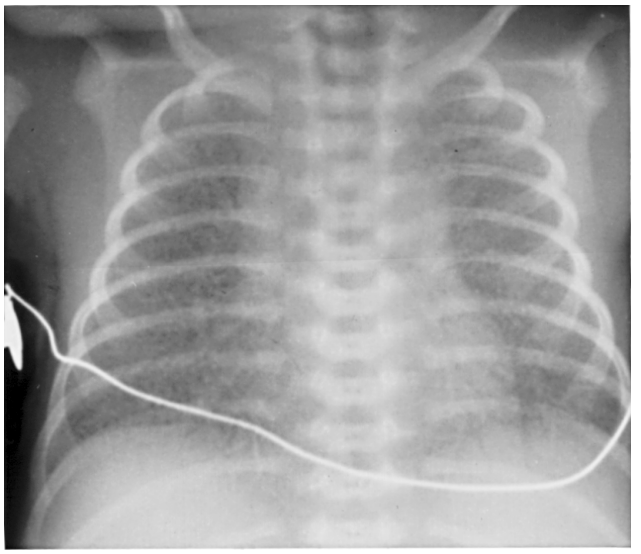
FIGURE 2-4
AP view of the chest of an infant with respiratory distress syndrome (hyaline membrane disease).

Note the reticulogranular appearance of the lung fields and the extension of air bronchograms.



use exceeds the rate of surfactant production. After 48–72 hours of age, most infants begin to show signs of recovery. Oxygenation and ventilation improve, while retractions and respiratory rate decreases. The timing of clinical improvement coincides with a spontaneous diuresis.

A different clinical course may be seen in infants treated with surfactant therapy. These infants often have rapid improvements in oxygenation and a decreased need for ventilator support.[8] Despite surfactant therapy, some extremely low birth weight infants may experience a worsening in their respiratory distress after an initial period of improvement. A postsurfactant slump has been described after the first week of life in infants who require increased oxygen and ventilatory support. Repeat doses of surfactant resulted in improvement in oxygenation and ventilation.[9]

Infants with RDS are predisposed to developing a symptomatic patent ductus arteriosus (PDA)—left-to-right shunting through the ductus arteriosus causing compromised cardiovascular or pulmonary function relative to the magnitude of the shunt. The incidence of a symptomatic PDA in infants less than 30 weeks gestational age with RDS is 75–80 percent.[10] In infants with the most severe RDS, a large left-to-right shunt may be present on the first day of life without the characteristic ductal murmur.

A significant degree of shunting through the patent ductus results in diminished blood flow to the lower aorta and systemic hypoperfusion. Most of the left ventricular output is diverted back to the lungs. The brain, gut, kidneys, and myocardium may not receive adequate perfusion. Tissue mottling, diminished capillary filling, acidemia, and oliguria may result, mimicking the clinical picture of septicemia, intracranial hemorrhage, or a metabolic disorder. In very small infants, pharmacologic measures may fail to close the PDA, resulting in a prolonged recovery phase and ventilator dependence. Surgical intervention becomes necessary for these infants.

Diagnosis: Radiographic Findings

Characteristic features of RDS can be identified on x-ray (Figure 2-4). The lung fields show a fine reticulogranular pattern and marked underaeration, leading to a small lung volume. The most distinguishing finding is peripheral extension and persistence of air bronchograms. Prominent air bronchograms represent aerated bronchioles superimposed on a background of nonaerated alveoli. Granularity is attributed to the presence of distended terminal airways (alveolar ducts and terminal bronchioles) seen against a background of alveolar atelectasis.[11] These characteristic features of RDS progress as the disease worsens, but initiation of mechanical ventilation and surfactant replacement therapy alter the natural progression of radiologic changes.

Treatment with positive-pressure ventilation commonly results in lung fields that appear coarser than before treatment was instituted. A pattern of small bubbles replaces the granularity. This finding reflects overdistention of the terminal airways. On expiration, these bubbles can empty, producing a "whiteout" effect. This pattern occurs because the alveoli are underaerated and lack residual air (functional residual capacity), which results in empty lungs on expiration. When RDS is severe, the lung fields may appear completely opaque, and it may be impossible to distinguish the borders of the heart.

In the recovery phase of RDS, alveolar aeration occurs, and granularity disappears as surfactant production and function improve. The lung fields clear from the periphery inward and from the upper to the lower lobes. The lungs become large and radiolucent and frequently appear hyperaerated.[12] Surfactant therapy usually results in more rapid clearing and aeration of the lungs for infants at 32 weeks gestation and older. Uneven clearing and aeration of the lungs result from

uneven distribution of the surfactant preparation.[11] Some infants with RDS develop chronic lung disease following treatment with supplemental oxygen, positive pressure ventilation, and surfactant replacement therapy. It may be difficult to distinguish the early x-ray findings in these infants from those of an infant in the recovery stages of RDS.

Treatment and Nursing Care

Therapy for infants with RDS begins with anticipation of the preterm birth and administration of antenatal corticosteroids. Once the infant is born, therapy is directed at providing support for respiratory and cardiovascular insufficiency. Surfactant replacement therapy is routinely used in many infants requiring intubation and mechanical ventilation. Immediate administration of appropriate therapy can be life saving. Preventing alveolar atelectasis, hypoxia, and hypercarbia are the main goals of therapy. General supportive measures must also be maximized. (See Chapter 4 for a detailed discussion of nursing care.) Maintenance of adequate oxygenation and ventilation are nursing care priorities. Meticulous attention must be paid to ensuring a thermoneutral environment. Fluid intake must be carefully balanced to avoid overload and complications related to a PDA. Acid-base disturbances, such as metabolic acidosis and respiratory acidosis, are frequently present in infants with RDS and require careful monitoring. Prophylactic antibiotic therapy may be used until the possibility of infection is ruled out.

Oxygen must be administered carefully to provide adequate amounts to tissues without risk of oxygen toxicity. (See Chapter 10 for a detailed discussion of complications of therapy.) An arterial oxygen tension (PaO_2) between 50 and 70 torr is satisfactory for most infants. A high inspired oxygen concentration may be required to maintain the arterial oxygen tension within an acceptable range. Frequent or continuous monitoring of arterial blood gases is essential during the acute phase of the disease. Pulse oximeters provide noninvasive means of obtaining immediate information on the infant's oxygenation status. Surfactant replacement is a major component of treatment for infants with RDS. Natural surfactant preparations are administered via an endotracheal tube using a side port or catheter to deliver the drug into the trachea. (See Chapter 11 for a discussion of surfactant preparations.) Prophylactic exogenous surfactant replacement may be initiated shortly after birth in infants at risk for RDS. This approach means that some infants receive therapy when their disease is mild or never develops. Prophylactic administration of surfactant is associated with a decreased risk of pneumothorax, pulmonary interstitial emphysema, and death. However, the risk of the infant's developing a PDA and pulmonary hemorrhage increases.[13] Some clinicians administer surfactant therapy as a rescue treatment once the diagnosis of RDS is confirmed. Infants requiring mechanical ventilation for respiratory distress shortly after birth have demonstrated a decreased incidence of chronic lung disease when surfactant was administered within the first two hours of life.[14] Some infants with severe RDS may require multiple doses of surfactant. Others may be intubated only for administration of surfactant and then extubated to nasal continuous positive airway pressure (NCPAP). The combination of surfactant therapy followed immediately by institution of NCPAP has been shown to shorten the duration of respiratory support and eliminate the need for later mechanical ventilation in some infants.[15]

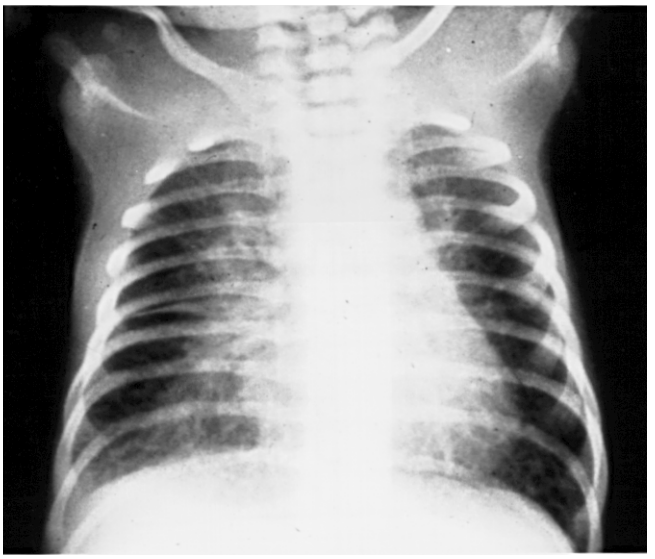
Timely transfer of infants with RDS to a special care unit should be considered when the infant is born in a facility where staff lack experience in caring for low birth weight infants with multisystem problems. Surfactant replacement therapy requires a person skilled in intubation and management of mechanical ventilation. Nursing and respiratory therapy personnel must be available to monitor the infant constantly. Institutional protocols for surfactant therapy should be available. Routine use of surfactant replacement therapy in facilities without a full range of services and expertise is not recommended.[16] Survival rates for very low birth weight infants are higher for those born in hospitals providing a high level of care to a high volume of sick infants.[17]

The decision to initiate ventilator therapy should be made on an individual basis. Variables that must be considered include birth weight, gestational age, postnatal age, results of the chest x-ray, progression of disease, and blood gas values. More immature and smaller infants, who will have a greater incidence of fatigue and apnea, are more likely to require mechanical ventilation even when their oxygen requirements are low. The goal of ventilator therapy is to provide the most effective gas exchange with the least risk of lung damage. Complications such as barotrauma, air leaks, oxygen toxicity, subglottic stenosis, pulmonary infections, cerebral hemorrhage, and retinopathy of prematurity are known to occur with intubation and ventilation. (See Chapter 10.)

Approximately one-third of preterm infants with RDS develop chronic lung disease.[18] However, rates

FIGURE 2-5
AP view of the chest in an infant with transient tachypnea of the newborn.

There is a typical pattern of streaky perihilar densities representing resorption of fluid through the pulmonary veins and lymphatics. The lungs are overaerated.



of chronic lung disease vary widely among neonatal intensive care units.[19] Use of conventional mechanical ventilation predisposes the infant with RDS to chronic lung disease as a result of lung injury from overdistention. Elective high-frequency oscillatory ventilation as initial ventilatory support has been studied, but no significant overall reduction in chronic lung disease has been identified. Adverse effects on short- and long-term neurologic outcomes remain a concern with this approach.[20] High-frequency oscillatory ventilation has been used to rescue preterm infants with severe RDS when conventional ventilation techniques have failed. However, there is concern that the benefit gained in terms of decreasing chronic lung disease is offset by the risk of an increase in the number and severity of intraventricular hemorrhages and the incidence of periventricular leukomalacia.[21]

A less severe form of chronic lung disease may be seen in low birth weight infants with only mild RDS. The cause of chronic lung disease in these infants is related to factors other than severity of the initial lung disease and need for mechanical ventilation with high inspired oxygen concentrations. Patent ductus arteriosus, nosocomial infection, and high fluid intake in the first days of life contribute to the development of chronic lung disease in infants with only mild RDS.[22,23] Although treatment options have increased since the mid-1980s, RDS continues to be a major problem for preterm infants. Advances in assisted reproductive technology have resulted in more multiple gestations. Since 1990, the rate of twin births has increased by 25 percent.[24] The rising multiple-birth rate is contributing to an increase in the number of infants born preterm. Use of tocolytic agents coupled with antenatal steroid therapy is reducing mortality, morbidity, and RDS in premature infants. However, preterm birth remains a major contributing factor for RDS. More research is needed to determine the best combination approach to treating RDS at specific gestational ages and degrees of disease severity. Surfactant type, timing of surfactant administration, and ventilatory support options are key elements in developing better protocols for practice that will improve outcomes for infants with RDS.