Respiratory Physiology and Support

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3.1 Introduction

Gas exchange between the environment and the tissues requires:

- Intake (inspiration) and release (expiration) of gases between the environment and the lung (ventilation, abbreviated as V)
- Diffusion of gases across a biologic membrane between the gaseous environment and the blood
- Blood flow to ventilated portions of the lung (perfusion, abbreviated as Q)
- The delivery of respiratory gases by the bloodstream to and from the body's tissues

3.2 Ventilation

Inspiration occurs when the pressure inside the lung becomes less negative than atmospheric pressure. Negative intrathoracic pressure results from expansion of thoracic volume in the presence of a relatively rigid box (the rib cage). In the normal lung under resting conditions, diaphragmatic contractions are the primary motive force responsible for expansion of thoracic volume, and the energy expenditure necessary for normal respiration during rest is relatively small. However, pathologic conditions that inhibit inspiration will significantly increase the energy expenditure required to maintain adequate inspiration (i.e., increased work of breathing). An important clue to the presence of these pathologic conditions is the use of accessory (intercostal, sternocleidomastoid, and abdominal) muscles of respiration.

Expiration in the normal lung at rest is passive and results from the elastic recoil of the lung. Thus under resting conditions in patients with healthy lungs, expiration requires no energy expenditure. However, conditions that increase airway resistance can also result in the use of accessory muscles of respiration and thus increase the work of breathing.

Gas exchange in the lung occurs only at the level of the terminal bronchioles and alveoli. Thus only a portion of the inspired air will be available for gas exchange. The volume of inspired gases that is not available for gas exchange is referred to as the physiologic dead space, which is the sum of the anatomic dead space (gas in airways not involved in gas exchange) plus the volume of gas entering alveoli that are not perfused (alveolar dead space). In the normal lung, the anatomic dead space is of relatively little physiologic consequence. However, conditions that prevent gas exchange at the level of the alveoli increase the alveolar dead space. These conditions will often induce an increase in respiratory rate and/or ventilation volumes to maintain adequate oxygen uptake and carbon dioxide elimination.

Expansion of alveoli requires a negative force that is sufficient to overcome the inherent recoil of the lungs. Due to the weight of the lung in the upright position pressing down on alveoli at the base, there is a tendency toward increased ventilation at the apices of the lung. However, the weight of the lungs in the upright position also results in a more negative pressure at the apex of the lung which causes the diameters of the alveoli at the apex to be slightly larger than at the base. Since the pressure-volume compliance curve of the lung is sigmoidal, such that compliance (change in volume per change in pressure) is lowest at smaller and larger alveolar volumes, the inherent compliance characteristics of the lung help to overcome an unequal distribution of inspiratory gases.

Finally, the law of Laplace states the pressure required to overcome wall tension in a sphere is inversely proportional to the volume. Accordingly, greater pressures are required to reexpand collapsed alveoli. Thus even at end expiration, a portion of the inspired air remains in the lung. This volume of gas that remains in the lung at the end of expiration is referred as the functional residual capacity (FRC). Factors that affect the volume of FRC include changes in airway resistance as well as alterations in lung and chest wall compliance.

Multiple pathophysiologic conditions will negatively impact ventilation. Some of these include factors that alter airway resistance (i.e., reactive airway disease, airway edema or foreign bodies, extrinsic compression from intrathoracic masses), lung compliance (i.e., pulmonary edema, interstitial lung disease), or respiratory dead space volume (i.e., atelectasis, pneumonia). In addition, conditions that alter respiratory mechanics will also cause ineffective ventilation (pneumothorax, pleural effusions, flail chest, significant abdominal distension, diaphragmatic eventration). Useful clues to the presence of these pathologic conditions are an increase in respiratory rate and the use of accessory muscles of respiration. Failure to recognize and treat the cause of altered ventilation puts the patient at increased risk of respiratory failure.

3.3 Diffusion

Respiratory gases (oxygen and carbon dioxide) enter and exit the circulation by diffusion across a biologic barrier (i.e., alveolar liquid surface, alveolar wall, interstitial tissues, and capillary wall). Diffusion is a passive process that occurs down a concentration gradient. The rate of diffusion is affected by the difference in concentration, the surface area available for the diffusion, the solubility of the substance that is diffusing, and the thickness of the barrier through which the substance must diffuse. Thus, efficient gas exchange requires a large surface area (50–100 m^2 in the adult lung) and a very thin layer (<1 μm) between the surface of the alveoli and the

circulation (blood-gas interface). In addition, the dense capillary network surrounding each alveolus maintains a concentration gradient between the alveolar lumen and the circulation by continuously delivering carbon dioxide and removing oxygen.

The alveolar surface is covered by a thin layer of liquid which is crucial for enabling gas exchange as well as clearance of inhaled extraneous particles. However this aqueous layer has a tendency to cause alveolar collapse due to the surface tension caused by the resultant air-water interface. Surface tension also has a tendency to draw fluid from the interstitium and alveolar capillaries into the alveolar lumen. Surfactant is a critical component of the liquid surface coating of the alveoli which helps to decrease surface tension. Surfactant is a mixture of lipids and proteins excreted by type II pneumocytes in the alveoli that forms a surface film at the air-water interface in alveoli. Surfactant deficiency, which occurs in the lungs of premature infants as well as in some lung injuries, causes atelectasis as well as alveolar flooding which can be difficult to treat without the availability of exogenous surfactant.

While carbon dioxide has high solubility in aqueous solutions, oxygen does not. Thus, conditions that increase the thickness of the blood-gas interface (i.e., pulmonary edema, surfactant deficiency) will generally affect circulating oxygen levels more than carbon dioxide levels. Due to the efficiency of carbon dioxide elimination, carbon dioxide levels in the blood are affected primarily by minute ventilation (respiratory rate X tidal volume). Thus increasing carbon dioxide levels in a patient in respiratory distress is an ominous sign of impending respiratory failure.

3.4 Perfusion

The pulmonary circulation is a high-volume, low-pressure system that in normal individuals receives 100% of the cardiac output. The high compliance (low resistance) of the pulmonary circulation is the result of a compliant pulmonary arterial tree (due to thin walls with relatively little smooth muscle), a large surface area of downstream vessels (alveolar capillary network), negative intrathoracic pressures (causing distension of extralobar vessels), and radial traction of connective tissues and alveolar septa on extra-alveolar vessels during lung expansion. In addition, at resting cardiac output, not all alveolar capillaries are perfused. These alveolar capillary beds can be recruited during periods of increased cardiac output (i.e., during exercise or stress), thereby expanding the volume of the downstream circulatory network, which helps to maintain low pulmonary vascular pressures even during periods of increased demand.

The pulmonary vasculature is responsive to both neural and humoral influences. Sympathetic and parasympathetic stimulation primarily affect vascular tone in large vessels, while humoral influences have greater effects on smaller pre- and postcapillary arterioles and veins. Humoral agents shown to affect pulmonary vascular smooth muscle tone include histamine, serotonin, acetylcholine, epinephrine, prostaglandins, endothelin- and endothelial-derived relaxing factor (EDRF, nitric oxide), and others. However, probably the most physiologically important influence on pulmonary vascular smooth muscle tone and thus local blood flow is hypoxia.

An important physiologic concept is ventilation/perfusion (abbreviated V/Q) matching. Ventilation of nonperfused alveoli increases the respiratory dead space, while perfusion of nonventilated alveoli (intrapulmonary shunting) results in inefficient gas exchange. The effects of gravity and lung compliance contribute to a balancing of ventilation and perfusion in the lung. Gravity has greater effects on pulmonary blood flow than on systemic blood flow due to the lower pressure within the pulmonary circulation resulting in greater blood flow to dependent portions of the lung. In turn, the unequal distribution of blood flow is matched by the effects of the sigmoidal curve of alveolar compliance, such that alveoli in nondependent portions of the lung remain relatively more distended at end expiration (i.e., on the flatter portion of the pressure/volume curve). Thus during inspiration, inhaled gases also tend to be distributed more toward the dependent portions of the lung.

While the anatomic considerations help to match ventilation to perfusion globally, local influences help to maintain V/Q matching locally. Hypoxic pulmonary vasoconstriction is probably the most important of these local control mechanisms. Hypoxic vasoconstriction causes increased vascular smooth muscle tone in the prealveolar arterioles of poorly ventilated regions of the lung resulting in a redistribution of blood flow to regions of the lung that are better ventilated. Hypoxic pulmonary vasoconstriction, however, can cause an increase pulmonary artery pressures (pulmonary hypertension) during global hypoxia, as can occur in infants with congenital diaphragmatic hernia.

3.5 Oxygen Delivery

After being taken up into bloodstream in the alveolar capillaries, oxygen must be transported to and released for use by the body's tissues. Carbon dioxide has high solubility in aqueous solutions and thus is transported to the lungs primarily dissolved in the serum. Oxygen however has poor solubility in aqueous solutions. Thus oxygen transport is primarily transported in the circulation bound to hemoglobin. Hemoglobin (Hgb) is a

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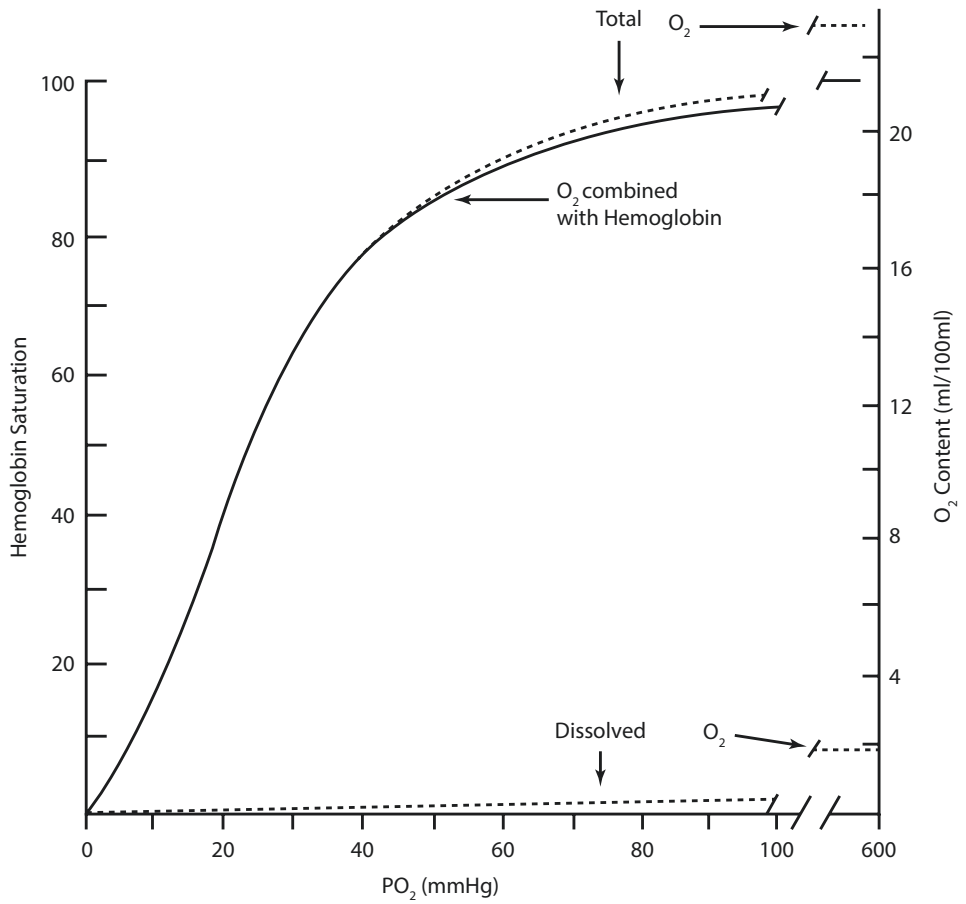
tetrameric polypeptide containing four protoporphyrin (heme) groups attached to a ferrous iron molecule. Each of the polypeptide chains can reversibly bind a molecule of oxygen. The binding of oxygen to hemoglobin occurs very rapidly. Once bound the oxygen is no longer in solution; thus, the partial pressure differential for oxygen diffusion across the alveolar-capillary membrane is maintained until the hemoglobin molecules become saturated. This typically occurs within about 0.25 s, which is about 1/3 of the time it takes blood to transit the pulmonary capillary under resting conditions.

Due to its low solubility in aqueous solutions (0.003 ml dissolved O_2 per ml of blood), oxygen is primarily transported in the bloodstream attached to hemoglobin (typically 1.34 ml O_2 per gm of Hgb). Thus the oxygen-carrying capacity of the blood is primarily determined by the hemoglobin content, while the total oxygen delivery to the tissues is dependent upon oxygen-carrying capacity and local blood flow.

The amount of hemoglobin bound to oxygen is dependent upon the partial pressure of oxygen. The relationship between partial pressure of oxygen and hemoglobin saturation (oxyhemoglobin dissociation curve) is curvilinear. At low partial pressures of oxygen, hemoglobin saturation increases more for each incremental change in oxygen tension than at higher oxygen tensions (i.e., curve flattens out at high oxygen tensions). This has the effect of allowing rapid loading of oxygen under conditions of high oxygen tension (i.e., in the lung) while allowing more oxygen delivery for each decrease in oxygen tension in low-oxygen environments (i.e., in the tissues). The oxyhemoglobin dissociation curve however is not static but can be shifted toward higher or lower affinity for oxygen. Factors that decrease the affinity of Hgb for oxygen (thus facilitating oxygen delivery at the tissue level) include high temperature, low pH, and high CO_2 and 2,3-diphosphoglycerate (2,3 DPG). 2,3 DPG is produced by erythrocytes during normal glycolysis. More 2,3 DPG production is increased during hypoxic conditions which facilitates the release of oxygen from Hgb. Variations in the structure of Hgb also affect their oxyhemoglobin dissociation curve. Specifically, fetal hemoglobin (HbF) has a higher affinity for oxygen (probably due to decreased affinity for 2,3 DPG) which helps with oxygen uptake in the low-oxygen environment of the placenta. However, the higher oxygen affinity inhibits oxygen unloading postnatally.



3.6 Pulmonary Physiology in the Neonate

Several unique aspects of neonatal pulmonary physiology related to lung maturation and growth as well as the transition from intrauterine to extrauterine life may significantly complicate management of the surgical neonate.

The structure of the bronchial tree is established by the 16th week of gestation, but alveolar maturation and growth continue throughout fetal life and into adulthood. Prenatal lung development is divided into four phases:

1. *Embryonic phase* (3rd through 6th weeks of gestation), during which the primitive lung bud forms
2. *Pseudoglandular phase* (7th through 16th weeks of gestation), during which the bronchial airways are established
3. *Canalicular phase* (16th through 24th weeks of gestation), during which the structure of the distal airways and early vascularization is established
4. *Terminal saccular phase* (24th week of gestation to term), during which primitive alveoli are formed and surfactant production begins

Throughout the period of prenatal lung development, interstitial tissue gradually decreases, resulting in thinning of the walls of the future alveoli. Even at birth, however, the lung does not contain mature alveoli; instead, it has approximately 20 million primitive terminal sacs. Postnatally, the relatively shallow, cuplike terminal saccules of the newborn lung gradually become the more spherical, thin-walled structure of mature alveoli. In addition, new alveoli continue to develop up to 8 years of age at which time approximately 300 million alveoli are present. After 8 years of age, lung growth is associated with increases in alveolar size but not number.

Lung hypoplasia is frequently associated with congenital surgical anomalies such as congenital diaphragmatic hernia or congenital cystic adenomatoid malformation that limits lung growth due to compression of the developing lung. Furthermore, because late fetal lung growth is stimulated by rhythmic lung expansion associated with fetal breathing, lung hypoplasia may also be associated with conditions that limit amniotic fluid volume (e.g., renal agenesis) and in patients with severe neurologic abnormalities (e.g., anencephaly). New bronchial development does not occur after the 18th week of gestation, so infants who experienced early inhibition of lung development will not develop completely normal lungs. Lung growth continues well after birth, however, so infants with adequate initial lung parenchyma to support extrauterine life may ultimately be left with little or no functional impairment.

Surfactant production in the fetal lung begins at about 20 weeks of gestation but is not secreted by the lung until about 30 weeks gestation. Surfactant consists of about 90% glycerophospholipids, of which dipalmitoylphosphatidylcholine (DPPC) is the most important. During late gestation, the ratio of phosphatidylcholine (PC or lecithin) to other lipid components (phosphatidylglycerol, sphingomyelin) changes, and thus the ratio of different lipid components of surfactant in the amniotic fluid can be used as an index of lung maturity, that is, a lecithin/sphingomyelin (L/S) ratio >2.0, which normally occurs around 35 weeks gestation and is associated with a low risk of respiratory distress syndrome (RDS). Infants born prior to the age of lung maturity are prone to atelectasis and pulmonary edema due to a relative lack of surfactant, which can result in the development of hyaline membrane disease.

Fetal lung maturation and surfactant production can also be affected by hormonal influences. Fetal stress associated with uteroplacental insufficiency accelerates lung maturation, probably as a result of the influence of elevated glucocorticoids and catecholamine levels, resulting in a relatively low incidence of RDS in these infants. Elevated insulin levels, however, inhibit surfactant production. Thus, even term infants of diabetic mothers may be prone to the development of RDS.

Due to the relatively greater tissue thickness in the normal newborn lung, lung compliance in the neonate is approximately equal to that of the adult. The chest wall of the newborn, however, is more compliant. Thus, the intrapleural pressure in the newborn is less negative (i.e., only slightly less than atmospheric pressure) than in adults. Given this relationship, one would expect the functional residual capacity (FRC) to be lower in the neonate than in the adult. However, the newborn infant augments FRC by maintaining inspiratory muscle activity throughout expiration thereby splinting the chest wall and by increasing airway resistance via glottic narrowing during expiration. As a result, the percent FRC of the neonate is similar to that of adults.

Lung expansion and intrapleural pressures affect airway diameters and thus airway resistance. With forceful expiration, increased intrapleural pressure compresses the airways, thus restricting air flow and potentially causing air trapping. In the lung of the adult and older child, cartilaginous support of the airways prevents complete airway collapse. Less cartilaginous support of the central airways in premature infants, however, may result in air trapping during periods of increased respiratory effort.

Hemoglobin in the fetus has a higher oxygen affinity than the hemoglobin found in the normal older child and adult. The increased oxygen affinity of fetal hemoglobin appears to be primarily due to a decreased affinity for 2,3-DPG. This increased oxygen affinity allows for greater uptake of oxygen from the placenta at the lower oxygen tensions normally observed in the fetus. Greater

oxygen uptake also reflects higher fetal hemoglobin concentrations. Postnatally, however, the increased oxygen affinity of fetal hemoglobin may limit the delivery of oxygen during periods of hypoxemia. In the newborn infant, the oxygen-hemoglobin dissociation curve gradually shifts to the right (toward decreased affinity) as adult hemoglobin levels increase and 2,3-DPG levels rise. Thus, by the time the child is 4–6 months of age, the oxygen affinity usually approximates that of an adult.

Hemoglobin concentrations also change during the first weeks after birth. The normal hemoglobin concentration of newborn infants varies between 16.7 and 17.9 g/dl. Postnatally, hemoglobin concentrations transiently increase initially but then gradually fall to reach minimum levels at 8–12 weeks of age. The primary explanation for the postnatal decrease in hemoglobin concentration is believed to be the decreased stimulus for hemoglobin synthesis associated with markedly decreased erythropoietin levels in response to the higher oxygen environment of the neonate.

During intrauterine life, the placenta functions as the organ for gas exchange. In the fetus only about 12% of right ventricular output circulates through the pulmonary circulation. The remaining right ventricular output is shunted to the systemic circulation through the ductus arteriosus and foramen ovale. Blood is shunted away from the lung due to the high resistance to flow in the fetal pulmonary vasculature, likely due to the combined effects of hypoxic pulmonary vasoconstriction, the local release of vasoconstrictor leukotrienes, and anatomic compression of the pulmonary vasculature by the surrounding liquid-filled lung.

At birth, the lung must immediately assume the role of gas exchange. This remarkable transition depends upon the completion of several simultaneous events. First, the collapsed, fluid-filled alveoli of the prenatal lung must be expanded with air, which begins with the first breath. At birth, more than 25 mm Hg of negative pressure is required to overcome the surface tension and open the alveoli for the first time. To accomplish this, the initial inspiratory efforts of the newborn infant are extremely powerful, generating negative pressures of up to 60 mm Hg. In addition, as the newborn's lung fills with oxygen, blood flow must be redirected such that poorly oxygenated blood returning to the right atrium preferentially flows through the pulmonary circulation. The redistribution of blood flow in the newborn occurs as a result of the combined effects of an increase in systemic vascular resistance and an eightfold decrease in pulmonary vascular resistance. The former is due to loss of the low-resistance placental circulation. The latter is due to expansion of the pulmonary vasculature as the lung expands and the pulmonary vessels are no longer compressed by the fluid-filled lung and due to vasorelaxation in response to increased alveolar oxygen tension. As a result of these adjustments, systemic pressure and left atrial pressure increase, while right atrial and pulmonary artery pressure decrease, resulting first in functional closure and then anatomic closure of the fetal shunts (foramen ovale, ductus arteriosus).

Newborn infants with significant impairments in lung function (e.g., RDS, pulmonary hypoplasia) that result in hypoxemia are prone to persistent pulmonary hypertension of the newborn (PPHN) due to hypoxic pulmonary vasoconstriction. In addition, abnormalities of lung structure are frequently associated with abnormalities of the pulmonary vasculature (i.e., pulmonary vascular hypoplasia), which may also contribute to pulmonary hypertension. As pulmonary blood pressure exceeds systemic blood pressure, blood flow will be shunted again through the anatomic fetal shunts (foramen ovale and ductus arteriosus), resulting in a condition referred to as persistent fetal circulation (PFC). The development of PFC further exacerbates hypoxemia as unoxygenated blood is shunted away from the pulmonary circulation to the systemic circulation (right-to-left shunt). Occasionally, PFC will respond to measures that increase systemic blood pressure or decrease pulmonary vascular resistance, such as inhaled nitric oxide or oxygen. However, if a significant shunt already exists, these interventions are less likely to be successful. Therefore, the optimal strategy is to recognize and treat alveolar hypoxia before pulmonary hypertension develops.

3.7 Clinical Correlations

The following scenarios present typical situations and suggested treatments for pediatric respiratory problems.

3.7.1 Case Scenario #1

3.7.1.1 Presentation

You are seeing a newborn infant at 36 weeks gestational age. The child was born to a nulligravid 18-year-old mother who presented with preterm labor. The child was born after a prolonged labor and difficult assisted vaginal delivery. At the time of rupture of the amniotic membranes, meconium-stained amniotic fluid returned. Examination of the placenta revealed evidence of a partial abruption. The infant's Apgar scores were 7 at 1 min and 8 at 5 min. Upon oropharyngeal suctioning in the delivery room, meconium-stained secretions were noted. The patient is tachypneic and has peripheral cyanosis. Auscultation reveals coarse bilateral breath sounds.

1. What is the likely cause of this patient's respiratory distress?
2. What are the options for supporting this patient?

3.7.1.2 Treatment

The newborn patient has respiratory distress syndrome. Given the difficult delivery and observed meconium staining of the amniotic fluid, it is likely this patient's respiratory distress is due to meconium aspiration syndrome. The management of patients with meconium aspiration syndrome is primarily supportive. Pulmonary physical therapy and frequent suctioning should be instituted to assist with clearance of the airways. Oxygen therapy with continuous positive airway pressures may improve the patient's cyanosis and decrease the atelectasis associated with disruption of surfactant function.

In many settings in Africa, the use of bubble continuous positive airway pressure, known as "bubble CPAP," may be an option in these types of cases. Bubble CPAP implies placing a short binasal pronged nasal cannulae into the nasal passages of newborns who need some extra airway pressure while their pathology improves and oxygenation increases. The nasal cannulae are attached to the oxygen wall outlet at 8–14 l/min in an effort to maintain pharyngeal pressure with a Y-connector so that an expiratory limb is produced. The expiratory limb can then be placed in 8 cm water pressure; bubbling that stops indicates an excessive loss of airway pressure and the need to confirm for leaks. The water pressure provides for continuous airway pressure, which could allow for these types of patients to improve without the need for intubation.

Steroid therapy may help to decrease airway inflammation, although corticosteroid therapy has not been shown to improve the course or outcome associated with this disease. In addition, antibiotic therapy should be instituted to prevent the frequent complication of secondary bacterial pneumonia, especially if steroids are used.

3.7.2 Case Scenario #2

3.7.2.1 Presentation

A 7-year-old boy is brought in after being rescued from a burning building. He was sleeping in his home when it caught fire. He was rescued by a neighbor who heard the child screaming for help and coughing. On examination, the child has soot around the nares and in the posterior pharynx, although there are no obvious facial burns. He is anxious and tachypneic, and his skin color is cherry-red.

1. What is the likely cause of this patient's anxiety and tachypnea?
2. What would be your initial treatment?

3.7.2.2 Treatment

This patient was exposed to a fire in an enclosed environment—a history that raises concern for an inhalation injury. Other findings including soot in the oropharynx and around the nares support the likelihood of inhalation injury, whereas the findings of the cherry-red skin and anxiety are consistent with carbon monoxide poisoning.

Carbon monoxide is a by-product of combustion. Inhaled carbon monoxide is rapidly transported across the alveolar membrane and preferentially binds to the hemoglobin molecule in place of oxygen. Binding of carbon monoxide to hemoglobin (carboxyhemoglobin) impairs unloading of O_2. Carboxyhemoglobin is bright red, which explains the cherry-red skin color, and the tachypnea and anxiety suggest tissue (central nervous system) hypoxia.

The most important first step in treating this patient is to provide supplemental oxygen in high concentrations. High oxygen concentration accomplishes two goals: (1) it optimizes oxygen delivery to ameliorate tissue hypoxia, and (2) it accelerates unloading of carbon monoxide from the hemoglobin molecule (the half-life of carboxyhemoglobin is about 90 min in 21% oxygen but decreases to 20–30 min in 100% oxygen).

An inhalation injury is not commonly due to direct thermal injury to the airways, but these injuries are associated with inhalation of toxic by-products of combustion, which can result in airway edema due to inflammation. Therefore, fluid resuscitation should be judicious, and the patient should have a bladder catheter placed to monitor urine output as an indicator of adequacy of hydration. Care should be taken, however, to avoid overhydration. At times, after fluid resuscitation, the airway can become edematous, and one needs to monitor for airway obstruction, which may make a definitive airway more difficult. Steroids have been used frequently in the past to attempt to decrease airway swelling. Their use, however, has not been shown to decrease the morbidity or mortality in patients with inhalation injury, and they may increase the risk of infections. Similarly, prophylactic antibiotics have also not been shown to decrease pulmonary complications or mortality in patients with inhalation injuries.

Key Summary Points

1. The primary role of the lungs is to allow for exchange of respiratory gases (intake of oxygen and elimination of carbon dioxide).
2. Pulmonary function requires a balance of ventilation, gas transport, and blood flow.
3. Surgical diseases can negatively impact gas exchange by altering any or all of these factors.
4. Severe derangements may overcome compensatory mechanisms, resulting in hypoxia and acidosis.
5. Due to differences in lung maturation and respiratory mechanics, neonates may be at increased risk of altered gas exchange.
6. Recognition and treatment of causes of dysfunction are key to improving patient outcomes.

Suggested Reading

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