Apnea of Prematurity

Apnea of prematurity (AOP) is the most common and recurring problem of respiratory control in the premature infant. AOP occurs in more than 85% of all infants born prior to 34 weeks gestational age. The incidence of AOP is inversely proportionate to gestational age at birth—as gestational age decreases, apnea becomes more prevalent.

In premature infants without respiratory distress syndrome (RDS), AOP may occur on the first day of life, but it may not present for several days in infants with RDS. Many perinatal and postnatal complications increase the infant's risk of developing AOP, including central nervous system insult or injury, respiratory insult or injury, metabolic disease, sepsis, congenital defects, inborn errors of metabolism, birth trauma, and maternal substance use (including smoking and alcohol consumption). Some evidence supports heredity as a risk factor.

Definition

AOP is most commonly defined as the cessation of breathing for more than 20 seconds, or 5–10 seconds in the presence of bradycardia (heart rate < 80 bpm or 30 bpm below baseline) or desaturations (SaO_2 < 80%–85%). Brief respiratory pauses that are less than 10 seconds in duration and not associated with bradycardia or desaturations can occur in conjunction with startles, movement, defecation, or asynchrony during feedings, and are usually self-limiting.

In the premature infant, apnea may be the presenting symptom accompanying altered homeostasis of nearly all organ systems. Temperature instability, asphyxia or hypoxemic events, sepsis, metabolic disturbances, respiratory compromise, patent ductus arteriosus or other heart defects, intracranial hemorrhage, feeding disruptions, hematologic disturbances, pain, and agitation are some examples. AOP is considered a diagnosis of exclusion because it often is the presenting symptom of other pathologic conditions and should be thoroughly investigated before being assigned this diagnosis.

Classification

AOP is distinguished by duration and hemodynamic dysfunction and is further classified into three categories based on the presence or absence of obstruction. *Central apnea* involves total cessation of respirations or the absence of respiratory muscle activity accompanied by the absence of airflow. *Obstructive apnea* is characterized by the presence of respiratory muscle activity in the absence of airflow that continues throughout the entire apnea episode. *Mixed apnea* consists of a combination of obstructed apnea and central apnea and is believed to represent the most common type of apnea in the newborn. Obstructive apnea may occur in the pharynx, the larynx, or in both areas of the upper airway. *Ideopathic apnea* is most commonly associated with prematurity.

Hypoxemic events resembling apnea have been detected in intubated, mechanically ventilated preterm infants. These episodes of hypoxemia are preceded by increased pulmonary resistance and decreased compliance similar to events occurring before apnea in unintubated infants. Subtle, spontaneous movements precede these episodes, and they are characterized by central respiratory depression and obstructed airflow. The events are a consequence of hypoventilation and are frequently associated with arousal.

Periodic Breathing

AOP should be distinguished from periodic breathing, in which the infant exhibits regular short cycles (10–20 seconds in length) of respiration that are interrupted by respiratory pauses of at least 3 seconds. The pattern recurs for at least 2 minutes followed by a stronger respiratory drive to restore normal ventilation and often is accompanied by mild hypoxemia. Periodic breathing is considered a benign developmental phenomenon, and medical treatment is not indicated. However, when preceded by significant hypoxemia or when associated with bradycardia or prolonged apnea with alveoloar hypoventilation, it is abnormal and may be a precursor to pathologic apnea.

AOP and periodic breathing are disorders that tend to decline in frequency with advancing postconceptual age and are treated with administration of methylxanthines.

Pathophysiology

AOP is a common disorder of respiratory control in premature infants. Apnea presenting independent of other pathology is most likely a maturational feature representing a physiologic rather than pathologic immaturity of respiratory control. However, a clear mechanism responsible for apnea in premature infants has not been identified.

Normal rhythmic breathing requirements include a patent airway; a central respiratory drive originating from respiratory centers in the brainstem (modulated by input from peripheral neural and chemical receptors); and coordinated, effective functioning muscles of respiration. Changes in arterial PCO_2, PO_2, and pH act on neural and chemical receptors from these centers and are integrated by the respiratory center in the brainstem, which sends signals to the respiratory muscles responsible for maintaining airway patency and regulating the level of ventilation. The immature brainstem respiratory centers in preterm infants have an attenuated response to carbon dioxide and a paradoxical response to hypoxia, which results in apnea rather than the normal hyperventilation response. Anatomical characteristics such as decreased number of synaptic connections, decreased dendritic arborization, and poor myelination result in functional immaturity of the brainstem, which improves after treatment with methyxanthines.

Obstructive apnea can be the result of poor pharyngeal tone, which can cause the pharynx to collapse with negative airway pressures generated during inspiration. Structurally, the airways are more compliant and smaller, both in diameter and length, and are at increased risk for blockage by malpositioning, edema, and excess mucus.

Genetic factors associated with a higher risk of occurrence in premature infants include being born to first-degree consanguineous parents, being monozygotic twins, and having a sibling who presents with complications of apnea.

Significant ventilatory and cardiovascular consequences can be associated with AOP. Prolonged apnea results in hypoxemia and hypercarbia, which is directly related to the frequency, duration, and intensity of the episode.

Apnea and Gastroesophageal Reflux

Gastroesophageal reflux (GER) is a common problem in premature infants and often is suggested as a component of AOP. Reflux of gastric contents into the larynx may induce apnea as a result of stimulation of the laryngeal nerve or other afferent pathways; however, this mechanism is not proven to either cause or prolong apnea. The frequency with which the two conditions coexist is debated, and the cause-effect relationship is multifactorial. The majority of apnea occurring before GER is central in origin, but when apnea occurs during or after a GER episode, it is more frequently mixed apnea. In some instances, apnea occurs prior to reflux, decreasing lower esophageal tone and lower esophageal sphincter pressure resulting in reflux. In the overall premature infant population, GER does not induce apnea, prolong the duration of apnea, or exacerbate apnea-related bradycardia or desaturations. Further, there is no clear evidence that pharmacologic agents that decrease gastric acidity or enhance gastrointestinal motility impact the frequency or duration of apnea.

Management

Management begins by eliminating factors associated with increasing risk of apnea, by taking measures such as ensuring a stable thermal environment, maintaining airway patency, and using proper positioning. Ensuring proper placement of nasal and oral gastric tubes is important, as malposition of these tubes has been implicated in association with apnea. Cue-feeding, pacing with feedings, and left-side lying position are good measures for parents to facilitate better feeding patterns, which may reduce the incidence of choking and apnea. Prone positioning of the preterm infant assists to "splint" the chest wall and facilitate slight neck extension positioning and stabilization of the head; this positioning has been shown to improve breathing. Prone positioning in the preterm infant also is associated with improved gastric emptying time. Prone positioning is indicated only with

the use of cardiorespiratory monitoring, and the importance of transitioning to supine positioning for home care cannot be over emphasized.

Administering continuous airway pressure is associated with decreased apnea. Evidence suggests it may serve as a "splint" for upper airways and the chest wall, increase oxygenation, and help maintain functional residual capacity. Many times, the flow is enough to support the infant with apnea, but sometimes administration of oxygen along with flow is necessary. Continuous positive airway pressure reduces the frequency of only mixed and obstructive apnea, with little or no effect on central apnea in infants. Infants unresponsive to these therapies or methylxanthines will require intubation and ventilatory support.

Methylxanthines are the mainstay of treatment for apnea. These agents have multiple pharmacologic and physiologic mechanisms of action, including increased minute ventilation, improved CO_2 sensitivity, decreased hypoxic depression, enhanced diaphragmatic activity, and decreased periodic breathing episodes. Treatment usually is initiated with a loading dose followed by maintenance therapy in either oral or intravenous (IV) preparation. Common side effects include tachycardia, feeding intolerance, emesis, jitteriness, restlessness, and irritability. Toxic levels may produce cardiac dysrhythmias and seizures. Methylxanthines increase metabolic rate and oxygen consumption, have a mild diuretic effect, increase cerebral metabolic rate, and decrease cerebral blood flow.

Thephophylline, aminophylline, and caffeine citrate have demonstrated effectiveness in the treatment of apnea of prematurity. Caffeine citrate is considered preferable because it is better tolerated and has fewer side effects, a larger margin of safety, a higher therapeutic index, and a longer half-life. The long half-life allows once-per-day dosing, and the larger margin of safety means monitoring levels at the recommended dosing is seldom necessary. Caffeine has been shown to reduce the rate of bronchopulmonary dysplasia and may have neuroprotective benefits as well.

Doxapram, another respiratory stimulant, has been used in infants with idiopathic apnea of prematurity refractory to methylxanthines. It acts through stimulation of a peripheral chemoreceptor and has been shown to increase minute ventilation, tidal volume, inspiratory flow, and airway pressure. Side effects include hypertension, irritability, hypoglycemia, gastric irritability, and in a small number of preterm infants, heart block. Doxapram is available as an oral drug, but it is poorly absorbed. Because of this, it is typically used as a continuous IV infusion. Benzyl alcohol is the preservative used in doxapram, although the concentration is considered low (0.9%/mL) and at recommended dosing, toxicity in the neonate is unlikely. Toxicity is associated with a potentially fatal side effect known as *gasping syndrome* in neonates. Due to the benzyl alcohol preservative and its potential side effects, use of doxapram is limited in the United States.

Anemia can lead to apnea of prematurity, desaturations, and bradycardia. The symptoms of anemia appear to be worse in more premature infants, and in infants with underlying disease processes. Red blood cell transfusion is a proposed mechanism to increase oxygen carrying capacity; however, blood transfusions also are associated with worsening bronchopulmonary dysplasia and necrotizing enterocolitis. Red blood cell transfusions should be reserved for infants with significant clinical signs and symptoms of anemia.

AOP often resolves and then resurges in response to other pathology. Retinopathy of prematurity exams, immunizations, and surgery are associated with recurrence of apnea.

Resolution

Apnea of prematurity resolves by around 36–40 weeks gestational age. However, in more premature infants it may last beyond 43–44 weeks gestational age and is a problem that frequently delays discharge.

Consequences

In premature infants, desaturations and bradycardia frequently occur along with apnea. Bradycardia most often

occurs after the onset of hypoxemia and may be accompanied by increased stroke volume. Prolonged apnea, bradycardia, and desaturations lead to decreased systemic blood pressure and cerebral hypoperfusion, which can contribute to hypoxic-ischemic injury of the immature brain. Untreated significant apnea often progresses and can lead to complications of the respiratory system, cardiac system, gastrointestinal system, central nervous system, and renal system.

Identifying the long-term consequences of apnea is difficult because of the numerous secondary causes of apnea. Neurodevelopmental outcome is less favorable in infants when apnea persists, when mechanical ventilation is required for longer periods of time, and when frequent apnea persists after discharge. Former premature infants with AOP may be at a higher risk to develop sleep-disordered breathing later in life.

Consistent and reliable evidence continues to support no relationship between persistent AOP and an increased risk of sudden infant death syndrome (SIDS). The use of home monitoring for prevention of SIDS in infants with AOP is not indicated by the American Academy of Pediatrics. However, when apnea persists, the use of home monitoring may be an alternative to delayed hospital discharge. Because the monitors are subject to false alarms and "missing" some apnea and bradycardia, this practice remains controversial.

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Apnea of Prematurity: Information for Parents

Apnea of prematurity is when your baby's breathing pauses. It is very common for this to happen in premature babies. The more premature the baby is, the more common apnea is. The pauses in breathing may happen alone, but more commonly they happen with drops in heart rate (bradycardia) or oxygen saturations (desaturations).

Apnea can happen just because the baby is premature, or it can be a symptom of some other illness or problem. When the apnea happens alone and only once in a while, your baby's provider will watch your baby very closely. When the apnea happens with bradycardia or desaturations, your baby's provider will run blood tests and possibly do other tests such as X rays, head ultrasounds, and heart sonograms (known as an *echocardiogram* or *cardiac echo*) to make sure nothing else is causing the apnea.

Many times, premature babies need medications to help their bodies remember to breathe, and sometimes they need more help from a nasal cannula, continuous positive airway pressure, or a breathing machine. Apnea often is the first symptom seen when a baby has an infection, so antibiotics may be started even before the test results come back.

Premature babies often are placed on their tummies, which helps support the chest (so they breathe easier) and helps with digesting feedings. In the neonatal intensive care unit, your baby is on monitors that will sound an alarm if the baby stops breathing or has a drop in heart rate or oxygen saturations. As your baby grows and the apnea (and other conditions) improve, your baby will be placed on his or her back because this is the safest way for your baby to sleep and rest as he or she gets closer to going home.

Apnea usually improves as your baby gets older, but it takes longer for it to improve in some premature babies. Sometimes even after the apnea seems to have stopped, it starts again. This can happen because the baby is still immature or because of necessary tests like an eye examination. Apnea may start again (briefly) after immunizations are given. The apnea that happens after immunizations is usually very mild. It is important that your baby has eye examinations and receives immunizations to protect him or her from serious problems later on.

Sometimes apnea continues as your baby is getting closer to going home. It is important to continue watching and caring for your baby in the hospital until it is safe for your baby to go home. Babies are sometimes sent home on the medications that help them remember to breathe.

Apnea of prematurity does not mean your baby is more at risk for sudden infant death syndrome (SIDS). Things that increase the baby's risk for SIDS are cigarette smoke; sleeping on their tummies; a lot of soft fluffy bedding (e.g., blankets, pillows, stuffed animals); keeping the room too warm; and sleeping with others.

It is important that you keep all of your follow-up appointments and that your baby receives immunizations at the scheduled times.