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Review

Apnea of prematurity

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Abstract

Apnea of prematurity (AOP) is one of the most frequent pathologies in the Neonatal Intensive Care Unit, with an incidence inversely related to gestational age. Its etiology is often multi factorial and diagnosis of idiopathic forms requires exclusion of other underlying diseases. Despite being a self-limiting condition which regresses with the maturation of the newborn, possible long-term effects of recurring apneas and the degree of desaturation and bradycardia who may lead to abnormal neurological outcome are not yet clarified. Therefore AOP needs careful evaluation of its etiology and adequate therapy that can be both pharmacological and non-pharmacological.

Keywords

Apnea of prematurity, idiopathic and secondary apnea, caffeine.

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Definition and pathophysiology

Apnea of prematurity (AOP) is defined as the cessation of breathing for over 15-20 seconds and is accompanied by oxygen desaturation (SpO_2 less than or equal to 80% for ≥ 4 seconds) and/or bradycardia (HR < 2/3 of the basic HR for ≥ 4 seconds) in neonates with a gestational age less then 37 weeks [1, 2].

The incidence of AOP has an inverse correlation to the gestational age (GA): 7% of neonates with a GA of 34-35 weeks, 15% of neonates with a GA of 32-33 weeks, 54% of neonates with a GA of 30-31 weeks, nearly 100% of neonates with a GA of < 29 weeks or weighing less than 1,000 g [3]. Apnea can be classified as central (10-25% of cases), obstructive (10-25% of cases) or, more frequently, mixed (50-75% of cases) [4]. Only one type of apnea predominates in each individual neonate.

Bradycardia can accompany apnea. It usually occurs after oxygen desaturation, a consequence of apnea, with incidence related to the length of the episode (75% in apneas longer than 20 seconds). Sometimes bradycardia can occur before apnea due to a vagal mechanism that is not mediated by hypoxemia.

The physiopathological mechanism underlying AOP is not fully clear, but is certainly linked to the immaturity of the central nervous system (CNS) of the preterm neonate, and particularly to a poor myelination of the immature brainstem, and for that reason it spontaneously improves as the GA increases [1, 2, 5]. The neurological control of respiration is located on the ventral medullary surface, where the chemoreceptors for CO_2 are found.

The preterm neonate has a very particular respiratory response pattern to hypercapnia and hypoxia. In response to hypercapnia, a preterm neonate, unlike an adult, does not increase respiratory frequency (Rf) or tidal volume, but prolongates the expiratory period, resulting in a lower volume/minute. This reduced response to hypercapnia is more marked in preterm neonates with AOP. The response to hypoxia takes place over two phases. Ventilation initially increases for 1-2 minutes then the Rf falls below the starting level. The cause of this depressive phase is unknown, but this type of response can persist for various weeks of post-natal life. It is unclear whether it plays a role in triggering apnea, but once hypoxia has occurred, it does aggravate apnea. Various neurotransmitters are involved in the hypoxic depressive response, as adenosine, endorphins and γ-aminobutyric acid (GABA). Neurotransmitter blockers (xanthines for adenosine, naloxone for endorphins) act before the late depressive ventilation phase [6].

Etiology

AOP is a diagnosis of exclusion: it can be idiopathic or be the epiphenomenon of other diseases of the premature infant. The idiopathic apnea is a developmental disorder that reflects the immaturity of the respiratory drive and a unbalanced tone of autonomic and parasympathetic system. It can be potentially harmful to the acute consequences on gas exchange and hemodynamic alterations. The apnea typically appears during active sleep, which is the primary condition of fetal well-being. The excitation threshold appears depressed compared to that of the quiet sleep. The prolonged apnea (> 20 sec) and recurrent may affect oxygenation, potentially exacerbate brain injury, especially if associated with bradycardia and desaturation. Often the initial apnea is the phenomenon that causes bradycardia and desaturation. When sleep apnea is obstructive or mixed (lack of air flow), it occurs as an episode of bradycardia with desaturation. The airway obstruction may also occur secondarily to an apnea that lasts more than 20 seconds. This explains why some neonates with central apnea that do not respond to CNS stimulants may respond to nasal continuous positive airway pressure (nCPAP) or because some neonates with mixed apnea may respond to CNS stimulants. Moreover, a bradycardia which appears as a primary event may be followed by desaturation which causes depression of the respiratory drive leading to apnea [5].

The secondary apnea can have different causes that require specific interventions:

- bacterial sepsis: especially if apneas appear in the first hours of life in relation to maternal-fetal infections or after the second week of life;
- viral infections;
- significant persistent ductus arteriosus (PDA);
- seizures;
- hypoxic-ischaemic encephalopathy;
- severe anemia or hypovolemia;
- maternal drugs;
- abdominal distension which reduces lung volume and increases vagal stimulation;
- pain;
- congenital malformations of the upper airways;
- nasal obstruction;
- metabolic disorders (hypothyroidism);
- hypoglycemia;
- hypocalcemia;
- hypothermia or hyperthermia.

Genetic basis of AOP

Recent studies showed the possible genetic basis for AOP, as demonstrated by its higher incidence in first degree relatives. One study [7] conducted

on 317 pairs of premature twins of less than 36 weeks has identified a higher concordance to AOP between monozygotic twins (87%, compared to 62% for dizygotic twins of the same sex) indicating a genetic susceptibility to AOP between twins of the same sex, especially male ones. Polymorphisms of genes A1 and A2A, genes for adenosine receptors, could be responsible for the variability of response to caffeine that is commonly seen in infants. In a recent work [8], the DNA of 115 g preterm infants < 34 weeks with respiratory distress treated with nCPAP or with intubation-surfactant-extubation (INSURE) were analyzed. Infants were divided into 2 groups, one with apneas treated or not treated with caffeine and a group without apneas. It has been shown that some single nucleotide polymorphisms, three in particular, of the gene encoding for the A2A receptor are associated with the highest risk of developing apnea, probably due to the increased expression of adenosine receptors in presence of these polymorphisms. Polymorphisms of genes for A1 and A2A can also contribute to the diversity of response to caffeine. The study shows that in infants with GA less than 28 weeks with AOP treated with caffeine, good response to therapy is associated with certain genetic polymorphisms, in particular the A1 gene. Certain gene polymorphisms of A2A and A2B receptors are associated with lower incidence of apneas and of bronchopulmonary dysplasia (BPD), while other polymorphisms are associated with increased incidence of BPD. Many are the links between these receptors and inflammation that is the basis of BPD: for example A2A receptors are expressed on inflammatory cells and modulate an anti-inflammatory activity; A2B receptors play instead a pro inflammatory action. Higher affinity of the A2B anti-inflammatory caffeine receptors could explain its beneficial effect on BPD.

Duration of apnea episodes

AOP usually begins in the first 2 days of life, at the latest within 7 days of life: beyond the first week it is not common. The lower is the GA at birth, the longer is the duration of AOP, which generally ceases at term. A study of 226 preterm infants born at 24-28 weeks of GA [9] has shown that the time of resolution of episodes of apnea/bradycardia is longer in neonates with lower GA at birth. These episodes frequently persisted beyond 36 weeks post-menstrual age (PMA). Apneas persisting beyond 38 weeks are seen more frequently in newborn of 24-27 weeks compared with those of 28 weeks. Infants born at 24 weeks continue to have a high incidence of apneas after 40 weeks (22% of cases), with a significant difference compared to those born at 28 weeks of GA. Consequently, the 24 weeks newborns are discharged from the hospital with a higher PMA (35.6 ± 2.4 wks) compared to the 28 weeks ones (34.4 ± 2 wks). The achievement of food autonomy and thermoregulation in open cradle correlates closely with the resolution of AOP.

Effects of apnea

In preterm neonates, oxygen desaturation/bradycardia episodes can clearly cause alterations in cerebral haemodynamics which may compromise the subsequent neural development of the neonate, even though it is hard to demonstrate a direct correlation between the two phenomena, given all the conditions associated with a potentially negative effect on the neurological outcome of this category of infants. In fact, neither the frequency nor the severity of apneas that lead to an increase in the risk of neural damage have been established. In a trial conducted on 175 neonates < 32 weeks of GA or weighing less than 1,250 g and monitored up to 3 years of age, A. Janvier [10] highlighted that the number of days of apnea, in addition to the male sex, has a significant association to the increased probability of an alteration in neural development.

Apnea and anemia

The pathogenesis of apnea is multifactorial and also anemia, resulting in the reduction of the ability to transport O_2, may have a role in its occurrence. The respiratory neuronal network is immature in neonates, especially if preterm, and characterized by a paradoxical response to hypoxia, as previously described. This phenomenon in preterm infants may be exacerbated by the presence of anemia (associated with a reduced release of O_2 in the CNS). The effect of anemia on the apnea is not yet clarified and studies showed conflicting results on the effect of red blood cells transfusion on the incidence of apneas. A very recent study [11] evaluated 67 very low birth weight (VLBW) infants (≤ 1,500 g) without or with minimal respiratory support (spontaneus breathing in room air or with O_2 in cot or nCPAP, but not intubated) and who have received one or more red blood cell transfusions (median 1, range of 1-6). These neonates were evaluated for the presence of apneas over a period of 6 days (3 days before and 3 days

after each transfusion of red blood cells). Every newborn had cardiac frequency (CF) and SpO_2 monitored and pneumography impedance was used for the measurement of central apneas that begin and end within about 50 seconds, within 25 seconds from the start of bradycardia and desaturation (CF < 100 beats/minute, SpO_2 < 80%). The authors have shown that transfusion of packed cells are followed by a statistically significant reduction in the number of apneas (lasting from 10 to 30 seconds, always associated to desaturation and/or bradycardia). The likelihood of having sleep apnea with these features in the next 12 hours after a transfusion is related to the hematocrit, both in neonates with GA > 32 weeks and < 32 weeks.

Apnea and GER

Both the gastro-esophageal reflux (GER) and apnea are common in preterm infants, but their relationship is controversial. The two phenomena do not appear temporally related, although there is evidence that physiological stimulation of laryngeal afferents induces central apnea and laryngeal adduction. Apnea and GER although co-existing in the same infant are often events separated in time [12]. When it is shown a GER, apnea (obstructive or mixed) is followed rather than preceded by reflux. The GER has an incidence of approximately 7% in the first year of life. The high incidence in the neonate is due in part to the constantly supine position which favors the incontinence of the gastro-esophageal junction, and in part to a relatively high intake of liquids, which is equivalent to 14 l/day of an adult. The main pathogenetic mechanism of GER is the transient relaxation of the esophageal sphincter, which is present in both symptomatic and asymptomatic GER, the latter being associated to a greater number of acid reflux. The GER can induce apnea, both central and obstructive, by activation of chemoreceptors laryngeal as already demonstrated in animals. The acid stimulation of laryngeal chemoreceptors induces a reflex that protects the airway from aspiration: rapid swallowing, apnea, laryngeal constriction, bradycardia and hypertension. Even the excessive secretions in the upper airway may induce central apnea. The non-acid reflux seem to be the main causes of apnea; regurgitations that appear immediately after a meal (when the stomach is still full of milk that easily flows back into the esophagus) could trigger apnea with a middle esophageal distension, causing central apnea. The acid reflux appears mostly in the post-prandial period when the stomach is partially empty: in this case the acidity that reaches the larynx triggers a laryngeal reflex, determining the apnea. There is little evidence that drug therapy of GER has positive effects on AOP and the use of anti-reflux drugs is not justified for the treatment of apnea crisis, although a subgroup of preterm infants with eating disorders seems to beneficiate from the therapy.

In one study [13] conducted on 119 preterm infants 28 weeks GA undergoing cardiorespiratory monitoring with plethysmography and pH-metry, only 1% of cases of GER episodes were associated with apnea and there is no difference in incidence of apnea before, during or after a GER. Moreover, the presence of a GER during apnea does not cause a prolongation of apnea or his worsening [13]. In 28 preterm about 30 weeks GA suffering from recurrent postprandial apneas, designed with a multichannel intraluminal impedance with pH and with polysomnography, the Gaviscon® administered after each meal (or 25 ml/kg) was effective in reducing the number of acid GER without affecting the number of non-acid GER, compared to non-treated. The frequency of GER-related apnea is not different between treated and untreated [14]. Also thickened formulas do not seem to reduce the acid and non-acid GER in preterm infants than those fed with not-thickened formulas [15].

Apnea and SIDS

Sudden infant death syndrome (SIDS) is defined as the death of an infant < 1 year of age who apparently occurs during sleep and remains unexplained, despite complete autopsy, examination of the death scene and review of the clinical history. SIDS is responsible for 11% of all neonatal deaths and 75% of SIDS occur between 2 and 4 months of age. Epidemiological studies have shown that there is a causal relationship between SIDS and AOP. Apnea usually resolves at PMA that precedes the onset of SIDS: apnea of longer duration, which affects most premature infants, generally extends up to a maximum of 43 weeks PMA. The average onset of SIDS is around 46 weeks PMA for infants born at 24-28 weeks and at 52 weeks PMA for those born at term. Apnea is not predictive of SIDS and previous apnea doesn't justify the use of home cardiomonitor [16].

Treatment

The idiopathic apnea does not seem to directly cause significant intracranial abnormalities or severe long term neurological disability. However, it may be associated with less favorable neurological and/or cognitive outcome or sleep disorders in older children. For this reason the AAP in 1985 had issued guidelines for the treatment of apnea episodes: a) > 20 sec; b) associated with bradycardia or cyanosis or pallor; c) with a frequency of > 1 per hour in a 12 hour period. The treatment can be pharmacological and non-pharmacological and acts with different mechanisms: 1) reduction of the work of breathing, 2) increase of the respiratory drive, 3) increase of the contractility of the diaphragm.

1. The reduction of the work of breathing is obtained by:
   a. maintaining the prone position: in this position, the chest wall is stable and the thoraco-abdominal asynchrony is reduced. Studies have shown that the prone position reduces the frequency of apneas in preterm infants; the prone position with the head raised to 15° is associated with a reduction of almost 50% of desaturation in a study, but in newborns already treated with continuous positive airway pressure (CPAP) or caffeine this position offers no further positive effects;
   b. CPAP or nasal intermittent positive pressure ventilation (NIPPV): generally with a peak inspiratory pressure (PIP) of 15-20 cm H_2O, positive end-expiratory pressure (PEEP) of 5-6 cm H_2O the extent of desaturation can be reduced by up to 50%.

2. The increased respiratory drive is obtained with:
   a. the administration of oxygen: the low flow oxygen reduces the degree of hypoxia and apnea. However, considering the O_2 toxicity there is an ideal level of O_2 that may be recommended;
   b. the increase in inspired CO_2: the increase of the concentration of CO_2 in the inspired air of 0.8% for 2 hours is able to reduce the amount of apneas;
   c. the transfusion of red blood cells, which causes an increase in tissue oxygenation;
   d. the use of caffeine: methylxanthines increase the sensitivity of chemoreceptors and then the respiratory drive and can also increase the contractility of the diaphragm. Caffeine has a better therapeutic range and fewer side effects of theophylline and therefore it is the most widely used drug;
   e. the use of doxapram: this drug stimulates the peripheral chemoreceptors in low doses and the central ones in high doses. Its effect is dose-dependent.

3. The increase in contractility of the diaphragm:
   • AOP may be due by muscle fatigue of the diaphragm and drugs that increase the contractility could be beneficial, but this has not yet been demonstrated in the newborn.

Pharmacological treatment

The drugs of choice are caffeine and theophylline [17]. Both increase the sensitivity of chemoreceptors to CO_2, increase the contractility of the respiratory muscles and increase the response to catecholamines. Xanthines are endogenous adenosine antagonists (which is a central respiratory depressant, but also a respiratory stimulant peripheral). The main effect of xanthines is therefore to increase the output of the respiratory center, which determines an increase in ventilation. Theophylline is generally less tolerated, causing tachycardia, and gastrointestinal dysfunction and the relationship between therapeutic/toxic dose is lower.

The efficacy of caffeine on AOP was discovered for the first time in 1977 by J.V. Aranda [18] who observed a reduction of apnea episodes on 18 neonates at a GA < 28 weeks treated with an initial bolus dose of 20 mg/kg followed by a maintenance dose of 5 mg/kg. After more than thirty years, the same author defines the drug as the "silver bullet in neonatology" because it is one of the safest and most effective drugs and has the best cost/benefit ratio among all those used in neonatology. The trials that have been conducted on the highest number of preterm neonates are those conducted by B. Schmidt in 2006 and 2007 [19, 20] which are multicenter, randomized, placebo-controlled trials in which the author recruited nearly 1,000 neonates weighing between 500-1,250 g and divided them into a group treated with caffeine and a group treated with a placebo. The caffeine group was treated with standard doses (20 mg/kg/day via bolus followed by 5 mg/kg/day) from 28 to 35 weeks of gestation, with an average treatment duration of 37 days. Schmidt demonstrated that caffeine treatment

reduces the duration of CPAP and duration of oxygen administration. In the caffeine group, the use of post-natal steroids and the need for red blood cell transfusions were also reduced. The recommended caffeine dose in treating AOP is 20 mg/kg by an initial bolus followed by a maintenance dose of 5 mg/kg/day, which can be increased if the treatment is unsuccessful. Some trials have demonstrated that higher doses lead to a better effect on apneas compared to lower doses. In a trial [21] comparing two groups of preterm neonates with a GA < 30 weeks, in which one group was treated with doses of 20 mg/kg/day and the other with doses of 5 mg/kg/day, the authors found that the group treated with the higher doses showed a significant reduction in the number of apnea episodes within a week from start of treatment, without presenting an increase in side effects. There is not enough data in scientific literature for this indication in the preterm neonate [22] in relation to the prophylaxis for apnea episodes.

Doxapram is a potent stimulator of breath: in adults it increases ventilation/minute by increasing the Rf. The mechanism of action is not well known: at low doses it seems to act peripherally at the level of the carotid glomus, whereas at high doses its action is mainly central. The number of stimulated centers increases with increasing dose. Its use in the newborn has been performed in limited and uncontrolled case series. The doses described are effective on apnea of 2.5 mg/kg/hour continuous infusion iv, although the trend is to give lower doses (max 1.5 mg/kg/hour). Rarely it was administered by mouth, in which case it should be given with tube in 1 hour (every 8 or 12 hours). Possible side effects during the infusion are: jaundice, convulsions, irritability, increased blood pressure, increased gastric residuals; three cases of atrioventricular block have also been reported. The long-term effects are not known but there are some data suspicion psychomotor retardation in VLBW in which it was used compared to those in which it had not been utilized. It is currently not recommended for the treatment of AOP [2, 23].

Non-pharmacological treatment

Posture: due to the hypotonia of muscles of the neck present in neonates, it is very important to avoid both the hyperextension and hyperflexion of the neck, that can trigger obstructive apnea.

The prone position in neonates with respiratory distress increases ventilation, reduces the incidence of gastric reflux and aspiration risk.

The elevated position of 15° reduces the hypoxemic events.

Body temperature maintained between 36.5 to 37°C (temperature values on the lower limits of the range seem to be more effective in reducing apneas more than higher values on the range).

Tactile stimulation: it reduces apneas, probably increasing external stimuli.

CPAP: it acts through several mechanisms in treating obstructive sleep apnea: stabilizes the rib cage and thus reduces neuronal inhibitory signal to the respiratory center; prevents the obstruction of the upper airway by splinting the pharynx (the CPAP is useful in the treatment of bronchial malacia); prevents hypoventilation improving functional residual capacity and the expansion of the alveoli, as demonstrated by the improvement in gas exchange [2].

Olfactory stimulation: introduction of a pleasant odor into the incubator reduced the incidence of apnea and bradicardia [24].

Conclusions

Apnea of prematurity is a developmental disorder, and then by definition self-limiting. However it can cause serious problems both during the hospital stay and probably long-term neurological or cognitive consequences, even if it has not yet been identified the lower limit beyond which the hypoxemia and or bradycardia increase the risk of impaired neurological development. The apnea can be defined idiopathic only after excluding a number of diseases of the preterm of which it may be an epiphenomenon. The etiological diagnosis is critical for an appropriate therapeutic treatment which may require the use of drugs, but can sometimes be also non-pharmacological.

Declaration of interest

The Authors declare that there are no conflicts of interest.

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