APNEA IN PRETERM NEWBORNS: DETERMINANTS, PATHOPHYSIOLOGY, EFFECTS ON CARDIOVASCULAR PARAMETERS AND TREATMENT

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Abstract

Apnea, especially in preterm newborns (AoP) is one of the common problems encountered at neonatal units. Numerous factors are likely to play a role in the etiology of apnea. Recent data sugest a role for genetic predisposition of AoP. It seems, that physiological rather than pathological immaturity of the respiratory, or cardiorespiratory control, play a major part in the pathophysiology of AoP. Immaturity of the brainstem, cerebral cortex, receptors of the lungs and the airways as well as of the chemoreceptors contribute to the development of apnea in preterm newborns. Several neurotransmitters (GABA, adenosin, endorphins) and their maturational changes are including in pathogenesis of apnea, too. The instability of the upper airway in preterm infants, asynchrony of musculature of the upper airway and diaphragm, pathological changes in the upper airway and malformations of the central nervous system might also contribute to the occurrence and severity of AoP.

In newborns, apnea occurs more frequently in active sleep than in quiet sleep and the frequency of apnea in active sleep is higher in the warm conditions. Durations of apnea correlate with the body heat loss.

Cardiovascular changes during apnea - bradycardia, peripheral vasoconstriction and various changes in peripheral blood flow and pressure occur together with changes in ECG. The standard clinical management of apnea includes non-pharmacological treatment (eliciting arousal reactions and reflex breathing by mechanical skin, or mucosa stimulations), pharmacological treatment (methylxanthines are preferred) and application of continuous positive airway pressure (CPAP) or in severe apnea - mechanical ventilation.

Keywods: apnea, apnea of prematurity, newborn, immaturity, chemoreflexes, heart rate, bradycardia, blood pressure, oxygen desaturation, methylxanthines, treatment of apnea

INTRODUCTION

In the early postnatal period start and stabilization of (air) breathing is a major developmental milestone for premature infants. These infants may have problems with temperature instability, hypoglycaemia, feeding, hyperbilirubinemia, gastrointestinal complications (1) as well as with cardiorespiratory control. One of the common respiratory disorder in the early neonatal period is apnea - spontaneous and transient arrest of the exchange of the air between atmosphere and alveolar compartments and/or the respiratory movements.

The *definition* of apnea of prematurity (AoP) has been changing in past years due to new views on its physiopathology. Apnea was defined on the basis of the presence of cessation in breathing > 20 seconds or shorter respiratory pauses accompanied by bradycardias (< 100 beats per minutes) and oxygen desaturations (<90%) (2).

Apnea duration varying from 2 (3) to > 15 seconds (4, 5) have been established to make more precise definition of apnea in newborns. At present, the most widely used definition of *apnea of prematurity* (in infants born less than in 37th week of gestation) is a cessation of breathing accompanied by heart rate and oxygen saturation changes, while there is a pause of breathing for more than 15-20 s accompanied by oxygen desaturation (SpO_2d“80% for >10s) and/or bradycardia (heart rate<2/3 of baseline for ≥4 s) (6).

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According to the mentioned definitions, the most apnea alarm devices in neonatal units are set up to detect apneas lasting for greater than 20 second (7), which are accompanied with bradycardia (< 80 beats/per minutes) and oxygen desaturation (80 %).

Apnea is usually divided into three main types: *central, obstructive* and *mixed*. In central apnea, there is a cessation of both respiratory effort and nasal airflow. With obstructive apnea, nasal airflow ceases as the infant makes increasing respiratory efforts in attempts to overcome partial or total upper airway obstruction. The third type of apnea is described as mixed and has both central and obstructive components (5). Central apnea in newborns accounts for approximately 10 % to 25 % of all cases of apnea, with obstructive apnea accounting for 10 % to 25 % and mixed for 50 % to 75 % (8).

DETERMINANTS OF APNEA

Heritability of apnea in preterm infants

Heritability determines many vital characteristics through determination of development, production and functions all body structures, receptors, neurotransmitters and molecules involved in regulation of body functions including cardiovascular and respiratory system (9). There is evidence that some infants may have a genetic prediposition towards experiencing apnea of prematurity (5). Tamim et al. (10) first reported a higher proportion of first-degree mating for infants with AoP compared with those without it. A genetic basis of apnea of prematurity has been demonstrated also in twin study (11), which suggesting apnea as a heritable disorders. The authors found greater concordance for apnea among monozygotic twins (87%) than same-gender dizygotic twins (62%). A gender-dependent model revealed that genetic factors accounted for 99% of the variance in male twins and 78% of the variance in female twins.

Predispositions and pathophysiology of apnea

Mechanism leading to obstructions of airways include several processes, such as the instability of the upper airway in preterm infants, asynchrony of the musculature of the upper airway and diaphragm activities, other pathological changes in the upper airway and also central nervous system disorders (5). The two most likely sites of loss of upper airway patency based on anatomical and physiological basis are the larynx and pharynx.

Pharynx

Patency of the airways depends on a perfect respiratory, pharyngeal and laryngeal muscles coordination. These muscle groups contract in synchrony during inspiration. The generation of negative airway pressure by the respiratory muscles, in normal situations, should be counteracted by contraction of upper airway muscles (7), mainly by genioglossus, sternohyoid and posterior cricoarytenoid. Reduced tone in these muscles, as one might expect in preterm infants may predispose to upper airway obstruction (12) and subsequently to apnea (mixed or obstructive).

Also spontaneous neck flection can lead to obstruction in healthy preterm newborns, as well as in situation where there are **anatomical abnormalities of the upper airway**, such can be seen in the Piere Robin and Down syndromes (5).

Nasal obstruction

Nasal area is the next typical location predisponing to the obstruction of the upper airway in preterm infants. Nasal edema or the presence of a nasogastric feeding tube causes nasal obstruction, that increases nasal airway resistance and can leads to apneic events in newborns (23).

Larynx

The newborn's larynx has a characteristic laryngeal vestibule, which is small in diameter, particulary in relation to the lumen of the trachea, making it anatomically a likely sites for obstruction (12). The obstructing structures seem to be disproportionaly large arytenoid masses and aryepiglotic folds.

Also the stimulation of *laryngeal chemoreflex* with bolus of fluid instilled into the oropharynx leads to the swallowing, airway obstruction (12) and apnea, bradycardia and hypotension may ocured in preterm infants (13). This reflex-induced apnea is mediated through superior laryngeal nerve afferents (14, 15). The role of this reflex is a protection of the airway and seems that apnea can represent an exaggeration of this protective reflex in preterm infants (12). It is interesting, that the severity of apnea depends of the degree of individual maturation. This finding has been examined by direct electrical stimulation of superior laryngeal nerve in monkeys, which produces glotic closure followed by prolonged apnea. Preterm and newborn monkeys having more accentuated apnea after stimulation that older monkeys (16).

Malformation of central nervous system such as meningomyelocele, Arnold-Chiari deformity, hydrocephalus, which result in paralysis of the abductor cord secundary to raised intracranial pressure, comonly increases incidence of the apnea and upper airway obstruction (5).

Muscle tone, sleep state and ambient temperature

The dominant inspiratory muscle in newborns is the diaphragm. Its position is higher than in adults, but this advantage is ofset by the low tone of intercostal muscles and soft and compliant chest. For the higher chest wall compliance are responsible soft ribs due to low mineralisation of bones and a low intercostal muscle tone.

Important changes in the respiration of the newborns occurs during *sleeping*. There are basically two types of sleep, quite, non-rapid eye movement (NREM) and active rapid eye movement (REM) sleep. While adults have approximately 80% of their sleep in NREM, premature newborn infants with less than 32 weeks have approximately 80% of their sleep in REM - active stage. The active stage is characterized by irregular breathing with intermittent respiratory pauses and apneas. During this active sleep, there is a central inhibition of all postural muscles inducing a generalized muscle hypotonia. The inspiratory intercostal muscles tone, which help to keep the thoracic cavity form, is affected, too. Hypotonia of these muscles leads to distortion of the rib cage during inspiration causing so called paradoxical inspiratory motion of the abdomen (abdominal paradoxical movements). This distortion results in an increase in the diaphragmatic work, which have to contract more to maintain adequate ventilation. Generalized muscle hypotonia also affects the upper airway muscles, and it is responsible for a significant increase in airway resistance and respiratory work. Moreover, the respiratory muscles (especially the diaphragm) of these babies are not well-developed, they have poor differentiation and low enzymatic capacity, what put the premature newborn infant at risk for muscular fatigue (7).

The influence of thermal drive on central sleep apnea was studied in newborns. Bader et al. (17) reported that the rate of apneic events in active sleep increased with warmer ambient air temperature in full-term neonates but not in preterm neonates. Likewise, Franco et al. (18) found that the apnea frequency significantly increased with a warmer ambient temperature during active sleep in neonates born between 37 to 41 weeks of gestation. In contrast, apnea episodes were less frequent and shorter in cold enviroment with higher metabolic rate and oxygen consumption even in premature newborns (19).

Immaturity

There is a strong negative reciprocal relationship between gestational age, birth weight and frequency of apnea. In 7% percent of neonates born at 34 to 35 weeks gestation, in 15% at 32 to 33 weeks, in 54% at 30 to 31 weeks (20) and nearly in all infants born at <

29 weeks gestation or < 1,000 g occur apnea of prematurity (21). The severity of apnea is quite variable among infants of similar age, which suggests that a variety of other factors may contribute to infant's susceptibility to apnoeic episodes (11). Apnea of prematurity (AoP) usually ocurs during the second and third rather than the first week of life (22).

Immaturity in the control of respiratory activity plays an important part in the pathophysiology of apnea in preterm newborns (12). In most cases, AoP likely reflects as a "physiological" rather than a "pathological" immature state of respiratory control (23). Signals for the control of breathing which maintain rhytmic ventilation originate in the brainstem (respiratory centre, brainstem generator of breathing), in the area of the medulla oblongata.

Brainstem generator

Evidence of brainstem immaturity comes from measures of neuronal function in preterm infants with apnea. Auditory evoked responses have been used to measure brainstem conduction times, which were significantly higher in babies with apnea compared with controls matched for gestational age (24). In preterm infants, post mortem histological examination was performed. The examination demonstrated a fewer synaptic connection, a reduce number of dendritic arborisation and a reduction in myelinisation (25).

Input into the respiratory center arises from three primary sources: chemoreceptors (*chemical regulation*), receptors of the lung and airways, and input from the higher CNS levels (*neural regulation*). Delay maturation of any of these areas could potentially result in apnea (5, 12).

Chemical regulation of breathing

To the chemical regulation of breathing by PaO_2, $PaCO_2$ and pH of blood are involved peripheral and central chemoreceptors also in newborns, however with some peculiarities. *Peripheral chemoreceptors* located in the carotid bodies are primarily responsible for the ventilatory response to hypoxia. Newborns also respond to changes in $PaCO_2$ and pH. The response to hypercapnia is hyperventilation and term newborns have ventilatory response to hypercapnia more pronounced than to hypoxia. Preterm newborns respond less to hypercapnia than term newborns what is likely centrally mediated. A decrease in arterial pH stimnulates ventilation in newborns independently of $PaCO_2$ and this reaction is expected to be centrally mediated (26).

Term newborns during the first week of life, and preterm newborns for the first 2-3 weeks of life typically show a biphasic reaction to hypoxia in that they have an initial rapid increase in ventilation followed by an inhibition of breathing (26, 27). It has been suggested that hypoxia affects ventilation in two different ways: a stimulatory effect through peripheral chemoreceptors and a direct depressive effect of hypoxia to the brainstem generator of breathing.

Several neurotransmitters have been implicated in the development of the central hypoxic respiratory depression. These include -aminobutyric acid (GABA), adenosine and endorphins (28). GABA is the major inhibitory neurotransmitter in the CNS (23) and GABAergic neurons were activated during hypercapnia, in piglets (29). Adenosine is a product of adenosine triphosphate and is formed as a consequence of metabolic and neural activity in the brain, especially during hypoxia (23). When the receptors for these neurotransmitters were blocked in animal models using bicuculline, methylxanthines or naloxone, respectively, the hypoxic respiratory depressive response was reduced (30) as well as respiratory rate in response to hypercapnia was increased (31). Experimental evidence suggests that adenosine and the inhibitory neurotransmitter GABA might interact with each other to cause apnea (30), because the binding of adenosine to its receptor may be involved with the release of GABA and thus inhibit respiration leading to apnea (32). Hypoxic respiratory depression may play a role in apnea of prematurity.

A key integrative function for *central CO_2 chemosensitivity* and modulation of afferent inputs from peripheral chemoreceptors and laryngeal afferents play the ventral surface of

the medulla and adjacent areas. Maturational change in medullary neurotransmitter function appears to contribute to the apnea of prematurity (28). Also the recent findings provides a detailed information about the postnatal changes in the incidence of hypoxemic events associated with apnea and an anecdotal evidence for a correlation with carotid chemoreceptor maturation. It also provides a hypothesis that sensitization of the carotid chemoreceptors could represent an important protective mechanism to defend against severe hypoxemia (33).

Neural regulation of breathing

Also neural regulation of breathing in newborns, especially in the preterm ones, has many peculiarities that are unique in their control of ventilation. The specific responses of the ventilation to different stimuli (distension of the lungs, changes in intrapulmonary pressure, etc.) may reflect and/or to be under the influence of the maturation process of the ventilatory control (34).

The Hering-Breuer inflation reflex (HBR), mediated by vagal stretch receptors in smooth muscles of the airways, appears stronger in newborns than in adults (35, 36). The HBR, as a simple control negative feedback system, may be used as a temporary regulator of breathing mainly in premature newborns.

Preterm infants also show special responses to mechanical or chemical stimulation of **irritant receptors in the bronchial mucosa,** which often result in reduced respiratory efforts and in apnea rather than the facilitatory response seen in mature infants (37). Mechanical stimulation of the oropharyngeal region evoked transient respiratory arrest in 25% of studied premature newborns (38) and this percentage was higher in premature newborns with respiratory distress syndrome (39).

Table 1. Factors exacerbating or causing apnea in newborns

Central nervous system	Intracranial haemorrhage Seizures Drugs *(sedatives, narcotics, postanaesthesia, prostaglandin E_2)*
Sepsis	Necrotizing enterocolities Meningitis Bronchiolitis
Metabolic abnormalities	Hypoglycaemia Hyponatraemia Hypocalcaemia Inborn errors of metabolism
Enviromental	Hyperthermia Hypothermia
Upper airway obstruction	Choanal atresia Micrognathia (Piere Robin sequence) Macroglossia Hypotonia of Down syndrome
Circulatory	Patent ductus arteriosus Heart failure Anaemia
Immunisation	

(Modified by Rennie)(5)

Apart from the reflexes described above, there are other sensory pathways (e.g. visual, acoustic, vestibular, tactile, thermal, pain, etc.) that could influence the pattern of breathing in newborns. For example, the breathing can be stimulated and apnea interrupted by mechanical stimulation of the skin (pain or tactile stimuli) or of the airway mucosa to evoke so called „reflex breathing." The described effect exceeds time of the stimulation and persists for several minutes. This is why Kattwinkel et al. (40) recommended that in premature newborns suffering from frequent apneic pauses, mechanical stimulation of the skin every 20 ÷ 30 minutes helped prevent the apneic pauses.

Another factors involved in apnea

There are many conditions that causing apnea, but most apnoeic episodes occur spontaneously in preterm babies who are otherwise healthy. It is due to a immaturity of their systems, mainly of the central nervous system. Therefore, it is necessary to exclude *secondary* causes of apnea before a diagnosis *apnea of prematurity* (AoP) is done (41).

There are many next conditions that cause or accentuate apnea (Table 1).

CHANGES OF CARDIOVASCULAR PARAMETERS

Timing of the cardiovascular changes in apnea

Usually, a gradual inbition of the respiratory movements for a few seconds before the onset of apnea occured or alternatively, breathing stopped abruptly without any prior change. Apnea may terminate spontaneously, but with increasing duration, stimulation and resuscitation is neccesary to restart breathing.

Storrs (42) by examination of cardiovascular changes during apnea in premature newborns found that apnea could be as short as five seconds in which cardiovascular changes occured. On the other side, Curzi-Dascalova et al. (43) described that in some cases the cardiac deceleration reactions preceed the respiratory arrest and therefore they are not at least at this initial stage a cosequence of the apnea. These results suggest close interconnections of functional integration of central structures that regulate breathing and circulation in newborns (44).

Clinically, after the onset of apnea the infant become bradycardic, cyanosed and hypotonic. Changes of cardiovascular parameters mainly relate to the heart rate, ECG, blood presure and blood flow even in immature infants with gestations as low as 27 weeks (42).

Exact determination of the timing - relationships between start of apnea and start/end of changes in cardiovascular parameters needs further study.

Heart rate

In adult experimental animals, stimulation of peripheral chemoreceptors by hypoxia elicits tachycardia which is reversed to bradycardia by peripheral vasoconstriction and hypertensive reaction. In newborns, inhalation of hypoxic mixture evokes tachycardia, spontaneus apneic pauses are accompanied usually by a deceleration of heart rate - apneic bradycardia.

As the definition of apnea, also definitions of bradycardia in the preterm infants are various. However, a fall in heart rate to less than 100 beats/min in preterm infant for over a 5 seconds is generally considered as a neonatal bradycardia (45). Alternatively, a fall in heart rate of more than 30% below baseline has been used as a criterion for bradycardia (46).

At present, there are different views about the mechanisms of the apneic bradycardia. One of the views is that bradycardia occurs before (43) or simultaneously with apnea without oxygen desaturation, possibly mediated by central structures, vagal nerve and not necessarily by hypoxemia (23).

However, in the majority of cases, there is apnea closely followed by a fall in oxygen saturation and almost all bradycardias begin after the onset of apnea and after the onset of desaturation (47, 48). Initially it was thought that this bradycardia accompanied by hypoxia is the direct result of cardiac depression. It is now clear that the bradycardia occurs too early in apnea to be due to this effect (49). Stop of the respiratory movements and of the cyclic distension of the lungs may also have a role in the development of the bradycardia, perhaps due to the lack of stimulation of a pulmonary inflation receptors (50) and loss of the respiratory sinus arrhytmia. It seems that mechanisms of the apneic bradycardia are complex, perhaps including baroreflexes in the cases when the hypertonic reaction during apnea occurs. These mechanisms should be studied in more details.

Bradycardia can influence both, hemodynamics as well as saturation of hemoglobin by oxygen (SaO_2). There is evidence, that apneic episodes in preterm babies not associated with bradycardia had a median 5% reduction in SaO_2, whereas those associated with bradycardia had a median reduction 9% (51). The relation between bradycardia and SaO_2 is mutual. The greather reduction in HR during apnoeic attacks had infants with poor baseline values of oxygenation, than those who were well oxygenated (51). Therefore is neccesary to keep infants with recurent apnoeic attacks well oxygenated.

ECG changes

Recently, analysis of electrocardiogram (ECG) for episodes apnea-bradycardia characterization was carried out on preterm infants. RR interval, R-wave amplitude and QRS duration were studied for periods at rest, before, during and after apnea-bradycardia episodes.

Results reveal modification in the amplitude of the R-wave and duration of the QRS complex, in meaning reduction of the R-wave amplitude and prolongation of the QRS complex. The first minor variations of the time series appeared after the onset of apnea, while the most significant changes were reflected during apnea-bradycardia episodes with their normalization after a short time of the heart rate returning to its rest value. Analysis of the first less significant changes in the first minutes of apnea, the authors try to detect a signal that is potentially useful for the early detection and characterization of these episodes (52).

Blood pressure

In adults, hypoxia usually causes peripheral vasoconstriction, redistribution - centralization of blood associated with hypertensive response, but in newborns were observed only variable changes in systemic blood pressure. Storrs (42) did not seen the consistent changes in mean blood pressure during apnea in preterm babies. Only a small rise (never more than 10 mmHg), or a small fall, or blood pressure remain unchanged. Sometimes, he also recorded a rebound rise in blood pressure associated with cardiac acceleration. In all infants he noted beat-to-beat variations (up to 33%) in pulse pressure (pulsus paradoxus) while breathing, which were eliminated during apnea.

Gootman (53), in experiments in newborn piglets found that during hypoxia is a rise of vascular resistance in the mesenteric circulation, but blood pressure in the aorta decreases. Older (bimonthly) piglets responded to hypoxia not only by the increase of the vascular resistance in the splanchnic area, but also by the rise of aortic pressure. It demonstrates the postnatal maturation of the cardiovascular regulation.

Recently, we study the changes in cardiovascular parameters during spontaneous apnea (Figs.1,2) in preterm newborns. Parameters are continously monitored by using device Portapres (FMS). The device enables registration of peripheral blood pressure non invasively so, it is possible to use this method also in newborns without indications for catheterization for invasive BP monitoring.

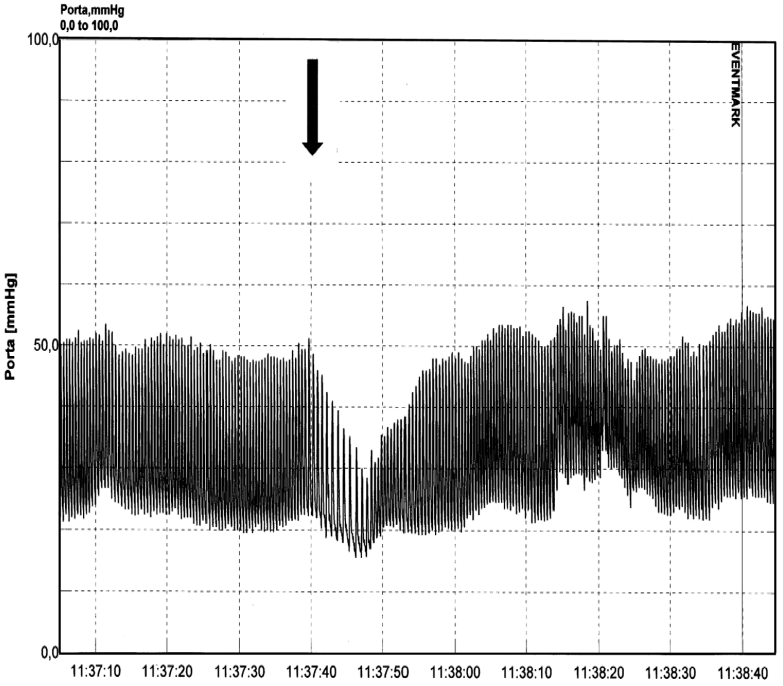

Fig. 1 Record of the blood pressure by means of Portapres. Blood pressure reaction during apnea (arrow) accompanied by a decrease $SatO_2$ to 89%.

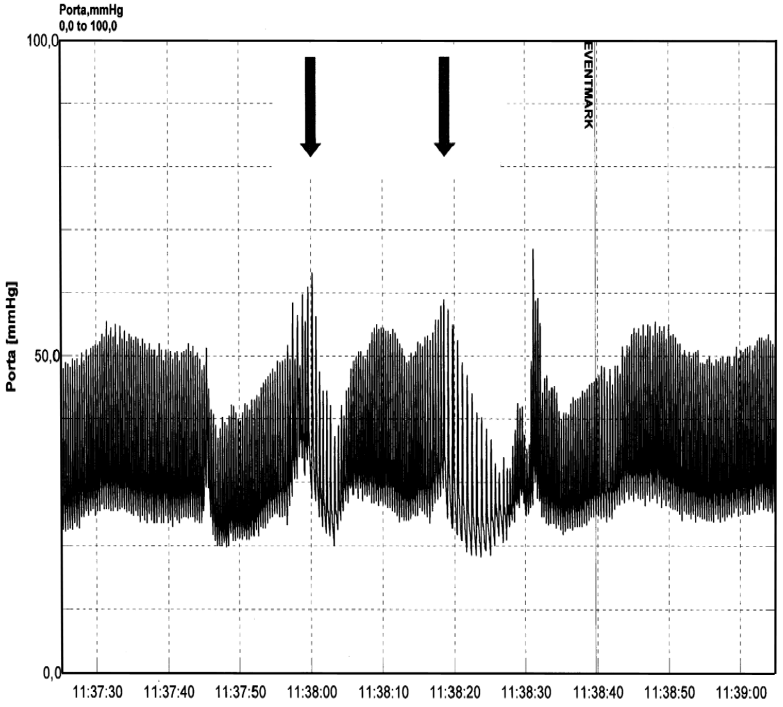

Fig. 2 Blood pressure recording in repetitive apneas accompanied by a decrease saturation ($SatO_2$ 88% and 78%) as well as by changes of blood pressure.

Blood flow

Changes in blood flow during apnea in premature newborns are influenced by the peripheral vasoconstriction and by a presence of transitional circulation in which the shunts may re-open.

In pulmonary circulation hypoxia can elicit vasoconstriction, but the effect may be modified by a blood flow through ductus arteriosus.

The effect of episodes of apnea with bradycardia on cerebral circulation was studied by measuring blood flow velocity in the anterior cerebral arteries (54). With episodes of apnea complicated by mild-to-moderate bradycardia, a decrease in diastolic flow velocity was noted with little or no change in systolic flow velocity. With episodes complicated by severe bradycardia (heart rate less than 80/min), the diastolic flow velocity as well as progressive decrease in systolic flow velocity also were observed. Accompanying the changes in cerebral blood flow velocity were similar changes in arterial blood pressure. These data clearly suggest potential deleterious hypoxic-ischemic effects from apnea on brain with severe bradycardia in the preterm infant. Therefore, apnea alarm limits should be set up to keep the heart rate above 80 beats/minute and to prevent oxygen desaturation (51).

TREATMENT OF APNOEA OF PREMATURITY

The management of apnoea of prematurity is influenced by the presence of any underlying conditions causing the apnoeic episodes and the mode of clinical interventions depends also on the type of apnoea (central, obstructive or mixed apnoea).

Apnoeic episodes with an underlying cause (generally referred to as secondary apnoea) should be eliminated by treating such a cause, including infection, patent ductus arteriosus, seizures, maternal or neonatal medication exposure and possibly gastro-oesophageal reflux.

Treatment of symptomatic idiopathic apnoea generally involves pharmacologic and non-pharmacologic approaches. Some management options have been demonstrated as beneficial, while other require further study. Therapeutic interventions with proven benefit are the use of continuous positive airway pressure (CPAP) and methylxanthines. Interventions requiring further study include body positioning, sensory stimulation, improving oxygen-carrying capacity and oxygen intake, control of hyperbilirubinaemia, nutritional supplementation (L-Carnitine, Creatine), Doxapram and anti-reflux medication (55).

CPAP

Apnoea of prematurity is frequently managed by the nasal CPAP. It has been found to decrease the incidence of obstructive and mixed apnoeic episodes, but its effect on central apnoea is less clear. The beneficial effects of nasal CPAP may be augmented by the use of the nasal intermittent positive pressure ventilation (NIPPV). It is a mean of respiratory support, when intermittent ventilator-derived inflations are superimposed on CPAP (55).

In the neonatal intensive care unit (NICU) reccurent apnea unresponsible to nasal CPAP or administration of methylxanthines is considered as a relative indication for mechanical ventilation, while prolonged apnea or sudden collapse with apnea and bradycardia, with failure to establish satisfactory ventilation after a short period of face mask ventilation is absolute indication to starting mechanical ventilation (56,57,58). Minimal ventilator settings should be used to allow for spontaneous breathing efforts and to minimize lung injury (55).

Methylxanthines

Methylxanthines (aminophylline, theophylline and caffeine) have been used for treatment of apnoea of prematurity for more than 30 years. Their clinical effects are equivalent, but caffeine is the preferred treatment because of its wider therapeutic index and longer half-

life that allows once-daily administration (59). Caffeine has appropriately been described as a "silver bullet" in neonatology (60). Methylxanthines acting both, peripherally and centrally, stimulate medullary respiratory centres, increase carbon dioxide sensitivity, induce bronchodilation and enhance diaphragmatic function. It leads to increased minute ventilation, improved respiratory pattern and reduced hypoxic ventilatory depression. Recent data indicate that initiation of caffeine treatment before a postnatal age of 3 days may have incremental beneficial effects on later outcomes (61). The recommended dosing for caffeine citrate is a loading dose of 20 mg/kg (10 mg/kg of caffeine base) followed by a daily maintenance dose of 5 mg/kg (59, 62). Treatment is typically discontinued by 33 to 34 weeks of postmenstrual age, following resolution of clinically apparent apnoea of prematurity. The CAP trial confirmed that caffeine is effective in reducing or eliminating of apnoea episodes in premature infants and in reducing the need for respiratory support. Moreover the treatment with caffeine results in reduced incidence of bronchopulmonary dysplasia and improved rates of survival without neurodevelopmental disability at 18 to 21 months (62, 63). Although the Cochrane review concludes that the available evidence does not supply the use of caffeine as prophylaxis to prevent apnoea, the CAP trial and other benefits of early caffeine therapy with minimal risk justify the use of early caffeine prophylaxis in premature infants (64). Infants with very low birth weight should routinely receive caffeine therapy and caffeine levels do not need to be obtained as a part of routine clinical management (59). Caffeine should be used in babies with apnoea and to facilitate weaning from mechanical ventilation (65). Caffeine should also be considered for babies at high risk of needing mechanical ventilation, such as those <1,250 g birth weight who are managing on non-invasive respiratory support (65).

Therapeutic interventions requiring further study

Body position can influence lung function. Probably the optimal body position for prevention of apnea in an infant with an accompanying lung disease is prone (55). The prone, head-up tilt position may be considered as a first-line intervention for infants with apnoea of prematurity (66). Nevertheless it should be avoided as the infant is being prepared for discharge. Several modes of *sensory stimulation* (somatic, olfactory or skin-to-skin contact) have been proposed for the prevention of apnoea of prematurity but there is a lack of data confirming their effectiveness. *Oxygen supplementation* with the aim to increase the baseline oxygen saturation as a strategy to prevent or treat clinical apnoea of prematurity has currently insufficient evidence. The results of clinical studies evaluating the impact of *red blood cell transfusions* on the incidence and frequency of apnoeic episodes in premature infants were conflicting. The presence of apnoea of prematurity on its own probably should not be the indication for blood transfusion but should be taken into account when forming guidelines for blood transfusion in premature babies. *Hyperbilirubinaemia* and transient bilirubin encephalopathy have been linked to an increased incidence of apnoea in premature infants but further research will be needed to demonstrate whether more strict control of neonatal jaundice can decrease the incidence of apnoea in such infants. *Gastro-oesophageal reflux* has been implicated in causing apnoea but treatment of reflux has been shown to have no effect on frequency of apnoea of prematurity in premature infants.

Doxapram is a respiratory stimulant used in some countries for the treatment of methylxanthine-resistant apnoea of prematurity. The use of doxapram is controversial due to the side effects. Short-term adverse effects include sleeplessness, jitteriness, seizures, feeding intolerance and life-threatening cardiac conduction disorders. Long-term adverse effects are related to the decrease in cerebral blood flow velocity and decrease in oxygen delivery, coupled with increased cerebral oxygen consumption in preterm infants receiving doxapram. Careful evaluation of risk and benefit must be used in prescribing this drug (55).

CONCLUSION

Apnea is one of the common problems encountered at neonatal units. Recent data sugest that in the etiology of apnea genetic predisposition can play a role. It seems, that physiological rather than pathological immaturity of the cardiorespiratory regulation and central integration of this control play a major part in the etiology and pathophysiology of apnea in premature newborns (AoP). Immaturity of the brainstem, receptors of the lungs and airways as well as peculiarities in chemoreflexes contribute to the development of apnea in preterm newborns. Several neurotransmiters (GABA, adenosin, endorphins) and their maturational changes are including in pathogenesis of apnea, too. The instability of the upper airway in preterm infants, asynchrony of musculature of the upper airway and diaphragm and other pathological changes might also contribute to the occurrence and severity of AoP.

Before, during and after apnea occur cardiovascular changes: bradycardia, peripheral vasoconstriction and various changes in peripheral blood flow/pressure together with changes in ECG. Typical finding is bradycardia, worsing perfusion of most organs and saturation of hemoglobin by oxygen.

The standard clinical management of apnea includes non-pharmacological treatment (eliciting arousal reactions and reflex breathing by mechanical skin, or mucosa stimulations), pharmacological treatment (methylxanthines are preferred) and application of CPAP or in severe apnea - mechanical ventilation.

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