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Apnoea of prematurity: causes, treatment, prevention, consequences and genetic basis

Dihalni premori zaradi nedonošenosti: vzroki, zdravljenje in preprečevanje, posledice ter genetska osnova

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Abstract

Apnoea (or apnoeic attacks, pauses) of prematurity is one of the most common diagnoses in neonatal intensive care units. Apnoeic attacks are transient in nature and are caused by a disruption in the adaptation of the respiratory centre and respiratory system to extrauterine life and immaturity of the receptors that detect partial oxygen and carbon dioxide pressure. They significantly prolong the duration of hospitalisation and have potentially adverse long-term consequences.

In our review article we provide a definition of apnoeic attacks of prematurity. We present the classification, epidemiology, pathophysiological background and cardiorespiratory monitoring of premature infants. We describe how to diagnose apnoea of prematurity, secondary causes of apnoea, and differential diagnostic options, as well as some conditions that are associated with apnoea of prematurity. A large part of the article is dedicated to presenting possible therapeutic interventions, including those that have not yet been implemented in general clinical practice as further research is needed to confirm their efficacy. The final part of the article provides an overview of the research on the genetic basis of apnoea of prematurity, and the presentation of their results.

Izvleček

Dihalni premori (ali apnoične atake, pavze, apneje) zaradi nedonošenosti so ena najpogosteje postavljenih diagnoz v neonatalnih intenzivnih enotah. Dihalni premori so prehodne narave in nastanejo zaradi motnje v prilagoditvi dihalnega centra in dihal na zunajmaternično življenje ter nezrelosti receptorjev, ki zaznavajo delne tlake kisika in ogljikovega dioksida. Pomembno podaljšujejo trajanje hospitalizacije ter imajo lahko škodljive dolgoročne posledice.

V preglednem prispevku opredeljujemo dihalne premore zaradi nedonošenosti. Predstavljamo klasifikacijo, epidemiologijo, patofiziološko ozadje in nadzorovanje srčno-dihalnih funkcij nedonošenčkov. Opisujemo, kako postaviti diagnozo dihalnih premorov zaradi nedonošenosti, sekundarne vzroke apneje in diferencialnodiagnostične možnosti ter nekatera stanja, ki so povezana z dihalnimi premori zaradi nedonošenosti. Velik del prispevka je namenjen predstavitvi možnih terapevtskih ukrepov, med njimi tudi takih, ki še niso prodrli v splošno klinično prakso, saj so za potrditev njihove učinkovitosti potrebne nadaljnje raziskave. Sklepni del članka ponuja pregled raziskav, v katerih so proučevali genetsko podlago dihalnih premorov zaradi nedonošenosti in predstavitev njihovih rezultatov.

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1 Introduction

Apnoea or apnoeic attack (pause) of prematurity is a condition in which a neonate, who was born before completing 37 weeks of gestation, completely stops breathing for 20 seconds or longer (1-5). This is often accompanied by haemoglobin desaturation, which is defined as a decrease in the saturation of arterial blood in oxygen (SpO_2) to 80% or less for at least four seconds, and bradycardia, which is defined as a fall in heart rate under 100 beats per minute for at least four seconds (1-3).

2 Classification

Traditionally, apnoea is divided into three types: central, obstructive and mixed (1-7). This division is based on whether the absent movement or flow of air through the upper respiratory tract is accompanied by respiratory efforts or not (7). With the central type, both the air movement and the respiratory efforts are absent. Absence of air movement in spite of respiratory efforts is characteristic for obstructive apnoea (2-7). The obstruction is generally a combination of a passive collapse of the pharynx and either a passive or an active tightening of the throat (3). With the mixed type, a short obstructive apnoea episode is followed by central apnoea or vice-versa; with the onset of the central phase of apnoea followed by an obstructive apnoea phase (2-7). Mixed type is dominant, representing 50–75% of all respiratory pauses resulting from prematurity. The central and the obstructive type each represent 10–25% of all the attacks (1,3) (Figure 1).

3 Epidemiology

The incidence of apnoea of prematurity is inversely proportional with gestational age and birth weight (1-3,5). Literature lists the onset of apnoea of prematurity with 7% of neonates who were born after 34 or 35 weeks of gestation, with 15% of those born after 32 or 33 weeks of gestation, with more than 50% of those born after 30 or 31 weeks of gestation and with nearly all born before 29th week. Apnoea of prematurity is suffered by more than a half of neonates with a very low birth weight (less than 1500 g), and 90% of those born with extremely low birth weight (below 1000 g) (1,3).

4 Pathophysiology

Numerous studies into the development of respiratory control of animals and people (preterm infants) have made it easier to understand apnoea of prematurity (1,2,4). As we understand this today, it is basically a physiological and anatomical impairment of the respiratory system (1-3,6,7). Anatomically, the impairment is manifested as a smaller number of synaptic links with less branching and axon myelination (1,3,4,8). Physiologically, the impairment is manifested as underdeveloped respiratory control and underdeveloped respiratory function of preterm infants (9).

4.1 Central chemoreceptors and weakened respiratory response to hypercapnia

With the increase in partial carbon dioxide pressure in the blood, adults, chil-

dren and neonates begin breathing faster and deeper (*hypercapnic respiratory response*), while preterm infants respond with a longer exhale, which results in lower minute ventilation (1,3,4,6). *Hypercapnic ventilatory response* is primarily signalled by the central chemoreceptors for CO_2. The incline of the curve on the figure displaying the measurements of the minute ventilation in relation to partial carbon dioxide pressure ($PaCO_2$), shifts to the right in neonates with apnoea, which means that at the same level of $PaCO_2$ the minute ventilation of neonates with apnoea is lower, compared to the ventilation of their peers without apnoea. They exhibit no differences in pulmonary mechanics, which points to the fact that the observed derogations are of central origin (4).

Also, with preterm infants, the threshold value of CO_2 for apnoea was close to the base value of the partial carbon dioxide ($PaCO_2$) pressure, unlike with adults, where the threshold value is significantly below the base value. Therefore, even a mild hyperventilation can lead to a fall in $PaCO_2$ and apnoea (1,4).

Additionally, in preterm infants, hypoxia with lower metabolism, and therefore lower formation of carbon dioxide, brings the treshold and base value even closer together, and leads to apnoea. (1,4).

4.2 Peripheral chemoreceptors and weakened respiratory response to hypoxia

Before birth, the peripheral chemoreceptors, whose main representative is the carotid body, only activate with very low oxygen values. Immediately after the birth, the activity decreases (physiological denervation) because of the sudden increase of partial oxygen pressure (PaO_2) from values below 30 mm Hg (4 kPa) to 50–70 mm Hg (6.7–9.4 kPa) and more. After birth, the peripheral chemoreceptors must be reset to higher partial oxygen pressures. From that point onward, chemoreceptors activate with values of PaO_2 50–70 mm Hg (6.7–9.4 kPa). Neonates may also stop breathing because the oxygen in their exhaled air increases significantly, as this causes a physiological denervation of the peripheral chemoreceptors (1,4,9,10).

With hypoxia, ventilation is increased (faster and deeper breathing) in adults. The NMDA (N-methyl-D-aspartate) glutamate receptors in the tractus solitarii nucleus (4) are key to this process. Unlike adults, preterm infants exhibit a two-phase breathing response. First, the ventilation increases for approximately 1–2 minutes, as the frequency and tidal volume increase, which is followed by a persistent decrease in ventilation (*hypoxic ventilation depression).* The two-phase ventilatory response persists for up to 4–6 weeks (1,3,4).

4.3 Afferent signals from the respiratory tract and an emphasized inhibition response

Afferent sensory signals from the upper respiratory tract can alter the motorics of ventilation (4). Chemoreceptors in the larynx, which have nerves from the superior laryngeal nerve, are located in the mucosa of the interarytenoid space at the entrance to the larynx. The stimulation of these receptors triggers the so-called *laryngeal chemoreflex*. This is essentially a protective reflex, protecting the respiratory tract from aspiration. With adults, its activation triggers a cough, while with preterm infants, an excessive response may lead to apnoea, bradycardia and even a cardiovascular collapse (1,4,11-13).

Afferent sensory signals originating from the upper and lower respiratory tract (pulmonary and laryngeal receptors) are contained in the nucleus tractus solitarii neurons and have an inhibiting effect on the motor neurons of the phrenic nerve. Some laryngeal fibres form monosynaptic connections with vagus fibres for the heart muscle, which can explain the simultaneous onset of apnoea and bradycardia during the simulation of afferent nerve endings in the larynx. Numerous

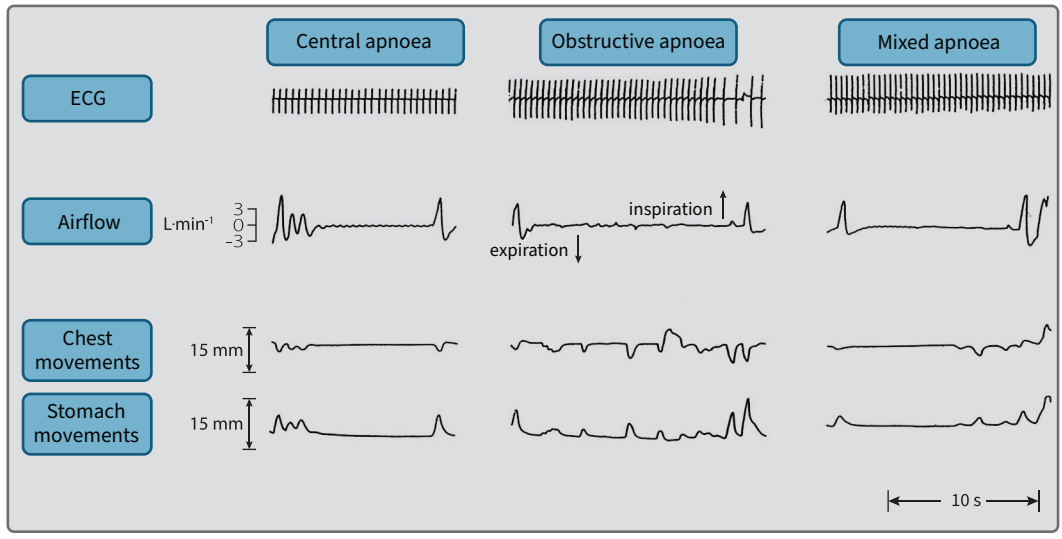

Figure 1: Central, obstructive and mixed apnoea (adapted from Ruben E. Alvarado) (15).

researchers established that we can trigger apnoea in tracheostomized animals by raising the negative pressure, the air flow into the isolated upper respiratory tract or liquid into the larynx, proving that afferent information inflow from the larynx to the brainstem significantly contributes to ventilation inhibition. However its role in the spontaneous onset of apnoea of prematurity has not yet been explained (4,11-13).

The primary source of afferent signals from the lower respiratory tract is the tenth cranial nerve *(n. vagus)*. Its *non-myelinated* C-fibres represent more than 90% of all respiratory afferent fibres from the lungs, and are part of the bronchoconstriction and bradycardia response related to apnoea or quick and shallow breathing (4).

There are two types of *myelinated* afferent fibres of the vagus nerve: slow and fast. The former are located in smooth muscles and evoke the Hering-Breuer inflation reflex (14). The second group of fibres is branched along the tracheobronchial epithelium and triggers coughing, reflexive bronchoconstriction and fast and shallow breathing. In studies, only a few preterm infants consistently exhibited the same response as adults. Most preterm infants had slowed their breathing, or an onset of apnoea occurred (4).

With animal neonates, including human, apnoea can be triggered by irritants, perfumes or water covering the face or nose. This reflex onset of apnoea is signalled by the trigeminal nerve *(n. trigeminus)* and is characteristically connected with bradycardia and laryngeal closure. Further research is needed to explain whether thermoreceptors for cold or mechanoreceptors are part of the reflex (4).

4.4 Neurotransmitters and apnoea

One of the characteristics of the respiratory system in preterm infants is also an increased sensitivity to inhibitory neurotransmitters, among which the most thoroughly researched are gamma aminobutyric acid (GABA) and adenosine. GABA is the main inhibitory neurotransmitter in the central nervous system. In experiments on pigs, GABAergic neurons were activated during hypercapnia. The inhibition of the $GABA_A$ receptors during hypercapnia blocked ventilation depression and increased breathing frequency (1).

Adenosine is a product of ATP and

forms as the results of the brain's metabolic and nervous activity. Its production is especially pronounced during hypoxia. Recently, it was reported that during breathing regulation, adenosine and GABA are mutually active. The discovery that adenosine receptors are expressed in neurons containing GABA has increased the probability that there is a connection between the two. Binding adenosine to its receptor could contribute to the release of GABA, and consequently to an inhibition in breathing that leads to apnoea (1).

4.5 Compliant chest wall

Because of lower mineralisation in neonates and especially in preterm infants, the chest wall is soft and highly compliant (7). This results in increased displacement of the diaphragm during inhalation, and consequently, and increased work of breathing, contributing to the development of diaphragmatic fatigue and onset of apnoea (3).

4.6 Feeding

Apnoea of prematurity is more frequent during feeding and immediately following, because of an immature coordination of breathing, suckling and swallowing, an irritation of the laryngeal adductor reflex, diaphragmatic fatigue and tympanites. The latter reduces the lung volume and increases work of breathing (3).

4.7 Sleeping

Sleeping phases have a major impact on respiration. During the active sleep phase, breathing pattern is typically irregular, while during calm sleep, it may be regular or irregular. The muscles of the larynx lose their phase and tonic activity, which makes the upper respiratory tract exceptionally vulnerable for collapsing, especially with preterm infants, and during inhalation, when the forces of negative pressure affect the respiratory tract. The overall gain of the respiratory system is decreased during sleep, which is manifested in a lower incline of the curve of the breathing response to CO_2. Preterm infants spend a large part of their sleep time in REM (rapid eye movement) sleep phase, during which apnoea is also the most frequent, due to the activation of GABAergic and deactivation of serotonergic neurons. During this phase, the breathing frequency declines, and with it ventilation, with more paradox breathing that carries a less stable base value of SpO_2. Waking from the REM sleep phase is most likely a precursor to apnoea, as in preterm infants coincides with haemoglobin oxygen desaturation, and the motor activity of closing the thorax. This means that waking from sleep in preterm infants rather causes apnoea than terminates it. (1,3,4).

5 Control of vital functions

All neonates, who are born before the completed 34th week of gestation, must be monitored for at least the first week of their life, or at least for seven days after the onset of the last apnoeic attack. In the neonatal intensive care unit, most neonates have constantly monitored heart rate and breathing frequency, as well as oxygen saturation non-invasively through their skin using a pulse oximeter (2).

We also use other devices for monitoring apnoea, such as breathing sensors, for example a ripple type mattress, mattress with sensory pad, and a pressure-sensitive capsule. These monitors interpret chest or abdominal movements as respiration. (2,4,5).

In order to monitor apnoea, we can also use monitors that detect changes in impedance of the chest during respiration. With respiratory inductive plethysmography, abdominal and thoracic movements during respiration are detected by abdominal thoracic bands or the Graseby capsule. All these devices are unreliable due to interference that occurs with body movements and heart activity; they also cannot

detect the obstructive apnoea type (2,4,5).

Currently, the use of the pulse oximeter in detecting apnoea of prematurity with accompanying bradycardias and desaturations it the most reliable method. (2,4,5).

6 Diagnosis and aetiology

Diagnosis of apnoea of prematurity is always exclusionary, and may only be set once we have excluded all other possible secondary causes of apnoea (3,5).

6.1 Secondary causes

Frequent secondary causes of apnoea in preterm infants are detailed in Table 1.

6.2 Causes of apnoea by age of onset

The causes of apnoea can be established fairly reliably with regard to age of onset of apnoea. Determining the cause is also necessary for selecting the right approach in therapy (16) (Table 2).

7 Differential diagnosis

7.1 Periodic breathing

Periodic breathing in a neonate can be confirmed when we can establish at least three apnoea lasting more than 3 seconds, with normal breathing intervals between them lasting less than 20 seconds, while at the same time, we do not notice any change to the heart rate or colour of the body. Periodic breathing is a normal condition reflecting the immaturity of the breathing system in neonates and does not require therapy. On the other hand, apnoea of prematurity is a pause in breathing that causes haemodynamic disturbance, therefore requiring appropriate therapy (4,5,17).

7.2 Infantile spasms

Apnoea is not a common clinical symptom in infantile spasms but may manifest alongside them. These are hidden spasms, and are more frequent in preterm infants. They are manifested by blinking,

Table 1: Overview of the most frequent secondary causes of apnoea in preterm infants (1,3,5).

Infection:	bacterial sepsis (early, late), pneumonia, meningitis, local infections (e.g. urinary tract infection), invasive fungal infection, viruses (RSV).
Respiratory:	congenital malformations of the upper respiratory tract (Pierre-Robin sequence), nasal obstruction, vocal cord paralysis, laryngotracheal stenosis due to overflexion of the neck, respiratory distress of the neonate, pulmonary haemorrhage, pneumothorax, hypoxemia, hypercapnia, bronchopulmonary dysplasia.
Cardiovascular:	open Botallo duct, cyanotic heart disease, congestive heart failure, increased vagotonia, extensive hypovolemia, hypo- or hypertension.
Neurological:	hypoxic-ischemic encephalopathy, intraventricular and intracranial haemorrhage, conditions that increase intracranial pressure, congenital mio- and neuropathies, congenital central hypoventilation syndrome, malformations of the central nervous system (Arnold-Chiari malformation, Dandy-Walker syndrome), spasms, pain, placental transfer of opioids, magnesium sulphate, general anaesthetics.
Metabolic:	congenital metabolic diseases (hyperthyroidism), acidosis, hypoglycaemia, hypocalcaemia, hypo- and hypernatremia, hypermagnesemia, hypo- and hyperthermia.
Gastrointestinal:	necrotizing enterocolitis, gastroesophageal reflux, abdominal distension.
Haematological:	severe anaemia.

Abbreviation: RSV – respiratory syncytial virus.

salivation, chewing, gazing, movements that mimic pedalling, automatic seizures and changes in the vasomotor response that most frequently include tachypnoea, tachy- or bradycardia, as well as apnoea (5,18).

8 Conditions related to apnoea of prematurity

8.1 Sudden infant death syndrome (SIDS)

Sudden infant death syndrome, abbreviated as SIDS, relates to the death of a child below the age of one, which occurs during sleep and remains unexplained in spite of a detailed autopsy, the investigation of the circumstances surrounding the death and a review of clinical history (3). Past research has pointed to a causal link between the two phenomena; however, while recent studies have shown that the risk for SIDS with premature neonates is three times higher, compared to those born on time, the risk factors for SIDS with preterm infants are linked to the age of the mother, smoking, meteorological factors and genetics, and not to apnoea of prematurity (1). Research has shown that only 2–4% of patients with SIDS have apnoea of prematurity in their anamnesis (5). It is also important to note that the two phenomena are separated by time. Long-lasting apnoea do not last longer than up to 43rd week of postconceptional age, while SIDS most frequently occurs at around 46 weeks (with preterm infants who were born between 24th and 26th week of gestation) or 52 weeks (with full term infants) of the postconceptional age. We can therefore conclude that apnoea of prematurity does not forecast SIDS and does not require constant monitoring of the cardiorespiratory functions at home. Cardiorespiratory monitoring after discharge from the hospital may be prescribed only to some premature infants with unusually long and repeating extreme episodes of apnoea, bradycardia and hypoxemia until they cease, which is mostly by the end of the 43rd week of postconceptional age (2,3).

Table 2: Causes of apnoea by age of onset (16).

The age of onset of apnoea	Causes of apnoea
A few hours	sedation of the mother, asphyxia, spasms, hypermagnesemia, neonatal respiratory distress
First week	atelectasis after extubation, open Botallo duct, near or intraventricular haemorrhage, prematurity
After the first week	post haemorrhagic hydrocephalus with elevated intracranial pressure, neonatal spasms
Between 6th and 10th week	anaemia

8.2 Anaemia in preterm infants

Anaemia in preterm infants is significantly included in the pathophysiology of apnoea of prematurity. Lower oxyphor blood capacity leads to lower tissue oxygenation, i.e. hypoxia, to which premature infants paradoxically respond with the so-called *hypoxic ventilation depression* (3). Points of view on using red blood cell transfusions in anaemic preterm infants with apnoea are nonetheless opposing. Studies have shown that after receiving a red blood cell transfusion, the number of apnoea decreases by a statistically significant amount for a short term, as the likelihood for the onset of apnoea in the 12 hours after receiving the transfusion depended on the haematocrit value; however, there is still no evidence on its long-term effectiveness (2,19). Transfusion of red blood cells also has no effect on bradycardia, and could even increase the risk of development of bronchopulmonary dysplasia and necrotizing enterocolitis (1).

8.3 Gastroesophageal reflux (GER)

Both apnoea and gastroesophageal reflux (GER) are frequent in preterm in-

fants, however the causal link between them remains inconclusive. Preterm infants have a hyperactive laryngeal chemoreflex response when irritated with an acidic content. It protects the respiratory tract from aspiration by fast swallowing, apnoea, laryngeal constriction, bradycardia, and hypertension. Apnoea with hypoxemia also lowers the tone of the upper oesophageal sphincter, thereby causing a reflux. Massive secretion in the upper respiratory tract can trigger a central apnoea type. Non-acidic reflux, which occurs immediately after a meal, may trigger apnoea through the mechanism of stretching the median part of the oesophagus. The acidic reflux, which occurs mostly when the stomach is basically empty, can cause the above-described laryngeal reflex, if it reaches the larynx. However, by using multichannel intraluminal impedance technology, it was recently established that the phenomena are often separated by time; GER does not extend or exacerbate the existing apnoea, nor does pharmacological therapy for GER decrease the risk for repeated apnoea in preterm infants. Quite the opposite; some studies have even demonstrated simultaneous increase in detected apnoea with pharmacological therapy for GER. Also, ranitidine, the inhibitor of histamine receptors H_2, is thought to increase the risk for necrotizing enterocolitis, infection and death of preterm infants (1-4,20-22).

9 Therapy

Literature includes numerous therapies for treating apnoea of prematurity. We divided them by the mechanism of action, as certain interventions reduce work of breathing, while others increase the respiratory drive, and third ones increase the diaphragm contractility (3). The other division is to pharmacological and non-pharmacological interventions, and the division by proven effectiveness (1,3) (Table 3).

9.1 Non-pharmacological interventions

9.1.1 Position of the body

Due to the hypotonia present in the neck muscles of neonates, it is very important to avoid both hyperextension and hyperflexion of the neck, which can trigger obstructive apnoea. When they are awake, lying on the stomach is recommended, as it has numerous positive benefits. It improves thoraco-abdominal respiratory synchronization, stabilizes the thoracic wall, increases ventilation, reduces the onset of gastroesophageal reflux and the onset of apnoea. It has also been established that extension of the neck by 15 degrees, i.e. a slightly head elevated position when lying on the stomach, reduces the number of hypoxemic events by nearly a half (1,3). However, lying on the stomach is related with an increased onset of the sudden infant death syndrome, and is therefore only suitable for neonates with cardiopulmonary monitoring in the neonatal intensive unit (3,23). It is recommended for all healthy neonates to lie on their backs after they are discharged from the hospital (3).

9.1.2 Non-invasive ventilation support

Among non-invasive ventilation support techniques, the most frequent one is continuous positive airway pressure (CPAP) (1). It is usually delivered through a mask or nasal contraptions (nCPAP) (5). Values of 4–6 cm H_2O have proven to be safe and effective for treating apnoea (1,2). This is a continuous positive pressure in the airway that passes through the neonate's pharynx into the lower airway, thereby preventing the collapse of the pharynx and alveolar atelectasis, stabilises the thoracic cavity, and consequently reduces the inflow of inhibiting nervous signals into the respiratory centre, increasing the functional residual capacity (FRC) of the lung, and reduces the work of breathing, which improves oxygenation and re-

duces bradycardia (1,3,4). It can also be used for reducing apnoea, which occurs in preterm infants after extubating (1,5). It is effective in treating apnoea of prematurity when episodes include an element of airway obstruction, i.e. in the obstructive and mixed type. It is not effective with central apnoea. Studies have shown that nCPAP with a variable airflow is more effective than with a constant airflow. CPAP is extended by using nasal intermittent positive pressure ventilation (nIPPV) and nasal synchronized intermittent positive pressure ventilation (nSIPPV) (1,5,24). In general, these two technics are used with the maximum inspiration pressure of 15-20 cm H_2O, and a positive final expiration pressure of 5-6 cm H_2O, and are also effective with the central type. They lower the frequency of apnoea and the need for artificial ventilation. Researchers have discovered that implementing them simultaneously for treating apnoea requires lower dosages of caffeine (3). Adverse effects of CPAP include barotrauma, abdominal distension, feeding intolerance and local nasal irritation (5).

An alternative to other forms of non-invasive ventilation support is using high-flow nasal cannulas (HFNC). These provide the inflow of a mixture of heated, moistened air and oxygen along the nasal cannula, maintaining a constant positive pressure in the airway and an open upper airway. In treating apnoea of prematurity, they achieve similar results to nCPAP, but, in general, infants tolerate them better (2-4,25).

Table 3: Mechanism of action of proposed interventions for the treatment of apnoea of prematurity (adapted from Picone F. et al.) (3).

Mechanism of action	Therapeutic intervention
Reduced work of breathing	Prone, head elevated body position nCPAP or nIPPV/nSIPPV
Increased respiratory drive stimulation	caffeine doxapram CO2 inhalations red blood cell transfusion tactile stimulations
Increased diaphragm contractility	caffeine branched-chain amino acids

Abbreviations: nCPAP – continuous positive airway pressure; nIPPV – nasal intermittent positive pressure ventilation; nSIPPV – nasal synchronized intermittent positive pressure ventilation.

9.1.3 Endotracheal intubation and artificial ventilation

When non-invasive ventilation support strategies and pharmacological therapy are not effective, neonates need to receive endotracheal intubation and artificial ventilation. This method is effective for all types of apnoea. If a neonate's lungs are normal, we ventilate with peak inspiratory pressure (PIP) of 10–12 cm H_2O; positive end expiratory pressure (PEEP) of 3–5 cm H_2O; low frequency of 20–25 inhales/min; short inspiration time of 0.35–0.40 seconds, and with a low fraction of inspired oxygen (FiO_2) (3-5).

9.2 Pharmacological interventions

9.2.1 Methylxanthines

The main group of drugs for pharmacological therapy of apnoea of prematurity are methylxanthines, which include caffeine, theophylline and aminophylline (1-5). They are strong stimulants of the central nervous system. The main mechanism of their action is non-selective competitive antagonism on adenosine receptors. Adenosine acts as a central depressor of breathing or an inhibition neuroregulator in the central nervous system. It is released during hypoxia. Methylxanthines block both inhibition adenosine receptors A_1 as well as excitation receptors A_{2A}, which are located on GABA neurons on the brainstem. The latter receptors should have a major role. Methylxanthines have numerous positive effects on breathing, as they increase minute ventilation, sensitivity to CO_2, nervous stimulation for breathing. (as they increase the number of sig-

nals) from the respiratory centre, improve diaphragm contraction, as well as the function of other muscles of respiration, reduce the periodic breathing and the hypoxic ventilatory depression (1,2,4,5). Until now, studies have not yet yielded data that would confirm the effectiveness of prophylactic use of methylxanthines in preterm infants with a risk for apnoea (2,5,26). Therapy also has certain adverse side effects, as methylxanthines may cause tachycardia, vomiting, tension and nervousness, spasms, and food retention in the stomach (1-5). Since they increase metabolic activity, oxygen and energy use, they may reduce the growth of preterm infants, which sometimes requires additional caloric intake (1).

9.2.1.1 Caffeine

Caffeine is the first choice among methylxanthines for the following reasons: it has fewer side effects, neonates handle it better, it has a broader therapeutic window, and due to a high level of safety, monitoring its serum concentrations is only seldom required when used with recommended doses (1,2,4,27). Its long half-life allows for a single daily dosage, and has numerous other positive effects. Research has found that it reduces the onset of bronchopulmonary dysplasia and also provides neuroprotection (1-4,27). With preterm infants who received caffeine therapy, there were fewer cases of cerebral palsy, and a better neurological development (27). Caffeine reduces the need for artificial ventilation, and allows earlier extubation, improves the survival of neonates with a very low birth weight, and is believed to have the best cost-benefit ratio among all medications used in neonatology. Due to the listed characteristics, scientists named it the "silver bullet in neonatology" (3,4,28). As caffeine citrate, it first came into use for treating idiopathic apnoea at the former neonatal department of the Division of Paediatrics at the University Medical Centre Ljubljana in the early 1980s (29).

Caffeine is the drug of choice for treating apnoea of prematurity; however, certain specifics related to its use have to be pointed out. We must pay attention to whether the baby is receiving any other medication that could affect its pharmacokinetics. Because caffeine is an antagonist of adenosine receptors, higher doses of adenosine are required for treating tachycardia when the neonate is also being administered caffeine (3).

Even though caffeine is a general drug that neonates handle well, overdosing can cause severe effects: serious tachycardia, irritation, jaundice, intolerance for food ingestion and polyuria. Serum values above 50 μg/ml can result in the onset of fever, tachypnoea, serum hyperosmolarity, vomiting, hyperglycaemia, spasms. Routine measurements of plasma concentration of caffeine are not necessary but are appropriate when we detect the signs that point to overdose, or when higher than usual therapeutic dosage is needed. Some studies report on lower blood supply to the brain and intestines in the first two hours after caffeine is applied, thereby increasing the risk for brain haemorrhage and necrotizing enterocolitis (3).

There are two unresolved questions related to caffeine use, namely dosage and therapy duration. Caffeine is usually available as caffeine citrate and the active component represents only 50% of the total dose (1). We generally dose it with the starting, bolus or loading dose, followed by a maintenance dose. Studies have shown that a higher dose of caffeine is more effective in preventing apnoea of prematurity, but higher dosages also have more adverse side effects. That is why they currently recommend the lowest still effective dosages, namely 10–20 mg/kg as the loading dose and 5–10 mg/kg/day as a maintenance dose. We can attempt a higher dosage with persistent apnoea that fail to respond to therapy (1). The other dilemma is when to stop caffeine therapy. It is advised to cease it before it may lead to unnecessary extended hospitalisation. One of the ap-

proaches could be an attempt to stop the therapy after a clinically apparent period without apnoea, lasting at least 5–7 days, or after the completed 33rd or 34th week of postconceptional age, depending on which condition was fulfilled earlier (2,5). It is important to cease the caffeine therapy at least 1–2 weeks before the discharge from the hospital due to its long half-life (3–4 days or approximately 100 hours), which may be even extended under certain circumstances (e.g. with cholestatic hepatitis). Discharge of preterm infants with a history of apnoea of prematurity from the hospital after ceasing caffeine therapy must be carefully planned (5,30). However, the long caffeine half-life begins to shorten rapidly with age. For an infant of about six months it is only three hours, and if there is a need for methylxanthine therapy in the postneonatal period, caffeine should be replaced with theophylline, which has a half-life of about 10 hours regardless of infant age (31,32).

9.2.2 Doxapram

Doxapram is a strong breathing stimulant. With smaller doses, it acts on peripheral chemoreceptors and increases the tidal volume and minute ventilation, and with higher doses, it acts directly on respiratory neurons in the brainstem (1,3,4,33). It is currently suitable only for treating apnoea, when there is no response to methylxanthine therapy and CPAP. Its effect is short-lived and lasts only up to two days (5). It is also connected to numerous adverse side effects, such as spasms, myoclonus, blood pressure increase, hyperactivity and irritability, hyperglycaemia, tympanites, milk retention in the stomach and vomiting (1,3-5,33). In the first week after birth, or when there are high values of serum bilirubin, it is not recommended due to potential exacerbation of jaundice, intraventricular haemorrhage and and bilirubin encephalopathy (kernicterus). Sources describing its use also list three cases of the atrioventricular block (AV-block) (3). The most important and potentially long-term dangerous side effect is decreased oxygenation and cerebral blood flow velocity, which decreases the blood supply and affects the developing brain and may lead to long-term developmental deficit (3). Because it is poorly absorbed, it has to be administered through a continuous intravenous infusion; when administered orally, which is rare, it is administered slowly through tube in one hour, every 8–12 hours (3). It contains 0.9% benzyl alcohol as a preservative, which is also one of the important reasons it is used seldom (4,5). An effective dose, which is 2.5 mg/kg/hour, contains 32.4 mg/kg/day benzyl alcohol, and even if this is below the toxic dose, which is 45 mg/kg/day, there are reports in literature about smaller doses resulting in certain cases of the so-called gasping syndrome, which can be caused in neonates by benzyl alcohol poisoning (5).

9.3 Other interventions with unclear effectiveness

Various sources list numerous other interventions whose effectiveness currently remains inconclusive, i.e. is not fully confirmed (1,3).

9.3.1 Kangaroo mother care

Kangaroo mother care, i.e. skin-to-skin care, is a method of caring for preterm infants aimed at returning the child to the mother and mother to the child. In practice this means nursing baby on the mother's bare bosom. With stable neonates, this has come into broad practice because of the calming effect shown on the infant's clinical status and vital signs. The effect of this approach in treating apnoea of prematurity remains inconclusive, as results of different studies show opposing outcomes. In certain studies, it was established that during kangaroo mother care there was less apnoea and bradycardia, while other studies established that there was more of it. Recently, studies has shown that this approach has the same effect on improving apnoea as does lying on the stomach (1,3).

9.3.2 Thermoneutral environment

A mild increase in body temperature in neonates increases the instability of their breathing pattern. A recent study has established fewer cases of apnoea with an incubator temperature of 30.4 °C than if the temperature is set to 32.5 °C. Certainly, there are numerous factors that effect the temperature in an incubator and a neonate's body temperature; however, overheating could be a risk factor for apnoea of prematurity, which is why there is the general recommendation of setting the temperature to the lowest value of the thermoneutral area and avoiding fluctuations of the environmental temperature. The specific environmental temperature that decreases the onset or severity of apnoea of prematurity is not known (1,3,5).

9.3.3 Branched-chain amino acids

Parenteral nutrition, rich with branched-chain amino acids (leucine, isoleucine and valine) *in vitro* has been proven to increase the diaphragm strength. This approach could be useful, as the increased work of breathing in preterm infants, due to the highly compliant chest wall, may lead to muscle fatigue that contributes to apnoea (3).

9.3.4 Sucrose

Oral intake of sucrose has an analgesic effect; since pain is a known stimulation for apnoea, sucrose is mentioned as a possible intervention. However, there has been no evidence that it would reduce the number of desaturations and bradycardias (3).

9.3.5 Using an orogastric feeding tube

Feeding through an orogastric feeding tube should have the advantage over inserting a nasogastric feeding tube, as the latter can increase resistance of the nasal part of the airway by up to 50%, which has an important role in apnoea of prematurity. However, recent studies have shown that the position of the tube does not have a major effect on bradycardia and desaturation. In one study transpyloric feeding, especially if limited only to breast milk, has proven to be a safe method for lowering apnoea and bradycardia episodes in preterm infants with suspected gastroesophageal reflux (1).

9.3.6 CO_2 inhalations

Carbon dioxide is a physical stimulant for breathing in mammals. Apnoea occurs when its value drops below the threshold value for apnoea. Its increase by 1–2 mm Hg above this value reduces apnoea or completely eliminates it. Studies have shown that inhalation therapy using low concentrations (as low as 0.8%) CO_2 is as effective as using theophylline for reducing apnoea of prematurity. Exposal to such low CO_2 levels also has no effect on the cerebral blood flow velocityand researchers also did not notice any side effects of inhaling CO_2 on preterm infants. However, there is high probability that neonates would quickly get accommodate to the inhaled concentrations, therefore the effect of long-term exposure remains uncertain (1,4,34).

9.3.7 Tactile stimulations

Tactile stimulations are thought to be useful in treating or preventing apnoea. Touch stimulates non-specific nervous activity in the brainstem centre and stimulates breathing. It is important for the strength of such stimulation to remain below the threshold for causing arousal from sleep to wakefulness. Research has shown that using special mattress with embedded actuators that deliver small stochastic displacements achieved a 65% reduction in duration of oxygen desaturation (1,3,4,16).

Olfactory stimulation has also been used for treating apnoea of prematurity. Pleasant smells stimulate breathing, while unpleasant smells during active sleep, when apnoea is the most frequent, reduce the respiratory effort. The study included 14 neonates with a gestational age of between 24 and 28 weeks, for whom apnoea

and bradycardia therapy with caffeine and doxapram was not effective. Fifteen drops of vanilla, a known stimulant for the olfactory nerve, were placed on the edge of the neonates' blankets, resulting in a 45% reduced frequency of apnoea and bradycardia. Unfortunately, only a small group of neonates was monitored, and the experiment lasted only 24 hours, so consequently we do not know how long this beneficial effect persists (1,3,4,15,35).

Kinaesthetic stimulation using water beds and oscillating bed mattress has so far not proven to be effective when treating or preventing apnoea of prematurity (5).

10 Resolution of apnoea of prematurity

Apnoea of prematurity is a self-limiting disease and resolves with advancing age and maturity (2,3). In general, the following rule applies: the lower the gestational age, the longer the period that apnea of prematurity persists (1). For most, namely for 92% of infants, apnoea is resolved by 36th week, and by the 40th week of postconceptional age, it is resolved for 98% of infants. However, with severely preterm infants, i.e. those born between 24th and 28th gestation week, and for those with bronchopulmonary dysplasia, apnoea can persist even after the 38th or 40th week of postconceptional age (1,5,36). Studies have shown that the reason for this can be found in delayed development, i.e. maturity, namely in synaptogenesis and myelination, which begin in the 33rd week in the solitary nucleus, the main respiratory centre of the brainstem (4,8). The myelination of the brainstem is deemed the physiological basis for the resolution of apnoea (4).

11 Consequences

Consequences of apnoea of prematurity are currently not well understood, because different sources present opposing results. Both short-term and long-term consequences are mentioned. With preterm infants, apnoea is often accompanied by oxygen desaturisation with hypoxemia and bradycardia. The latter usually follows hypoxemia. First, it is accompanied by the increase of the heart volume, as the longer-lasting apnoea and bradycardia lower the blood pressure, which also affects the brain haemodynamic. There is a reduced blood supply to the brain, and the resulting hypoxic-ischemic injuries of the not yet mature cerebral tissue. Long-term consequences can be even more controversial, as it is difficult to prove a direct connection between apnoea and poor neurological development, because preterm infants may also face a number of conditions related to the negative effect on their neurological development (1,3). First studies did not exhibit any differences in the neurological development between preterm infants with apnoea and those without it. Both groups did have delayed mental and motor development. Recent studies have shown that higher frequency and severity of apnoea of prematurity are linked with a higher incidence of adverse effects or death, which was explained with the mechanism that the numerous hypoxia and bradycardia conditions that follow apnoea of prematurity may cause long-term cerebral damage and problems in the neurological development, such as cerebral palsy and even blindness (1).

12 Genetic predisposition

Due to observed higher prevalence of apnoea of prematurity among first-degree relatives, studies have stated the hypothesis that there is a certain genetic predisposition to apnoea of prematurity (3,37). A retrospective study of twins included 217 pairs, of which 56 were monozygotic, and 161 were dizygotic, who were born before completing the 36th week of gestation. The assessment of heredity was based on the simultaneous onset of apnoea in each of the twins or the onset of apnoea within a pair. Among the monozygotic twins there

was a simultaneous onset of apnoea in 87% of cases, while among dizygotic twins of the same sex, it stood at 62%. It was also established that genetic factors contribute to 99% with male twins and 78% with female twins. Other significant risk factors for apnoea of prematurity established in the study were low birth weight, caesarean delivery and conception through assisted reproductive technologies (38).

Due to different responses of patients with apnoea of prematurity to caffeine therapy, some studies opted to research the role of genetic polymorphisms of adenosine receptors A_1 and A_{2A} to the onset of apnoea and to their role in individual differences in the response to caffeine therapy (2,3,39). The researchers took samples of cord blood from neonates who were born between the 24th and 34th week of gestation and divided them into two groups. The first group counted 60 and included neonates without apnoea, while the second counted 55 neonates with apnoea. This second group was then divided into two subgroups, namely to 30 neonates who responded to caffeine therapy, and to the subgroup of 25 neonates who did not respond to the caffeine therapy. Six single nucleotide polymorphisms (SNP) were selected for gene typing. It was established that apnoea patients, older than 28 weeks of gestation, who responded to the caffeine therapy, carried the rs16851030 C/C genotype rather than the C/T or T/T genotype. An analysis using logistic regression also showed a significant correlation between C/T and T/T genotypes rs35320474, and apnoea, and also with the development of bronchopulmonary dysplasia. Based on this study, we can conclude that specific polymorphisms in genes for adenosine receptors A_1 and A_{2A} affect the susceptibility to apnoea and bronchopulmonary dysplasia, as well as individual variability in response to caffeine therapy (39).

13 Conclusion

Apnoea of prematurity is one of the most common diagnoses in neonatal intensive care units. In spite of the frequency, there are still a lot of open questions that pertain to the pathogenesis, the most effective form of monitoring preterm infants, the most effective therapeutic and preventive approaches and any potentially harmful, both short-term and long-term consequences of this self-limiting developmental disease. Past research had yielded numerous conflicting findings. This is why apnoea of prematurity remains a major challenge for neonatology and an encouragement for further studies that could clear many doubts in the future, thereby contributing not only to a better understanding of this phenomenon, but also to unifying the guidelines for its therapy and prevention.

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