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Chapter 4

Respiratory Care of the Neonate

Štefan Grosek and Petja Fister

Additional information is available at the end of the chapter

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Abstract

The respiratory distress is a very common condition both in term and in preterm neonates and the most frequent reason for admission to the neonatal intensive care unit (NICU). The aetiology greatly depends on the maturation of neonate's organs and perinatal events. The clinical picture is sometimes scarce and very nonspecific for the etiologic determination. Treatment of neonatal RD begins first with the application of a mixture of oxygen and air, then with different modes of non-invasive respiratory support methods. Non-invasive respiratory support can be sustained with nasal continuous positive airway pressure, bi-level positive airway pressure and high-flow nasal cannula ventilation. Non-invasive ventilation with high-frequency oscillations through nasal cannula or masks is also possible with some respiratory devices. Non-invasive ventilation is usually combined with the application of natural surfactant and other therapeutic means, like methylxanthine therapy, prevention and closure of patent ductus arteriosus, and control of infection. In the case of non-invasive ventilation failure, different kinds of invasive ventilation methods are available and being practiced in NICUs. The invasive respiratory support can be maintained by controlled or intermittent mandatory ventilation combined with different supportive synchronous positive inspiratory ventilation, offered by modern respirators.

Keywords: neonate, respiration, ventilation, oxygenation, perfusion, evidence-based therapy, surfactant, respiratory distress

1. Introduction

The lung is the only organ during foetal development that remains dormant, although foetal breathing occurs; gas exchange is performed by the placenta, but the lung is completely ready for transition to extra-uterine life. Its development and maturation are precisely regulated

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during foetal life and needed to accomplish readiness for extra-uterine exchange of gases. During labour, different obstetric and non-obstetric factors may affect lung inflation in transitional period to extra-uterine life.

Even mature neonates have smaller diameter of the airways in comparison to infants, children and also adults; their chest wall is more compliant and the lung volume at the end of expiration is the same as the closing volume. Therefore, their lungs are prone to collapse. Besides, the neonates have fewer alveoli with ventilation perfusion mismatch, but a two–three–fold increase in oxygen demand in comparison to adults [1]. They have relatively inefficient respiratory muscles due to lack of red respiratory muscles and more white ones, which get tired faster. Their pulmonary vascular wall contains more muscle fibres and is therefore more prone to vasoconstriction. The sudden falls in partial oxygen pressure result quickly after short hyperpnoea in hypopnoea or apnoea. The foetal haemoglobin binds oxygen with greater affinity than adult haemoglobin. Neonates also have immature immune system with lack of the acquired immunity against microorganisms and are thus more prone to infection. In a premature infant, all these differences in lung development are more prominent in comparison to the term neonate and further influence the transitional period of extra-uterine life.

Because of all the above-mentioned developmental immaturity of the lungs, heart, blood vessels, circulation and immune system, neonates are more prone to develop idiopathic respiratory distress (RD) at the beginning of the life but also in later days and weeks and these differences are even more pronounced in premature and very premature neonates. The aetiology and pathophysiology of the RD differ between mature and premature infants [2]. In the most extreme prematurity, several forms of RD syndrome or hyaline membrane disease (HMD) may develop because of lack of surfactant and underdevelopment of the lung.

RD is very common in neonates, affecting about 10% of them [3]. Some of them have disorders of transition from foetal to extra-uterine life; others have RD caused by congenital or acquired infection or congenital malformations of different organs (thoracic and extra-thoracic). Regarding perinatal and labour history, gestational age and appropriateness of birth measures, the aetiology of the neonatal RD could be suspected. Clinical picture of neonatal RD is rather nonspecific in regard to the aetiology of it and also the management is quite universal. RD may develop immediately and acutely after birth or more slowly in the next few hours depending on the cause of neonatal breathing difficulties [4].

According to the situation in the delivery room, we have to decide how to approach the neonate with breathing difficulties. A well-equipped and trained neonatology team should be available during all difficult or premature deliveries which have to follow recommended resuscitation care of the neonate. The first golden minutes are the most important not only to properly recognize a neonate who needs our support but also to apply appropriate, sufficient and not too aggressive support if not needed. Appropriate inspiratory pressure and oxygen therapy during artificial ventilation in the delivery room may prevent immediate and later complications especially in the most vulnerable extreme premature infants. Prevention of hypothermia, in premature neonates with plastic bag, is also one of the important preventable methods because it may prevent severe metabolic derangements due to hypothermia, harmful for all organs [5].

2. Methods

We conducted electronic searches of articles on respiratory management and care of neonates with RD, using key terms: neonate, respiration, ventilation, oxygenation, oxygen, evidence based therapy, caffeine, surfactant, respiratory distress in the PubMed data base from the years 2000 to 2017 and reported the most relevant ones. Also, consensus guidelines on neonates with RD were reviewed [6]. The article describes transition from intra- to extra-uterine life, lists the methods for assessment of neonates with RD, describes the respiratory support in the delivery room, treatment with methylxantines, oxygen and surfactant, and the non-invasive and invasive tools for artificial ventilation.

This chapter includes the impact of optimal ventilation, tissue oxygenation and perfusion on the non-invasive and invasive respiratory management of neonates with RD. Also, the short- and long-term outcome in respect of respiratory management of neonates in the neonatal intensive care unit (NICU) is addressed.

3. Transition from foetal to extra-uterine life

The transition from foetal to extra-uterine life is a process of rapid physiologic changes in the neonate that begin in utero as the foetus prepares for transition from intrauterine placental support to extra-uterine self-maintenance. The process can last for up to 12 h after birth and depends on the gestational age, placenta, maternal health and congenital anomalies of the neonate. The foetus is preparing to the transition by foetal breathing, producing surfactant storing glycogen in the liver, producing catecholamines and depositing brown fat. After the umbilical cord is cut, placenta no longer does the work of lungs as they begin to exchange gasses. The first breath inflates the lungs and causes circulatory changes: the resistance to blood flow through lungs falls and more blood flows through pulmonary arteries to the lungs. Three foetal shunts close and this results in neonatal circulation. The three processes of the transition—(1) the replacement of amniotic fluid in the alveoli with air, (2) the onset of regular breathing and (3) the increase in pulmonary blood flow—may all be deranged soon after birth and RD ensues [7]. The failure of alveoli fluid clearance results in transient tachypnoea of the newborn (TTN) and causes in turn decreased lung compliance. The deficiency of surfactant mainly in preterm neonates or in term infants of diabetic mothers causes collapse of the alveoli and diffuse and progressive atelectasis that result in decreased lung compliance and small functional residual capacity (FRC) and cause HMD. The abnormal persistence of elevated pulmonary vascular resistance either due to underdevelopment, maldevelopment or maladaptation of pulmonary vessels results in persistent pulmonary hypertension of a newborn (PPHN). PPHN is often associated with congenital anomalies (i.e. congenital diaphragmatic hernia) or chronic intrauterine stress (meconium aspiration syndrome (MAS)).

At the time of birth, the umbilical cord is still pulsating. For term and preterm neonates, delayed cord clamping is recommended. The preterm neonates born before 32 weeks of gestation with delayed cord clamping had better neuro-developmental outcomes at the age of 18 months [8, 9]. Too early umbilical vein clamping, even before the first breath of the neonate,

may lead to a prolonged period of low cardiac output, which along with the undeveloped self-regulation system leads to a reduction of brain blood flow. Delayed cord clamping allows blood to enter the neonate's circulation and by that enhances the performance of the left ventricle, which is the most important for the normal cardiac output and stable haemodynamics especially in foetal distress with compromised haemodynamics at birth [10].

4. Assessment of the respiratory distress of the neonate

The evaluation of a neonate with RD is based on clinical, laboratory and radiologic investigations. In clinical evaluation, the respiratory effort, breathing efficacy and the breathing effect on other organs are assessed (**Table 1**). Signs of respiratory effort may be less pronounced or not visible in three cases: (1) the neonate, who has had RD for a long time, eventually becomes tired and signs of respiratory effort are reduced. Tiredness is a pre-terminal sign of respiratory failure. (2) A neonate with central nervous depression because of either intoxication, or encephalopathy, brain malformation, or increased intracranial pressure, breathes insufficiently without increased respiratory effort. These neonates breathe insufficiently due to reduced breathing impulse. (3) A neonate with neuromuscular disease may have respiratory failure without a significantly seen respiratory effort.

Classic laboratory signs of respiratory failure include acidosis (pH < 7.25), hypoxia (PaO_2 < 50–60 mm Hg (6.7–8 kPa), FiO_2 0.6–0.8) and hypercapnia ($PaCO_2$ > 60 mm Hg (8 kPa)) which are late signs of RD. Radiologically, neonatal chest may be scanned by X-rays [11, 12] or, lately more in use, by ultrasound (US) waves [13–17]. In utero, routine foetal US scan following development and screening for malformations may reveal intra- or extra-thoracic malformations, better differentiated by magnetic resonance imaging (MRI). Combining the risk and etiologic factors for neonatal RD, gestational age and radiologic investigations, the pulmonary disease causing the RD may be diagnosed (**Table 2**), since the clinical picture and laboratory signs are almost not of any help in defining the aetiology of neonatal RD.

	Respiratory effort	Breathing efficacy	Effect on other organs
1.	Breathing rate	Chest movement	Heart rate
2.	Intercostal, jugular, supraclavicular or subcostal retractions	Chest auscultation	Skin colour: cyanosis, paleness, mottled skin
3.	Auscultatory phenomena	Arterial blood oxygen saturation	Disturbance of consciousness
4.	Feeding difficulties		
5.	Expiratory grunting		
6.	Use of auxiliary respiratory muscles		
7.	Nasal flaring, head nodding		
8.	Gasping		

Table 1. The clinical assessment of airway and breathing in a neonate.

Pulmonary disease	Gestational age, risk factors	Aetiology	Roentgenogram	Ultrasound
Hyaline membrane disease	• Preterm • Neonates of diabetic mothers	Lack of surfactant	Diffuse reticulogranular ground glass pattern with air bronchograms and small-lung volume; grading from mild (grade 1) to the most severe pattern (grade 4)	Coalescent B-lines-'white lung', thickened and irregular pleural line
Transitional tachypnoea of the newborn	• Late preterm • Elective caesarean section	Failure of adequate alveoli fluid clearance at birth	Bilateral perihilar linear streaking, patchy infiltrates	Compact B-lines in the inferior and less compact in the superior fields (double lung point) or bilateral numerous noncompact B-lines and normal pleural line and pleural sliding
Persistent pulmonary hypertension	• Term > preterm • Perinatal depression	Persistence of elevated pulmonary vascular resistance	Clear lung fields with decreased pulmonary vascularity	Echocardiography
Meconium aspiration syndrome	• Term • Perinatal depression	Meconium-stained amniotic fluid	Patchy infiltrates	Pulmonary consolidation with air bronchograms, pleural line anomalies, pleural effusion, B-lines in non-consolidation area
Pneumonia	Infection of the mother	Bacterial or viral infection	Non-symmetric bilateral patchy infiltrates	Subpleural consolidation
Pneumothorax	Preterm > term	Air entrance into the pleural space	Edge of collapsed lung	Absence of pleura sliding and B-lines, subpleural consolidation
Congenital heart defect	Term > preterm		May be diagnostic	Echocardiography diagnostic
Congenital malformation of organs	Term>preterm		Diagnostic	
Metabolic, neuromuscular diseases	Term > preterm		Normal	
Genetic defect of surfactant proteins	Term, preterm	lack of surfactant proteins	Diffuse reticulogranular ground glass pattern with air bronchograms and small lung volume; grading from mild (grade 1) to most severe (grade 4) Chronic lung disease of different patterns	

Table 2. The etiologic and radiologic assessment of respiratory state of a neonate.

5. Respiratory support in delivery room

Routine care in delivery room depends on whether we expect and take care of extreme premature neonates or near term or term neonates with breathing difficulties. In case of near term or term neonates, care starts with providing warmth, clearing airway if necessary, drying and stimulating the neonate. Care of preterm infants is different because we immediately place him/her into a heated polyethylene bag with small opening for the nose and mouth and further stabilize him/her under the heater to assure normal body temperature, prevent hypothermia and desiccation [18]. The stabilization of the neonate with RD in the delivery room comprises proper head positioning with wiping of the mouth, and rarely, in the case of more secretion, not removed by wiping, we may perform gentle suction of the neonate's mouth, then nose. We have to avoid the deep insertion of the catheter and vigorous suctioning of mouth which may cause reflex bradycardia. In the case of meconium staining and aspiration, suction of trachea under visual inspection with laryngoscopy guidance is needed first and then intubation and further washing out meconium from the trachea. In case of apnoea, gasping or bradycardia of <100 beats/minute, it is necessary to ventilate neonate's lungs with positive pressure ventilation considering the use of lowest effective inspiratory pressures and volumes to prevent damage to the lungs (barotrauma and volutrauma). Ventilation should fill neonatal lung with a gas mixture of air and oxygen. To prevent and reduce the oxidative stress, caused by excessive use of oxygen in the inspired air, it is necessary to be careful with the use of oxygen. For measuring the arterial oxygen saturation (SpO_2) in the peripheral blood, the pulse oximeter should be attached to the right wrist [19]. Latest guidelines recommend starting ventilation of term neonates with FiO_2 0.21 and later increasing the FiO_2 according to the value of the measured SpO_2. Ventilation of preterm neonates should be started with FiO_2 of 0.21, gradually rising the FiO_2 in accordance with the measured value of SpO_2. Ventilation of the extremely premature infants (born before 28 weeks gestation) should be started with FiO_2 0.30, while of very premature infants (28–31 weeks of gestation) with the FiO_2 from 0.21 to 0.30. If neonate is spontaneously breathing, the constant positive pressure is applied for the stabilization of respiration (continuous positive airway pressure) of 6 cm of H_2O through a mask, nasal tubes or endotracheal tube using neonatal respirator (neonatal resuscitator; T-piece device), intended for stabilization of the neonate in the delivery room. The maximum positive inspiratory pressure should not exceed 20–25 cm H_2O, which is used only in the case of apnoea or bradycardia [6]. No differences in mortality and morbidity of premature neonates have been demonstrated in comparing resuscitation starting with low (FiO_2 ≤0.30) or high levels of oxygen (FiO_2 ≥0.6) [20]. Currently, there is insufficient evidence of sustained lung inflation efficacy and safety in the cardiopulmonary resuscitation and stabilization of the neonate in the delivery room [21, 22].

6. Methylxanthines

Methylxanthines stimulate the respiratory centre to increase its responsiveness to the partial pressure of carbon dioxide in the blood and reduce respiratory depression by hypoxia. They also improve respiratory muscle strength. Therapy with caffeine has proven to reduce the

duration of artificial ventilation and oxygen demand and decrease risk for bronchopulmonary dysplasia (BPD) and the need for patent ductus arteriosus (PDA) ligation [23, 24]. At the age of 2 years, positive effects on cognitive development were observed, but in the same group of children at the age of 5 years they were no longer detected [25]. In a premature neonate with RD, the less invasive artificial ventilation and surfactant therapy are usually combined with early prophylactic intravenous administration of caffeine to achieve the highest level of respiratory support in the least invasive form [26, 27]. Since methylxanthines affect the diaphragmatic activity and increase the tidal volume, we may use them to increase the muscle strength in floppy neonates [28].

7. Treatment with oxygen

Oxygen is necessary for aerobic metabolic processes in the body. The excess of oxygen is detrimental to neonates, particularly the premature infants with immature antioxidant, anti-inflammatory mechanisms and a greater amount of free iron. Hyperoxia affects not only the lung but also other organs, with the greatest effects to central nervous system (convulsions) and eyes (retinopathy of prematurity (ROP)). In comparison with a 'higher' level of SpO_2 (91–95%), the 'lower' level (85–89%) has been shown to diminish the risk of ROP and BPD, but unfortunately at the same time increase mortality, the incidence of necrotizing enterocolitis and poor neuro-developmental outcome [29]. Based on research, current recommendations propose the SpO_2 of preterm infants who require oxygen therapy to be between 90 and 94%, setting alarm limits to 89 and 95% [6]. The SpO_2 of term neonates who require oxygen therapy should be above 92%.

Hypercapnia is associated with acidosis and compromised cardiovascular function, while hypocapnia decreases cerebral blood flow. There is some conflicting evidence on higher $PaCO_2$ levels and the impact on mortality, severe intraventricular haemorrhage (IVH), BPD, ROP and neurodevelopmental outcome [30, 31]. Therefore, the optimal target carbon dioxide levels are not established; based on available data, it should be between 46 in 60 mm Hg (6.1–8 kPa) for ventilated neonates.

Blood gas is monitored in arterial samples, so an indwelling arterial line is necessary in taking care of a neonate with moderate or severe RD. Venous and capillary samples are not appropriate for PaO_2 measurements. They may be of use for $PaCO_2$ monitoring, although they slightly overestimate it, and pH monitoring, although they slightly underestimate it.

8. Surfactant

Pulmonary surfactant, a macromolecular lipoprotein complex, secreted by the alveolar epithelial cells type II, reduces the surface tension in the pulmonary alveoli at the end of exhalation. Sufficient amount of surfactant in the mature lungs prevents complete collapse of the lungs at the end of exhalation. A part of the inhaled air remains to be 'trapped' in the pulmonary alveoli, what is called the FRC. In each subsequent breath, it is not necessary to re-open

the lungs from the total collapse, which greatly reduces the work of breathing and with that fatigue and respiratory failure. A thin layer of a surfactant in the walls of the pulmonary alveoli at the end of each inspiration is not completely waterproof, some liquid passes through the pores being in contact with the air in the lung alveoli, increasing the surface tension and preventing the overdistension of the alveoli at the end of inspiration. The lung surfactant is rapidly adsorbed and easily distributed in the form of a thin film on the surface between the liquid layer and the air in the lung alveoli [32].

Several animal surfactants of bovine or porcine origin are used in Europe (**Table 3**).

Currently, a double-blind study of a synthetic surfactant, CHF5633, with the same effect in the treatment of RD as poractant alpha, but a stronger anti-inflammatory and a more favourable effect on the cerebral haemodynamics, is being conducted [33].

Early publications recommended the application of surfactant in developed RD as a 'rescue' or therapeutic administration or prophylactically for the prevention of RD in very premature infants in the first few minutes after birth. Criticism of the prophylactic administration of surfactant was that likely 27–60% of preterm infants receive surfactant unnecessarily [34, 35]. Recommendation nowadays is to stabilize the respiration of a spontaneously breathing neonate by using CPAP and early selective surfactant administration. When an endotracheal intubation is needed due to progressive RD, the neonate should obtain surfactant as soon as possible [6, 36].

Another way of avoiding lung barotrauma and especially volutrauma, techniques to shorten the duration of artificial ventilation or even completely avoiding it, has been developed in recent years. The first of such methods of fast and non-invasive surfactant application was **IN**tubate—**SUR**factant—**E**xtubate (INSURE). The extubation was followed by non-invasive respiratory support [37, 38]. In comparing early INSURE method with CPAP without the administration of the surfactant, certain advantages were found in the INSURE group. Not enough evidence was found to conclude that one of the two methods is better than the other [39].

Type of surfactant	Company name	Origin of surfactant	Lipids (%)	Proteins (%)	Dose (body mass)
Poractant alfa	Curosurf®	Extraction from porcine lungs	99	SP-B, SP-C 1%	100–200 mg/kg (1.25–2.5 ml/kg) in suspension
Bovactant	Alveofact®	Lavage from bovine lungs	99	SP-B, SP-C 1%	50 mg/kg (1.2 ml/kg) in suspension
Beractant	Survanta®	Extraction from homogenized bovine lungs	88–90	SP-B, SP-C 1%	100 mg/kg (4 ml/kg) diluted before use

Table 3. Surfactants, registered for therapy of RD in Europe.

Less **I**nvasive **S**urfactant **A**dministration (LISA) and **M**inimally **I**nvasive **S**urfactant **T**reatment (MIST) are other two less invasive methods of surfactant application. With LISA, the preterm neonate who is supported by CPAP via nasal prongs, the larynx is opened by laryngoscope and by the Magill forceps a thin and soft aspiration tube is inserted below the level of the vocal cords, and then the surfactant is applied in two to four aliquots while the neonate is spontaneously breathing. With MIST, the tube for surfactant application is somewhat stiffer and bent so it can be inserted into the larynx without the Magill forceps. According to the authors, MIST is an easier method for less skilled doctors [40]. To confirm the hypothesis that less invasive surfactant administration combined with the respiratory support by CPAP is more successful in neonates who have some natural surfactant and not effective in those who have too little of their own surfactant, a blind, multicentre, randomized study in premature neonates between 25 and ≤28 weeks gestation, requiring CPAP and a low percentage of oxygen in the inhaled air (FiO_2 from 0.30 to 0.45) during the first 6 h after birth, is currently underway. The research group is being treated with poractant alpha at a dose of 200 mg/kg body weight, and the control group receives placebo [41]. None of the above-described methods can avoid laryngoscopy.

The methods of surfactant aerosolization have up to date been more or less unsuccessful. With the **C**atheter **A**nd **L**aryngeal **M**ask **E**ndotracheal **S**urfactant **T**herapy (CALMEST) the surfactant is administered by a catheter and the laryngeal mask [42].

The oxygen requirement higher than the FiO_2>0.3 after 2 h of breathing with CPAP has a high positive-predictive value of a respiratory failure at 6 h after birth. Therefore, the recent recommendations suggest an early less invasive surfactant administration before the neonate requires high proportions of oxygen in the inspired air [43]. If no improvement is seen after the first dose, the surfactant application is repeated for the second or third time. In this case, the poractant alpha at a dose of 200 mg/kg body weight is supposed to have better effect as a lower dose of poractant alpha or beractant (100 mg/kg body weight).

Late-preterm and term neonates besides rarely having a primary surfactant deficiency due to genetic defect of surfactant proteins, they more often suffer from secondary surfactant deficiency in conjunction with MAS, pneumonia and pulmonary haemorrhage. In those cases small studies have shown improved oxygenation, gas exchange and a reduced need for extracorporeal membrane oxygenation (ECMO) [44].

9. Non-invasive respiratory support

The best and most frequently used treatment of neonatal RD nowadays is CPAP through nasal spouts (nasal mask, nasal cannula and nasal tube) with the addition of the interfaces by using various physical processes to insufflate and exhale the mixture of air and oxygen into and out of the respiratory tract of a neonate [45]. It has been proven to reduce side effects that neonates could suffer if they were ventilated by the invasive methods of artificial ventilation. Until now, a variety of techniques applying positive pressure of constant pressure

(CPAP), the intermittent insufflation of positive pressure (nasal intermittent positive pressure ventilation, NIPPV), which can be time determined or synchronous triggered by inhalation (synchronous nasal intermittent positive pressure ventilation (SNIPPV)) and ventilation at two levels of positive pressure (bi-level positive pressure ventilation, Bi-Level) or even with high-frequency oscillations (high-frequency oscillation ventilation (HFOV)) have been developed. Different randomized studies have explored the advantages or disadvantages of one method of non-invasive ventilatory support over the other. In comparing the non-invasive ventilation with NIPPV to the nasal CPAP, fewer respiratory failures and the need for intubation in the NIPPV group were found [46]. Meta-analysis of the use of different devices and interfaces for CPAP has elucidated differences in outcome depending on the use of nasal adapters or interfaces, requiring further research [47]. Similarly, there is an open question whether breathing with the help of bi-level CPAP is better than breathing with CPAP alone and does it pose an advantage of better exhaling CO_2, better oxygenation or other physiological indicators [48].

If higher mean inspiratory pressures are required for the lungs to remain inflated, the potential non-invasive ventilation using HFO via nasal tubes or cannulas may be used since even long-term studies have confirmed advantages of HFO non-invasive ventilation over other invasive ventilation methods.

Ventilation of neonates using high-flow rates (high-flow nasal cannula (HFNC)) has some advantages over CPAP due to less damage to the nose and nasal septa and less pneumothorax (PTX) [49]. A multicentre study being conducted in nine centres in Australia and Norway might give answers as to which breathing support is better in very preterm infants, CPAP or HFNC [50].

Nose requires special attention because the prolonged nasal respiratory therapy may cause decubitus and malformations of the nose. Regular changes of devices and protection of the nose skin and mucosa with skin-protective strips and/or creams prevent those problems. Gastric distension has to be prevented by an opened nasogastric tube and regular checking of gastric over distension which decrease compromise of diaphragm contractions. Neonatal care in term neutral environment incubators or warm beds and preventive positions like Cocoonababy® Nest or similar home-made products besides frequent changes of neonate's positions improve ventilation during the period of acute respiratory problems. Kangaroo care is a useful method to improve bonding between the neonate and the mother or father but has to be carried out cautiously during non-invasive ventilation [51]. During kangaroo care, observations have to be made whether apnoeic spells are more frequent and whether bradycardia occurs.

Non-invasive respiratory ventilation enables non-aggressive approaches, without sedation, analgesia, tracheal intubation and mechanical ventilation. Complications of non-invasive ventilation are mainly pressure sores of skin around the nose, ulceration and necrosis of the septum, much less likely hyperinflation of the lungs, restlessness, PTX, stomach distension or food intolerance. Non-invasive ventilation failure may be predicted by the use of neonatal chest US [52].

10. Invasive artificial ventilation of the neonate

Nowadays, the invasive artificial ventilation of the neonate represents a continuation of treatment in cases where non-invasive ventilation with or without the use of surfactant is not possible or successful. In invasive mechanical support ventilation with a respirator, CPAP is usually supplied in combination with intermittent mandatory or synchronized artificial ventilation (i.e. intermittent mandatory ventilation (IMV); synchronized intermittent mandatory ventilation (SIMV)). Ventilation can be sustained at two different positive pressure levels (variable/bi-level positive airway pressure, bi-level (BiPAP)). Other forms of artificial ventilation include ventilation by releasing the pressure (airway pressure release ventilation (APRV)), neuronal-mediated respiratory support (neurally adjusted ventilatory assist (NAVA)), and so on. In the case of the artificial ventilation, one should always set the concentration of a mixture of the inspired oxygen and air, the frequency of the ventilation, the ratio of duration of the inspiration and expiration or time of inspiration, the end-inspiratory pressure or the tidal volume and the end-expiratory pressure. Each respirator is equipped with the heater and humidifier in order that neonates breathe moist and warm mixture of air and oxygen. In cases of severe pulmonary disease with severe RD, high-frequency oscillating ventilators, which use very low inspiratory volumes that do not damage the lung tissue, may be used.

High-frequency oscillation ventilation is a method of artificial ventilation, which in cases of severe RD can be the least harmful way of ensuring good oxygenation and due to the active exhalation wash out carbon dioxide as well. High-frequency oscillation ventilation will only be successful if the pulmonary alveoli are optimally opened prior to the start of oscillations. In HFO, the optimization of lung volume is achieved by small increments of continuous positive distending airway pressure and the pressure in lung alveoli. Gradually, the increase of continuous positive distending airway pressure leads to opening of the small, collapsed non-ventilated lung and by that to the increment of the FRC of the lungs that ensure good ventilation and oxygenation. Consequently, the optimally opened lung tissue is then oscillated with very small tidal gas volume (order of the neonate's dead space of the lungs), which regulates the exhalation of carbon dioxide from the lungs. Oscillations with small volumes are less harmful for the delicate lung parenchyma and do not damage it, thereby preventing the secondary injury such as barotrauma and volutrauma. When lung function improves, the neonate's ventilation can be switched to conventional artificial ventilation again [53].

The most important factor in invasive artificial ventilation of the neonate is to prevent the lung over-distension, because it injures the delicate lung tissue and causes air leakage outside the airway with the development of pulmonary interstitial emphysema (PIE), PTX or pneumomediastinum (PM) and other even more severe forms the air leakage into the chest. When lungs become more compliant, the pressure-guided artificial ventilation may lead to lung over-distension, therefore many of the neonatal respirators are programmed to the restriction of tidal volume (volume-targeted ventilation; volume-guaranteed ventilation (VGV)). Care should be taken not to cause hypocapnia during ventilation since it decreases the brain blood flow and causes periventricular leukomalacia (PVL) and IVH which jeopardize the neurological development. The volume-targeted artificial ventilation was shown to shorten the duration

of artificial ventilation and hypocapnia, lessen the incidence of BPD, IVH grade III/IV, PTX and PVL in comparison to the pressure-controlled ventilation in preterm neonates. The mortality rate was unaffected by the mode of artificial ventilation [54].

During intubation and invasive ventilation, neonates are prone to cardio- and cerebrovascular instability. The intensive invasive therapy subjects neonates to more infections and the invasive ventilation to volu-, barotrauma and shear stress. Common complications due to intubations and invasive ventilation are hoarseness, aphonia, tracheal stenosis, and feeding and perioral sensation disorders.

11. Additional supportive therapies for neonatal respiratory distress

For treating pulmonary hypertension in different pulmonary diseases of the neonate the inhaled nitric oxide, pulmonary artery dilator, has been shown to have some beneficial effects [55]. On the other hand it has not been shown to be beneficial in preterm neonates with RD in reducing BPD or mortality [56]; though most NICUs are using it nowadays when hypoxic respiratory failure in extreme premature cannot be solved by other means [57].

The ECMO pumps the blood through an artificial lung back into the bloodstream, providing heart-lung bypass support outside of the neonatal body. ECMO is applied in neonates with severe RD due to congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), pneumonia, air leak problems or PPHN [58]. Veno-venous ECMO is preferred to be used in infants with hypoxic respiratory failure unless an arterio-venous ECMO is needed due to combined cardio-respiratory failure. ECMO support should be used only in neonates weighing ≥2 kg of body mass.

General supportive care of a neonate with RD encompasses optimization of thermal neutral environment, fluid and nutritional management and a stable hemodynamic state ensuring adequate oxygenation and perfusion of neonatal organs.

12. Conclusion

RD of a neonate has almost identical clinical picture irrespective of many etiologic entities it originates from. The perinatal history, labour course, the gestational age and appropriateness of birth measures for the gestational age should all be taken into account in diagnosing the aetiology of the RD.

The modern management of neonatal RD is minimally invasive. In the delivery room, neonates are being stabilized. The respiratory support is primarily non-invasive ventilation as well as the surfactant is applied with less invasive methods not involving intubation and artificial ventilation. If intubation is required, the time of artificial ventilation should be as short as possible. Hyperoxia and hypocapnia should be avoided. Further studies will show whether such non-invasive treatment is also going to affect the incidence of BPD, neurodevelopmental outcome and other long-term consequences of intensive neonatal therapies.

Author details

Štefan Grosek[1,2]* and Petja Fister[3]

*Address all correspondence to: stefan.grosek@kclj.si

1 Department of Pediatric Surgery and Intensive Therapy, Surgical Service, University Medical Centre Ljubljana, Ljubljana, Slovenia

2 Department of Pediatrics, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

3 Department of Neonatology, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia

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