The effect of respiratory management on neurodevelopmental outcome in preterm infants
Vliegenthart, R.J.S.

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General introduction and outline

RJS Vliegenthart
W Onland
AH van Kaam
Prematurity
The World Health Organization defines preterm birth as being born before 37 weeks of gestation. Globally, 10% of all infants are born prematurely, corresponding with approximately 15 million preterm infants born every year. The gestational age (GA) of these preterm infants is inversely related to mortality and morbidity: infants who are born with a lower GA have a higher risk of dying or enduring complications during the neonatal period. With decreasing GA, the incidence of adverse long-term neurodevelopmental outcome also increases. Only 5% of the surviving infants with a GA between 32-36 weeks will develop an adverse neurodevelopmental outcome, compared to about a quarter of the infants with a GA between 28-31 weeks, and up to more than half of the infants with a GA below the 28 weeks. The increased morbidity in preterm infants is associated with increased hospital admissions in the first years of life, increased health care costs and prolonged negative effects on emotional and psychosocial functioning of families.

A preterm infant is at risk for mortality and morbidity due to an underdevelopment of all organ systems, both structural and functional. Already during embryonic formation, a process called morphogenesis shapes the rudiments of all organ systems. During fetal life, these organ systems quickly develop into full functioning systems, ready to face extra-uterine life after 38 weeks of gestation. When an infant is born prematurely, the development of for example the brain, the heart, and the lungs will not be completed yet.

The central theme of this chapter will be the underdeveloped respiratory system, its complications after preterm birth, the treatment options during the neonatal period and the effect of all these components on neurodevelopmental outcome later in life.

The developing respiratory system
The respiratory system develops in different stages. Four weeks after conception, a lung bud (or respiratory diverticulum) emerges from the foregut of the embryo, bifurcating into a left and right diverticulum, laying the foundation of the left and right lung. During the next weeks, these buds will branch out further into the different lobes of the lung. From 16 to 28 weeks of gestation, respiratory bronchioles and vasculature arise, and the lining of the lung (the lung epithelium) begins to differentiate into specialized cells, such as type II pneumocytes which produce surfactant. This stage of lung development is called the canalicular stage (Figure 1). In the following saccular stage – starting from 26-28 weeks gestation onwards – the respiratory system evolves into fully developed functional gas exchanging units, i.e. alveoli.

When an infant is born prematurely, lung development will still be in the saccular or canalicular stage. Since the alveoli are fewer and larger compared to term infants, the surface area between air and blood vessels is reduced, therefore, effective pulmonary
gas exchange is complicated. In addition, the underdevelopment of type II pneumocytes results in a surfactant deficiency. Surfactant is a mixture of phospholipids and proteins, which reduces surface tension in the alveoli. This reduction in surface tension helps to avoid alveolar collapse. A surfactant deficiency results in a decreased compliance and a low end-expiratory lung volume. The latter is augmented by the fact that the preterm chest has a high compliance, limiting its ability to resist a decrease in end-expiratory lung volume caused by the surfactant deficiency. The overall effect will be a compromised gas exchange and a higher work of breathing.

In addition to differences in lung mechanics, preterm birth is also accompanied by an underdeveloped central control of breathing, located in the ventral brainstem. Central control of breathing is a complex dynamic process which is modulated by feedback from peripheral chemoreceptors monitoring carbon dioxide (CO₂) levels in the blood. In preterm infants, these peripheral chemoreceptors are not yet equipped to respond adequately to abnormal CO₂ levels, leading to an impaired control of breathing and subsequently leading to apnea of prematurity (AOP). AOP is defined as a cessation of breathing longer than 20 seconds leading to oxygen desaturation below 80% and/or a bradycardia with a heart rate below 100 beats per minute. Three classes of AOP can be distinguished: central, obstructive or mixed AOP. During central apnea, there is no or insufficient respiratory drive due to immaturity of the breathing center in the brainstem. Obstructive apnea are characterized by a lack of air entry into the lungs despite breathing efforts of the infant, due to an obstruction of the (upper) airways. Mixed apnea consist of a combination of central and obstructive apnea. With decreasing GA, the incidence of apneic episodes increases. Prolonged intermittent hypoxemia is associated with death and disability at 18 months of age.
It is clear that the above described changes in the respiratory system make the preterm infant highly susceptible for respiratory failure. As a result, most preterm infants need respiratory support to restore gas exchange. For a long time, invasive mechanical ventilation (IMV) was the first choice of treatment.

**Invasive mechanical ventilation**

In the 1950s, ventilators for pediatric use were quickly developed, because the polio-epidemic caused respiratory insufficiency. This also resulted in the introduction of IMV on the neonatology ward in the 1960s. IMV appeared to be very effective in treating respiratory insufficiency in preterm infants and soon, most preterm infants were supported with IMV from birth onwards. However, the first papers on adverse effects of IMV appeared shortly after its introduction, both in animal models and in clinical studies. Over the course of the following decades, multiple adverse effects of IMV have been identified.

The short-term complications of IMV are air leak syndromes, ventilator associated pneumonia, and airway injury leading to subglottic stenosis. However, the most important complication of IMV is called ventilator induced lung injury (VILI). Risk factors for VILI, mainly identified by animal studies, are volutrauma, atelectotrauma and biotrauma. Volutrauma is caused by alveolar overdistension due to high tidal volumes. The presence of a low end-expiratory lung volume leads to collapse of lung units (atelectasis); repetitively opening and collapsing during inspiration and expiration respectively, will cause atelectotrauma. Finally, the administration of high levels of supplemental oxygen leads to oxygen toxicity. As result, damage to the epithelial cells induces an inflammatory cascade (biotrauma) with pulmonary edema. This inflammatory cascade with subsequent injury can also be induced by systemic inflammation such as septicemia.

IMV and subsequent VILI is considered an important risk factor in the development of the two most common complications after preterm birth, namely bronchopulmonary dysplasia and adverse neurodevelopmental outcome. In the next two paragraphs, we will discuss these complications in more detail.

**Bronchopulmonary dysplasia**

The development of bronchopulmonary dysplasia (BPD) starts at being born with an underdeveloped respiratory system. In 1967, Northway et al. described BPD for the first time. Thirty-two patients were described with a mean birth weight of 1893 grams, in need of IMV with high pressures and high oxygen levels for respiratory distress syndrome (RDS). Thirteen of the 32 patients needed prolonged oxygen supplementation, of which nine survived beyond four weeks of age with pulmonary disease. Four of them developed chronic pulmonary disease during neonatal admission, slowly becoming asymptomatic during the following months. Based on chest X-rays and post-mortem
examination of the infants who died after prolonged pulmonary disease, BPD was described as chronic lung disease with extended inflammation and fibrosis of the lung parenchyma, hypertrophy of peribronchiolar smooth muscle cells and atelectatic areas throughout the lungs (Figure 2a). As a result of this publication, BPD was defined as needing supplemental oxygen more than 28 days. In terms of pathophysiology, classic BPD was almost exclusively linked to high pressure, high oxygen ventilation.

Since the introduction of antenatal steroids to promote lung maturation and the possibility to treat RDS with exogenous surfactant, most preterm infants with a GA > 30 weeks now survive without residual lung disease. These improvements in neonatal care have also resulted in an increased survival rate of extremely preterm infants (GA < 28 weeks), who’s lungs are in the canalicular and saccular stage of development. Exposed to less and more gentle ventilation, these infants develop another type of chronic lung disease, characterized by development arrest and simplification of the lung architecture and not so much lung fibrosis. This type of chronic lung disease is called ‘new’ BPD36-38 (Figure 2b).

The underlying pathophysiology of ‘new’ BPD is much more complex than the etiology of ‘old’ BPD (Figure 3). Although IMV remains an extremely important risk factor in the development of BPD, other risk factors have also been identified, such as chorioamnionitis, genetic susceptibility, intra-uterine growth restriction, lower GA, AOP, pulmonary fluid overload and poor nutrition32, 39, 40. Based on these changes, it was clear that a new definition was necessary for diagnosing BPD. As a result, an international consensus meeting in 2001 redefined the criteria for BPD41. During this meeting, it was also decided that the dichotomous definition for BPD did not take into account the fact that the severity of BPD – and thus the risk of complication – can differ considerably between infants. This resulted in the following severity-based definition for BPD:

- The need for supplemental oxygen during more than 28 cumulative days and
  - Mild BPD: no need for supplemental oxygen at 36 weeks postmenstrual age (PMA)
  - Moderate BPD: the need for < 30% oxygen at 36 weeks PMA
  - Severe BPD: the need for ≥ 30% oxygen or positive pressure support at 36 weeks PMA

The compromised lung function in BPD infants increases the risk on pulmonary complications throughout childhood, such as prolonged primary hospitalization, recurrent respiratory infections, asthma diagnosis and reduced lung function persisting into adulthood42-45. A large cohort study showed that the severity-based diagnosis of BPD was an adequate predictor for pulmonary outcome, with an increasing risk on adverse outcome with every increasing severity level of BPD46.
Figure 2. a. Lung parenchymal damage in old BPD. b. Lung parenchymal damage in new BPD. Reproduced with permission from Baraldi E, Filippone M. N Engl J Med 2007;357:1946-1955. Copyright Massachusetts Medical Society.
Interestingly, several studies have shown that BPD is also an independent risk factor for adverse neurodevelopmental outcome, as will be discussed in more detail in the next paragraph.

**Neurodevelopmental impairment**

Neurodevelopmental impairment (NDI) is a composite outcome, aggregating adverse cognitive, neurological, neurosensory and often motor outcomes. To assess neurodevelopmental outcome accurately, standard tests with trained professionals are performed. The follow up team usually includes a developmental psychologist, a neuro- or developmental pediatrician and a child physiotherapist. Depending on the corrected postnatal age of the infant, different tests are used to assess development. Internationally, NDI is usually defined as having either a mental or psychomotor development impairment, having some form of cerebral palsy (CP) or having a visual or hearing impairment. However, neurodevelopmental impairment is not always classified in the same manner. Different studies use different cut-off scores of impairment, with or without including motor scores, which makes it difficult to compare the results of different studies with each other.

Most studies assess the neurodevelopmental outcome in former preterm infants for the first time at two years corrected age (CA), because CP can be accurately diagnosed at this time. Furthermore, at two years CA, cognitive development is more and more distinguishable from motor development and language development has started. At this time, most infants are assessed with the Bayley Scales of Infant and Toddler Development (BSID). Combining different items of the test, the performance of an infant can be summarized by a Mental Development Index (MDI) and a Psychomotor Development

![Diagram of the pathogenesis of BPD](image_url)
Index (PDI). Both tests are standardized with a score of 100 being the mean. Impairment is defined as having a score below 85 (-1 standard deviation (SD)), with a score below 70 (-2 SD) being considered a severe impairment. Over time, the developmental test has been adapted as indicated by the different versions \(^47,48\). Comparison of the different versions of the BSID is challenging. The international community has agreed on adding 5 points to the MDI and 10 points to the PDI of the second version of the BSID to compare it with the third version \(^49\).

CP as assessed by a pediatrician is the final common pathway of having any disorder in the development of posture and motor control, using standardized diagnostic criteria \(^50,51\). The severity of CP is classified in five levels by the gross motor function classification score, ranging from mild coordination problems (level 1) to severe disability needing assisting technology in every aspect of life (level 5) \(^52\).

Neurosensory impairment is also one of the components of adverse neurodevelopmental outcome and is mostly defined as visual impairment leading to blindness in at least one eye and hearing impairment needing hearing aids.

The next important age to assess neurodevelopmental outcome is at five years CA. By this age, children are starting primary school, and this is the first time that cognitive development can be assessed in its different domains, e.g. verbal intelligence quotient (IQ), performance IQ and processing speed, combined in the full scale IQ score. For this assessment, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) \(^53\) is most often used. Similar to the BSID, this test needs to be assessed by a trained psychologist and scores are standardized with a score of 100 as the mean, score 85 as -1 SD (impaired) and score 70 as -2 SD (severely impaired). The movement Assessment Battery for Children (movement ABC) \(^54\) is used to assess motor development. The movement ABC is used to investigate fine motor, ball, and balance skills. A standard score ≤ 7 is considered as abnormal, a standard score of ≤ 5 is cut-off for impairment. CP and neurosensory impairment are diagnosed in the same standardized manner as at age two. Initially, most published literature on neurodevelopment reported the outcome at age two. However, it became clear that neurodevelopmental assessment at two years did not always predict neurodevelopment at five years age accurately. In fact, studies have shown, that for the general preterm population, the correlation between cognitive and motor functioning at two and five years of age is only fair \(^55\). For this reason, it is now recommended to extent follow-up of preterm infants at risk to at least five years of age.

**IMV, BPD and neurodevelopmental outcome**

As previously mentioned, both IMV and BPD are independent risk factors for developing NDI later in life \(^35,46\). Multiple hypotheses have been suggested to explain the underlying mechanism for the association between IMV and NDI.
First, brain damage might be caused by IMV itself. Five days on IMV in an animal model using preterm baboons resulted in a higher incidence of cerebral injury compared to one day on IMV\textsuperscript{56}. This might have been due to a delay in myelination or increased radial glia throughout the subventricular and ependymal zones in the ventilated animals. The clinical relationship between duration of IMV and NDI has been established in a large cohort study published in 2005. That study by Walsh et al. showed that every additional week of IMV increased the risk on adverse neurodevelopmental outcome with 18\%\textsuperscript{35}. It is important to emphasize that this study was conducted in an era when preterm infants were primarily started on IMV, with a median duration of 18 days in the total cohort, up to 23 IMV days in the surviving infants.

Second, the effect of IMV on neurodevelopmental outcome could be mediated through BPD. As described above, IMV is an important risk factor for the development of BPD. Multiple large cohort studies identified BPD as one of the major risk factors for adverse neurodevelopmental sequelae later in life\textsuperscript{46, 57, 58}. Infants with BPD are prone to experience more chronic hypoxia compared to preterm infants without BPD. As demonstrated in animal models, chronic hypoxia is associated with progressive ventriculomegaly\textsuperscript{59}, decreased cortical thickness and white matter\textsuperscript{60}, and loss of glial cells\textsuperscript{61}. To treat chronic hypoxia, administration of supplemental oxygen is often necessary. However, hyperoxia is associated with the induction of apoptotic neurodegenerative reactions in the fore-brain of rat models, due to the production of reactive oxygen species (ROS) and altered gene expression of proteins controlling neuronal survival\textsuperscript{62}. In addition to the already increased inflammatory state of infants with (developing) BPD and the increased risk of intra-uterine infection and neonatal sepsis during admission on the neonatal ward, ROS induce an inflammatory response\textsuperscript{63, 64}. The released inflammatory mediators cause white matter dysmaturation\textsuperscript{65}, increasing the risk on NDI later in life. The studies reporting on the relationship between BPD and neurodevelopmental outcome mostly used the old, binary definition of BPD. More recent studies also used the new severity-based definition of BPD to assess its impact on NDI at two years CA. These studies have shown conflicting results, one study showing increasing risk on adverse outcome with every increasing severity level of BPD\textsuperscript{15}, while another study could not confirm this finding\textsuperscript{66}. To date, no study has been published exploring the relationship between severity of BPD and neurodevelopmental outcome at five years CA.

Although the limited correlation between outcome at two and five years CA has been established for the general preterm population, it is unknown whether this is also true for the selected population of infants with BPD, which can be considered a subgroup with the highest risk of adverse neurodevelopmental outcome. In addition, it is also unclear if this correlation differs depending on the severity of BPD.
Changes in respiratory support practices

It is clear that the above described complications of IMV and BPD have changed respiratory support practices in the neonatal intensive care unit (NICU). Aiming to reduce the risk on BPD and adverse neurodevelopmental outcome, the focus of respiratory support has shifted from IMV to modes of non-invasive support. The different options of non-invasive support are described in this section.

Non-invasive respiratory support

**Nasal continuous positive airway pressure** (nCPAP) provides positive pressure via the nose to splint the upper airways and is an effective way to give respiratory support to preterm infants. It reduces the frequency and severity of obstructive and mixed AOP. Furthermore, nCPAP increases functional residual lung capacity and end-expiratory lung volumes improving gas exchange at alveolar level. Randomized controlled trials (RCTs) have shown that starting respiratory support with nCPAP in the delivery room (DR) instead of IMV significantly decreases the risk on mortality and BPD. **Nasal intermittent positive pressure ventilation** (nIPPV) is an intensified mode of nCPAP, in which positive pressure inflations are intermittently administered in addition to nCPAP. This method is more effective in reducing AOP and extubation failure in preterm infants compared to nCPAP. Synchronizing nIPPV with the breathing effort of the infant decreases breathing effort and is more effective in preventing intubation compared to nCPAP.

Pharmacological treatment

One group of drugs aims to improve the condition of the lung. **Antenatal corticosteroids** promoting intra-uterine lung development have proven to be effective in reducing the duration of mechanical ventilation and reducing the need for supplemental oxygen in preterm infants. Since inflammation is a large modulator in the pathogenesis of lung injury and BPD, **postnatal corticosteroids** might help to attenuate the inflammatory response. A variety of treatment regimens have been studied, most of them showing a positive effect on extubation rate and BPD incidence. However, the safety of postnatal corticosteroids on long-term outcomes is questioned. Therefore, routine use of postnatal steroids is not yet recommended. **Diuretics** reducing pulmonary fluid overload improve lung compliance, but do not affect BPD incidence. In the first days postpartum, a lack of endogenous surfactant can cause RDS, in which case **exogenous surfactant** can be administered. Surfactant therapy reduces the risk on air leak syndromes, mortality and BPD in preterm infants with RDS, by reducing surface tension of the alveoli and improving lung volumes. Over the last years, a new technique was developed to administer surfactant by inserting a small flexible catheter in the trachea just below the vocal cords, omitting the need for intubation to administer surfactant...
therapy. This minimally invasive surfactant therapy (MIST) rapidly improves lung volumes. Meta-analysis showed that MIST is more effective in reducing the need for IMV and BPD incidence compared to invasive surfactant administration.

Another group of drugs aims to reduce respiratory failure caused by AOP. In the first weeks of life, preterm infants are likely to develop apnea. The standard choice of treatment for AOP is caffeine, from the pharmacological group of methylxanthines. Although the mechanisms of action are not completely understood, methylxanthines are inhibitors of the adenosine receptor, modulating the central respiratory drive.

Reported physiological effects of caffeine are stimulation of the central nervous system and increased peripheral chemoreceptor responsiveness to CO₂, increased diaphragmatic activity and increased tidal volumes. A large placebo-controlled trial shows that caffeine reduces AOP frequency, the need for IMV and the risk of BPD. Also, caffeine treatment is associated with reduced risk of NDI at 18-21 months CA and with improved motor coordination even at eleven years of age. A caffeine concentration of 15-20 mg.L⁻¹ is considered therapeutic. Usually, a loading dose of 20 mg.kg⁻¹ caffeine citrate and 5 mg.kg⁻¹.d⁻¹ is prescribed in preterm infants. To maintain the therapeutic caffeine concentration > 15 mg.L⁻¹, a pharmacokinetic model showed that this dose needs to be increased based on increasing GA, postnatal age and weight, or that a higher maintenance dose of 10 mg.kg⁻¹.d⁻¹ needs to be administered following a loading dose of 20 mg.kg⁻¹.d⁻¹. However, this has not been investigated in neonatal practice, and thus, the optimum dose of caffeine treatment remains unknown.

If AOP persists during caffeine treatment, doxapram can be added, in order to stimulate the central breathing center and the peripheral chemoreceptors in the carotid bodies. Although doxapram appears to be effective in reducing apnea frequency, some observational studies report on short-term adverse effects and possible neurodevelopmental delay after doxapram treatment. Due to these reports, doxapram is not used as first choice of treatment of AOP, although there are large differences in the use of doxapram across the world. However, observational studies investigating doxapram are always confounded by indication: the infants who receive doxapram will always have a higher incidence of AOP and higher risks of other morbidities. The described associations between doxapram and long-term outcomes have not been corrected for these confounders. The true long-term effect of doxapram on preterm infants is therefore still unknown, since current evidence of doxapram has not been systematically reviewed nor has the relationship between doxapram and neurodevelopmental outcome been corrected for confounders.

Although the above described treatment options should enable clinicians to implement a restrictive IMV policy, it remains unclear whether this is feasible in daily clinical practice and what the effects of such a policy are on the incidence of BPD and the risk of NDI. It needs to be considered that such a policy may also have possible adverse effects.
on NDI, mediated for instance through accepting a higher rate of AOP and the increased use of doxapram. Furthermore, the association between IMV and NDI was established in an era when IMV was the primary mode of respiratory support in preterm infants. It is unknown whether this association still exist in an era of non-invasive respiratory support.

Implementation of a non-invasive respiratory strategy in Amsterdam

Taking the growing evidence into account that IMV should be avoided in preterm infants, the NICU of the Emma Children’s Hospital/Academic Medical Center (AMC) in Amsterdam implemented a non-invasive respiratory support policy over the last years, aiming to reduce mechanical ventilation and subsequently BPD and NDI. The newly advocated policy includes major changes in both DR and NICU management. Infants in the DR are only to be intubated if they need resuscitation with chest compressions after persistent bradycardia. Exogenous surfactant is administered when an infant has signs of respiratory distress and has a prolonged need for > 30% oxygen, primarily using MIST. Criteria for intubation on the NICU are:
- Fraction of inspired oxygen > 0.40 with signs of respiratory distress and/or
- > 1 apnea/hour requiring vigorous stimulation or bag-and-mask ventilation and/or
- Hypercapnia causing a pH < 7.2

Open-lung high-frequency ventilation is started when an infant meets the intubation criteria. The aim is to transfer patients back to nCPAP within the first 12 hours of life. Caffeine, non-invasive ventilation and permissive hypercapnia are used to keep infants on non-invasive support. Doxapram can be used as a secondary treatment in all infants who fail the aforementioned treatment options.

Implementation of this strategy allows us to answer many of the unresolved issues on respiratory support policies as mentioned in this chapter, and as listed in the aims and outline of this thesis.
Aim of this thesis

The aim of this thesis is to assess the effect of a restricted respiratory management policy on neurodevelopmental outcome in preterm infants by answering the following questions:

1. Is it feasible to implement a restrictive IMV policy in preterm infants born with a GA below 30 weeks?
2. Does the implementation of a restrictive IMV policy lead to a reduction in the incidence of BPD and adverse neurodevelopmental outcome at two years CA?
3. Does the association between IMV duration and neurodevelopmental outcome still exist in an era of restrictive IMV?
4. Is BPD severity associated with neurodevelopmental outcome at two and five years corrected age and how are the outcomes at these two time points correlated?
5. What is the optimum dosage of caffeine treatment?
6. What is the effect of doxapram treatment on neurodevelopmental outcome?
7. Is doxapram treatment for AOP effective and safe on short and long-term outcomes?

OUTLINE

Based on the growing evidence that IMV in preterm infants induces long-term pulmonary morbidity as well as neurodevelopmental sequelae, as discussed in Chapter 1, a restrictive mechanical ventilation policy was introduced in the AMC.

In Chapter 2, the feasibility and effectiveness on long-term neurodevelopmental outcome of this policy are assessed, by comparing a cohort before and after implementation of the restrictive IMV policy.

In the era of restrictive ventilation, it is unclear whether the association between duration of IMV and adverse neurodevelopmental outcome still exists. Therefore, Chapter 3 explores the association between duration of mechanical ventilation and neurodevelopmental outcome at two years CA.

The relationship between BPD severity and neurodevelopmental outcome at two years CA has been studied, but results are conflicting. Furthermore, no study assessed this association at five years CA. Therefore, in Chapter 4, we explore the association between BPD severity and NDI at two and five years CA in a cohort of preterm infants. Moreover, Chapter 4 assesses whether the outcome at two years accurately predicts outcome at five years CA in BPD infants.
In 2017, an article was published in the New England Journal of Medicine on lung function at eight years in extremely premature infants. This article described three epochs of preterm infants, concluding that there was no significant decline in oxygen dependence at 36 weeks PMA and no significant improvement in lung function in childhood over time, despite the decreased use of mechanical ventilation in the neonatal period. **Chapter 5** consists of a letter to the editor, proposing an alternative explanation for these reported results.

In order to achieve a non-invasive respiratory policy in preterm infants, pharmacologic agents such as caffeine and doxapram are used to decrease AOP. In **Chapter 6**, a systematic review describes and appraises all published RCTs reporting on different dosages of caffeine, in order to find the optimal dosage of caffeine.

Doxapram is known as an effective agent to reduce AOP, but several small studies reported short and long-term adverse effects after doxapram treatment. The case-control study in **Chapter 7** explores the association between doxapram and NDI at two years CA.

Although a Cochrane review summarized RCTs on doxapram\textsuperscript{94}, there is also a considerable amount of non-randomized studies, which have not been reviewed. To evaluate the safety of doxapram treatment in preterm infants, **Chapter 8** will systematically review all existing evidence on doxapram treatment, including non-randomized evidence.

**Chapter 9** discusses the most important findings of this thesis and provides future perspectives for practice and research. A Dutch summary can be found in **Chapter 10**.
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