From the Department of Women´s and Children´s Health
Karolinska Institutet, Stockholm, Sweden

NEWBORN RESPIRATORY SUPPORT USING DISTENDING PRESSURE: THE EFFECT OF INTERFACES AND SYSTEM DESIGN ON PERFORMANCE AND OUTCOME

Sonja Baldursdottir

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Newborn respiratory support using distending pressure: the effect of interfaces and system design on performance and outcome
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Sonja Baldursdottir

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Principal Supervisor:
Professor Baldvin Jonsson
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Neonatology, Obstetrics and Gynecology

Co-supervisor(s):
Associate Professor Thomas Drevhammar
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Neonatology, Obstetrics and Gynecology

Snorri Donaldsson, PhD
Karolinska Institutet
Department of Women´s and Children´s Health
Division of Neonatology, Obstetrics and Gynecology

Opponent:
Professor Colm O´Donnell
School of Medicine & Medical Science, University College Dublin

Examination Board:
Associate Professor Kajsa Bohlin-Blennow
Karolinska Institutet
Department of Clinical Science, Intervention and Technology
Division of Pediatrics

Associate Professor Ola Andersson
Lund University
Department of Clinical Sciences
Division of Neonatology

Associate Professor Stefan Johansson
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology

To my family

POPULAR SCIENCE SUMMARY OF THE THESIS

Infants, especially those who are born to soon, may need help breathing after birth. Mechanical ventilation has saved many lives, but it also causes trauma to the lungs which can increase the risk of developing chronic lung disease. Therefore, it is preferable to support the infants own breathing and avoid mechanical ventilation. Continuous positive airway pressure (CPAP) is a gentler way of providing breathing support. It gives a continuous flow of air into the nose of the infant creating pressure that aids lung expansion and prevents small airways from collapsing. Different CPAP systems as well as interfaces are available.

Just as breathing through a stuffy nose or a thin straw can be difficult, the tests carried out in study I showed that some interfaces can be hard to breathe through. The use of narrow tubes in some CPAP system designs can cause a higher pressure than intended to be delivered to the infants´ lungs. In contrast, leakage of air between the nose and the CPAP interface can cause less pressure to be delivered to the lungs. These aspects may affect the likelihood of the newborn failing to breathe on CPAP and needing mechanical ventilation. In study II leakage was measured during CPAP treatment in 50 infants with the two most commonly used types of nasal interfaces. We found that leakage was common. However, an encouraging finding was that it was often possible to reduce the leakage by simple adjustments by the caregiver.

Infants that do not breathe after birth need to be ventilated. This is usually done with a T-piece system that gives breaths through a face mask that needs to be held in place over the newborns nose and mouth. A new system that can be used with a nasal interface has been developed. In study III we found that infants, that were born more than 3 months to early and received help with the new system in the delivery room, were less likely to need mechanical ventilation during the first week of life. The study did not reveal a difference in the development of chronic lung disease.

Infants that need help breathing after birth are often separated from the mother and moved to a special table. In study IV we found that a new simplified system could be used to give both nasal CPAP breathing support and assisted breaths after birth, if needed. This could be done while the newborn was skin-to-skin with the mother thus minimising the mother-child separation during the first hours after birth.

Hopefully some of the insights gained can be used to improve CPAP treatment even where resources are lacking and help more newborns breathe without needing mechanical ventilation. A system with a nasal interface that can give assisted breaths as well as CPAP and fixated with a cap may facilitate skin-to-skin care and reduce separation of infants from their mothers. More research is needed to explore the relationship between the way of supporting breathing after birth and the development of chronic lung disease.

ABSTRACT

Preterm infants often require respiratory support after birth due to lung immaturity. The preferred method of providing respiratory support to breathing infants in respiratory distress is non-invasively with continuous positive airway pressure (CPAP). This has been associated with less mortality and morbidity compared to invasive mechanical ventilation. The continuous distending pressure that improves lung aeration and gas exchange can be generated with different CPAP systems and is usually applied through either nasal mask or prongs in the neonatal intensive care unit while face mask has been the most used interface in the delivery room.

The overall aim of this thesis was to evaluate how different interfaces and system design affect the quality and outcome of CPAP respiratory support for neonates in the delivery room and neonatal intensive care unit.

In study I the literature was reviewed regarding differences in bubble CPAP systems intended for use in low-resource settings. Tests in a mechanical lung model showed how using an interface with high resistance or expiratory tubing with a narrow diameter can lead to increased imposed work of breathing and higher delivered mean airway pressure.

Study II was a randomised clinical cross-over study with the aim of measuring leakage during CPAP treatment in newborn infants with nasal mask versus nasal prongs. Measurements revealed a greater leakage for nasal mask compared with prongs. Although some leakage was common with both interfaces it could often be reduced with simple care adjustments.

Study III was a follow up study of extremely preterm infants included in the randomised CORSAD study in Stockholm. Medical records of the infants that had been randomised to initial respiratory support with either rPAP using nasal prongs or T-piece with face mask were reviewed up to 36 weeks of postmenstrual age. Infants in the rPAP group were less likely to be intubated and receive mechanical ventilation during the first week of life. At 36 weeks of postmenstrual age there was no statistically significant difference found in mortality or bronchopulmonary dysplasia.

Study IV was a feasibility study evaluating a simplified version of the rPAP system for delivery room stabilisation and continued support during transportation and after arrival in the neonatal unit. The system could be used for stabilisation both skin-to-skin and on a resuscitation table as well as for continued support the first hours after birth. The study did not reveal problems with the system or safety.

LIST OF SCIENTIFIC PAPERS

I. **Baldursdottir S**, Falk M, Donaldsson S, Jonsson B, Drevhammar T. Basic principles of neonatal bubble CPAP: effects on CPAP delivery and imposed work of breathing when altering the original design. Archives of Disease in Childhood – Fetal and Neonatal Edition. 2020;105(5):550-4.

II. Falk M, Gunnarsdottir K, **Baldursdottir S**, Donaldsson S, Jonsson B, Drevhammar T. Interface leakage during neonatal CPAP treatment: a randomised, cross-over trial. Archives of Disease in Childhood – Fetal and Neonatal Edition. 2021;106(6):663-7.

III. **Baldursdottir S**, Donaldsson S, Palleri E, Drevhammar T, Jonsson B. Respiratory outcomes after delivery room stabilisation with a new respiratory support system using nasal prongs. Acta Paediatrica. 2023;112(4):719-25.

IV. **Baldursdottir S***, Gunnarsdottir K*, Donaldsson S, Jonsson B, Drevhammar T. Facilitating skin-to-skin stabilisation and late cord clamping of preterm infants: feasibility of a new and simplified rPAP system. Submitted manuscript. *shared first author

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LIST OF ABBREVIATIONS

bCPAP	Bubble Continuous Positive Airway Pressure
BPD	Bronchopulmonary Dysplasia
CDP	Continuous Distending Pressure
CPAP	Continuous Positive Airway Pressure
DR	Delivery Room
FRC	Functional Residual Capacity
GA	Gestational Age
GCP	Good Clinical Practice
HFNC	High Flow Nasal Cannula
ILCOR	International Liaison Committee on Resuscitation
IQR	Interquartile Range
IUGR	Intrauterine Growth Restriction
IVH	Intraventricular Haemorrhage
iWOB	Imposed Work of Breathing
LMIC	Low- and Middle-Income Countries
MV	Mechanical Ventilation
NEC	Necrotizing Enterocolitis
nCPAP	Nasal Continuous Positive Airway Pressure
NICU	Neonatal Intensive Care Unit
PDA	Patent Ductus Arteriosus
PEEP	Positive End Expiratory Pressure
PMA	Postmenstrual Age
PPV	Positive Pressure Ventilation
RDS	Respiratory Distress Syndrome

1 INTRODUCTION

Successful respiratory support is crucial for the survival of infants experiencing problems adapting after birth. Mechanical ventilation has contributed to the increased survival of preterm infants with respiratory distress, however mechanical ventilation can cause lung injury increasing the risk of developing bronchopulmonary dysplasia (BPD) (1). BPD is one of the most significant morbidities seen after preterm birth.

A less invasive mode of respiratory support, continuous positive airway pressure (CPAP) treatment first described by Gregory et al (2), has become the preferred method of respiratory support in neonates during the last decades. (3, 4) First, observational studies reported associations between increased use of CPAP and lower rates of BPD. (5-8) Later, meta-analysis of randomised clinical trials showed a reduction in the combined outcome of death and BPD when respiratory support was started with CPAP compared to intubation and mechanical ventilation in very preterm infants with respiratory distress after birth. (9-13) Based on this, CPAP is recommended by international guidelines for spontaneously breathing preterm infants with respiratory distress in the delivery room rather than intubation and intermittent positive pressure ventilation. (14-16) CPAP treatment has also been shown to reduce the need for re-intubation when used post-extubation. (17)

CPAP treatment is based on providing a positive airway pressure during both inspiration and expiration with the aim of stabilising the ribcage and airways of the infants (18), aiding lung expansion (19) and preventing alveolar collapse, thereby increasing the pulmonary surface area and optimising gas exchange. Common indications for CPAP treatment in newborn infants include respiratory distress syndrome (RDS) (15), apnea of prematurity (20), meconium aspiration syndrome (21, 22) and transient tachypnea of the newborn (23).

The interfaces and systems used to provide CPAP have changed over time and still vary between countries and centres depending on preferences, resources, and availability. This thesis summarises the evidence behind the use of different interfaces and CPAP system designs intended for stabilisation in the delivery room (DR) and respiratory support in the neonatal intensive care unit (NICU).

2 LITERATURE REVIEW

2.1 INTERFACES FOR CPAP DELIVERY

Through the years, different interfaces have been used for providing CPAP to infants with respiratory distress. In its first description, CPAP was delivered via endotracheal tube or head box. (2) Subsequently the use of face masks (24) and chambers (25) was reported. However, due to complications associated with the application of tight fitting masks and boxes requiring a seal at the neck, (26) nasal interfaces became more popular. These included single nasal and nasopharyngeal prongs that were later replaced by short binasal prongs as they showed favourable results in randomised trials (27-29) and subsequent meta-analysis (30), plus were perceived to be better tolerated by the patient and easier to insert.

Currently the recommended interfaces are nasal mask and nasal prongs. (15) The nasal mask covers the nose while prongs are short binasal tubes that are fitted into the nostrils. Both interfaces should fit tightly to avoid leakage and a resulting drop in CPAP pressure. A good fit without causing excessive pressure on the underlying tissue risking skin injury, a well-known complication of nasal CPAP treatment. (31) The choice between a nasal mask or prong interface can potentially affect the comfort and effect of CPAP treatment. However, evidence on which interface is better is scarce and guidelines still recommend the use of either nasal mask or prongs. (15) Therefore, the choice of a nasal interface seems to have been largely influenced by individual preferences and local traditions, rather than evidence.

Figure 1: *Nasal masks and prongs.*

During recent years there has been an increased interest in the research area of devices and interfaces used for providing CPAP. Publications have reported favourable clinical outcomes in infants receiving CPAP with nasal mask vs prongs without explaining what this difference in outcome is due to. (32) The following subchapters summarise the clinical research available on the two interfaces, their physiological properties and effects in vitro.

Factors that might reveal possible properties that explain the differences between them in clinical settings.

2.1.1 Interface resistance

The resistance to airflow in the nasal interface can cause a drop in pressure with less actual pressure in the patient airway than the pressure measured in the delivery circuit of the CPAP system.

Two studies measured the resistance of different sizes of prongs and nasal masks. (33, 34) Both were conducted in vitro and showed the highest resistance to flow in the smallest sizes of prongs and lowest for nasal masks. Nasal prongs from different manufacturers vary in internal diameter and length and as these factors affect resistance, prongs of the same size from different manufacturers can vary in resistance. Infant Flow prongs were found to have lower resistance than Fisher & Paykel and Hudson prongs. RAM cannula were found to have high resistance at all sizes and flow rates leading to a large drop in pressure. (34) RAM cannula is an interface that has gained popularity during recent years and although only approved for use with low/high flow humidified oxygen it is being used for CPAP treatment in some centres. The study by Green et al. (34) together with another study showing the delivery of 60% lower pressure than set CPAP level (35) indicate that the use of RAM cannula for CPAP treatment should be discouraged.

2.1.2 Interface leakage

As CPAP treatment is dependent on the actual distending pressure delivered to the lungs, which is determined by the gas flow and leakage at the nasal interface (36), leakage might be an important factor affecting the efficacy of CPAP treatment.

In a trial by Hückstädt et al (37), most of the patients treated with CPAP had leakage. However, the trial did not provide details on leakage or compare interfaces. No prior studies reporting direct measurements on leakage during neonatal nCPAP treatment with nasal mask and prongs were found. One study used other indirect methods to identify interface leak: a reduction in bubble amplitude on the nasal pressure signal and a fall in mean airway pressure and correlated this to intermittent hypoxia in preterm infants that were alternated between nasal mask and prongs. The researchers found no difference in % time with interface leak, hypoxia or bradycardia between the interfaces. (38)

2.1.3 Delivered airway pressure

Three studies published in 2019 (39) and 2020 (38, 40) aimed to compare delivered pressure during CPAP treatment with different interfaces by different methods. Cakir et al

(39) calculated transpulmonary pressure from measured esophageal pressure and used this as a surrogate for the pressure in the distal airways during CPAP support. The measurements performed on 62 newborns with transient tachypnea randomised to CPAP with prongs vs nasal mask showed no significant differences between the interfaces. Sharma et al (40) measured oropharyngeal pressure in preterm neonates with gestational age between 28 and 34 weeks on CPAP with RAM cannula, Hudson prongs and nasal mask. They found that oropharyngeal pressure was lower than set CPAP level for all studied interfaces but correlated the best with nasal mask. The most recently published study on 20 extremely preterm infants (25-27 weeks GA) with postnasal age 14-24 days recorded episodes with hypoxaemia, bradycardia, and pressure loss at the interface (CPAP circuit pressure measured immediately proximal to the nasal interface) in each patient with both nasal mask and prongs. The order of interfaces was not randomised. The recordings were similar for both interfaces and the authors concluded that nasal mask and prongs can be used interchangeably for providing CPAP to preterm infants after 72 hours of age. (38)

2.1.4 CPAP failure

A frequently studied outcome in clinical trials comparing efficacy of CPAP delivery in preterm infants with nasal mask vs prongs is CPAP failure, as defined by the need for intubation and mechanical ventilation, within 72 hours. The studies identified included between 60-178 preterm infants who were randomised to receive CPAP with nasal mask vs prongs for respiratory distress, either as primary respiratory support or post extubation. (32, 41-45) All studies showed either equal or favourable outcomes for nasal masks. Two studies (32, 43) reached statistical significance and three meta-analyses including these randomised controlled trials reveal a lower rate of CPAP failure within the first 72 h after treatment initiation in preterm infants randomised to nasal mask compared to prongs. (46-48) A Cochrane systematic review published in 2022 concludes that available data provide low-certainty evidence that providing CPAP with nasal mask may reduce CPAP failure compared with prongs. (49)

2.1.5 BPD

The literature search identified one randomised controlled trial with the primary aim of comparing the incidence of moderate and severe BPD in preterm infants randomised to CPAP delivered with nasal mask vs prongs. (50) The study that included 149 preterm infants with GA between 26-32 weeks revealed a lower incidence of moderate and severe BPD in the group of infants randomised to nasal mask although no difference in the overall BPD was seen. Other studies have included BPD as a secondary outcome and a meta-

analysis evaluating BPD among other outcomes did not show a statistically significant difference in BPD as defined as the need for oxygen or respiratory support at 36 weeks postmenstrual age after CPAP delivered via nasal mask vs prongs. (48)

2.1.6 Nasal injury

Nasal injury is a well-known and common complication of nasal CPAP treatment. It can occur in different locations and vary in severity from local erythema of the skin to necrosis with irreversible injury and nasal deformity, causing pain as well as increased risk of bacterial infections. (51)

The first study comparing the incidence of nasal trauma caused by nasal mask compared with prongs was published in 2005 and included 89 very low birth weight infants (<1501g).(31) It showed that nasal trauma was common, with no significant difference in incidence between groups (mask 29% vs prongs 35%, P=0.5). However, the location differed with nasal mask primarily causing trauma to the junction between the nasal septum and the philtrum while prongs mostly affected the walls of the nasal septum. The study also found a significant correlation between nasal trauma and duration of nCPAP treatment. Since then more studies comparing nasal masks and prongs have included nasal injury as an outcome (32, 41-45, 50, 52) and two studies (53, 54) have randomised preterm infants in 3 groups to compare nasal mask with prongs or rotation of the interfaces. While Newnam et al (53) found no statistically significant difference in mean Neonatal Skin Condition Scale (NSCS) total scores, the study by Bashir et al (54) revealed significantly less injury with nasal mask compared with prongs or rotation of the two. A meta-analysis including the studies mentioned above showed a RR of 0.64 (95% CI 0.55-0.74) for nasal injury with nasal mask compared with prongs (48) and a Cochrane review also concluded that nasal mask may reduce risk of nasal injury compared with prongs. (49)

2.2 INTERFACES FOR DELIVERY ROOM STABILISATION

Neonatal resuscitation guidelines recommend positive pressure ventilation for infants that fail to establish spontaneous breathing after birth. (55, 56) The most used interface to provide positive pressure ventilation in the delivery room has been face mask. However, mask ventilation is often complicated by leakage and airway obstruction which can cause less effective ventilation and delayed establishment of lung aeration. (57-60) Furthermore, placement of the mask over the infants' nose and mouth has been shown to induce apnea (61) which might be triggered by the trigeminocardiac reflex. (61-64) These factors could possibly increase the need for intubation.

To get around the disadvantages of mask ventilation as discussed above, studies comparing nasal interfaces to face mask have been conducted. In 2005, a study by Capasso et al, indicated that nasal prongs might be an advantageous alternative to face mask for providing positive pressure ventilation to neonates with moderate asphyxia after birth. (65) Later two randomised trials enrolling preterm infants compared face mask to a single nasal tube ending in the nasopharynx and found no difference in intubation rates. (66, 67) Two meta-analysis (68, 69) including these heterogenous studies concluded that nasal interfaces might offer some advantages over face mask for neonatal resuscitation in the delivery room, but further testing was needed.

Van Vonderen et al found that when a single nasal tube ending in the nasopharynx was used, it took the caregiver longer to start PPV and airway obstruction occurred more frequently, and leak was greater leading to inadequate tidal volumes compared with face mask. (70) Previously, studies have shown favourable results for short binasal prongs compared to single nasal or nasopharyngeal tube for applying CPAP. (27-30) This could be explained by the increased resistance of the longer nasopharyngeal tube and possible leakage from the contralateral nostril. According to this, short binasal prongs might be a better alternative even for delivery room stabilisation.

The rPAP system, that is a new system for delivery room stabilisation, can be used with either short binasal prongs or face mask. The CORSAD trial that randomised extremely preterm infants to initial respiratory support with the rPAP with short binasal prongs versus T-piece with face mask showed lower rates of DR intubation or death in the rPAP group. (71) As the mechanism of CPAP generation also differs, it is impossible to determine to which extent the favourable outcome is attributable to the nasal interface compared to face mask.

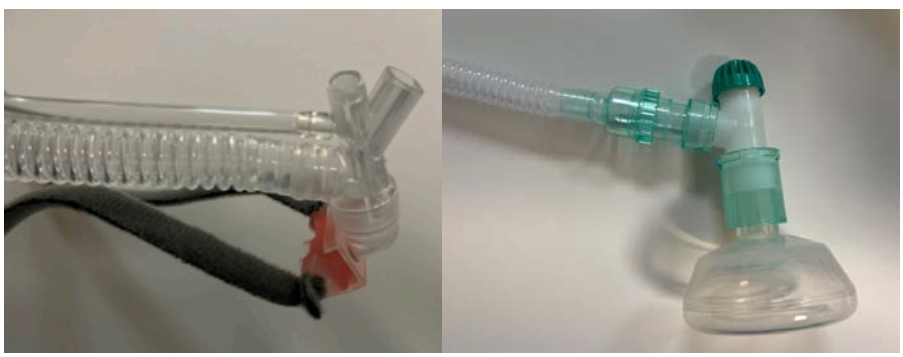

Figure 2: *rPAP with nasal prongs and T-piece with face mask*

Nasal prongs have been suggested as an alternative to face mask for positive pressure ventilation during delivery room stabilisation in international guidelines. (72, 73) A recently published Cochrane review agrees with these guidelines and concludes that nasal interfaces offer a comparable option for respiratory support in the delivery room and may reduce delivery room intubations. (74)

2.3 CPAP SYSTEMS

2.3.1 CPAP generation

There are various systems available for generating CPAP. These fall mainly into two categories: variable-flow CPAP and continuous-flow CPAP.

2.3.1.1 Continuous flow

Ventilator derived CPAP and bubble CPAP are examples of continuous flow systems where the pressure is generated by a resistance on the expiratory limb of the breathing circuit.

In ventilator derived CPAP this resistance is controlled by changing the orifice size of the exhalation valve. The T-piece works in a similar way where the exhalation orifice on the device is manually adjusted by the user to set the CPAP pressure.

In bubble CPAP the resistance is created by submersing the distal end of the expiratory tubing in water and the pressure is decided by the depth of submersion in cm water. (75)

2.3.1.2 Variable flow

The Benveniste device and Infant Flow Driver are examples of variable flow CPAP devices that generate pressure with a gas jet proximal to the infant's nares. The Benveniste technique to deliver CPAP to neonates was described in 1976 (76) and was first applied with face mask or endotracheal tube and later with a nasal interface. Another variable flow device, later marketed as Infant Flow was described by Moa et al in 1988. (77) The device was designed with a fluidic flip mechanism to achieve a constant airway pressure to optimise lung expansion and minimise the work of breathing. The mechanism of pressure stability has been shown with simulated breathing and computational fluid dynamics to be based on the jet of air supporting inspiration being deflected to the outlet on expiration. (78)

2.3.2 CPAP systems in low resource settings

Each year an estimated 15 million babies are born preterm and more than 60% of preterm birth occur in Africa and South Asia. (79, 80) The use of CPAP for newborns with respiratory distress is one of the actions WHO recommends to improve outcome of preterm

birth. (81) However, availability of commercial CPAP devices is limited in many low-resource settings.

Due to its simple design and lower cost than ventilator derived CPAP, bubble CPAP is ideal for use where resources are limited. In recent years, new devices marketed as bubble CPAP have been designed and targeted for low-resource countries. (82) Also, devices are being built locally from available equipment. (83, 84) Many of these devices deviate from the original design and concerns have been raised about this increasing use of CPAP without regulation (79) often without prior testing for reliability and safety.

The bubble CPAP design as described by Sahni and Wung (75) has a low resistance interface connected to the expiratory tube that is submersed in a water bottle. In this design there is minimal dead-space, low resistance to breathing and the pressure is determined by the submersion depth of the distal end of the expiratory tube. As the pressure can be read from the water bottle in cm of water no other pressure meter is necessary.

Some new versions have a large dead-space (82) or use high resistance tubing (85). Other use interfaces such as the RAM cannula or an oxygen cannula with one end submersed in water. (83, 86) As resistance is directly proportional to the length of the tubing and inversely proportional to the radius to the fourth power, changing the diameter or length of the tubing can affect the resistance to breathing. This needs to be kept in mind when designing new devices.

2.4 CPAP AND WORK OF BREATHING

Physiologic work of breathing consists of the work required to overcome the elastic and resistive forces of the lung tissues and airways. (87) Low lung compliance due to surfactant deficiency in combination with increased compliance of the chest wall and narrow, flexible airways are factors that contribute to increased physiologic work of breathing in preterm infants. The aim with CPAP treatment is to splint the upper airways and increase end-expiratory volume thereby stabilising the chest wall and reducing work of breathing. (18, 88) However, resistance to flow contributed by the device, for example due to narrow diameter tubing or interfaces, gives rise to the additional imposed work of breathing required to breathe through the device. The imposed work of breathing varies between different devices. (89-91) The total work of breathing is the sum of the physiologic and imposed work of breathing.

2.5 RESPIRATORY SUPPORT AND BRONCHOPULMONARY DYSPLASIA

BPD is a chronic respiratory disease with the highest occurrence in the most preterm infants, born during the late canalicular or saccular stage of lung development. Besides prematurity, mechanical ventilation is one of the strongest risk factors for BPD. Both BPD and prolonged mechanical ventilation have been associated with neurodevelopmental morbidity. (92) CPAP treatment has been shown to reduce the need for mechanical ventilation and the incidence of BPD and is therefore the recommended first choice for respiratory support in preterm infants with respiratory distress. (15, 93)

Since BPD was first described by Northway et al in 1967 (94), both the pathophysiology and clinical presentation have changed secondary to the introduction of antenatal corticosteroids, surfactant and more gentle ventilation strategies. In line with this, new definitions and ways of grading BPD have been proposed. (95, 96) BPD has classically been defined by the need for supplemental oxygen or respiratory support for more than 28 days or at 36 weeks of postmenstrual age (PMA). (97-99)

BPD is often used as an outcome in clinical studies. A shortcoming of using BPD as an outcome when comparing different treatments and outcomes between centres, is that the outcome is defined by treatment instead of a diagnostic test. In this way the prevalence of the outcome can be affected by saturation targets and variations in clinical practice instead of only reflecting disease severity. Walsh et al wished to address this and proposed the physiologic definition using an oxygen reduction test. (100) In 2018 further refinements of the BPD definition were proposed to take into account the increased use of high flow nasal cannula (HFNC) as well as preterm infants dying from respiratory failure secondary to severe parenchymal lung disease prior to 36 weeks PMA. (101)

Jensen et al have since compared 18 definitions of BPD. They found that BPD graded by level of respiratory support at 36 weeks PMA regardless of current or prior oxygen supplementation best predicted death or serious respiratory morbidity at 18-26 months corrected age. According to this definition, as used in study III in this thesis, infants breathing room air without support at 36 weeks PMA do not have BPD. Those with nasal cannula ≤2 L/min have grade 1 BPD, those with nasal cannula >2 L/min or non-invasive positive airway pressure have grade 2 BPD, while those on invasive mechanical ventilation have grade 3 BPD. (102)

2.6 SUMMARY OF AVAILABLE EVIDENCE AND KNOWLEDGE GAPS

Systems for CPAP delivery differ in their way of generating distending pressure. Bubble CPAP is an example of continuous flow system that is well suited for use in a low resource setting, due to the simplicity of its original design. However, during recent years reports of new systems deviating from the original design that are used in low resource settings without prior testing have been published. This is a concern that has been pointed out by the World Health Organisation. (79)

Guidelines recommend the use of a nasal mask or short binasal prongs for delivering CPAP to newborn infants with respiratory distress. Numerous studies have compared the interfaces, and the evidence indicates that the use of nasal mask may reduce CPAP failure and nasal injury compared with nasal prongs. Still, it is unclear what may explain the improved treatment effect experienced with nasal mask in these studies. The studies have not measured factors such as delivered CPAP pressure or leakage which are factors that are, at least theoretically, important during CPAP treatment.

The interface most used for giving respiratory support in the delivery room is face mask. However, the recent CORSAD trial showed less need for delivery room intubation and death when extremely preterm infants were stabilised with a new respiratory support system using nasal prongs compared with T-piece with face mask. Then new questions arise “how does this affect later need for respiratory support?” and “can a system using nasal prongs be used for continuous respiratory support from birth, during transport and after arrival in the NICU?”

3 RESEARCH AIMS

The overall aim of this thesis is to evaluate how different interfaces and system design affect the quality and outcome of CPAP respiratory support for neonates in the delivery room and neonatal intensive care unit.

Specific aims:

I. To describe components and design of bubble CPAP systems intended for use in low- and middle-income countries and evaluate the in-vitro effects on performance when altering the original bubble CPAP design.

II. To measure and compare leakage during nasal CPAP treatment with nasal mask vs prongs in term and preterm infants and evaluate if leakage can be reduced with simple manoeuvres.

III. To evaluate need for mechanical ventilation and later respiratory morbidity in extremely preterm infants stabilised with a new respiratory support system with low imposed work of breathing using nasal prongs compared to a T-piece with face mask.

IV. To perform a clinical feasibility trial of using a simplified respiratory support system for delivery room stabilisation and continued support during transport and in the NICU for the first hours after birth.

4 MATERIALS AND METHODS

This thesis includes an in vitro study with tests in a mechanical lung model, a randomised clinical study, a follow-up study of a randomised controlled trial and a clinical feasibility study. The methods used in the different studies will be described in the following sections.

4.1 BUBBLE CPAP - TESTS IN A MECHANICAL LUNG MODEL (PAPER I)

The original bubble CPAP design has a low resistance interface directly connected to wide bore expiratory tubing that is submersed in water. This results in a system with low resistance and minimal dead-space and the delivered pressure is reflected by the submersion depth.

By reviewing the literature, several publications describing bubble CPAP devices intended for use in low resource settings that deviate from the original design were found. Three main alterations thought to be of importance were increased dead space, the use of high resistance interface and narrow bore expiratory tubing. Dead space can lead to rebreathing and accumulation of carbon dioxide and should be avoided. The effect of different interfaces and expiratory tubing diameter on mean CPAP and imposed work of breathing was tested in a mechanical lung model.

4.1.1 Mechanical lung model

Measurements were performed using a mechanical lung model (ASL5000; Ingmar Medical, Pittsburgh, Pennsylvania, USA) with simulated breathing at a respiratory rate of 60 breaths/min. Three interfaces were tested to study the effects of interface resistance on delivered CPAP, measured as the average delivered pressure to the lung simulator, and resistance to breathing, measured as imposed work of breathing (mJ/breath). Expiratory tubing with internal diameters of 3, 4, 6, 8, 10 and 12 mm were tested to study the effect of expiratory tubing diameter. The tubing from the Fisher & Paykel bubble CPAP system was included for reference. Expiratory tubing was submersed 5 cm in an open top canister of water. Tests were performed with fresh gas flows of 6 and 8 L/min with non-humidified air at room temperature, without leakage.

4.1.2 Statistical analysis

Data were collected and processed in the test lung software and exported to SPSS. Mean values with 95% confidence intervals were calculated for 19 consecutive breaths and compared using unpaired t-test for the two flow rates and ANOVA with Games-Howell post hoc test when comparing different interfaces and internal diameters. $P<0.05$ was considered statistically significant.

4.2 MEASURING LEAKAGE, A RANDOMISED CLINICAL TRIAL (PAPER II)

4.2.1 Population and setting

In this randomised, clinical, cross-over trial we measured and compared leakage during nasal CPAP treatment with nasal mask vs prongs in 50 newborn infants and evaluated if leakage could be reduced with simple manoeuvres.

Patients were recruited at the neonatal intensive care units (NICU) of the Karolinska University Hospital and the Östersund Hospital, Sweden, between August 2018 and October 2019. Eligible for inclusion were stable neonates with postmenstrual age (PMA) over 28 weeks, receiving CPAP treatment, regardless of the reason for respiratory support. Exclusion criteria were cardiac or respiratory malformations, facial defects, or injuries, FiO2 >0.5, circulatory instability, recent surgery or recent extubation.

4.2.2 Measuring flow and leakage

Leakage in L/min was recorded with the flow through technique, with one flow meter on the fresh gas flow and another on the patient expiratory limb. This avoids the addition of dead space present with flow meters in the in-line position. (103) Flowmeters were calibrated for the FiO2 level the infant was receiving. A software calculated the leakage from information on the flow through the two flow meters, before and after the patient. A pressure sensor measured the pressure at the patient interface.

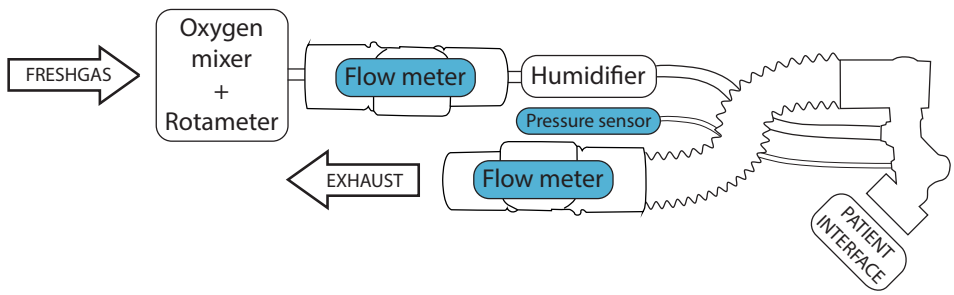

Figure 3: *Schematic equipment setup with flow meters in the flow-through position, one on the fresh gas flow and one on the expiratory limb. (104)*

4.2.3 Intervention

In part 1, we measured and compared leakage with a randomised cross-over design. The order in which interfaces were tested was randomised with assignment notes in sequentially numbered opaque envelopes. Patients were stratified according to gestational age (GA) above or below 34 weeks and presence of a nasogastric tube or not. The CPAP system, with the randomised interface and flowmeters connected in the flow through position (Figure 3), was applied and adjusted by experienced NICU staff blinded to the outcome variable, leakage. When they were satisfied with the position of the interface, they were asked to evaluate if no,

little or much leakage was present. After a few minutes of stabilisation, leakage in l/min was recorded.

In part 2, simple measures to reduce leakage were explored. If leakage > 0.2 L/min was present, the research team applied simple adjustments with the aim of reducing leakage and recorded the lowest level of leakage. This included closing the infant's mouth, adjusting the position, or changing the size of the interface. Part 1 and 2 were then repeated for the other interface.

To avoid staff observing what adjustments affect leakage and influencing care of infants enrolled at a later stage, the NICU staff were not allowed to participate in part 2.

4.2.4 Statistical analysis

As absolute leakage during nasal CPAP treatment in neonates has not been previously reported, no sample size calculation could be performed. A sample size of 50 infants, where each infant acted as its own control, was chosen based on previous, experimental neonatal CPAP cross-over trials.

Data were analysed with parametric (independent samples and paired samples t-test) and non-parametric (Mann-Whitney U and Wilcoxon signed-rank) tests. In the regression analysis, PMA was removed due to co-linearity with weight and the stratification on nasogastric tube was removed as almost all infants had a nasogastric tube. A p value < 0.05 was considered statistically significant.

4.3 FOLLOW UP OF THE CORSAD COHORT IN STOCKHOLM (PAPER III)

4.3.1 Population and setting

In the multicentre, randomised controlled CORSAD trial, extremely preterm infants were randomly assigned to initial respiratory support in the delivery room with a new respiratory support system rPAP using nasal prongs vs standard T-piece with face mask. The primary outcome was delivery room intubation or death and the follow up period was 72 h after birth. Study III was a single centre follow up of extremely preterm infants included in the CORSAD trial at the Karolinska University Hospital in Stockholm up to 36 weeks PMA.

4.3.2 Clinical variables

Data on respiratory support and outcome as well as other neonatal morbidities and death were collected from medical records up to 36 weeks PMA.

BPD is multifactorial and the diagnosis is set at 36 weeks PMA. This results in a long interval between the studied intervention and outcome. We collected information regarding mechanical ventilation during the first three and seven days as a proxy of severity of respiratory disease closer to the intervention. Data on if infants had received any mechanical ventilation before 36 weeks PMA was also collected since mechanical ventilation has been linked to BPD but can occur for other reasons than primary pulmonary disease.

BPD was defined and graded by mode of respiratory support administered at 36 weeks PMA irrespective of oxygen use by the Jensen definition (102). This definition, found to best predict early childhood respiratory morbidity, considers the use of high flow nasal cannula, and does not require information on the amount of oxygen delivered.

To explore if treatment effect was associated with maturity, need for DR intubation and mechanical ventilation was also analysed after stratification on gestational age group.

4.3.3 Statistical analysis

Independent t-test or Mann-Whitney U and Chi-square or Fisher´s exact test was used as appropriate when comparing clinical variables between the groups of infants randomised to each system. Generalised linear model with identity link was applied to calculate risk differences with 95% confidence intervals for respiratory outcomes and mortality between the two groups. Analysis was based on intention to treat and p-value < 0.05 was considered statistically significant.

4.4 CLINICAL FEASIBILITY TRIAL (PAPER IV)

4.4.1 The simplified system

The simplified rPAP system has one tube for the fresh gas flow that is delivered by an air/oxygen mixer and another tube connected to an adjustable pressure limiting (APL) valve and a manometer. This simplifies humidification and eliminates the need for a dedicated driver unit. The system can be used with nasal prongs and attached to the infants´ nose like regular CPAP systems. This could enable the system to be used hands-off for continued support beyond the initial stabilisation in contrast to commonly used T-piece resuscitation systems.

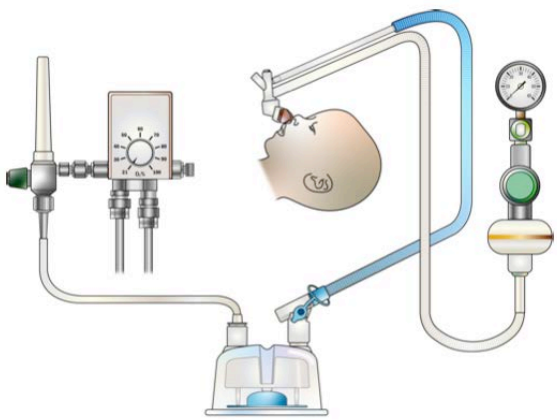

Figure 4: *The simplified rPAP system setup with humidification. Illustration by Mats Ceder.*

4.4.2 Study design

The Feasibility of Uninterrupted Infant Respiratory Support Treatment (FUIRST) trial was a single centre, non-randomised feasibility trial of a simplified rPAP system with humidification. The purpose was to evaluate if the system could be used for stabilisation skin-to-skin or on a resuscitation table and continued respiratory support during transport and in the NICU for up to 4 hours after birth. Collected data aimed to evaluate ease of use and safety. This included information on level of respiratory support, oxygen saturation, heart rate and temperature, interruptions in CPAP treatment, ease of use regarding system set up, airway and respiratory support management, fixation, and transport, need for change to backup respiratory support system or other rare or adverse events such as pneumothorax, need for intubation or chest compressions and problems related to equipment or the research protocol.

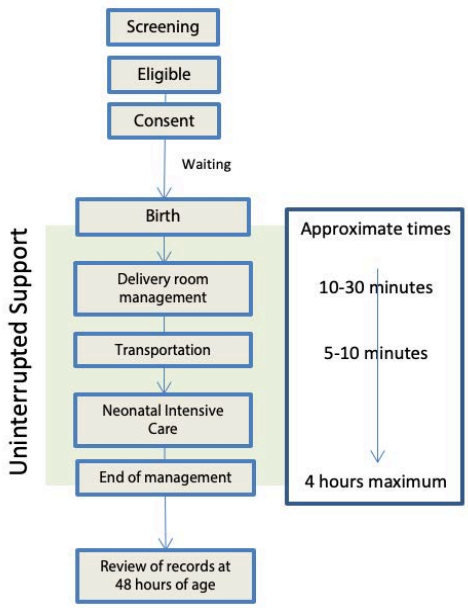

Figure 5: *Flow diagram for the feasibility study (paper IV).*

4.4.3 Population

Newborn infants in need of respiratory support after vaginal delivery at GA between 28+0 and 34+6 weeks and days or caesarean section at GA between 28+0 and 37+6 weeks and days were included when investigators were available. Inclusion required antenatal parental consent.

The study was not designed to estimate treatment effects and no power calculations were performed. Thirty-two infants born both vaginally and by caesarean section, some of whom had required positive pressure ventilation and received support with the study system for the maximum of 4 hours, were included.

4.4.4 Statistical analysis

Descriptive statistics were used to summarise the data. Categorical variables were presented with counts (percentages), normally distributed continuous variables as mean□SD and not-normally distributed as median (IQR). Normal distribution was tested with Shapiro-Wilk test.

4.5 ETHICAL CONSIDERATIONS

Paper I (bCPAP): No ethical approval needed as the study was performed in an in vitro setting, not involving any patients or patient information.

Paper II (ToNIL): Neonates receiving CPAP treatment in the neonatal department at the Karolinska University Hospital were included after written informed parental consent. The risk for deterioration during measurements was minimised by not including infants with high oxygen requirement or circulatory instability. The time required for measurements was short and planned in consultation with the parents and nursing staff to suit the infants sleep and mealtimes. The study was approved by the Swedish Ethical Review Authority, Dnr: 2016/2449-31.

Paper III (CORSAD Stockholm): Extremely preterm infants were enrolled in the CORSAD trial at birth in the Karolinska University Hospital after antenatal written informed parental consent. Both the original CORSAD trial and the follow up study were approved by the Swedish Ethical Review Authority, Dnr: 2015/927-31/4 and 2019-01122 respectively.

Paper IV (FUIRST): Infants in need of respiratory support at birth were enrolled after antenatal written informed parental consent. The system used is a slightly modified version of the rPAP system that had been evaluated in extremely preterm infants and is already in use internationally in neonatal intensive care units. As in the ToNIL study, the separation of infant from the parents was minimised through encouraging the parents to participate and have the infant skin to skin if the infants condition allowed. The study was approved by the Swedish Ethical Review Authority, Dnr: 2019-05581.

5 RESULTS

5.1 PAPER I – BUBBLE CPAP

5.1.1 Interface resistance

The interface with the highest resistance, the RAM cannula, had the highest imposed work of breathing (Figure 6) while small differences in delivered mean CPAP were seen between the three interfaces (Figure 7).

5.1.2 Internal diameter of expiratory tubing

Tests with expiratory tubing with internal diameters less than 8 mm led to increased imposed work of breathing (Figure 6) and delivered CPAP exceeding the submersion depth (Figure 7). This was even more pronounced with higher gas flow as seen in tests with 8 L/min fresh gas flow compared with 6 L/min. The flow rate had less effect when expiratory tubing with wider internal diameter was used.

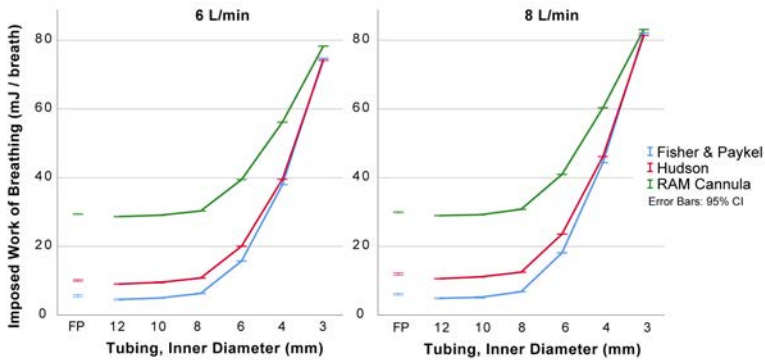

Figure 6: *Effect of different interfaces, flow, and expiratory tubing diameters on iWOB. (105)*

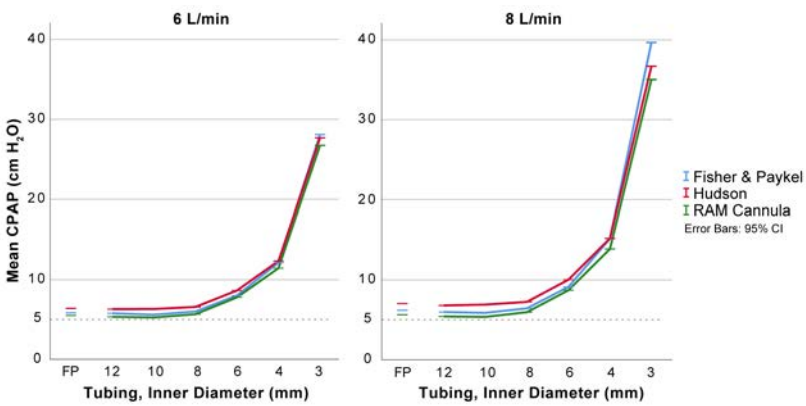

Figure 7: *Effect of different interfaces, flow and expiratory tubing diameters on mean CPAP. (105)*

5.2 PAPER II – INTERFACE LEAKAGE

Leakage was measured during CPAP treatment with both nasal mask and prongs in 50 infants with a median PMA of 33 weeks (range 28-42). Details on screening and inclusion is found in Figure 8. The infants were stable during measurements and the median time connected to the measuring equipment was 25 min (IQR 21-30) for each infant.

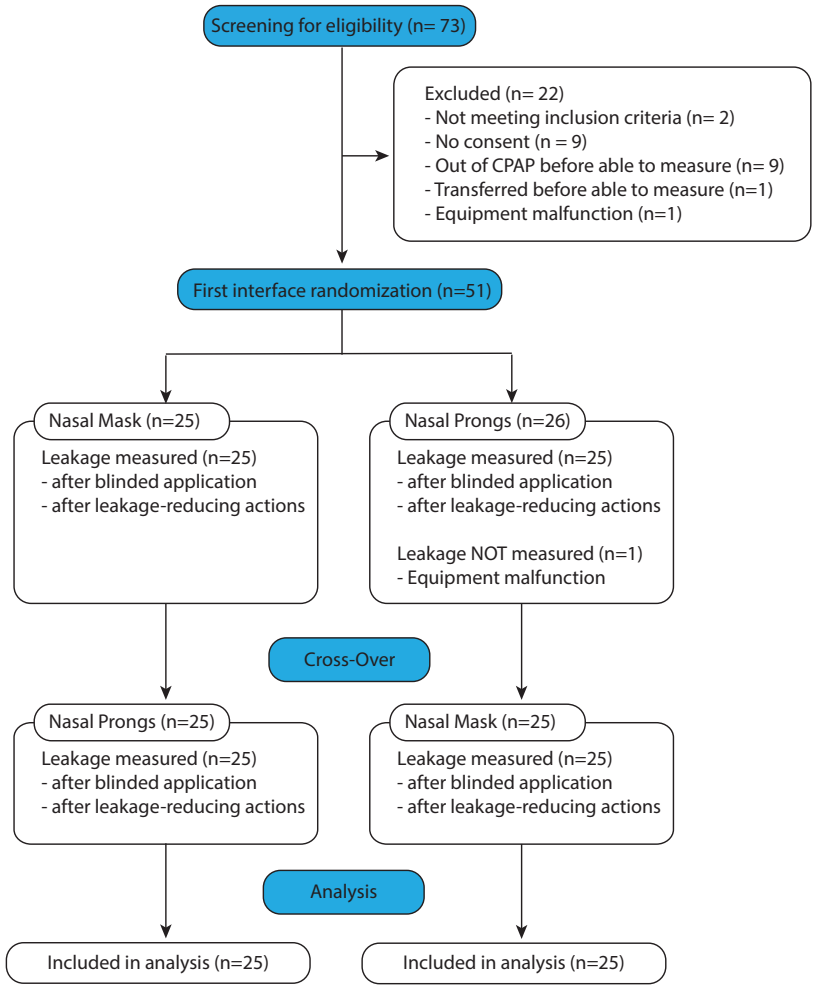

Figure 8: *CONSORT flow diagram for the ToNIL study. (104)*

Leakage was common and a leakage above 0.2 L/min was present with at least one interface in all patients. A significantly lower leakage (mean difference 0.86 L/min, 95% CI 0.07 to 1.65, p=0.034) occurred with nasal prongs (median 2.01 L/min, IQR 1.00-2.80) than nasal

mask (median 2.45 L/min, IQR 0.99-5.11). Leakage was associated to the set CPAP level for both interfaces, but not with the PMA or weight of the infant.

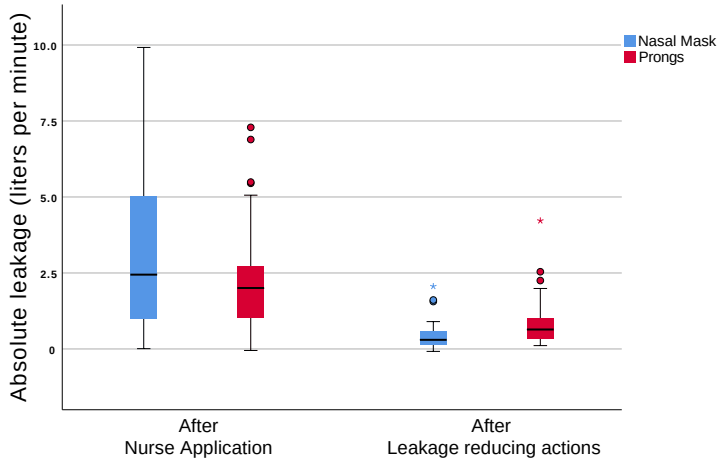

Figure 9: *Leakage for each interface, after nurse application and after leakage reducing actions by investigators. (104)*

Leakage could be reduced with non-blinded leak-corrective manoeuvres in 96% of the measurements with prongs and 98% with nasal mask. A reduction in leakage was most often achieved by adjusting the seal of the interface by adjusting the angle, straps, or bonnet, or by applying light pressure on the interface at the feeding line entry.

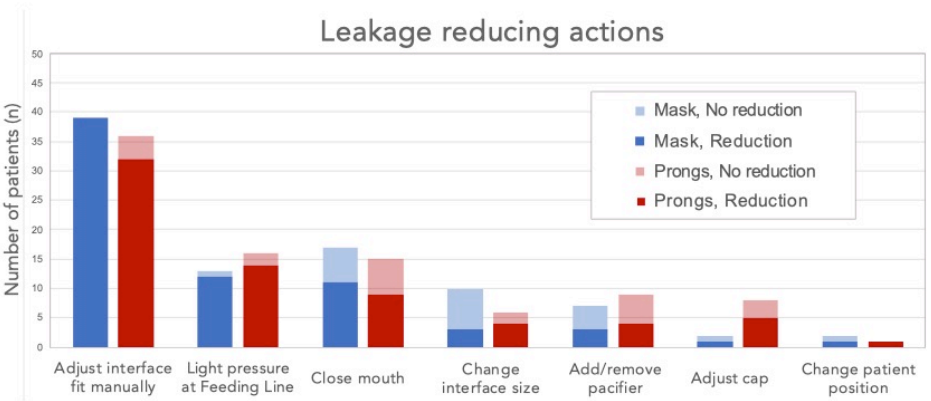

Figure 10: *Actions attempted to reduce leakage by investigators guided by current leakage. The actions were not randomised and not all actions were attempted on every infant. (104)*

5.3 PAPER III – CORSAD STOCKHOLM

In total, 94 infants, with a median (IQR) GA of 25.3 (24.6-26.4) weeks were included in the CORSAD trial in Stockholm, 46 in the rPAP group and 48 in the T-piece group. The groups were balanced regarding baseline characteristics except for intrauterine growth restriction which was more common in the rPAP group. Follow up information to 36 weeks PMA was available for all infants.

Stabilisation with the rPAP system compared to T-piece was associated with a significantly lower rate of DR intubation (28 vs 54%, p=0.008) and less mechanical ventilation during the first 72 h (52 vs 73%, p=0.034) and 7 days of life (63 vs 81%, p=0.045). At 36 weeks PMA, a majority of infants in both groups had received any mechanical ventilation, 76% in the rPAP vs 90% in the T-piece group (p=0.079) and there was no difference in the rate of BPD (28 vs 27%) or death (20 vs 23%) between the rPAP and T-piece group respectively.

Although the number of infants receiving surfactant was similar, the timing of first administration differed, with infants in the rPAP group receiving the first dose at a median age (IQR) of 120 (9-325) min vs 10 (6-120) min in the T-piece group.

No significant differences were seen in rates of air leak, pulmonary haemorrhage, culture-positive sepsis, intraventricular haemorrhage, necrotising enterocolitis, retinopathy of prematurity and patent ductus arteriosus treatment between the groups.

	New system (n=46)	T-piece (n=48)	Risk difference, % (95% CI)	p value
Intubated in the delivery room, n (%)	13 (28.3)	26 (54.2)	-25.9 (-45.1 to -6.7)	**0.008**
Surfactant, n (%)	29 (63.0)	35 (72.9)	-9.9 (-28.7 to +8.9)	0.31
First dose in the delivery room	13 (28.3)	25 (52.1)	-23.8 (-43.0 to -4.6)	**0.022**
First dose in the NICU	16 (34.8)	10 (20.8)	+13.9 (-4.0 to +31.9)	0.15
Age at first dose in minutes, median (IQR)	120 (9-325)	10 (6-120)		**0.045**
Any MV during the first 3 days, n (%)	24 (52.2)	35 (72.9)	-20.7 (-39.9 to -1.6)	**0.034**
Any MV during the first 7 days, n (%)	29 (63.0)	39 (81.3)	-18.2 (-36.0 to -0.42)	**0.045**
Any MV before 36 w PMA, n (%)	35 (76.1)	43 (89.6)	-13.5 (-28.5 to +1.5)	0.079
Death or BPD, n (%)	22 (47.8)	24 (50.0)	-2.2 (-22.4 to +18.0)	0.83
Death, n (%)	9 (19.6)	11 (22.9)	-3.4 (-19.9 to +13.2)	0.69
BPD, n (%)	13 (28.3)	13 (27.1)	+1.1 (-16.9 to +19.3)	0.90
Grade 1, n (%)	3 (6.5)	7 (14.6)		
Grade 2, n (%)	9 (19.6)	6 (12.5)		
Grade 3, n (%)	1 (2.2)	0		

Table 1: *Comparison of outcomes between groups in the CORSAD Stockholm cohort. Adapted from paper III. (106)*

5.4 PAPER IV – FEASIBILITY TRIAL

A total of 109 parent couples were approached of which 75 couples consented to study participation and 32 infants were included. The infants had a mean (SD) GA of 33.4 weeks (□1.2) and a median (IQR) birth weight of 2118 g (476).

Figure 11: *Set up for initial stabilisation at a caesarean section.*

All infants received nCPAP and nine received PPV with the simplified rPAP system in the delivery room. Respiratory support with the simplified system was continued during transportation and in the NICU in 31 out of 32 infants. One infant did not need continued respiratory support after initial stabilisation in the delivery room. Minor interruptions of CPAP support, most commonly due to placement of nasogastric tube, occurred in all infants.

Out of 17 infants born vaginally, 13 were stabilised skin-to-skin. The remaining infants, including those born by caesarean section were stabilised on a resuscitation table. Twenty-four (75%) received skin-to-skin contact at some point during the study period while receiving respiratory support with the simplified system. The median (IQR) cord clamping time was 300 (708) sec after vaginal birth and 50 (25) sec after caesarean section.

There were no cases of pneumothorax or hypothermia and no infants needed intubation, chest compressions or use of T-piece backup system for stabilisation.

The system was easy to set up and use for respiratory support. In five cases we experienced minor problems related to fixation of the system during transportation.

CPAP/PPV started age (minutes)	
Median (IQR)	1.4 (1.6)
Received PPV	
n (%)	9 (28)
PPV duration (seconds)	
Median (IQR)	120 (125)
Cord clamping time (minutes)	
Median (IQR)	1.5 (4.4)
(min-max)	(0.25-21)
Place of stabilisation	
Skin-to-skin, n (%)	13 (41)
Resuscitation table, n (%)	19 (59)
Apgar score	
5 minutes, median (IQR)	9 (2)
10 minutes, median (IQR)	10 (1)
FiO2 at 5 minutes	
Median (IQR)	0.25 (0.09)
Saturation at 5 minutes %	
Median (IQR)	85 (19)
Temperature when leaving DR C□	
Mean (SD)	37.0 (0.4)
Temperature on arrival in NICU C□	
Mean (SD)	36.9 (0.3)
Number of interruptions in CPAP	
Median (IQR)	3 (1)
Duration of interruptions (seconds)	
Median (IQR)	15 (20)

Table 2: *Neonatal outcomes in the feasibility study of the simplified system (paper IV).*

6 DISCUSSION

Since its description by Gregory et. al. (2) continuous positive airway pressure has become the standard of care in neonatal intensive care units. The treatment builds on a continuous flow of air to the lungs creating a distending pressure that prevents the collapse of small airways thereby optimising gas exchange. This thesis includes studies in the in vitro and clinical settings that aimed to evaluate how different aspects of CPAP system design affect the properties of the respiratory support and a follow-up study to explore the potential effect on outcome.

The European Consensus Guidelines on the Management of Respiratory Distress Syndrome recommend stabilising breathing babies with CPAP of 6-8 cm H_2O.(72) In study I and II we have shown how various factors such as interface leakage and resistance of the interface and expiratory tubing can result in a different pressure being delivered compared to what is expected. This can go unnoticed when pressure and leakage are not measured. Even if pressure is measured it is usually proximal to the interface and does not necessarily reflect the pressure delivered to the infant's airways.

Bubble CPAP is a simple way of creating continuous positive airway pressure without expensive and fragile technical equipment. This makes bCPAP ideal for use in low resource settings. During recent years, new systems that are specifically aimed for use in low resource settings have been built. One of these systems was the first version of the Pumani system that had an alternative design with the bubble bottle on the inspiratory limb. The system was studied by members of my research group and found to be pressure unstable and pose risk of rebreathing with accumulation of carbon dioxide (85). The design was subsequently revised. This finding lead to the idea for study I with the aim to identify other alterations to the original bubble CPAP design and to test the effect of these changes on the delivered mean CPAP level and imposed work of breathing in a mechanical lung model. Through literature review, three major alterations were identified. These are summarised in Figure 11.

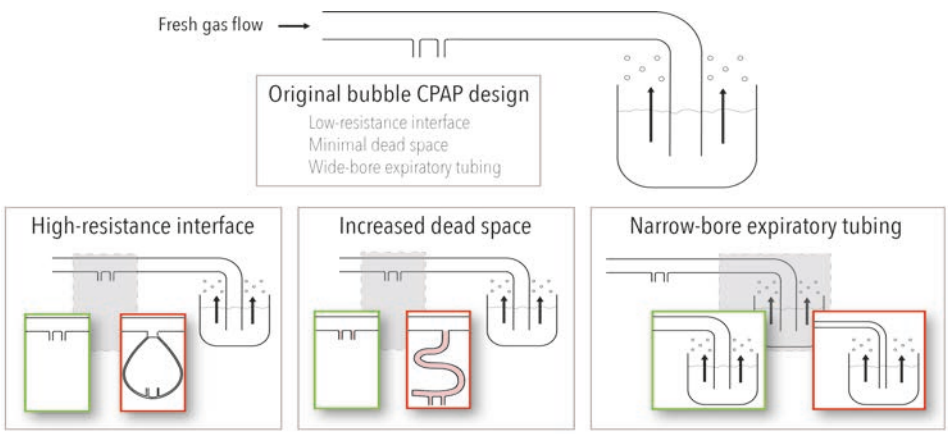

Figure 11: *Three major alterations from the original bubble CPAP design; high resistance interface, increased dead space and narrow bore expiratory tubing. (105)*

The discoveries made in study I are worrying, particularly when seeing examples in the literature of systems with high resistance being combined with methods to prevent leakage. It requires increased work to breathe through a system with high resistance and exhalation is likely to occur through the mouth or through leakage at the interface. Such systems resemble HFNC, which are designed to have leakage at the interface opposed to CPAP systems which have tight fitting interfaces. It is important to know the properties of the system you are using to be better able to choose the appropriate system for the individual patient and use it in the right way. For example, if the system has properties similar to HFNC the interface should allow leakage to avoid unintentionally high pressure and work of breathing. Studies have shown that HFNC can sufficiently support breathing in a large proportion of newborn infants with respiratory distress. Ideally, some CPAP systems should be available for those who fail high-flow therapy and may benefit from rescue CPAP. (107, 108)

The success of CPAP treatment is thought to be dependent on the actual distending pressure delivered to the lungs (36), which theoretically is determined by the gas flow and leakage at the nasal interface. Yet, studies on leakage during CPAP treatment have been lacking. The aim of study II was to measure leakage during nasal CPAP treatment in infants with nasal mask and prongs and evaluate if it could be reduced with simple adjustments. We found that leakage was common for both interfaces and in our cohort, more leakage was seen with nasal mask.

We observed that leakage could often be reduced by gently pressing one finger on the interface at the entry of the nasogastric tube. It seems possible that the nasogastric tube could have a larger effect on the mask form and therefore could increase the leakage for nasal masks compared with prongs. Studies that have shown less CPAP failure with nasal mask compared to prongs often do not mention if the included infants had a nasal- or oral gastric tube and leakage degree was not measured. (32, 43) This makes it difficult to put our results into context with these studies and to draw conclusions about the effect of leakage on the outcome.

While finding it encouraging that leakage could be reduced with simple adjustments of the interface, the risk of nasal trauma needs to be considered. In our trial, no signs of skin irritation were seen, however, the duration of the intervention was short. All adjustments aimed at reducing leakage that result in increased pressure on the infants´ nose and this needs to be weighed against the risk of causing injury. Nevertheless, there are other possibilities that may help to reduce leakage and maintain the pressure, such as offering a pacifier to infants that are not at ease or possibly changing from nasal to oral gastric tube.

In study III we compared the combined outcome of BPD or death at 36 weeks of postmenstrual age in extremely preterm infants that had received initial respiratory support with the rPAP system using nasal prongs versus a standard T-piece system with face mask. Since BPD and death are competing outcomes, we also compared the outcomes separately. A causal relationship between delivery room stabilisation and BPD could be direct through an effect on the lung tissue during stabilisation, and/or mediated through the need for

mechanical ventilation. Although respiratory distress due to pulmonary disease is the most common reason for mechanical ventilation during the first week of life, other factors such as infections, effects of the patent ductus arteriosus and NEC start playing a larger role thereafter. Therefore, mechanical ventilation at different time points, administration of surfactant and other neonatal morbidities were also compared between the two groups. As the cohort of infants studied came from the randomised CORSAD trial and the groups were balanced regarding other known potential confounding factors such as gestational age and antenatal steroids, no adjustments were made for these in the analysis.

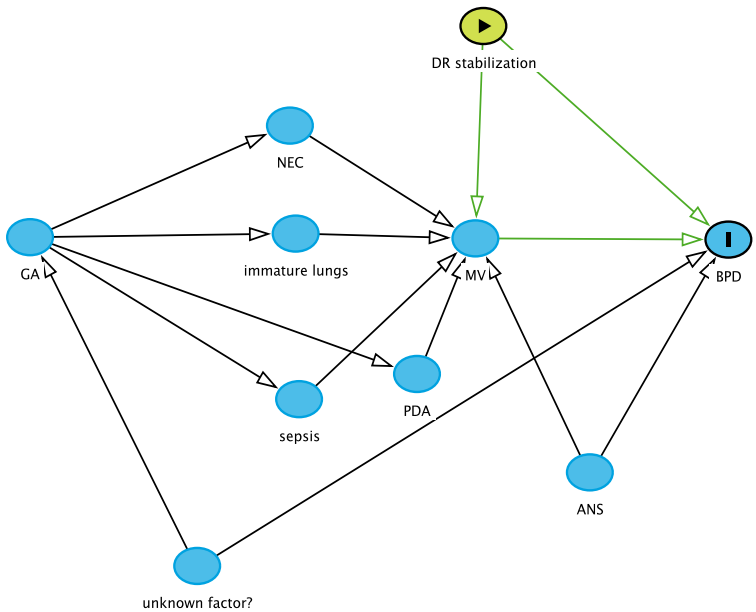

Figure 12: *BPD is multifactorial. Theoretically DR stabilisation could have a direct causal relationship with BPD or mediated through less need for mechanical ventilation.*

We found that the extremely preterm infants in the rPAP group were less likely to receive mechanical ventilation during the first week of life compared to infants in the T-piece group. At 36 weeks PMA, a majority in both groups had received any mechanical ventilation and there was no statistically significant difference in the diagnosis of BPD or death.

The intervention in the CORSAD trial was not blinded. This could have led to bias and withholding of intubation in the rPAP group at the cost of greater instability in CPAP. However a secondary analysis did not support this theory. (109)

The simplified rPAP system has the same properties with low imposed work of breathing and can be used with nasal prongs as the original rPAP system, previously tested in a randomised trial.(71, 110) Study IV was the initial step in evaluating the use of the simplified rPAP with humidification for stabilisation followed by continued CPAP support as well as during skin-to-skin contact. That is, a test of the feasibility of the approach using the system. The system

was successfully used for the described purpose in 32 preterm infants. The infants were normothermic and there were no cases of pneumothorax.

The ability to stabilise infants skin-to-skin enables physiological cord clamping and reduces separation of the mother and infant. Previously, skin-to-skin contact has been initiated after stabilisation. Recent studies have shown that immediate skin-to-skin contact is safe even in preterm and low birth weight infants and may contribute to increased cardiorespiratory stability as well as reduced mortality in low- and middle-income countries. (111, 112) In line with this, the World Health Organisation now recommends CPAP and kangaroo mother care for preterm and low birth weight infants as soon as possible after birth. (113) Further, skin-to-skin contact together with use of heated humidified gases may reduce the risk of hypothermia which has been associated with increased mortality and morbidity in preterm infants. (114-117) The simplified system may provide a favourable option for stabilisation and continued respiratory support skin-to-skin with heated humidified gases. However, adequately powered randomised studies are needed to establish the efficacy of this approach compared to other approaches.

6.1 STRENGTHS AND LIMITATIONS

The study on effects of changing the bubble CPAP design (paper I) was carried out in the in vitro setting without leakage. As seen in the ToNIL study (paper II), leakage is common in the clinical setting and could protect the infant from the possibly harmful effects of high pressure and resistance to breathing, given that specific measures to avoid leakage such as chin straps and seal at the interface have not been applied.

We acknowledge that the small sample size is a limitation to the ToNIL study (paper II), and results need to be confirmed in a larger context with a longer registration, preferably with and without nasogastric tube. The randomised cross-over design allowing each infant to act as its own control can be considered a strength. Both term and preterm infants were studied, however, no infants below 28 weeks gestational age were included. Therefore, the results may not be representative for this group of extremely preterm infants for whom it can be hard to find a properly fitting prong and resistance starts playing a larger role.

The second part of the ToNIL study was non-randomised and not all infants underwent the same interventions to reduce leakage, as the purpose was to explore ways to reduce leakage without analysing the effect of each of them separately. Further, as removing the nasogastric tube for the purpose of the study was not considered feasible, we could not assess the effect of its presence on leakage.

One of the limitations of the CORSAD Stockholm study (paper III) was the lack of power to detect a difference in the outcome of BPD and that it only included infants from one of the centers in the multicenter CORSAD trial. The lack of power would have remained when analysing the whole CORSAD cohort. While the predefined inclusion and exclusion criteria and computer randomisation in the CORSAD trial are factors that can increase the validity of the study by reducing risk of selection bias and confounding, the fact that the intervention

was not blinded might introduce risk of bias. Although we can expect the results to be generalisable to extremely preterm infants in countries with similar health care systems that follow the same treatment guidelines, the results may differ depending on baseline intubation and BPD rates. A limitation of the generalisability of studies requiring antenatal consent is that infants that tend to have the worst prognosis, owing to the need for acute delivery in the absence of antenatal steroids, are often not included.

All infants included in the CORSAD trial in Stockholm received initial respiratory support with the randomised system. However, two infants crossed over to T-piece before intubation during the intervention period. Analysis of results by intention to treat should reduce the risk of bias while per protocol analysis could have exaggerated the positive treatment effect of the rPAP system.

Study IV has the limitations of a non-randomised feasibility study in not being able to give information on the effect of the given treatment in comparison to other approaches.

7 CONCLUSIONS

- The development of new techniques for non-invasive respiratory support can lead to improved outcome for newborn infants, however proper testing is important before implementation into clinical practice.
- Altering the design can affect the properties of the CPAP system and may result in unforeseen changes in delivered mean CPAP level and add to the work required to breathe through the device.
- An interface with low resistance and expiratory tubing with internal diameter of at least 8 mm (for a 1,5m long tube) should be used if aiming to build a bubble CPAP system that is easy to breathe through and delivers stable pressure at a level equal to the submersion depth of the expiratory tubing. In addition, the dead space needs to be minimised to reduce the risk of carbon dioxide accumulation.
- Leakage is common during nasal CPAP treatment and can be affected by the choice and position of the nasal interface. In our cohort of infants, most of whom had a nasogastric tube, more leakage occurred with nasal mask compared to nasal prongs.
- Stabilisation with the rPAP system that has low imposed work of breathing using nasal prongs is associated with less need for DR intubation and mechanical ventilation during the first week of life in comparison to stabilisation with T-piece with face mask. We did not find a statistically significant difference in mortality or the diagnosis of BPD at 36 weeks of PMA. Further adequately powered studies are needed.
- It is feasible to stabilise preterm infants with the simplified rPAP system skin-to skin or on a resuscitation table and continue respiratory support with the same system during transportation. Stabilisation skin-to-skin can enable physiological cord clamping and reduce separation of the mother and her newborn.

8 POINTS OF PERSPECTIVE

Since the publication of paper I, more articles addressing the use of different bubble CPAP systems in low resource settings have followed. Hopefully this increased awareness has led to improved and safer respiratory support of newborns even where commercial CPAP systems are lacking.

Information on leakage during CPAP treatment has been gained. However, knowledge on how this is connected to treatment effect and failure is still lacking. Randomised studies assessing both leakage and/or delivered pressure as well as treatment failure could lead to increased understanding.

While stabilisation of extremely preterm infants using a system with low imposed work of breathing and nasal prongs has been shown to reduce the need for delivery room intubation and mechanical ventilation during the first week of life, more research is needed on the relationship between respiratory support early in life and later respiratory morbidity.

A system with low imposed work of breathing that can provide PPV and CPAP and be fixated with a cap could be a good alternative for stabilisation and continued respiratory support skin-to-skin and facilitate physiological cord clamping.

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