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THE PRETERM INFANT: EVALUATING AND DEVELOPING NON-INVASIVE RESPIRATORY STRATEGIES TO AVOID MECHANICAL VENTILATION

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To my family.

ABSTRACT

Avoiding mechanical ventilation of preterm infants is important to prevent morbidity and mortality. Non-invasive ventilation and CPAP has been shown to be superior to intubation and mechanical ventilation in preventing chronic lung disease in very preterm infants.1 . CPAP for infants was first used in the early 70's. Since then, several different CPAP devices have been developed. Some of them are designed to give long term respiratory support while others are designed for initial support, with the possibility to give positive pressure ventilation (PPV) if needed. Some are expensive and complicated with several add on features while other are cheap, with simple mechanisms and easy to use.

The goal for CPAP treatment is to give continuous airway pressure to the infants in order to minimize the work of breathing and improve gas exchange. But are all CPAP systems the same? Do all CPAP systems deliver stable airway pressure which helps the infants with their work of breathing?

The overall aim of this thesis was to evaluate existing and newly developed devices for non-invasive respiratory support used in neonates in the DR and the NICU. The focus was on device resistance, pressure stability, imposed work of breathing and interfaces used.

The aim of Paper I was to examine the in vitro performance of a new system (rPAP) and to perform a clinical feasibility trial, comparing a T-piece system with face mask, and the new system with face mask or nasal prongs, for initial stabilization of preterm infants. The new device was shown in a mechanical lung model to be pressure stable and have low imposed work of breathing compared to the T-piece. The feasibility trial comparing these devices revealed no safety issues when stabilizing preterm infants with the new device.

The aim of Paper II was to examine the in vitro performance of the Medijet CPAP reusable and disposable generators and compare them to other CPAP systems. The main mechanism of CPAP generation for the disposable Medijet generator was shown to be resistance. The Medijet systems shows increasing resistance to breathing with each design generation. Our results suggest that the disposable Medijet should be used cautiously in patients where low-resistance and pressure-stable CPAP is believed to be clinically important.

The aim of Paper III was to compare the revised Pumani CPAP system with two traditional bubble CPAP systems, focusing on in-vitro performance and safety. The revised Pumani system had high resistance, high imposed work of breathing and submersion depth had almost no impact on the delivered pressure which is the main CPAP generating mechanism of true bubble CPAP systems.

The aim of Paper IV was to evaluate if using the new system (rPAP) with nasal prongs as interface, could reduce the need for intubation of extremely preterm infants in the DR compared to using the standard T-piece system with face mask. The CORSAD randomized controlled trial showed that using the new system decreased delivery room intubations in extremely preterm infants and creates thereby a possibility to avoid mechanical ventilation.

LIST OF SCIENTIFIC PAPERS

I. **Donaldsson S**, Drevhammar T, Taittonen L, Klemming S, Jonsson B. Initial stabilisation of preterm infants: a new resuscitation system with low imposed work of breathing for use with face mask or nasal prongs. *Arch Dis Child Fetal Neonatal Ed.* 2017;102(3):F203-f207.

II. Falk M, **Donaldsson S**, Jonsson B, Drevhammar T. Return of neonatal CPAP resistance – the Medijet device family examined using in vitro flow simulations. *Acta Paediatr.* 2017;106(11):1760-1766.

III. Falk M, **Donaldsson S**, Drevhammar T. Infant CPAP for low-income Countries: An experimental comparison of standard bubble CPAP and the Pumani system. *PLoS One.* 2018;13(5):e0196683-e0196683.

IV. **Snorri Donaldsson**, Thomas Drevhammar, Yinghua Li, Marco Bartocci, Siren Irene Rettedal, Fredrik Lundberg et al. Comparison Of Respiratory Support After Delivery in infants born before 28 weeks gestational age -The CORSAD Randomized Clinical Trial. Manuscript, accepted for publication

Scientific papers not included in the thesis

Donaldsson S, Falk M, Jonsson B, Drevhammar T. Imposed Work of Breathing for Flow Meters with In-Line versus Flow-Through Technique during Simulated Neonatal Breathing. *PLoS One.* 2015;10(7):e0133432.

Hinder M, McEwan A, Drevhammer T, **Donaldson S**, Tracy MB. T-piece resuscitators: how do they compare? *Archives of Disease in Childhood - Fetal and Neonatal Edition.* 2019;104(2):F122.

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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.

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CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
bCPAP	Bubble CPAP
BPD	Bronchopulmonary Dysplasia
CDP	Continuous Distending Pressure
CPAP	Continuous Positive Airway Pressure
DMC	Data Monitoring Committee
DR	Delivery Room
FRC	Functional Residual Capacity
GA	Gestational Age
GCP	Good Clinical Practice
ILCOR	International Liaison Committee on Resuscitation
iWOB	Imposed Work Of Breathing
nCPAP	Nasal CPAP
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PEEP	Positive End Expiratory Pressure
PPV	Positive Pressure Ventilation
RD	Risk Difference
RDS	Respiratory Distress Syndrome
SAE	Serious Adverse Event

1 INTRODUCTION

Being born, taking the first breath and continue breathing is challenging, especially if a baby is born prematurely. Providing adequate respiratory support is essential and potentially lifesaving. Continuous positive airway pressure or CPAP is the most common respiratory support given to a new-born infant. CPAP applies a continuous distending pressure to spontaneously breathing infants by means of an interface, to facilitate lung expansion and make breathing easier.

Non-invasive ventilation and CPAP has been shown to be superior to intubation and mechanical ventilation in preventing chronic lung disease in very preterm-born infants.[1] Different strategies and different devices have been developed, all aiming to improve the non-invasive approach and to avoid mechanical ventilation. Since Gregory's first infant CPAP device[2], several different CPAP devices have been developed. Some of them are designed to give initial support, with possibilities to give positive pressure ventilation (PPV) if needed. Other are designed to give long term respiratory support in the neonatal intensive care unit (NICU). Some are cheap, developed for low-income countries, whilst others are complicated and expensive, with add on features such as bi-level pressures and high frequency oscillating pressures. The ultimate goal for every device is the same: to provide a stable, continuous airway pressure to minimize the work of breathing and improve gas exchange. But are all CPAP systems the same? Do all CPAP systems deliver stable airway pressure which helps the infants with their work of breathing?

This thesis will focus on CPAP devices that have been developed for neonatal use in the last decades. Aspects such as pressure stability, imposed work of breathing (iWOB) and different interfaces will be discussed.

2 LITERATURE REVIEW

2.1 PHYSIOLOGICAL EFFECTS OF CPAP

Continuous positive airway pressure is a method for applying a Continuous Distending Pressure (CDP) to spontaneously breathing patients during inspiration and expiration.[3] CDP increases transpulmonary pressure, which in newborn infants helps to establish and maintain Functional Residual Capacity (FRC) and facilitate gas exchange.[4-6] CPAP splints the upper airway , decreases the upper airway resistance and reduces the risk for obstructive apnea.[7,8] With improved oxygenation and a stable FRC, CPAP may also reduce the risk of severe central apnea.[9-11] CPAP lowers work of breathing, decreases thoraco-abdominal asynchrony, and conserves surfactant and facilitates its function.[12,13] The CDP is also the driving force required to overcome elastic, flow-resistive, and inertial resistance of the respiratory system.[14]

The most common understanding when referring to CPAP in neonates is that it is non-invasive with a nasal interface (nCPAP). The major difference in providing CDP non-invasively (nCPAP) versus invasively (mechanical ventilation) is that the non-invasive support is ineffective during apnea. However, as mentioned above, CDP itself can decrease the occurrence of apnea and with pleural pressure changes, spontaneous breathing increases venous return, improves cardiac output, and improves lung aeration with alveolar recruitment and stabilization.[15-17]

2.2 THE HISTORY OF CPAP DEVICES

In 1914, Von Reuss published in a textbook a description of Von-Tiegel's "over- pressure apparatus".[18,19] It consisted of hoses, an oxygen gas source, a tight-fitting face mask, and a water-filled receptacle. A metal tube was connected to an expiratory hose that was submerged into the receptacle and pressure was controlled by adjusting the tube depth according to a centimeter scale.

More than 50 years later, Gregory et al reported successful CPAP treatment of spontaneously breathing preterm infants with RDS.[2] The CDP was created with a resistor clamp on the expiratory limb of the system. It had a water submersion pop-off pressure valve and has therefore often been mistaken for a bubble CPAP (bCPAP) system. Sahni and Wung[20] were first to describe the original bCPAP system. This design has wide bore expiratory tubing submersed in water without a resistor clamp. It had short binasal prongs as interface connected directly to the tubing. This made the system more pressure stable than the Gregory CPAP and was believed to be easier to breathe through. In 1976, the Benveniste valve was introduced as a nasal CPAP device.[21] It was originally designed to protect infants from high breath volumes and inflation pressures common in the crude ventilators used at the time.[22] The Benveniste valve was the first variable flow system used for nasal CPAP in infants. A new variable flow system for infant was introduced by Moa et al in 1988.[23] It had short nasal prongs as interface and used jets to generate pressure stable CPAP and was later marketed as the Infant Flow CPAP. Many other systems have been introduced and built on similar

designs. In addition to all these different CPAP systems, modern ventilators are also capable of delivering CPAP by a Y-piece and a patient interface. All the above techniques for CPAP generation are still in use. Studies comparing CPAP systems are limited and the few comparisons that have been undertaken have not shown clear differences between system performance.

2.3 CLASSIFICATION OF CPAP SYSTEMS

CPAP is derived from either variable or continuous gas flow. In variable-flow CPAP devices, pressure is generated proximal to the infant's nares. Turbulence is created to oppose expiration and aid inspiration and uses the Venturi effect to redirect the gas flow to create constant pressure. In continuous-flow CPAP, the gas flow is directed against a resistance in the expiratory limb of the breathing circuit.

2.3.1 Variable-flow CPAP

The Infant Flow and the Arabella CPAP system is an example of a device that uses dedicated flow drivers and gas generators with a fluidic-flip mechanism (Coanda effect) to create variable flow. Pressure stability is achieved by the Venturi effect in combination with the fluidic flip, and the patient is connected to the patient with binasal prongs or nasal mask.[23,24] The original Infant Flow system was designed by Gunnar Moa and Kjell Nilsson in the 1980's. The flows within the geometry have recently been investigated by computer simulations (Figure 1).[25]

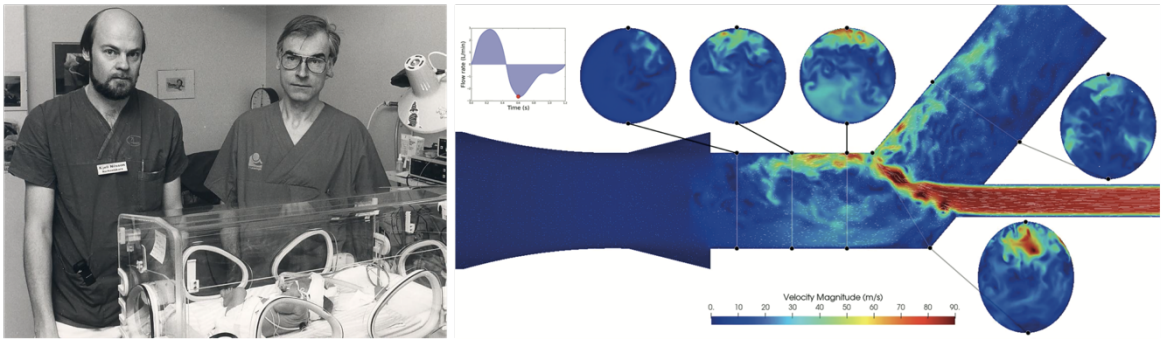

Figure 1: *The inventors of the original Infant Flow (Östersund, 1988) and flows within the driving geometry investigated using computational fluid dynamics at KTH (Stockholm, 2020).*

The Benveniste valve and the original Medijet are examples of alternative variable-flow system that also use the Venturi effect to create stable pressure but do not have a fluidic flip mechanism. A blended gas source provides a fresh-gas flow that is directed towards an orifice which generates variable flow. The device is connected to the patient via nasal prongs.[21]

2.3.2 Continuous-flow CPAP

Bubble CPAP is a continuous-flow system with wide bore tubing and low-resistance nasal prongs. Blended gas is humidified and heated before patient. The expiratory tubing is submersed distally in a water bottle and the depth of submersion reflects the delivered CPAP pressure in centimetres.[20]

Another example of continuous flow CPAP is ventilator-derived CPAP. By varying the ventilator's expiratory orifice size CPAP is increased or decreased. Pressure, flow and the exhalation valve works in synchrony to maintain the desired CPAP level. A summary of different CPAP generation is shown in Table1.

Mechanism	History	Flow	Mechanism	Stable CPAP?
Resistor	Gregory's CPAP T-Piece resuscitator	Constant and not used to adjust CPAP	Resistance on expiratory limb or device to adjust CPAP	Depending on level of fresh gas flow
Bubble	Used by Wung, Columbia, USA	Constant and not used to adjust CPAP	Submersion of expiratory tubing	Depending on tube dimensions
Flow opposition	Benveniste Infant Flow rPAP	Variable, used to adjust CPAP level	Turbulent flow opposing exhalation and aiding inspiration	Related to quality of design
Ventilator	Used for mechanical ventilation	Constant or variable, adjusted by inspiratory valve	Controlled expiratory limb valve resistance	Highly related to ventilator performance

Table 1: *Principles for CPAP generation. Some CPAP systems display features of several mechanism e.g. the Medijet is both a resistor and flow opposition system and the Pumani is both a resistor and bubble CPAP system.*

2.4 PATIENT INTERFACES

There are several interfaces in use to deliver nCPAP in infants (Figure 2). These include single and binasal prongs, short and long versions and also nasal masks. Hudson, Argyle and Infant flow are examples of short nasal prongs, and nasopharyngeal tubes and Duotube are examples of long nasal prongs. Older CPAP interfaces such as endotracheal tubes, head boxes, face chambers, and full-face masks are no longer in use in modern day NICU's. Nasal cannulas are sometimes used as CPAP interfaces but they are not marketed or tested for CPAP use and should therefore not be used as such.

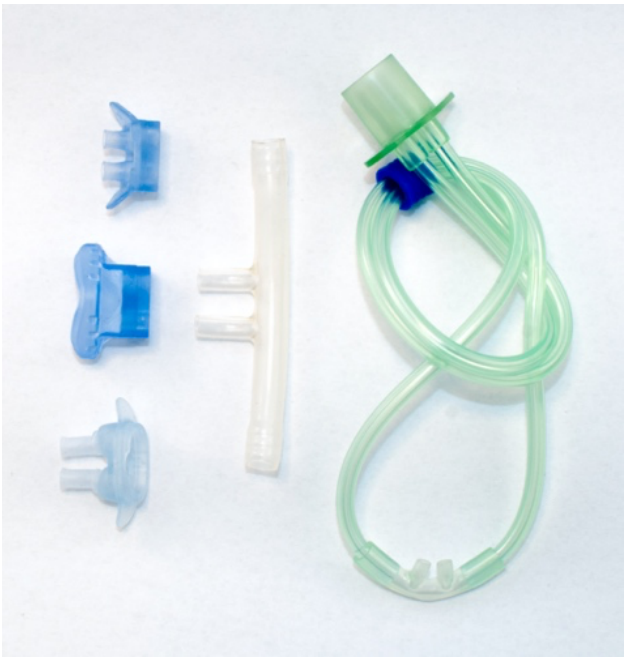

Figure 2: *A variety of nasal CPAP interfaces.*

In recent years, evidence has shown that short nasal prongs and nasal mask seem to be superior to long nasal prongs. De Paoli et al. compared, in vitro, different interfaces for nCPAP treatment in neonates. Short binasal prongs had the lowest resistance to flow, and the authors concluded that large pressure variations could occur in clinical settings.[12] In a clinical study by Davis et al., using short binasal Hudson prongs lead to significantly lower incidence of respiratory failure within seven days post extubation compared with using a single long prong.[26] Roukema et al. compared short binasal prongs with nasopharyngeal prongs and reported a lower rate of reintubation for short prongs.[27] A Cochrane review concluded that short binasal prongs are more effective than single prongs in reducing the rate of reintubation in preterm neonates.[28] A trial comparing nasal prongs and nasal masks for delivering CPAP to preterm infants <31 weeks of gestational age showed that the nasal mask was more effective than nasal prongs for preventing intubation within 72 h of starting therapy.[29] Green et al compared, in vitro settings, different brands of short nasal prongs, masks and even included the RAM cannula. They concluded that use of interfaces with high resistance results

in a greater drop in delivered airway pressure in comparison to set circuit pressure and this could have impacted clinical efficacy.[30]

The 2019 European RDS guidelines recommend using short binasal prongs or nasal mask when commencing CPAP treatment for preterm infants.[31]

2.5 PRESSURE STABILITY AND IMPOSED WORK OF BREATHING OF CPAP DEVICES

When breathing through a device, the airway pressure will fluctuate during the breathing cycle. Inspiration will lead to a decreased airway pressure and expiration will lead to an increased airway pressure. It is the patient that generates theses pressure changes and they represent the extra work needed to breathe through a device. This extra work is called imposed work of breathing (iWOB). For CPAP systems that are pressure-unstable, the fluctuations will be large and the iWOB will be high. Investigate pressure stability can be done in a number of ways but they all reflect the relation between pressure and flow for a device (Figure 3).

Pressure can be measured at a given time, flow or volume, for example during one breath. Imposed work of breathing is an integration of pressure over volume for one breath. It can be divided into an expiratory and inspiratory part. Every breath has a pressure-volume loop in the same way as we see on the screen of ventilators, and the work of breathing can be calculated from the area within a single breath. Imposed work of breathing can be averaged over time or per volume.[32]

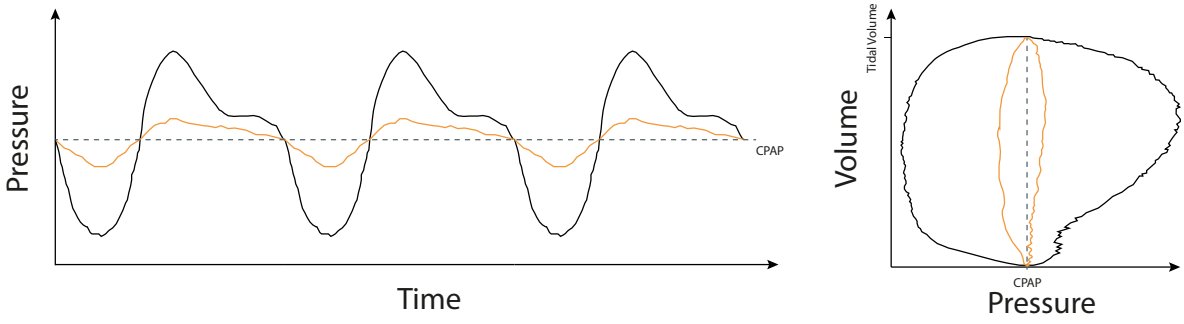

Figure 3: *Illustration of pressure stability during spontaneous breathing. High amplitude of the pressure fluctuations during breathing (up/down) corresponds to a wider pressure-volume loop (left/right) and a larger iWOB. The illustration in black has a higher resistance to breathing, with larger pressure swings and higher iWOB.*

2.6 METHODS USED TO MEASURE PRESSURE STABILITY AND IWOB

2.6.1 Static tests

A simple way to describe resistance is the pressure changes at a given flow. This simple static model makes experiments easy to perform and understand, without the need to accurately reproduce flow profiles or volumes.

2.6.2 Dynamic tests

Mechanical lung simulators are needed for dynamic tests. These can simulate spontaneous breathing, allowing us to compare the pressure stability of different devices and variables. Simulations can be either non-compliant (volume or flow pump) or complex (including compliance and resistance).

2.6.3 In vitro comparison of CPAP devices

Moa et al compared a new system (Infant Flow) to a continuous flow CPAP system and showed that the new system was more pressure stable and less sensitive to leakage.[24] Klausner et al used a mechanical lung model to compare a variable flow system (Arabella) to a continuous flow system and showed lower iWOB for the Arabella system.[33] Drevhammar et al compared seven CPAP systems.[34] They showed large variations in iWOB and pressure stability with AirLife and Infant flow having the lowest iWOB while NeoPuff and Medijet had the highest.

2.7 CPAP DEVICES IN LOW RESOURCE SETTINGS

Providing respiratory support for infants in low-income settings is challenging. Access to inexpensive CPAP respiratory support is highly prioritized by the World health organization (WHO), which in a 2012 statement highlighted this as an area in need of innovation and implementation.[35] Bubble CPAP has major advantages compared to CPAP provided by more expensive devices such as existing variable flow systems or modern ventilators. The combination of low price, simple technique, well-proven clinical effect, and no need for pressure monitoring makes bubble CPAP ideal for use in lower-middle countries. In the last decade, new devices have been designed for use in low resource settings. Almost all are based on the original bubble CPAP design, often with modifications. The development of new systems has not been without concerns. The WHO stated: ‘Increasing use of CPAP without regulation is a concern. Many devices are in the “homemade” category; several low-cost bubble CPAP devices are being developed specifically for low-income countries but need to be tested for durability, reliability and safety’.[36] It is of great importance to conduct quality research on the effectiveness, sustainability and safe implementation of bCPAP design alterations for use in low resource settings.

2.8 RESPIRATORY SUPPORT DEVICES FOR DELIVERY ROOM MANAGEMENT

The delivery room management of the preterm infant is moving towards a less invasive approch.[37] The benefit of non-invasive management was first noted in observational studies[38,39] and then in a randomized trials , such as the COIN, CURPAP, VON and SUPPORT trials.[40-43] A Cochrane review from 2016 concludes that prophylactic nasal CPAP in very preterm infants reduces the incidence of BPD or BPD and death, compared to intubation and mechanical ventilation.[1] The European guidelines for the treatment of RDS 2019 and The International Liaison Committee on Resuscitation (ILCOR) consensus document 2020, recommend using CPAP rather than intubation and mechanical ventilation for initial stabilization of spontaneous breathing preterm infants with respiratory distress.[31,44]

To establish stable spontaneous breathing in a newborn preterm infant, positive pressure ventilation (PPV) is often needed. The techniques available for non-invasive PPV are T-piece resuscitators, self-inflating bags or flow-inflating bag systems.[45] All are used with a facemask as patient interface. The T-piece systems can be used to provide CPAP and bag systems can have a built-in positive end expiratory pressure (PEEP) valve. For some of these bag and PEEP valve systems, this design is quite ineffective and PPV needs to be delivered at a high rate in order to create PEEP and CPAP cannot be generated during spontaneous breathing.[45-47] Animal studies have shown convincingly that PEEP is beneficial in creating FRC[48], however clinical studies have failed to show marked clinical significance with the devices used today.[44] Animal studies have also shown that when preterm rabbits are apnoeic the larynx is closed which makes both PEEP and PPV ineffective.[49] PPV even triggered closure of the larynx in rabbit pups who already had a stable breathing pattern. The authors concluded that very preterm infants could benefit from focusing on spontaneous breathing rather than providing PPV with face mask. It is known that stimulation of the trigeminal nerve in infants, can cause a cessation of breathing pattern, bradycardia, peripheral vasoconstriction and closure of the larynx.[50,51] In 2018, Martherus et al[52] speculated in a review, that using a facemask as an interface could influence the breathing pattern of infants via the trigeminal nerve. Apnea after the placement of facemask in newborn infants was later confirmed by Kuypers et al in a retrospective study reviewing resuscitation video recording.[53]

A new system, the rPAP, was recently introduced. It is a variable flow device and has a marked reduction in imposed work of breathing (iWOB) compared to the traditional T-piece.[54] The system is handled in a similar way as the standard care T-piece system, delivers of PPV by occlusion at an aperture on the device, and can be used with nasal prongs/mask as the patient interface.

The combination of various devices and interfaces for CPAP support complicates the process of deciding which systems are best suited for neonatal use. The ILCOR guidelines highlight this problem: "Interpretation of human studies is further complicated by varying interfaces (e.g., face mask versus endotracheal tube) and methods of generating PEEP (e.g., self-inflating bags with PEEP valve versus T-piece resuscitator)".[55] The clinical effect of using

different interfaces and devices, and the impact of the CPAP level given in the delivery room has been insufficiently studied and high quality randomized controlled trials in preterm infants are needed.

3 RESEARCH AIMS

The general aim of this thesis was to evaluate existing and newly developed devices for non-invasive respiratory support used in neonates in the DR and the NICU. The focus was on device resistance, pressure stability, imposed work of breathing and interfaces used.

Specific aims:

I. To describe the performance of a new system(rPAP) “in vitro”, then to perform a clinical feasibility trial comparing a T-piece system with face mask, and the new system with face mask or nasal prongs, for initial stabilization of preterm infants.

II. To describe the “in vitro” performance of the Medijet CPAP reusable and disposable generators and compare this to the Neopuff resistor system and two non-resistor systems (the Infant Flow and Benveniste valve).

III. To compare the Pumani system with two traditional bubble CPAP systems, focusing on “in-vitro” performance and safety.

IV. To evaluate if a new system, with low iWOB and nasal prongs as interface, could reduce the need for intubation of extremely preterm infants in the DR compared to the standard T-piece system with face mask.

4 MATERIALS AND METHODS

The studies that this thesis is based on include both preclinical in vitro experiments as well as clinical trials. Device testing was performed in our lab at Östersund Hospital, Sweden and clinical trials at the Karolinska University Hospital in Stockholm, Sweden and (in paper IV) six other centers in Europe.

4.1 THE NEW RESUSCITATION SYSTEM

The new resuscitation system, now called rPAP, was designed in a collaboration with our research group. The original prototype was designed by Kjell Nilsson and Thomas Drevhammar. The author of this thesis, among others, gave clinical feedback on the design and function. Minor design alterations were made before the device was CE certified. The new system is driven by two flows, one jet flow and one bias flow. The jet flow creates the CPAP and the addition of the bias flow enhances the inspiratory rise time during PPV. The system can be used with either face mask or nasal interface.

4.2 IN VITRO EXPERIMENTS (PAPER I, II AND III)

The "in vitro" experiments were performed with either dynamic tests (paper I-III) or static tests (paper II and III).

4.2.1 Dynamic tests

A mechanical lung model (ASL 5000, IngMar Medical, Pittsburg, Pennsylvania, USA) was used in dynamic experiments and to simulate breathing for all test systems. To simulate breathing, a simple noncompliant flow pump mode was used. We used a fixed volume syringe and a calibrated pressure transducer (VT PLUS HF, Fluke Biomedical, Everett, Washington, USA) to standardize the accuracy of volumes and pressures. Sinusoidal flow profiles with respiratory rate of 60 per minute and an inspiratory-to-expiratory time ratio of 1:1 were used. A tidal volume of 32 mL were used in all in vitro experiments. In addition, 16 mL tidal volume was also investigated in paper I. All systems were tested at different CPAP levels and with non-humidified air at room temperature. iWOB was calculated for each breath from the area within the pressure volume loop (modified ASL V.3.1 software). This method has been described in detail by Banner[32] and Drevhammar[34].

4.2.2 Static tests

The static experiments performed in paper II and III examined pressure changes due to resistance both with and without simulated airway flow. In paper II the effect of directing flow through the driver port with the patient interface closed was compared to doing the opposite, that is delivering fresh gas flow through the patient interface with the driver port occluded. This was done to investigate whether the Medijet generator created CPAP due to

variable flow (Coanda effect) or simply due to resistance. The pressure stability of the devices was investigated at 5 cm H2O of CPAP with simulated airway flow from -10 L/min to + 10 L/min, with negative flow representing inspiration and positive flow representing expiration. In both paper II and III devices were compared with regards to pressure changes when increasing the fresh gas flow, gradually from 0-10 L/min through the driver port with the patient interface closed, at a set CPAP level or submersion depth. In paper III the effect of the submersion depth was investigated for different devices. In addition, the resistance of tubing of the Pumani system was tested by gradually dissembling the connections at 6 different points.

4.2.3 Statistical analysis

Statistical analyses were performed using ANOVA with Bonferroni correction and mean data was presented with standard deviation (supplementary tables) or 95% confidence interval(figures). $P < 0.05$ was considered to be statistically significant.

4.3 CLINICAL FEASIBILITY TRIAL (PAPER I)

The clinical feasibility trial comparing the newly developed system to standard T-piece system started in 2012. From 2012 to 2015, 36 infants with gestational age between 27w-34w, were recruited. Informed consent was obtained from mothers with threating preterm labour and the infants were randomized into 3 groups. The groups were new system with prongs, new system with face mask and standard T-piece system with face mask. The trial was a feasibility trial and therefore not designed to estimate treatment effects and no power calculations were performed. The intervention was CPAP for at least 10 min after birth and PPV if needed. The intervention ended with either establishment of stable spontaneous breathing or intubation. Outcomes included respiratory and safety parameters and the follow up period was 72 hours after birth.

4.3.1 Statistical analysis

Normal distribution was tested with Shapiro-Wilk test. Normal distributed data was presented as mean (SD) and differences were tested with ANOVA. Non-normal distributed data was presented as median with inter quartile range and differences was tested with Kruskall-Wallis test. Nominal data were tested with Fisher's exact test. $p < 0.05$ was considered statistically significant.

4.4 THE CORSAD TRIAL (PAPER IV)

The CORSAD (Comparison Of Respiratory Support After Delivery on infants born before 28 weeks gestational age) Trial was a two armed, nonblinded, randomized trial in seven centers

in five countries. The study had local ethical consent in each of the five countries. It was funded by unrestricted academic research grants and no corporate funding was allowed.

The trial was performed according to Good Clinical Practice (GCP) following the principles of the Declaration of Helsinki[56] and registered at clinicaltrials.gov before the start of the trial. Before each study site initiation, on site DR training was performed and web-based training module introduced. Infants were recruited after screening and informed consent of mothers with threatening preterm labor before 28 w GA in absence of prespecified exclusion criteria. Informed consent was prospective in all cases. Randomization was stratified on center, antenatal steroid treatment and GA. Patients were randomized with a computer genericide randomization system shortly before birth in a 1:1 ratio to either the new system group with nasal prongs or the standard T-piece system with facemask. The same system was used for multiple births infants.

The delivery room intervention was CPAP for the first 10-30 minutes after birth and PPV as needed. Intervention ended when the infant had established stable breathing on CPAP or was intubated. CPAP pressures allowed were 5-8 cm H2O and PIP pressures 20-25 cm H2O. Routine DR care for thermal regulations, oxygenation, monitoring and post intervention care followed International Guidelines[31,44] and local protocols.

The primary outcome was intubation or death in DR within the time frame of 0-30 minutes. The intubation criteria included persistent bradycardia, apnea, poor respiratory effort and inadequate oxygenation. Secondary outcomes included respiratory and safety variables.

The trial was conducted according to GCP to increase data quality but this was not required since both systems were CE-labelled. An independent Data Monitoring Committee (DMC) reviewed data on safety, progress and study conduct on a regular bases during the trial period. All adverse event and deaths were reviewed by the DMC.

4.4.1 Statistical analysis

We calculated the number of patients needed from a baseline intubation rate of 60% in extremely preterm infants born in Sweden prior to the trial.16 Estimated treatment effect was not known,so an 20% absolute reduction was judged to be clinically important. The calculated number of infants was 195 with a binary outcome superiority trial design at significance level (alpha) of 5% and power (1-beta) of 80%. This was increased to 250 patients to accommodate stillborn, protocol violations, baseline intubation rate changes, and center differences. The primary outcome was analyzed using a logistic regression model adjusted for stratification variables. The model was also used for estimating an adjusted risk difference. A multivariate GEE logistic regression model, adjusting for multiple births was also performed. Binary outcomes and demographic variables were compared by chi-square or Fisher's exact test as appropriate. Continuous data were compared using t-tests or non-parametric test after tests of normality. Risk ratios and risk difference for secondary outcomes with 95% CI were calculated using cross tabulation risk function or in Excel version 16 (Microsoft, Redmond, WA, USA). Kaplan Meier method was used for cumulative incidences

of DR primary outcome followed by NICU mechanical ventilation or death up to 72 h. All analyses were two-sided, based on intention-to-treat and $p<0.05$ considered statistically significant. No adjustments for multiple comparisons were made and secondary outcome results should be interpreted as exploratory.

5 RESULTS

5.1 PAPER I

The in-vitro simulations showed that the new system had better pressure stability and a marked reduction in iWOB compared to standard T-piece systems represented by GE and Neopuff. With a tidal volume of 16 mL/breath and 4 cm H2O of CPAP, the relative iWOB reduction was over 85% both for the new system with and without prongs when compared to T-piece. Increasing CPAP level led to increased iWOB for the T-piece systems but decreased iWOB for the new system.

In the clinical feasibility trial, a total of 39 infants were randomized, of whom 36 needed support. 12 infants received support with T-piece, 12 infants the new system with facemask and 12 infants the new system with prongs. There was a statistically significant imbalance between the groups with respect to gestational age. All patients received the randomized system until at least 10 min of age except for 1 patient who was intubated. There were no statistically significant differences in DR outcomes between the groups. In NICU, more infants treated with the new system and prongs received surfactant in the first 72 hours. However, the infants in this group were also statistically more immature with a median GA of 30w+5d compared to 33w+0d for T-piece and 32w+2d in the other new system group. Two infants, both w 27 GA, in the new system with prongs developed pneumothoraxes. In both cases, pneumothorax developed after intubation in NICU. There were no other patient safety issues detected, and no problems related to equipment or usage.

5.2 PAPER II

The disposable Medijet differed from the other variable flow devices when simulated airway flow was tested both through the prongs versus the driver port. The resistance was comparable feeding air from either side so the mechanism for pressure generation resembled more a continuous flow resistor system than a variable flow system. This was not seen the for the Infant Flow, Benveniste valve nor reusable Medijet with or without the clip. In the static tests with a prespecified CPAP level the Neopuff and the Medijet disposable generator had the highest resistance, the Infant flow and Benveniste the lowest and the reusable Medijet in the middle. The reusable Medijet showed lower resistance without the clip. The dynamic tests showed the same pattern as for resistance, with the highest iWOB for the disposable Medijet and Neopuff. Because the Neopuff system has an adjustable resistor valve, by increasing flow and loosening the valve, iWOB decreases and pressure stability increases at any given CPAP level.

5.3 PAPER III

The original Pumani system was designed without a bleed valve with the risk of rebreathing and carbon dioxide accumulation. A bleed valve was added after communication with our research group and the system tested in this paper was the revised Pumani system with a

bleed valve. We tested the bleed valve flow and even at low CPAP pressures the flow exceeded 1 l/min so the risk for rebreathing is minimal in this revised design.

When tested for the effect of submersion the conventional bCPAP systems (the Diamedica and the Fisher and Paykel), CPAP was dependent mainly on submersion depth and fresh gas flow only had marginal effect. For the Pumani system, submersion depth had almost no effect on delivered pressure and was dependent on fresh gas flow instead.

When tested for resistance, the Fisher and Paykel system had the lowest resistance and the Diamedica slightly higher. The Pumani system tubing had substantially higher resistance. The resistance was higher than the resistance of an uncut 3.5 mm endotracheal tube that was used for comparison. The Pumani tubing system contains multiple connections. Disconnecting parts decreased resistance measured after every connection. The resistance of the revised Pumani system tubing, without fresh gas flow or submersion, was higher than in both conventional bubble CPAP systems. The resistance was higher than an uncut size 3.5 endotracheal tube. Disconnecting parts of the revised Pumani tubing reduced resistance. Submersion depth and fresh gas flow had now effect on the resistance of the Pumani system and the prongs used for the system also had high resistance. The Pumani system had the highest iWOB of the systems tested, including NeoPuff that was also measured for comparison as a true resistor system.

In summary, the revised Pumani system had high resistance, high imposed work of breathing and submersion depth had almost no impact on pressure delivered which is the main CPAP mechanism of true bCPAP systems.

5.4 PAPER IV

A summary of screening, inclusion, randomization and treatment is found in Figure 4. The two groups were similar in respect to demographics and clinical characteristics. Exposure to antenatal steroids was high, with over 98% receiving at least one dose in both groups. Intra uterine growth retardation (25.0% vs 18.0%), multiple births (21.0% vs 18.9%) and general anesthesia during C-section (16.1% vs 7.8%) was more common in the new system group. Humidification, which was optional to centers if used in both groups, was 46.3% in the new system group and 53.7% in the T-piece group.

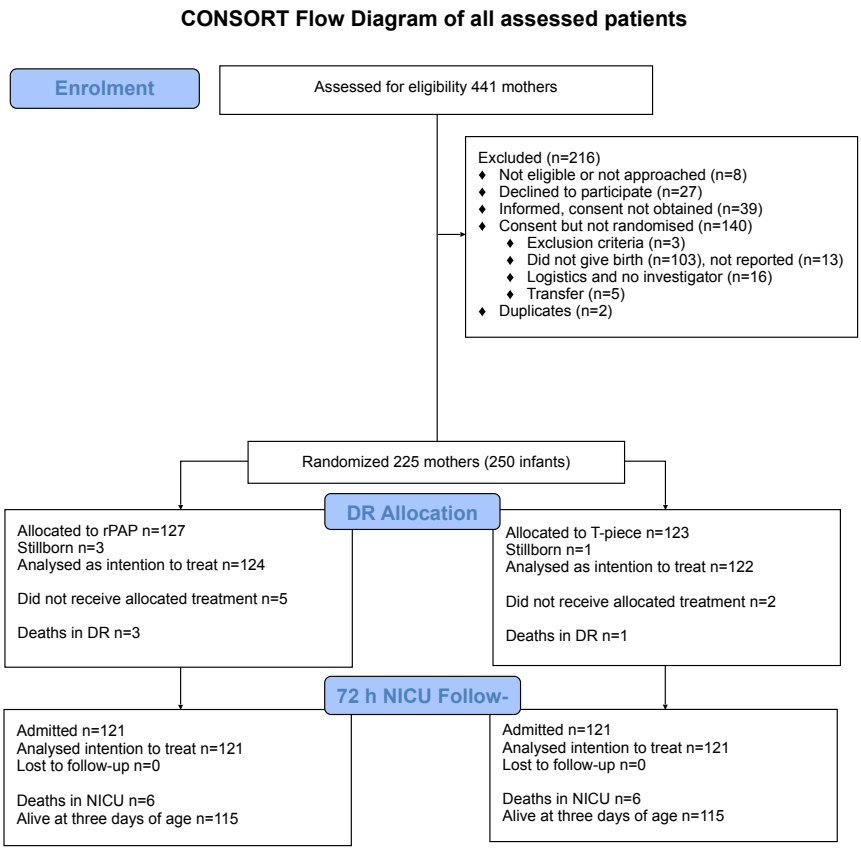

Figure 4: *Flow diagram of patients in the CORSAD study.*

The primary outcome was defined as intubation or death in the DR within the time frame of 0-30 minutes. In the new system group 33.1% (41/124) of the infants were intubated or died in DR and 45.1% (55/122) in the T-piece group. The adjusted odds ratio was statistically significant after adjusting for stratification variables (adjusted OR= 0.53, [95% CI 0.30 to 0.94], P= .03; adjusted RD = -14.6% [CI -26.5% to -2.6%]). One infant in the new system group was intubated at 45 minutes in the DR but did not meet the primary outcome criteria because this was after the prespecified time frame of 0-30 minutes. One additional infant in the new system group was born with malformations that were not known prior to delivery, got treatment limitations at 2 minutes of age and died at 66 minutes of age.

None of the secondary outcomes were statistically significant after correction for multiple comparisons. There were a total of 4 deaths in the DR, 3 in the new system group and 1 in the T-piece group. 12 infants died within 72 hours in the NICU, 6 in each group. Allocated treatment violations, reports of AE and technical issues more frequent in the new system group. Interface was changed in 9 infants from prongs to facemask in the new system group. The DMC did not find that deaths or serious averts events (SAE) were connected to devices used nor the trial protocol. In Figure 5 important safety secondary outcomes are shown as odds ratio.

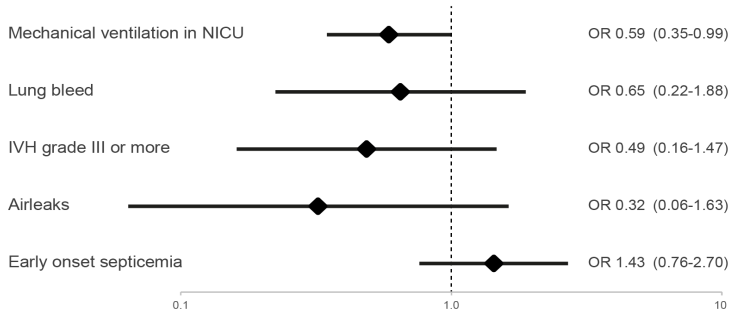

Figure 5: *Secondary NICU outcomes of the CORSAD study. OR below 1.0 favors the new system. There were no statistical differences after adjustment for multiple comparisons, n= 121 in each arm.*

6 DISCUSSION

Since the first CPAP for use in newborns was designed and described by Gregory in the 1970', numerous devices and techniques have been developed to give non-invasive respiratory support to newborn term and preterm infants. It became clear early on that a simple resistor system as the Gregory CPAP would be hard to breathe through and a simple but brilliant solution emerged. It involved changing from a resistor clamp to submersing the exhaustion tube in water to generate the CPAP pressure. Since then, the bubble CPAP design has prevailed and is still a very good alternative to more modern and expensive CPAP devices that have been developed. Research on new devices used for neonatal non-invasive respiratory support is suboptimal, and in some cases lacking entirely. The responsibility of manufacturers is unclear and the regulatory body is not up to standard compared to for example new pharmaceuticals.

This thesis focuses on evaluating existing CPAP devices and technique and also comparing a newly developed device for resuscitation to the standard device recommended in International guidelines. We have been involved in the design of the new device, performed a pilot study using the device and completed a multicenter randomized controlled trial with focus on important clinical outcomes for newborn extremely preterm infants.

When devices are developed and marketed, it is important that the devices actually perform in the way they are intended to, and that they are used correctly. The T-piece device is a resuscitator, labelled as such and is not marketed as a CPAP device and is designed to use with a facemask. It is pressure unstable and has high imposed work of breathing.[34] It is not meant as CPAP for intermediate nor long term respiratory support. Therefore, attention to pressure stability or iWOB has not been in focus in its design. However, the T-piece is widely used for longer periods of time than it takes to stabilize an infant, as during transport from the DR to the NICU and also in rural areas that do not have standard CPAP devices on site.[57] This prolonged respiratory support with a T-piece is of unsure risks and benefits.

In papers II and III we have evaluated the design and performance of two commercially available CPAP devices. The Medijet and the Pumani CPAP devices are described and marketed in a certain way. The original Medijet was built on the Benveniste valve technique.[58] One of the concerns with the Benveniste valve was the noise because of its open design. To make the Medijet device more attractive and modern, modification were successively made over the years to minimize noise and make the device disposable. This redesign however had costs when it comes to performance. The disposable Medijet is said to be a variable flow device. We have shown, when tested in the lab, that it has almost none of the qualities that are the hallmark of variable flow devices. Pressure instability, high imposed work of breathing and mechanisms resembling classic resistor devices make it unlikely that the disposable Medijet is a variable flow CPAP device. It has never been proven in trials that pressure stability and iWOB is of clinical importance, nevertheless it is still important for manufacturers to describe their product in the right way so the users can tailor their treatment

accordingly. For example, higher CPAP pressure leads to higher imposed work of breathing when using the Medijet but not for the Infant Flow in. For some infants this could potentially be important.

The revised Pumani tested in paper III was described as a bubble CPAP device.[59] The traditional view on the mechanism of bCPAP is that the submersion level reflects the pressure delivered to the patient. When we tested the Pumani, the submersion level had no correlation to the pressure delivered.[60] Pressure was mainly created by the resistance of the tubing system. Placing the submersion bottle in the circuit ahead of the patient interface and a bleeding valve makes it understandable that the submersion level would have minimal impact. When the Pumani was presented in a conference in 2015, there was no bleeding valve and the tubing had a blind end after the patient interface. After reaching out to the researcher and creators of the system and pointing out the risk for rebreathing, the bleeding valve was added. At the same time, we pointed out that the tubing of the system had high resistance and that the submersion level could not be used to set delivered pressure. After the publication of our paper and measurements in their own lab, the RICE 360 group changed the design of the Pumani again and it now has the original bubble CPAP design with the submersion bottle placed after the patient interface.[61]

In paper I and IV we evaluate a new system that is now marketed and sold under the name rPAP. This system was designed with pressure stability and low iWOB in focus.[54] Drevhammar et al noticed in an in vitro simulation that the traditional T-piece was pressure unstable and had high iWOB in comparison with traditional CPAP devices such as Infant Flow and bubble CPAP.[34] The interface for the T-piece is a face mask, the same as for other resuscitation devices such as the self-inflating ambu bag. Capasso et al had shown in a clinical study that a nasal interface was an alternative to a face mask.[62] In that study fewer intubations were observed when using nasal prongs compared to using face mask for resuscitating newborn infants. The ILCOR guidelines included the alternative of using a nasal interface instead of facemask in their guidelines already in 2010 and successive guidelines.[44,55,63] Designing and testing a device that is pressure stable, with low imposed work of breathing and a nasal interface was therefore an attractive next step in our research. In paper I, the in vitro tests of the new rPAP design clearly showed that there was a substantial difference in iWOB between two different brands of T-piece systems and the new system. It also showed that whilst the iWOB increased for the T-piece with increased CPAP level the iWOB decreased for the new system. The small feasibility trial showed that the new system was easy to use and did not reveal any safety issues when using the device, neither with face mask or prongs. The groups were imbalanced with regards to GA but this could be expected due to randomization, sites and a small sample size.

In paper 4 we were able to show that using the new system with nasal prongs decreased DR intubation of extremely preterm infants compared with using a traditional T-piece. Using the primary outcome of DR intubation or death instead of the traditional outcome of BPD or death in similar trials[40-43,64] is debatable. However, the BPD diagnosis criteria have been

criticized in recent years and at least 2 new definitions are currently discussed in different forums.[65,66] The outcome of DR intubations for extremely preterm infants has been graded as important in the newest update of the ILCOR guidelines in 2020.[44] Creating a window of opportunity for avoiding intubation and mechanical ventilation and giving surfactant using minimally invasive techniques or non-invasively, is worth pursuing.

Reassuringly, none of the secondary outcomes were significant or showed a trend towards poor safety issues or worse clinical outcomes for the new system in the first 72 hours.

As mentioned earlier, despite evidence from the adult populations[67], imposed work of breathing has not been shown to have clinical significance in neonatal setting. This is mainly due to insufficient research in the area, with no control over important factors such as leakage and equal experience off trial staff using different systems. It has repeatedly been shown that the resistance, size and iWOB of different nasal interfaces and prongs differ and that this may have clinical importance.[12,26,28,30] On the other hand, hard evidence for or against this view is not readily available. Based on both our own research and other groups research, I believe that it is wrong to assume that all modern CPAP generators and tubing systems have minimal resistance and minimal imposed work of breathing. Making such assumption could, in a worst-case scenario lead to harm for newborn patients.

Delivering non-invasive long-term respiratory support via the nose to infants, has been standard with CPAP, high flow and low flow nasal cannula and has been so for a long time in the NICU setting. Infants are “preferred nasal breathers” [68]and therefore ,the optimal and least invasive route giving respiratory support is through the nose. However, traditionally, non-invasive respiratory support in the DR has been delivered via facemask with the possibility of giving PPV. Using a facemask for stabilization can be challenging. Mask leakage and airway obstruction are common when using a face mask, often undetected by the user.[69-72] A few trials in the past 20 years, have investigated whether nasal interfaces are better suited to deliver this initial respiratory support after birth.[62,73-75] Recently, 2 systematic reviews have been published on the subject, to see which is more effective and favorable, nasal interfaces or the face mask. Although both conclude that nasal interfaces may be more favorable, both were inconclusive.[76,77] In an editorial in Resuscitation, concerns about using the facemask as interface is raised and pointed out that more trials comparing facemask and nasal interfaces are needed.[78]

Caring for extremely premature babies is very expensive but the number of patients is limited. There are very few drugs that are tested and approved for use on these patients. The same applies to medical technology. This is because it is difficult to conduct studies in this patient group, and because the potential market is small. It is an ethical dilemma that research on premature babies is relatively neglected, despite its importance from a patient, relative and care perspective. The evidence-based care that we seek is difficult to achieve in practice. However, it is our duty as physicians and researcher to test and evaluate newly developed devices and, preferably, without the direct involvement of the Med Tech industry. Seeking consent with parents is important, however recently it has been pointed out that the use of

waiver of consent and retrospective consent might be crucial moving forward in DR resuscitation trials and generate reliable evidence for the future.[79]

6.1 LIMITATIONS

The in vitro tests used in paper I, II and III are limited by the artificial nature of such models. In our model there was no leakage, a symmetrical sinusoidal flow pattern (i:e 1:1) was used and the model was non-compliant. In vitro tests like these can be criticized for not reflecting how devices are used, how the total work of breathing may change, and whether the results are clinically relevant. Simulations may underestimate iWOB for systems which are pressure unstable with large pressure swings because of tube compliance and gas compression, which will lead to a reduction in delivered volumes. Correcting for this artifact is complicated and was not attempted in our measurements. Large differences in iWOB between devices were seen and this was regardless of the specified tidal volume. It is therefore plausible that the difference will be present if other profiles than the tested tidal volumes are used. Despite the limitations of modelling, it is still useful to describe the true quality and mechanism of a devices, and the findings can be easily reproduced by other research groups.

In the clinical feasibility trial (paper I), the absence of stratification and the small number of patients resulted in an imbalance between the treatment groups. The group treated with the new system and prongs had significantly lower gestational ages. This must be considered when interpreting the results of the trial. Furthermore, the inability to perform a blinded trial always leads to the risk of bias, especially with only a few investigators involved in the trial. The small number of patients also makes it hard to draw definite conclusions about the safety and treatment effect of the new system.

The RCT in paper IV has several limitations. First, the trial was not blinded which leaves a potential for selection bias. This is a universal problem for all intervention trials of newborn infants in the DR. Despite clinical management guidelines and criteria for intubations this risk for bias can never be excluded. In an attempt to reveal possible bias secondary outcomes were included, such as time to intubation after initial stabilization. Secondly, only including infants to mothers that gave antenatal consent is also a risk factor for bias, because it excludes the sickest infants born (for example) after admission with emergency c/sections due to either mother or infant indications. These infants are often not subjected to the beneficial effect of antenatal cortisone, which could potentially affect how applicable our results/findings are more generally.

7 CONCLUSIONS

Devices used for non-invasive neonatal respiratory support are diverse and vary in their construction as well as function. Resistance, pressure stability, interfaces and imposed work of breathing differ markedly. However, these aspects are still of uncertain clinical importance. In the 2010 ILCOR guidelines the following questions were asked: “What is the appropriate interface to effectively ventilate infants…? What is the optimal device for delivering PEEP and CPAP?”. Eleven years later, I believe that the findings presented in this thesis have brought us one step closer in answering these questions.

- A new device (rPAP), was shown in a mechanical lung model to be pressure stable and have low imposed work of breathing compared to the T-piece. The feasibility trial comparing these devices revealed no safety issues when stabilizing preterm infants with the new device.

- The main mechanism of CPAP generation for the disposable Medijet generator is resistance. The Medijet systems shows increasing resistance to breathing with each design generation. Our results suggest that the disposable Medijet should be used cautiously in patients for whom low-resistance and pressure-stable CPAP is believed to be clinically important.

- The revised Pumani system had high resistance, high imposed work of breathing and submersion depth had almost no impact on the delivered pressure which is the main CPAP generating mechanism of true bubble CPAP systems. After the publication of our results the system has been revised again and has now the conventional bubble CPAP design. This paper highlights the continued need for critical review and testing of new CPAP designs with uncertain clinical implications before they are released on the commercial market.

- Using a new system (rPAP), which has low imposed work of breathing and nasal prongs as interface, decreased delivery room intubations in extremely preterm infants compared with using the T-piece and face mask. This creates a window of opportunity to give surfactant in a non- or minimal invasive way hence avoid mechanical ventilation.

8 POINTS OF PERSPECTIVE

We have continued evaluating devices and interfaces.[80-84] This is of great importance especially when regulations and notifying body for medical devices are sub-standard. Understanding the mechanism of how devices work and measuring their performance is of value. Performing clinical trials to test the importance of resistance, leakage and imposed work of breathing is urgent, especially for our smallest infants, for whom the margins between life, death and serious morbidity are minimal. We have several trials completed and underway looking at devices and their qualities.

When we started our journey 10 years ago with a new device, intended to stabilize the preterm infant in a gentle and non-aggressive way we were swimming against the stream. Sustained inflation with high inflating pressure and an aggressive approach in the DR was gaining momentum and thought to be the way forward to lower morbidity and mortality in the smallest infants. Since then, studies have showed that this aggressive approach can have serious consequences and even increase mortality. The new approach with early CPAP, avoiding PPV if possible and physiological cord clamping is gaining popularity. The new device we have designed and tested is optimal for such support. New DR studies should focus on a bundle of non-aggressive stabilizing methods and giving our smallest and most vulnerable infants the chance of a smooth start in life.

9 SUMMARY IN SWEDISH

Att undvika mekanisk ventilation i neonatalperioden kan minska sjuklighet och dödlighet hos förtidigt födda barn. Att istället använda icke-invasiv ventilation och CPAP har visat sig vara bra för att undvika intubation och mekanisk ventilation. CPAP användning kan förhindra utveckling av kronisk lungsjukdom hos mycket förtidigt födda barn. CPAP som andningshjälp för nyfödda barn började användas tidigt på 70-talet. Sedan dess har flera olika CPAP system utvecklats. Några av systemen är utvecklade för att ge långvarigt andningsstöd medan andra är utvecklade för initialt stöd, med möjlighet att ge övertrycksventilation (PPV) om det behövs. Vissa CPAP system är dyra och komplicerade med flera tilläggsfunktioner medan andra är billiga, med enkla mekanismer för att generera tryck och är användarvänliga.

Målet för CPAP-behandling är att ge spädbarn kontinuerligt luftvägstryck för att minimera andningsarbetet och förbättra gasutbytet. Men är alla CPAP system likadana? Levererar alla CPAP system stabilt luftvägstryck som hjälper spädbarn med deras andningsarbete?

Avhandlingens övergripande syfte var att utvärdera befintliga och nyutvecklade system för icke-invasivt andningsstöd som används hos nyfödda i förlossningsrummet och på neonatalavdelningar. Tryckstabilitet, extra andningsarbete samt patientgränssnitt var i särskilt fokus.

Syftet med arbete I var att undersöka egenskaper och prestanda för ett nytt system (rPAP) i mekanisk lungmodell. Dessutom att göra en klinisk pilotstudie där det nya systemet jämfördes med traditionellt T-stycke, vid initial stabilisering av förtidigt födda barn. Det nya systemet visade sig vara tryckstabilare och ha lågt påfört andningsarbete jämfört med T-stycket. Pilotstudien visade inga säkerhetsproblem i samband med användning av det nya systemet.

Syftet med arbete II var att undersöka in vitro-prestanda för olika generationer av Medijet CPAP systemen och jämföra dessa med andra CPAP-system. Huvudmekanismen för CPAP-generation för Medijet-engångsgeneratorn visade sig vara motstånd. Medijet-systemen visar successivt ökande andningsmotstånd för varje designändring. Våra resultat tyder på att Medijet engångsgeneratorn bör användas med försiktighet till patienter där låg resistens och tryckstabilitet av andningshjälpen tycks vara av vikt.

Syftet med arbete III var att jämföra det reviderade Pumani CPAP-systemet med två traditionella bubbel CPAP-system, med fokus på in vitro-prestanda och säkerhet. Det reviderade Pumani-systemet hade högt motstånd och högt pålagt andningsarbete. Nedsänkningsdjupet som är den huvudsakliga CPAP-genereringsmekanismen för sanna bubbel CPAP-system hade minimal påverkan på levererat tryck för Pumani systemet.

Syftet med arbete IV var att utvärdera om användning av det nya systemet (rPAP) med näsprångar som gränssnitt, skulle kunna minska behovet av intubation av mycket förtidigt födda barn direkt efter förlossning. Det traditionella T-stycket med ansiktsmask användes som jämförelse. Den randomiserade kontrollerade CORSAD-studien visade att användning av det nya systemet minskade intubationer i förlossningsrummet hos mycket förtidigt födda barn och kan därför ge möjlighet i fortsättningen att undvika mekanisk ventilation.

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