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PERFORMANCE OF NCPAP SYSTEMS FOR NEONATAL USE AND DEVELOPMENT OF A NEW SYSTEM FOR INFANT RESUSCITATION

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Performance of NCPAP systems for neonatal use and development of a new system for infant resuscitation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Sara, Knut, Einar and Sven

ABSTRACT

Objective

Nasal continuous positive airway pressure (NCPAP) is the most commonly used respiratory support for newborn infants. It is a technique for non-invasive respiratory support of both term and preterm infants with respiratory distress. NCPAP is preferred to mechanical ventilation in preterm infants after several clinical trials showed equal or improved outcome when it is used as primary support. Finding treatment strategies that reduce the need for intubation and mechanical ventilation to improve outcome and survival, have been a core theme in neonatal research.

There is a wide range of NCPAP systems and little information to facilitate the choice. This leaves the clinician with multiple options and uncertainties. Research on performance as well as optimising and combining NCPAP with resuscitation systems, has the potential to further reduce the need for mechanical ventilation and improve outcome. The aim of this thesis is to describe the performance of continuous positive airway pressure (CPAP) systems (1), to evaluate techniques for measuring flows during CPAP treatment (2) and to develop a new system for neonatal resuscitation (3).

Methods

1) A mechanical lung model was used to measure pressure stability and the imposed work of breathing (WOB) during simulated breathing. The tests of CPAP systems included different levels of CPAP, breathing profiles and leakage.

2) Flow meters were evaluated in the mechanical lung model using the in-line and the flow-through placement technique.

3) Infant resuscitation system prototypes were designed, manufactured in 3D printers and tested for pressure stability in the mechanical lung model. The final design was tested in a clinical feasibility trial.

Results

1) The tested CPAP systems showed large differences in pressure stability and imposed WOB.

2) The flow meters intended for neonatal use had a higher resistance and lower dead space than the other tested flow meters. In-vitro tests in the flow-through position showed that resistance generated CPAP. Two flow meters with low resistance had acceptable flow recording quality in the flow-through position.

3) In simulated spontaneous breathing, the new resuscitation system (prongs or facemask interface) had a marked reduction in imposed WOB compared to standard T-piece resuscitators. The clinical feasibility trial of 36 preterm infants did not reveal any problems with safety or usage of the new system.

Conclusions

1) The clinical importance of pressure stability for CPAP systems and imposed WOB is unclear but has been suggested as an important factor for some premature infants. This should be considered when choosing CPAP systems, designing trials and interpreting results.

2) Measuring breathing during nasal CPAP seems possible with the flow-through technique. This should result in measurements with no added WOB or dead space.

3) The new infant resuscitation system has low imposed WOB and will allow future investigations of the importance of imposed WOB, patient interfaces and CPAP levels.

LIST OF SCIENTIFIC PAPERS

I. Drevhammar T, Nilsson K, Zetterstrom H, Jonsson B.
Comparison of seven infant continuous positive airway pressure systems using simulated neonatal breathing.
Pediatr Crit Care Med. 2012;13(2):e113-9.

II. Drevhammar T, Nilsson K, Zetterstrom H, Jonsson B.
Comparison of nasal continuous positive airway pressure delivered by seven ventilators using simulated neonatal breathing.
Pediatr Crit Care Med. 2013;14(4):e196-201.

III. 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.

IV. 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
Archives of Disease in Childhood Fetal & Neonatal Edition (in press).

CONTENTS

LIST OF ABBREVIATIONS

BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CLD	Chronic lung disease
CPAP	Continuous positive airway pressure
ET-tube	Endotracheal tube
FRC	Functional residual capacity
GA	Gestational age
I:E	Inspiratory-expiratory time ratio
ILCOR	International Liaison Committee on Resuscitation
INSURE	Intubate surfactant extubate
iWOB	Imposed work of breathing
NCPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
NIPPV	Non-invasive positive pressure ventilation
OR	Odds ratio
PEEP	Positive end expiratory pressure
PPV	Positive pressure ventilation
RCT	Randomised controlled trial
RDS	Respiratory distress syndrome
RIP	Respiratory inductive plethysmography
SpO_2	Peripheral capillary oxygen saturation
TV	Tidal volume
VLBW	Very low birth weight
WOB	Work of breathing

1 INTRODUCTION

Preterm birth is a major cause of death and disability worldwide. Approximately ten percent of infants are born prematurely and the absolute number of preterm infants is increasing.[1] There has been a remarkable progress in respiratory support for the preterm neonate since nasal continuous positive airway pressure (NCPAP) was introduced by Gregory in 1971.[2] The decreased mortality and morbidity has been attributed to a number of factors including non-invasive respiratory support, improved antenatal care and intensive care in general.

NCPAP is used in both term and preterm infants with respiratory distress. In preterm infants it is commonly used after birth and after extubation (following a period of mechanical ventilation).[3,4] NCPAP was, on average, used for more than a month in extremely preterm infants born in Sweden in 2014 (Swedish Neonatal Quality Register annual report 2014).

A core aim for neonatal research has been to find techniques or strategies to reduce the need for mechanical ventilation. The approaches include both pharmaceutical therapies and respiratory support techniques. Intubating and mechanically ventilating infants has been associated with worse outcome compared to using NCPAP.[5] Optimising existing NCPAP treatment has the potential to further improve respiratory care of preterm infants. This may reduce the number of infants that fail on NCPAP and the need for mechanical ventilation. A high risk of failing on NCPAP is seen in infants born at lower gestational age, when receiving NCPAP directly after birth or when extubated from mechanical ventilation.[6,7]

The development of new tools for respiratory support and optimisation of non-invasive management could allow more infants to breathe on their own and reduce the need for intubation and mechanical ventilation (invasive). The research presented in this thesis concerns basic questions on the performance of NCPAP systems, flow measuring techniques and resuscitation equipment. In order to be meaningful the preclinical investigations have to result in clinical research.

2 BACKGROUND

2.1 EFFECTS OF NCPAP

NCPAP applies a continuous distending pressure to the spontaneously breathing infant through a non-invasive interface. The positive effects of NCPAP have been explained using physiological reasoning in combination with studies in animals and humans.[8,9] These include:

- Splinting of upper airway leading to decreased resistance and avoidance of obstructive apnoea
- Splinting of the thorax attenuates chest wall distorsion during inspiration
- The distending pressure leads to increased functional residual capacity (FRC) with improved oxygenation and elimination of carbon dioxide
- Decreased shunting and improved ventilation
- Improved compliance and lower work of breathing
- Conservation of surfactant
- Reduced apnoea

Negative effects of NCPAP are risks of pneumothorax, lung over-inflation (leading to decreased compliance, increased work of breathing (WOB), reduced ventilation and reduced venous return) and gas entering the gastrointestinal tract. The patient interface poses a risk of nasal damage.[9]

2.2 HISTORY OF NCPAP

The concept of CPAP to support infants is more than a hundred years old. In 1911, Engelmann provided a detailed description of an infant face mask resuscitation system with bubble CPAP developed from von Tiegel's apparatus (original illustration on the thesis cover).[10] The manuscript focused on infant resuscitation with positive pressure ventilation (PPV) and positive end expiratory pressure (PEEP) but it also mentioned CPAP support during spontaneous breathing. The system was included in 'Die Krankheiten des Neugeborenen', a textbook by August Ritter von Reuss published in 1914, translated into English in 1921.[11,12]

In 1971, Gregory described CPAP as a primary treatment for preterm infants with respiratory distress syndrome (RDS).[2] After initial success the use and popularity declined. Mechanical ventilation was generally seen as a better alternative in North America and the UK but NCPAP remained popular in Denmark, Sweden and some centres in North America. The controversy between these two competing treatment traditions has been described by Lagercrantz.[13]

The first observational study that reported differences in outcome related to the use of NCPAP was Avery in 1987.[14] They described a lower incidence of bronchopulmonary dysplasia (BPD) and a less frequent use of mechanical ventilation in Columbia University, New York compared to seven other leading centres in North America. A subsequent

observational study by Horbar investigated the variability of BPD and mortality in 11 centres. Columbia reported good results and was the only centre practicing early CPAP instead of mechanical ventilation. The authors could not find a clear association between ventilation strategy (as reported by questionnaire) and outcome.[15]

In a subsequent case-control study, Marter investigated predictors of chronic lung disease (CLD) comparing Boston and Columbia in infants born with a birth weight between 500 and 1500 g.[16] NCPAP was used as primary treatment in 11% in Boston vs 63% in Columbia. The CLD incidence (supplemental oxygen at 36 weeks postmenstrual age) was 22% in Boston vs 4% in Columbia. They concluded that "CLD was predominantly associated with the decision to use mechanical ventilation".

In Scandinavia, Kamper reported a comparably low incidence of BPD in a cohort of Danish infants 24 to 34 weeks of gestation treated with NCPAP.[17] Jonsson reported outcome and treatment for 687 very low birth weight (VLBW) infants born in Stockholm 1988-93.[18] The majority of patients could be managed without mechanical ventilation (59%) compared to 20-30% in North American network reports. The CLD incidence in Stockholm was low compared to centres using more mechanical ventilation. The use of antenatal steroids in the cohort was low (20%) and during the study period routine surfactant became available (after 1990).

In a comparison between infants treated in Boston and Stockholm 2001-2003, the more invasive management in Boston was not associated with better outcome.[19]

2.3 MECHANICAL VENTILATION, NCPAP AND SURFACTANT

In the early 90's, the use of NCPAP increased but there were still no randomised controlled trials (RCT) comparing the effectiveness and safety of non-invasive ventilation to mechanical ventilation. At the same time the first trial of the delivery of surfactant in combination with NCPAP were published by Verder.[20] In the following years, trials investigating invasive and non-invasive management of respiratory distress of premature infants had to address both respiratory support mode and surfactant treatment.

2.3.1 Clinical trials comparing mechanical ventilation and NCPAP

Initial respiratory support management of preterm infants include mechanical ventilation or non-invasive NCPAP support. The International Liaison Committee on Resuscitation (ILCOR) 2015 consensus document suggests the initial use of CPAP rather than intubation and mechanical ventilation (weak recommendation, moderate-quality evidence) referring to the COIN, SUPPORT and VON trials.[21] The European RDS guidelines have the same recommendations referring to the COIN and SUPPORT trials.[22]

Morley (COIN, 2008) randomised 610 infants (25-28 weeks of gestation) to either intubation or NCPAP.[23] The intubation rate in the NCPAP group was 46% and surfactant could only be given after intubation. There was no difference between the groups in primary outcome in

terms of BPD or death (odds ratio (OR) in favour of CPAP 0,8 (0,58-1,12 95% confidence interval (CI))). There were differences in secondary outcome variables in favour of NCPAP (time on mechanical ventilation, death or oxygen therapy at 28 days of age). A safety concern was the higher incidence of pneumothorax in the NCPAP group.

Finer (SUPPORT, 2010) randomised 1316 infants before delivery (24-27 weeks of gestation) to early CPAP or early intubation with surfactant.[24] The intubation rate in the CPAP group was 32,6% in the delivery room and in total 83%. There was no difference between the groups in primary outcome in terms of BPD (OR in favour of CPAP 0,95 (0,85-1,05 95% CI)). There were differences in secondary variables in favour of CPAP (alive and free from the need for mechanical ventilation day 7, fewer days of ventilation). There were no safety concerns and no higher incidence of pneumothorax in the CPAP group. A post-hoc analysis of infants 24-26 weeks of gestation showed a lower rate of death in the CPAP group.

Dunn (VON or sometimes DRM, 2011) randomised 648 infants (mean gestational age (GA) of 28 weeks) before delivery to 1) intubation, surfactant and minimum 6 h of mechanical ventilation 2) intubation-surfactant-extubation (referred to as ISX by the authors) or 3) NCPAP without surfactant.[25] In the first hour after birth, 83,3% in the ISX group could be extubated and 82,1% in the NCPAP managed without intubation. The overall intubation rate was 59% in the ISX group and 52% in the NCPAP group. There were no differences between the groups in primary outcome of BPD or death. There were no safety concerns or higher incidence of pneumothorax in the NCPAP or ISX group. In other trials, intubation-surfactant-extubation (ISX) is usually referred to as INSURE.

The primary research question of these trials concerned mechanical ventilation and NCPAP. In summary these trials individually showed no negative effects of less invasive management on primary outcomes and some potential advantages on secondary outcomes. In meta-analyses the trials showed a reduction in mortality and BPD (section 2.3.3).

2.3.2 Clinical trials on NCPAP and Surfactant

In 1994, Verder attempted to further reduce the need for mechanical ventilation in infants with RDS treated with NCPAP.[20] They randomised 68 infants (25-35 weeks GA) to receive INSURE (intubation-surfactant treatment-extubation) or to continue NCPAP treatment. Infants that received INSURE were treated with NCPAP after extubation. The trial was stopped early because of the less frequent need for mechanical ventilation in the infants who received INSURE.

The INSURE concept of rescuing patients on NCPAP that develop RDS has been investigated in several trials. The questions of delivering surfactant during NCPAP are complex and the effects of treatment depend on several factors including 1) use of antenatal steroids and the gestational age 2) timing of delivery (level of respiratory distress) 3) technique of delivery.

2.3.2.1 Prophylactic or selective treatment

The early success of surfactant was investigated at a time when antenatal steroid use was low and many infants were intubated. Surfactant treatment can be given *prophylactically* to all patients and this has been compared to *rescue* (or selective) treatment to patients who developed respiratory distress. Rojas-Reyes highlighted the change in practice in a Cochrane review on prophylactic versus selective surfactant treatment; "In recent years, the increased utilisation of antenatal steroids, more gentle resuscitation in the delivery room and the routine use of early delivery room CPAP may have changed the risk/benefit analysis".[26] The review had to include several subgroup analyses based on routine CPAP application, use of antenatal steroids and infants less than 30 weeks gestation. In summary, the benefits of prophylactic surfactant treatment are diminished in trials with routine application of CPAP and high use of antenatal steroids. Based on data from VON and the SUPPORT trial they conclude "in fact, the risk of CLD or death is lower in the arm that allowed stabilisation on CPAP and selective treatment with surfactant compared with the prophylactic arm".

2.3.2.2 Timing of selective treatment

One factor that has influenced the outcome in trials of surfactant rescue during NCPAP is the timing.[27,28] The threshold for giving surfactant has been lowered and early rescue has been favoured over late rescue.[27]

In a trial by Verder (1999) they randomised 60 infants (trial stopped early) with RDS on NCPAP to either early surfactant treatment or waiting until they were more affected (late treatment).[29] The early treated infants had better outcomes.

The Cochrane review of surfactant prophylaxis versus rescue excluded two trials due to an 'early strategy'.[26] The CNRN trial was excluded because the prophylaxis arm had signs of RDS at randomisation and was considered to be early strategy rather than prophylaxis.[30] The CURPAP trial was excluded because the rescue arm was given surfactant as an early selective strategy rather than at established RDS.[31]

Rojas (CNRN, 2009) randomised 279 infants with signs of respiratory distress (27-31 weeks of gestation) to NCPAP or NCPAP with prophylactic surfactant (INSURE) at 15-60 minutes of age.[30] There was a difference in the primary outcome of mechanical ventilation in favour of prophylactic surfactant (OR 0,69 (0,49-0,97 95% CI)) and fewer pneumothoraces (OR 0,25 (0,07-0,85 95% CI)). The NCPAP group received very late surfactant rescue at Fraction of inspired oxygen (FiO_2) of >0,75 and this may have affected the outcome in the NCPAP control group. The difference could not be seen in the CURPAP trial or in the VON trial.

Sandri (CURPAP, 2010) randomised 208 infants (25-28 weeks of gestation) at an age less than 30 minutes to NCPAP or NCPAP with prophylactic surfactant (INSURE).[31] There was no difference in the primary outcome of mechanical ventilation within five days (33,0% NCPAP and 31,4% prophylactic surfactant) or any safety outcomes. 50 out of 103 (48,5%) of the patients in the NCPAP group needed surfactant (median age 240 minutes) and 16 of these

could be extubated (INSURE). In summary, they showed that the infants (spontaneously breathing, high use of antenatal steroids (78% complete and 19% incomplete course) and 25-28 weeks of gestation) could be managed with NCPAP and selective surfactant administered to infants with respiratory distress.

These two trials (CNRN and CURPAP) used *early strategy or early selective strategy*. This is presented in reviews as a promising way to further improve non-invasive management.[26,27] The review by Rojas highlights the reduced incidence of pneumothorax in early surfactant rescue (vs later).[27]

An alternative to INSURE is to maintain spontaneous breathing and deliver surfactant without intubation and positive pressure ventilation. These techniques include intra-tracheal catheters, nebulisation and laryngeal devices.[32] Delivery of surfactant by an intra-tracheal catheter placed by laryngoscopy (without mechanical ventilation) has received most attention. This has been investigated in several trials eg Göpel (AMV, 2011) and Kanmaz (Take Care, 2013).[33,34] Even though some trials have shown promising results, a concern has been raised regarding laryngoscopy (without or with minimal sedation) of infants with respiratory distress.

Nebulisation of surfactant to a spontaneously breathing infant has advantages in theory but has been difficult to achieve.[35,36]

2.3.3 Meta-analysis of less invasive NCPAP approach

Schmölzer performed a meta-analysis and included 4 trials (COIN, SUPPORT, CURPAP and VON) with a total of 2780 preterm infants (<32 weeks GA).[37] The pooled results for the combined outcome death or BPD showed a reduction in favour of delivery room NCPAP compared to intubation with a relative risk 0.90 (0.83-0.98 95% CI) and numbers needed to treat (NNT) of 25.

Fischer and Bürer performed a review of strategies for avoiding intubation and BPD.[5] This meta-analysis included three additional trials (in total 3289 patients) and showed a relative risk of 0,83 (0,71-0,96 95% CI) in favour of the NCPAP group. The authors concluded that "Regardless of the population studied and the strategy used, avoiding endotracheal mechanical ventilation consistently led to a reduction in the incidence of death or BPD in all trials, with odds ratios ranging from 0.63 to 0.97". The authors also reviewed evidence from observational studies and animal models and found further support for avoiding mechanical ventilation.

There are still some controversy regarding the efficacy of NCPAP to reduce BPD. Jain and Bancalari refer to evidence as equivocal for NCPAP as preventing BPD (not considering the combined outcome of BPD or death) even when citing the meta-analysis by Fischer and Bürer.[5,38]

2.4 NCPAP SYSTEMS

Since the introduction of CPAP by Gregory, many systems and interfaces for CPAP support have been developed.[2] Early systems used expiratory resistors on the expiratory limb and a constant fresh gas flow (bias flow). The resistor was later replaced by submerging the expiratory limb into water to create a bubble CPAP. The next development was variable-flow CPAP systems. In these systems, CPAP is generated in the patient device, close to the interface, and adjusted with the fresh gas flow. In addition to these systems modern ICU ventilators are also capable of delivering CPAP by a Y-piece and a patient interface. All these techniques for CPAP generation are still in use.

The wide range of systems and traditions leaves the clinician with multiple options and uncertainties. Even though the non-invasive NCPAP approach has proven superior to intubation and mechanical ventilation, there is little information to facilitate the choice of NCPAP system, prongs and the consequences of leakage or adjustment of CPAP level.

Two other options of non-invasive treatment have also evolved. These are high-flow nasal cannulae and non-invasive positive pressure ventilation (NIPPV). Their clinical uses overlap with NCPAP treatment. The development of high-flow cannulae has been driven by creating more lightweight systems that are easier to apply and have less risk of nasal trauma without losing the benefits of NCPAP treatment. The aim of NIPPV development has been to avoid failure on NCPAP and further decrease the number of infants who need mechanical ventilation. Finding the boundaries and benefits of these alternatives to NCPAP is a major research challenge. These alternative treatment options will not be discussed in this thesis.

2.4.1 Parts of NCPAP systems

NCPAP systems can be constructed in several ways but generally consist of a fresh gas flow source, an interface and a CPAP generator.[9] The CPAP generator can be positioned far away from the patient by using a Y-piece. This connects the expiratory and inspiratory tubing to the interface. Examples of the use of Y-piece connectors are the bubble NCPAP systems or NCPAP generated by ventilators. The variable-flow NCPAP systems use generators integrated with the patient interface. These were developed to increase pressure stability and the CPAP level is adjusted with the fresh gas flow.

2.4.1.1 Fresh-gas flow source

The fresh-gas flow allows adjustment of inspired oxygen concentration and usually provides an option for gas conditioning (heat and humidification). In ventilators and dedicated NCPAP drivers, recording of the delivered airway pressure allows features such as automatic adjustment of CPAP in response to leakage or high pressure alarms.

2.4.1.2 Patient interface

The original CPAP described by Gregory used endotracheal tubes for 18 patients and head chambers for two patients.[2] In the following years, several non-invasive alternatives evolved.

A tight fitting face mask was reported in an abstract by Harris in 1972, Shannon in 1972 and Rhodes in 1973.[39-41] Nasal masks were used by Chernick in 1973 and Cox in 1974.[42,43] There were earlier reports of nasal interfaces, but they were used for pulmonary function tests and not for NCPAP.[44-47]

Bilateral tubes in the posterior pharynx was used by Novogroder in 1973 and shorter binasal prongs by Kattwinkel in 1973, Agostino in 1973, Caliumi-Pellegrini in 1974 and Wung in 1975.[48-52]

Single nasal (cut endotracheal tubes (ET-tubes)) have also been used to provide CPAP. In a study by Field in 1985 it was said to have been used in "more recent years".[53]

2.4.1.3 Techniques for CPAP generation

NCPAP systems have been classified according to if the fresh-gas flow is constant or variable.[9,54,55] This classification is difficult to apply to modern ventilators where adjustments of the inspiratory valve and fresh-gas flow are hidden from the user. Below is a classification of the principle mechanism for NCPAP generation.[3]

Resistors placed on the expiratory limb will generate a CPAP when obstructing the bias flow. This resistor type of system was used by Gregory and referred to as a "modified Ayres T-piece" anaesthetic circuit.[2,56] Gregory added a pressure meter and safety "underwater pop-off ". It may be because of this safety feature that Gregory's system sometimes has been incorrectly referred to as a bubble CPAP system.[3,54,55,57-60].

NCPAP resistor systems have been replaced by other techniques that are more pressure stable but are still being used in T-piece resuscitation systems. In the T-piece system the CPAP is generated by a valve situated on the patient end of the system. The resistance of this valve is adjustable but does not change during the breathing cycle (ie fixed but adjustable.

The fixed area valves (such as the expiratory limb screw clamp used by Gregory) have sometimes been replaced by spring-loaded valves. This development was used by Wung in 1975 and allows the valve area to increase and accept higher flows.[52] From a pressure-stability point-of-view the use of spring-loaded valves (or moving mechanical parts) for CPAP in neonates are problematic because of the small tidal volumes (TV) and rapid breathing. The spring-loaded valves are still in use when providing PPV with T-piece resuscitation systems or in anaesthetic circuits but generally not for NCPAP in infants.

CPAP generated by ventilators are presented under a separate heading even if they use an expiratory valve (resistor) to generate CPAP.

Bubble NCPAP uses a submerged tube as an expiratory limb resistor. The patient is connected to a Y-piece and the inspiratory limb connected to a bias flow. This modification of Gregory's circuit was mentioned by Novogroder and Caliumi-Pellegrini.[48,51] Shannon used bubble CPAP in combination with a face mask a few years earlier and in their manuscript

they mention its use without referring to it as an invention.[40] The first description of bubble CPAP for newborn infants was by Engelmann in 1911.[10]

The fresh-gas flow (bias flow) is adjusted to a level at least high enough to compensate for maximal inspiratory flows. The tube submerged in water works as a pop-off valve. This gives a more pressure-stable NCPAP since the submerged tube has a large maximal area and no mechanical parts. The bubbles generate pressure oscillations in the respiratory circuit and possible benefits of this phenomenon have been discussed.[61]

Variable-flow CPAP devices generate CPAP close to the patient interface. Most variable-flow CPAP systems use turbulence to oppose expiration and aid inspiration. The first technique for this type of CPAP generation was developed in Denmark by Benveniste and Pedersen.[62] The Benveniste valve uses a fresh-gas flow that is directed towards an orifice that is attached to the endotracheal tube. It was originally designed to work as a valve protecting intubated infants from ventilators and allowing spontaneous breathing with CPAP and low dead space. The Benveniste valve is a typical variable-flow CPAP device where CPAP can be increased or decreased by adjusting the fresh-gas flow. Even if it was originally described (1968) for invasive ventilation it was also used for non-invasive support (1976).[63] There were other research groups working on similar concepts and in 1974 a light-weight low-resistance Venturi system was presented by Carden.[56] This could "of course, easily be connected to nasal prongs or nasal mask, etc., if this less invasive method of delivering CPPB [continuous positive pressure breathing] is preferred".

In the late 1980´s, a variable-flow generator was developed in Östersund, Sweden. This design used two short bi-nasal prongs connected to small "engines" that use turbulent flow to generate CPAP (Fig. 1).[64] Pressure stability was achieved by the Venturi effect in combination with a "fluidic flip". This gave a light-weight system with increased pressure stability and low imposed work of breathing (iWOB). The system was later marketed as Infant Flow and the design has inspired other variable flow systems.

The variable flow devices can be driven by any source capable of generating a fresh-gas flow. This can be a rotameter, an NCPAP driver or a ventilator. Electronically controlled drivers can be used to adjust the fresh-gas flow to compensate for leakage or to provide NIPPV by increased fresh-gas flow during inspiration.

There is an overlap between variable-flow CPAP devices and resistor systems. This is a potential source of confusion for two reasons: 1) Any resistance on the expiratory side of a variable flow device will produce a system that is more similar to a resistor system 2) Increasing the fresh-gas flow to a resistor system will increase the delivered CPAP. An example of this is the Medin generator. It is based on resistance but referred to as a variable-flow NCPAP (manuscript in preparation).

Ventilators generate CPAP by balancing fresh-gas flow in the inspiratory limb with an expiratory valve on the expiratory limb. The patient is connected using a Y-piece. The

balance (inspiratory flow and expiratory resistance) is usually hidden from the user. If pressures are increased during inspiration NIPPV can be provided. Some ventilators provide NIPPV in CPAP mode.[65]

The technical challenge of generating pressure stable NCPAP using a Y-piece is great because of tube compliance and system resistance in combination with rapid neonatal breathing and potential leakage at the interface. This is probably the reason why some ventilator manufacturers, instead of using a Y-piece, use the ventilator as a variable-flow NCPAP driver. The Y-piece and patient interface may look similar to variable-flow NCPAP devices which may be confusing.

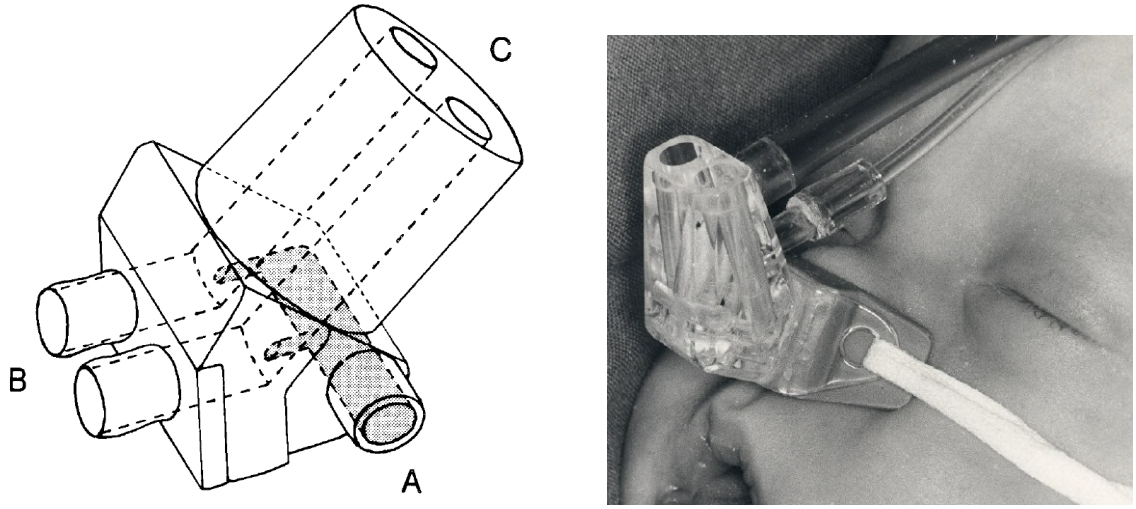

Figure 1: The original design of the variable flow NCPAP system developed by Gunnar Moa and Kjell Nilsson in Östersund. The device was later marketed as Infant Flow. A) Fresh gas flow inlet B) Connection to prongs C) Outlet. Left illustration from Moa with permission from Wolters Kluwer Health.[64] Right photograph from Moa and Nilsson with permission from John Wiley and Sons.[66]

2.4.2 Measuring pressure stability in-vitro

When an infant is breathing through a CPAP device, the pressure in the patient's airway will fluctuate. During inspiration the airway pressure will decrease, whereas it will increase during expiration. These pressure changes are generated by the infant and represent the added work needed when breathing through a device, the so called imposed WOB. For pressure-unstable systems the fluctuations are larger and the additional work needed higher. This is not only applicable to NCPAP systems. The same principles apply in patients with endotracheal tubes, tracheostomies and airway obstruction. A typical example is the clinical concern when adding workload to the patient by the use of a narrow bore endotracheal tube.

There are several ways to investigate pressure stability but they all reflect the relation between flow and pressure for a system or interface.

2.4.2.1 Static tests

Pressure changes at a given flow is a simple way to describe resistance. Resistance was often described at one flow level for the first CPAP systems. For instance, Carden reports 3 mm H_2O at 10 L/min (presumably expiratory flow) for their Venturi system and Kattwinkel reports less than 1 cm H_2O at 3 L/min (direction of flow not stated) for their nasal unit.[49,56] Testing at multiple flow levels gives a more complete description. Goldman used a graphical display of prong resistance at flows 0-120 mL/s.[67] De Paoli investigated prong resistances at 4-8 L/min inspiratory flow with no CPAP applied.[68] They showed that prongs with narrow internal diameter and greater length had higher resistance.

An example of static tests is presented in figure 2. Neopuff and Infant Flow systems were tested at 5 cm CPAP with flow ranging from -10 to 10 L/min. The tilt and shape of the graph represents the resistance. The relation between pressure and flow is not linear or symmetrical. The advantage of static compared to dynamic testing is that the experiments are uncomplicated and do not require accurate reproduction of flow profiles or volumes.

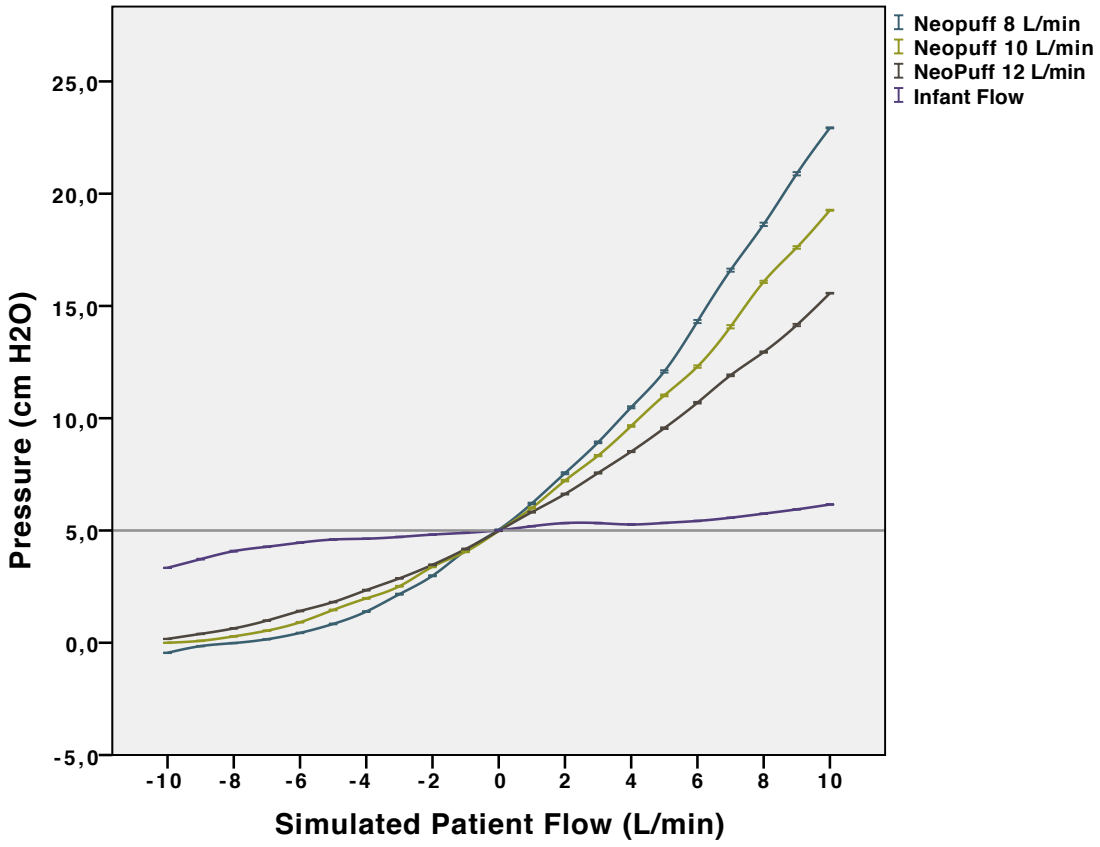

Figure 2: Example of static tests of two CPAP systems at 5 cm CPAP. Neopuff was tested at three levels of fresh-gas flows. Negative flows (ie inspiration) gives a reduction in delivered pressure. The slope represents pressure stability. Neopuff is less pressure stable than Infant Flow and the pressure stability is depending on fresh-gas flow. Lines represent means with error bars (95% CI). Data from manuscript in preparation.

2.4.2.2 Dynamic tests

Dynamic tests use mechanical lung models. These can reproduce breathing and allow comparison of pressure stability during simulated breathing. Simulations can be either non-compliant (volume or flow pump) or complex (including compliance and resistance).

- Non-compliant models reproduce a flow or volume pattern. Variations in delivered volume or flow are only related to gas compression and compliance or resistance of tubing (if used). *The use of these models aims at minimising the flow and volume variations during testing.*
- Models with compliance and resistance. Compliance and resistance can be achieved mathematically (programming of lung model) or physically (by deliberately adding resistors and compressible volumes). The delivered flow and volume will depend on changes in pressure and flow. This means that NCPAP systems that are not identical will not be tested at identical flows or volumes. *The use of these models aims at mimicking in-vivo conditions.*

Models with compliance and resistance are difficult to work with since the standard variables for reporting pressure stability are dependent on reproducible flows and volumes. This problem has been highlighted by Natalini.[69] They showed that attempts at compensating for variations in volume by using a volume adjusted work of breathing (WOB/L) were inappropriate. They also suggested a way to "eliminate the influence of the variable TV from the measure of WoB [Work of Breathing]" but the suggested correction has other disadvantages. Less complex variables such as the pressure difference during one breath (pressure swings) or pressure time product (PTP) also rely on reproducible volumes and do not solve the problem.

Complex models have been used in studies that aim to simulate physiological work of breathing rather than just imposed work of breathing. For example in-vitro generation of Campbell diagrams.[70]

There are few publications using compliant models. Cook used this method to investigat four CPAP systems.[65] Their main outcome was TV delivered at the end of expiration and pressure drop during inspiration. One of the tested systems was a ventilator that provided not only CPAP but also low-level pressure support. Since they used a compliant model, the end expiratory TV (main outcome) will directly relate to end expiratory pressure. This methodological weakness will favour systems with pressure support (rather than CPAP). The other outcome variable, pressure drop during inspiration, will not be measured at identical flows. These problems were not discussed as limitations and not mentioned in the related editorial.[54]

2.4.2.3 Measuring pressure stability in non-compliant dynamic models

Models that aim to reproduce flow (or volume) allow direct comparison of variables that represent pressure stability.

Pressure: The pressures at a given time, flow or volume. For example, the lowest pressure (pressure decrease) or highest pressure (pressure increase) during one breath.

Pressure time product: Integrating pressure change over a given time. This is rarely used and will not be discussed any further.

Imposed work of breathing: Integration of pressure over volume for one breath.[71] Total imposed WOB can be divided into an expiratory and inspiratory component. The work of breathing for any breath corresponds to the area within that single breath's pressure-volume loop. Imposed work of breathing can also be averaged over time or per volume.

2.4.3 In-vitro performance of NCPAP systems

Moa (1988) compared a new device with a resistor system at three levels of CPAP and TV of 30 mL.[64] Pressure stability was measured as pressure changes and imposed WOB. The new device were more pressure stable than the resistor system and had a higher tolerance for leakage.

Banner (1990) presented mechanical comparisons of CPAP delivered by ventilators and resistors in two abstracts.[72] They showed highest imposed WOB with the Babybird and lowest with the Seachrist ventilator. In the resistor experiments they tested different valves in combination with the Seachrist or Babybird ventilator.[72,73] The abstracts were never published as manuscripts.

Klausner (1996) used a mechanical lung model to compare Arabella (Hamilton Medical) and a conventional resistor system with Hudson prongs.[74] They used lower TV (12,1 mL) than Moa. The authors incorrectly refer to Arabella as the same system tested by Moa. Pressure stability is only reported as inspiratory imposed WOB (expiratory imposed WOB not reported) and pressure fluctuations (no detailed report). The results show a reduction in inspiratory imposed WOB for the Arabella device compared to the conventional resistor system.

Nikischin (2011) reduced TV further (1-9 mL breaths) and investigated three systems at 5 cm CPAP in a custom built mechanical lung model (Dräger).[75] A mono-nasal pharyngeal tube (3,0 mm internal diameter), Baby Flow nCPAP (Y-piece from Dräger) connected to a conventional ventilator (type and model not reported) and the Infant Flow system. Measured variables were pressure increase and decrease (from CPAP) and imposed WOB. They showed that mono-nasal pharyngeal tube had the highest imposed WOB followed by Baby Flow with a 20% reduction and Infant Flow (TV 4 mL) with 45%. They also performed simulations with leakage. The method of generating leakage exposed the systems to uneven test conditions with higher leakage for the more pressure stable Infant Flow system (not recognised nor discussed by the authors). A limitation to their description is that the Baby

Flow interface can be used with most ventilators and that the choice of ventilator will affect imposed WOB.

Wald (2011) investigated expiratory resistance for seven NCPAP systems (TV 6 mL, peak flow 0,46 L/min) at a PEEP of 6 mbar (6,1 cm H_2O).[76] Resistance was measured by pressure change during expiration. They showed that the resistance was lowest with the Infant Flow device and highest with Neopuff (low fresh gas flow). The reduced expiratory resistance at higher flows with Neopuff is discussed in great detail. The fundamental problem with focusing on expiratory resistance is that the relation between resistance and total imposed WOB (expiratory and inspiratory) is lost. In the discussion the authors state that "The increase in PEEP during the expiration period demonstrated in our study causes a further increase in the RE [expiratory resistance] and should thus be considered an advantage for the patient". This controversial statement was left without further comments.

Summary

Tests of performance of NCPAP systems show that some systems consistently are more pressure stable than others despite large variations in methods and quality. The Infant Flow system has been reported as a pressure stable system with low imposed WOB in all publications.

A problem in these in-vitro studies is that several authors generalise the performance of one system to a group of systems. For example, Cook drew conclusions on ventilator generated CPAP in general when they only tested one ventilator and Wald discuss the performance of jet systems in general when the two tested systems showed very different performance (Medijet and Infant Flow).

2.4.4 Clinical importance of pressure stability and imposed WOB

The differences in performance of NCPAP systems found in mechanical lung models could have clinical implications. Imposed WOB has been described as a factor that could affect outcomes such as failure on NCPAP and the subsequent need for mechanical ventilation.[9,67]

The clinical effects of using different CPAP systems have been investigated with 1) cross-over designs and short term physiological outcomes and 2) randomised controlled trials with clinical outcomes.

Different hypotheses have driven this research. The compared systems have rarely been selected for their pressure stability but more often based on the type of CPAP generator, type of interface or local traditions.

Pressure stability is only one of several factors that could affect outcome when comparing devices. The quality of the NCPAP delivered and the clinical effect will be a result of an interaction between the patient, interface and CPAP generator system. Trials of longer duration are also highly dependent on nursing care, training and the population studied.

2.4.4.1 Cross-over trials with physiological outcomes

The effects of CPAP systems on physiological variables have been investigated in several cross-over trials (Table 1).[60,77-85] The trials vary in the selected patients, outcomes, CPAP systems, patient interfaces, duration of treatment and CPAP levels.

Five manuscripts were published between 2001-2011 by a group with Courtney and Habib as co-authors in all manuscripts (Courtney, Pandit and Liptsen in Table 1).[60,78-81] They have investigated different CPAP systems using RIP standardised by pneumotachograph and oesophageal balloon catheter. In all studies, the systems were investigated at different CPAP levels. The duration at each level was approximately 5 minutes.

A group in Lille, France, investigated the effects of CPAP levels on lung volumes and breathing patterns in two studies using RIP (without oesophageal balloon) and Infant Flow.[86,87] They showed increased FRC (end-expiratory lung volume by RIP) and changes in breathing pattern (lower respiratory rate, loss of expiratory braking) with increased CPAP level. These effects are largely consistent with other reports.[60,78-81] The same group published a randomised cross-over comparison of Infant Flow, the Dräger Babylog 8000 ventilator and no NCPAP in 13 infants weaned from mechanical ventilation (Boumecid in Table 1).[84] Their main findings were higher TV, less expiratory braking and less thoraco-abdominal asynchronies with Infant Flow.

One trial used direct measurement of breathing (Huckstadt in Table 1).[83] They compared Infant Flow (short binasal prongs) and Babylog 8000 (single cut ET-tube, other nostril occluded) in newly extubated infants who needed NCPAP. Tidal breathing parameters were obtained from the airway flow using flow-through technique after a minimum of five minutes of accommodation. 20 infants were included after excluding 49 patients (leakage in 46 patients, irregular breathing in two patients and apnoea in one patient). Infant Flow showed less pressure swings, increased peak flows and increased TV. They concluded that Infant Flow improved ventilation.

Pickerd performed a trial on infants during weaning from CPAP (Pickerd in Table 1).[85] They used a novel electromagnetic inductance plethysmography (EIP) (FloRight, Volusense AS, Oslo, Norway) and not the traditional RIP used by other groups. This included serial measurements of tidal breathing but they also performed a 15 min cross-over comparison of 1) bubble CPAP 2) Infant Flow and 3) NIPPV (Infant Flow SiPAP). For Infant Flow there was an increase in tidal volumes and a reduction in respiratory rate when increasing CPAP from 5 to 7 (or 9) which was not seen in the bubble CPAP. Apart from the differences in tidal volume at higher CPAP levels there were no other significant differences between the devices.

	Systems compared	n	Patients	Duration	CPAP	TBP	Main Outcome	Findings
Ahluwalia (1998)	Pharyngeal tube (Sechrist ventilator) Infant Flow	20 (22)	28 (24-34) GA at 12 (1-75) days of age and FiO2 0,40 (0,30-0,78)	2 h (twice for each system)	Not changed: 6 cm H2O(3-8)	No	FiO2 needed to 90-95% SpO2	No differences
Courtney (2001)	INCA prong (ventilator) Pharyngeal tube (ventilator) Infant Flow	32	29±2 GA at 13±12 days of age and FiO2 0,29±0,10	3-5 min (10-15 min on 8 cm)	8-6-4-0 cm H2O	RIP	Lung volume and breathing pattern parameters	Infant Flow increased lung recruitment
Pandit (2001)	INCA prong (ventilator) Infant Flow	24 (35)	29 (25-31) GA at 8 (2-48) days of age and FiO2 0,26 (0,21-0,55)	3-5 min (10-15 min on 8 cm)	8-6-4-0 cm H2O	RIP	WOB and breathing pattern parameters	Infant flow larger TV, increased recruitment, lower WOB
Courtney (2003)	Arabella Infant Flow	18	27,9±2,0 GA at 4,6±4,3 days of age and FiO2 0,28±0,08	>5 min	8-6-4-0 cm H2O	RIP	WOB and breathing pattern parameters	No differences
Liptsen (2005)	Bubble CPAP (Hudson prongs) Infant Flow	18	28,1±1,6 GA at 9,4±10 days of age and FiO2 0,25±0,06	5-10 min (5-10 min on 8 cm)	8-6-4-0 cm H2O	RIP	WOB and breathing pattern parameters	Infant Flow decreased resistive work and thoracoabdominal asynchronies
Courtney (2011)	Bubble CPAP (Hudson prongs) VIP Bird ventilator (Hudson prongs)	18	28 (26-33) w GA at 10 (4-28) days of age and FiO2 0,21 (0,21-0,40)	5 min	3-5-7-4-2 cm H2O	RIP	WOB and short-term respiratory outcomes	No differences in WOB or breathing parameters but TcO2 higher in bubble CPAP
Pantalitschka (2009)	Leoni ventilator (Hudson prongs) Bubble CPAP (Hudson prongs) Infant Flow Infant Flow (ns-IPPV)	16	28 (24-29) GA 18 (3-70) days of age	6h	CPAP 5-6 cm IPPV 15 cm (Leoni) and 10 cm H2O (Infant Flow)	No	Apnoea	Infant Flow showed less apnoea
Huckstadt (2003)	Pharyngeal tube (nostril occluded) Babylog 8000 Infant Flow	20 (69)	27 (26-40) GA at 6,5 (1-125) days of age (<3 days after extubation)	>5 min	Not changed: 0,4 (0,3-0,6) kPa	FFT	Tidal breathing parameters	Infant flow showed less pressure swings, increased peak flows and TV
Boumecid (2007)	Infant Flow Dräger Babylogg 8000 No CPAP	13 (19)	29 (1 IQR) GA at 3 (±1) days of age	30 min	5 cm H2O	RIP	Tidal breathing parameters	Infant Flow showed higher TV, less expiratory braking and less thoracoabdominal asynchronies
Pickerd (2014)	Bubble CPAP (Fischer and Paykel) Infant Flow Infant Flow (Graseby capsule s-IPPV) No CPAP	29 (39)	28±2 GA at 28±28 days of age and FiO2 0,23-0,3	10-15 min	CPAP 5-7-9 cm and IPPV 7-9 cm over 5 cm H2O	EIP	Tidal breathing parameters	No differences between systems. Infant Flow showed increased TV and reduced RR at higher CPAP.

Table 1: Cross-over trials with physiological outcomes. Gestational age (GA) in weeks. Values as mean±SD or median (range or interquartile range (IQR)). The pharyngeal tube refers to a mono nasal cut ET-tube. The IPPV was non-synchronised (ns-IPPV) in the trial by Pantalitschka and synchronised (s-NIPPV) in the trial by Pickerd. Tidal breathing parameters (TBP) was obtained by respiratory inductive plethysmography (RIP), flow-through technique or electromagnetic inductance plethysmography (EIP).

In summary, trials with cross-over methodology and short term physiological outcomes show changes in breathing parameters that could be related to imposed work of breathing and pressure stability. The most consistent finding is increased tidal volumes and reduced respiratory rate for pressure stable systems like Infant Flow. In most studies, but not all (for example Lipsten), these effects increase at higher CPAP. The trials that determine work of breathing (Courtney, Habib et al. group) show increased work of breathing with less pressure stable systems. The clinical relevance of increased tidal volumes and reduced respiratory rate is not known. For instance, Huckstad interpret this as improved ventilation and Pickerd as potentially disadvantageous.[83,85]

There were no results in these trials that contradict pressure stability as a factor that affects breathing parameters, but some system comparisons show little or no difference. The authors mention several explanations when differences could not be found: 1) The difference between the systems were not large enough or 2) the infants were not small or sick enough.[80,81] The trials included relatively few patients and most variables had large variability (high variance). This could be because of a heterogeneous patient population, method related or due to a high natural variance.

2.4.4.2 Randomised controlled trials with clinical outcomes

NCPAP after extubation

Two trials frequently referred to were only published as abstracts (American Pediatric Society meeting 1999). Sun and Tien performed an RCT on 73 infants post extubation comparing Infant Flow to conventional NCPAP (Medicorps interface, not short binasal).[88] They showed less extubation failure in the Infant Flow group (16% vs 54%). Roukema performed an RCT on infants post extubation comparing Infant Flow to nasopharyngeal CPAP.[89] The failure rate was lower in the Infant Flow group (18/48 vs 27/45).

Davis (2001) performed an RCT comparing single prong (2,5 cm inserted Portex tube) to short binasal prongs (Hudson) after extubation in 87 infants at 26 weeks of gestation.[90] CPAP was provided by a ventilator (manufacturer not stated). Lower failure rate was seen with binasal (24%) compared to single-nasal prongs (57%).

Stefanescu (2003) performed an RCT comparing Infant Flow to a ventilator connected by INCA prongs after extubation in 162 infants <1000 g.[91] There were no differences in successful extubation (61,7%), death, BPD or time on CPAP. The Infant Flow group showed shorter hospital stay and fewer days on supplemental oxygen. The authors note that the ventilator CPAP group was slightly heavier and older than the Infant Flow group (not significant).

Gaupta (2009) performed an RCT of post-extubation support comparing bubble CPAP to Infant Flow.[92] They randomised 140 infants (approximately 27 weeks of gestation (1,07 kg)). There were no differences in the primary outcome of extubation failure (27,5% Infant Flow

and 16,9% bubble CPAP) for the whole population. In a subgroup analysis of infants <14 days on ventilator, there was a difference in favour of bubble CPAP. Reduced duration of CPAP treatment was seen in bubble CPAP but not after including infants who died in the analysis.

NCPAP after birth

Mazzella (2001) performed an RCT comparing Infant Flow to single pharyngeal prong interface (bubble CPAP) in 36 infants.[93] Patients were <36 weeks of gestation and those who had received antenatal steroids were excluded. Treatment was started at a median age of six and seven hours for the pharyngeal prong and Infant Flow respectively. There were lower oxygen requirements and lower respiratory rates in the Infant Flow group. There was no difference in the number of infants who failed on NCPAP (five on nasopharyngeal tube and one on Infant Flow).

NCPAP after birth and after extubation

Bober (2012) performed an RCT comparing Infant Flow to the ventilator Babylog 8000 (Hudson prongs) in 276 infants (approximately 28 weeks GA and 1,1 kg) who were started on NCPAP <6 h after birth (n=119 elective group) or after extubation (n=157 weaning group).[94] The main outcome was failure on NCPAP (intubation or reintubation). The trial was stopped early because of nasal injuries in the ventilator (Hudson prongs) group. There was a non-significant trend towards less failure in the weaning group for the Infant flow system but no difference in the elective group. The safety outcomes showed that the infant flow group had more pneumothoraces and the ventilator group had more necrotising enterocolitis and severe nasal injuries.

Summary of randomised trails with clinical outcome

In summary the RCTs comparing NCPAP systems or interfaces show conflicting results. This has been noted in several reviews and, apart from recommending short binasal prongs, reviews do not guide the users as to which systems to use.[3,22] The importance or non-importance of pressure stability as a factor affecting outcome cannot be judged from the randomised controlled trials. Pragmatic trials reveal important clinical outcomes other than NCPAP failure. For instance, the trial by Bober had 17,8% (24 of 135 patients) severe nasal injuries in the ventilator (Hudson prongs) group.

2.4.5 Summary

An array of systems for CPAP generation and patient interfaces are available. Data on differences in performance and pressure stability have been published, but the clinical importance remains uncertain. There are no hard data on the importance of providing pressure stable CPAP or using systems with low imposed WOB even if physiological reasoning and expert opinion suggest that this may be an important factor for avoiding mechanical ventilation and failure on CPAP.

2.5 MEASURING AIRWAY FLOWS IN INFANTS

The measurement of airway flow is used for basic description of tidal breathing parameters to complete infant pulmonary function testing. There is a need to standardise technology and measurement techniques to allow data from different centres to be pooled or compared.[95,96]

In adults the technology for measuring airway flow is widespread but its use in neonates is limited mainly because of the following technical challenges:

- rapid respiratory rate and small tidal volumes
- low tolerance for increased resistance
- low tolerance for adding dead space
- sensitivity to airway manipulation and problems with leakage at interface
- low tolerance for adding bulky equipment close to the patient

The most commonly used approach is to measure airway flow directly by using a patient interface attached to the flow-meter equipment. The European Respiratory Society/American Thoracic Society (ERS/ATS) Task Force document is limited to these direct measurements.[95] Indirect techniques do not rely on direct flow measurement and are described by the task force as difficult to standardise.

A potential advantage of indirect measurements is that they avoid problems with airway manipulation, leakage, resistance and dead space. Examples of techniques that measure flow indirectly are face-out body plethysmography and respiratory inductive plethysmography (band plethysmography).[97] New techniques such as electrical impedance tomography, electromagnetic inductive plethysmography and optoelectronic plethysmography have recently been developed.[98-100] These are mainly research tools and have limited use in the clinical setting.[101]

Measuring flow during NCPAP with a direct technique would be a useful tool for further studies on the importance of imposed WOB and the effects of NCPAP.

2.5.1 Measuring airway flows without CPAP

Airway flow can be measured at two positions in respiratory support systems or circuits (Fig. 3). Flow measurement can be either between the patient interface and the respiratory support system (in-line) or on the expiratory limb (flow-through).

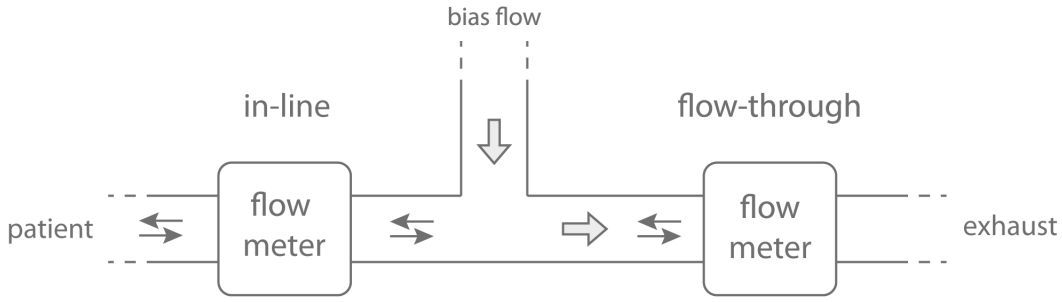

Figure 3: In-line and flow-through position of the flow meters. The in-line position adds dead-space. The flow-through position does not add dead-space if the bias flow is sufficient. The flow-through position is technically more challenging since the bias flow has to be subtracted to measure breathing. Figure from Paper III.

The advantage of the *in-line* position is that it is technically simple and insensitive to the compliance and resistance of the circuit (or NCPAP system). The disadvantage is that the volume inside the flow meter will add extra dead-space and rebreathing. To minimise dead space, the internal volume has to be small and the flow meter be placed as close to the patient as possible. Most variable-flow NCPAP systems do not allow fitting of a flow meter between the NCPAP generator and the patient interface because of their small size and integrated prongs.

The advantage of the *flow-through* position is that it will not add dead-space since it is positioned on the expiratory side (limb). The bias flow prevents rebreathing by constantly washing out the CO_2. The disadvantage is that it is technically more difficult since the bias flow has to be subtracted, and the tube compliance and resistance of the circuit or NCPAP system will affect measurements.

The first measurements of lung function in newborn infants were performed many years before the development of NCPAP. In 1956, Berglund and Karlberg used a face mask and helium dilution to determine functional residual capacity. Volumes were determined by spirometers.[44] The problems with resistance and adding dead-space seem well-recognised at the time. As an example of this, in 1966 Silverman presented resistance (static flow comparisons) and dead-space volumes (0,4 to 0,9 mL) for four devices.[47] They solved the problem of rebreathing by using valves or non-rebreathing anaesthetic circuits.

The problem of rebreathing and resistance is still a concern. Systems with high resistance and large dead-space are still in use. An example is the use of flow meters (in-line position) with CPAP by T-piece resuscitation devices.[102] When used with spontaneous breathing, both the dead-space and resistance for these devices are high compared to what was state-of-the-art more than 50 years ago for measurements without CPAP.[47]

The first measurement of airway flow using *flow-through* technique in preterm infants was in 1972 by Brady and Rigatto.[103] They developed and tested a flow-through system that had low dead space (0,06 mL) and low resistance (Fig. 4). They describe the relation between resistance and dead space for in-line measurement as "if dead-space is kept at a minimum, resistance tends to be high, and if resistance is kept at a minimum, dead-space tends to be large. In both instances minute ventilation and the work of breathing are increased". They report the use of their new flow-through system in 40 preterm infants (1-2 kg).

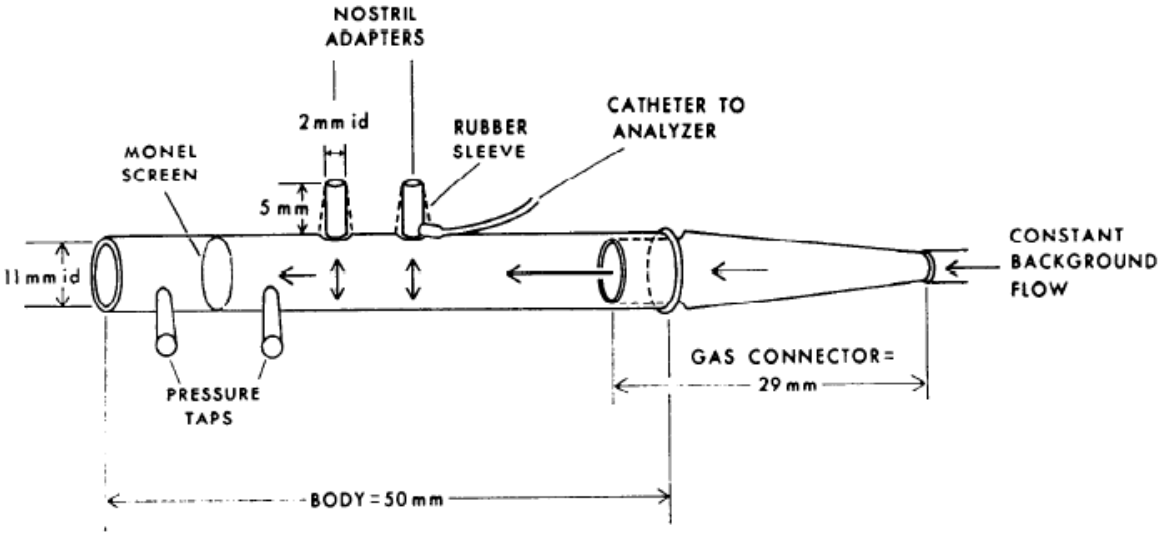

Figure 4: Flow-trough system used by Rigatto and Brady: "Nosepiece used with a constant background flow of gas to measure ventilation in preterm infants. To body of nosepiece, a segment of the barrel of a 5-ml syringe, we added a Monel screen (resistance element), two nostril adapters, and a removable gas connector".[103]

The system was used a few years later by Lahiri in an investigation of infants born at high altitude.[104] They measured the ventilatory response to changes in oxygen concentration of newborn infants at 3850 m (Puno) and 800 m (Tacna) in Peru.

In 1981 Ruttimann further developed the Rigatto system by adding a second pneumotachograph on the inspiratory tubing.[105] This allows for compensation when 1) fresh-gas flow varies or 2) in measurements where pressure variations and tube compliance affect measurement (as in mechanical ventilation or pressure-unstable CPAP). They investigated in-vitro performance and tested the system in intubated rabbits.

In 1983 Thomsson used a similar double pneumotachograph system to investigate lung compliance in spontaneously breathing intubated preterm infants (mean weight 1200 g).[106] Their main finding was that a simplified method of oesophageal balloon catheters recordings, used to estimate compliance, did not give correct estimates in sick infants. In the healthy

control infants, they did not use the double pneumotachograph system, but a standard in-line measurement.

None of these studies used flow-through technique in combination with non-invasive CPAP in spontaneously breathing infants.

2.5.2 Measuring airway flow during CPAP

The first reported use of flow-through measurements and CPAP was in 1988 by Andreasson.[107] They investigated lung mechanics after extubation in premature infants and used a face chamber with flow-through technique (constant bias flow of 7 L/min). A similar interface had been used earlier but the CPAP generator was modified with addition of a high-flow fan dedicated to feeding the resistor.[108,109]

The only use of flow-through measurements in combination with a variable flow NCPAP generator (Infant Flow with nasal prongs) were by Huckstadt in 2003.[83] They performed a randomised cross-over comparison of Infant Flow (short bi-nasal prongs) and Babylog 8000 (single cut ET-tube, other nostril occluded). 46 of 69 infants had to be excluded because of air leaks in one or both recordings (33 for Babylog and 37 for Infant Flow). Three more infants were excluded because of apnoea (n=1) and irregular breathing (n=2). For the remaining twenty infants they concluded that Infant Flow improved ventilation with less pressure swings, increased peak flows and increased TV.

The Huckstadt group have published work on the flow-through technique since 1995.[110,111] The first description in English is from 1998 with a detailed study on the effect of leakage on measurements.[112] After the problems with leakage in the Huckstadt manuscript (2003) they seem to have discontinued the work on the flow-through technique and in their publications from 2008-2009 in-line measurements are used instead.[113-115]

2.5.3 Summary

Measuring airway flow with the flow-through technique can achieve almost dead-space free measurements and has been used with CPAP by two groups. Andreasson used a face chamber and Huckstadt nasal prongs.[83,107] Reliable measurement of flow seems possible but leakage is a major problem with the prong interface.

2.6 RESUSCITATION OF THE NEWBORN INFANT

2.6.1 Transition to breathing and resuscitation

In the first minutes after being born, the infant goes from having full placental support to managing breathing and gas exchange on its own. The physiological changes during this transition are dramatic. Air breathing requires the lungs to be cleared of fluid and gradually expand. The surfactant secreted by the Type II pneumocytes facilitates the increase in FRC by reducing surface tension and increasing compliance. The cardiovascular system switches

from foetal circulation, where the ventricles work in parallel, to a circulation where they work in series.[116,117]

In term infants, 85% start to breathe unaided and 10% require stimulation. Respiratory support is needed for the last 5%, out of which 3% will breathe after PPV and 2% need to be intubated.[21] The number of infants who need support is higher in preterm and extremely preterm infants.

Failure to breathe and establish FRC is an emergency that requires immediate attention. Managing ventilation is the first priority in all resuscitation guidelines.

2.6.2 Premature infants and non-invasive support

2.6.2.1 Systems for PPV and CPAP

CPAP during resuscitation has been suggested to be advantageous. The reasons are the same as when it is given to an infant in respiratory distress (section 2.1 Effects of NCPAP). Infants who do not breathe, or have inadequate breathing, need ventilation with PPV. This is not possible with standard NCPAP systems. The three techniques available for PPV are T-piece resuscitators, self-inflating bags or flow-inflating bag systems.[118] The flow-inflating bag is considered to required more experience to handle.[119]

The T-piece systems can be designed to provide CPAP and bag systems can be equipped with a CPAP valve. However, for at least some bag and CPAP valve systems, PPV needs to be given at a high rate in order to deliver PEEP and the systems cannot generate CPAP during spontaneous breathing.[118,120]

When providing guidelines or conducting research, the use of different devices and interfaces for CPAP support complicates interpretation. The ILCOR consensus document recognises this problem: "Interpretation of human studies is further complicated by varying interfaces (eg, face mask versus endotracheal tube) and methods of generating PEEP (eg, self-inflating bags with PEEP valve versus T-piece resuscitator)".[21]

Regarding the use of CPAP during resuscitation the ILCOR consensus "suggest using PEEP ventilation for premature newborns during delivery room resuscitation (weak recommendation, low-quality evidence)". ILCOR could not make any recommendations for term infants.[21]

2.6.2.2 Interface during resuscitation

Short bi-nasal prongs are recommended for NCPAP but there are few publications using bi-nasal prongs during resuscitation.[3] The clinically most commonly used interface is the face mask.

Short bi-nasal prongs for resuscitation were first used by Capasso in 2005.[121] They compared Argyle prongs to a face mask in 617 infants who needed PPV. Interfaces were used with a self-inflating bag and no CPAP in mainly term infants. Patients ventilated with prongs had fewer intubations (0,6% vs 6,4%), less chest compressions, deaths and neonatal intensive care unit (NICU) admissions. They have been criticised for the use of a triangular shaped face mask (Redell-Baker) rarely used in other centres.[122]

Lamberska presented an abstract of a cohort study of prongs during resuscitation and a comparison to historical controls.[123]

Paz presented a single-centre clinical experience from patients using bi-nasal RAM-cannulas with a T-piece resuscitator.[124] They acknowledge a weak study design and conflict of interests.

There are more publications using a unilateral nasal tube (pharyngeal, cut ET-tube). Kamlin performed an RCT of 363 infants born at 24-29 weeks of gestation.[125] They compared a cut ET-tube (size not mentioned, inserted 3-4 cm) to a face mask connected to a T-piece resuscitator. There were no differences in intubation rates (54% and 55%) and the trial was stopped early because of futility. To minimise leakage, they occluded the mouth and contralateral nostril.

McCarthy also compared a unilateral nasal tube (5 cm cut ET-tube, size 2.5 to 3.0) to a face mask connected to a T-piece resuscitator.[126] The RCT included 144 infants (<29 weeks of gestation) and there was no difference in intubation rates (15% in both groups).

2.6.2.3 Human RCTs of PPV and CPAP

The ILCOR consensus document recognises the weak evidence for recommending T-piece in favour of bag systems during resuscitation.[21] Reliable (but not pressure stable) CPAP can only be provided with T-piece systems. The bag systems cannot maintain CPAP when the infant starts to breathe or provide reliable PEEP during PPV.[120] The ILCOR consensus document refers to two RCTs when recommending T-piece systems:

Dawson investigated PPV delivered by T-piece or a self-inflating bag (no CPAP) in an RCT of 80 infants (<29 weeks of gestation).[127] They showed no difference in primary outcome of oxygenation at 5 minutes.

Szyld performed a cluster randomised controlled trial comparing T-piece to a self-inflating bag (with a PEEP valve in six out of 11 participating centres) in infants >26 weeks of gestation.[128] 195 patients were VLBW (<1500 g) and the distribution of these were uneven with more VLBW infants in the self-inflating bag group. They were not able to detect any difference in their primary outcome of the proportion of patients with a heart rate above 100 at two minutes. Secondary outcomes showed that the T-piece patients had fewer intubations and lower delivered maximum positive inspiration pressure.

3 AIMS

The overall aim of this thesis is to understand and improve neonatal NCPAP respiratory support. This includes investigations of existing techniques for respiratory management as well as development of new respiratory support systems for research and clinical use in this field.

The specific aims of the included studies were:

- To compare existing systems used for NCPAP care using simulated neonatal breathing and determine imposed work of breathing (Paper I and II)
- To evaluate systems and techniques used for measurements of neonatal breathing focusing on the in-line versus the flow-through position and its effects on imposed work of breathing in a mechanical lung model (Paper III)
- To develop a system for respiratory support during neonatal resuscitation and test this device in a clinical feasibility trial on preterm infants (Paper IV)

4 METHODS

4.1 MECHANICAL LUNG SIMULATION (PAPER I-IV)

4.1.1 Methods, introduction and comment

The pressure stability of NCPAP support can be measured by mechanical reproduction of breathing. These mechanical lung models are standard tools used by manufacturers of ventilators and researchers interested in respiratory support systems. The main advantages of mechanical lung models, compared to animal or human studies, are high reproducibility with low variability, low costs and uncomplicated ethics. The main disadvantage is that the tests are performed in an artificial setting and have limited clinical value.

Imposed work of breathing is the added work needed to breathe through a device. This can be illustrated by the shape of a pressure-volume loop for a spontaneously breathing infant or in the simulated breathing of a mechanical lung model. Examples of alternative variables to describe pressure stability are direct measurements of pressure changes during the breathing cycle or pressure time product (section 2.4.2.3).

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4.1.2 Technical description

4.1.2.1 Breathing profiles

The method used in all papers include a mechanical lung model (ASL 5000 from IngMar Medical, Pittsburg, USA) that can reproduce flow patterns. The mechanical lung model was used in flow-volume mode. This reproduced a series of identical breaths without simulated compliance or resistance.

The breath profiles used in Paper I and II were from two separate infants. The flow recordings from the term infant (3,4 kg) were from the manuscript by Moa and the preterm infant recordings were obtained from medical records (routine dynamic spirometry recording during quiet sleep in a 1,3 kg infant).[64] In Paper III and IV, symmetrical sinusoidal flow patterns were used.

4.1.2.2 Experimental set-up

The CPAP system, with or without interface, was attached to the lung simulator using a standard 22 mm connector. Adhesive putty was used for airtight fixation. The CPAP level was adjusted before simulation was started.

Leakage was generated by applying a constant leak between the system and the lung simulator (at the 22 mm connector). Use of variable leakage was not attempted since it does not allow for identical test conditions.

4.1.2.3 Data collection and software

The mechanical lung model is a piston pump that measures volume (using the position of the pump) and pressure (in the piston chamber). The volume is corrected for gas compression in the piston chamber but not for volume or compliance outside the mechanical lung model. The accuracy of the mechanical lung volume variables was confirmed by fixed volume syringes and calibrated flow-pressure measurement equipment (VT PLUS HF from Fluke Biomedical, Everett, USA).

Imposed work of breathing was calculated by integrating the area within the pressure-volume loop for a single breath.[71] This variable was not calculated in the standard software and the manufacturer provided a modification for this purpose. Manual calculation of loop area was used to confirm that the software integration was correct.

The data were recorded and processed by the modified software. The software saved data on individual breaths and these could be compiled for further analysis. The main variables used in papers I-IV were delivered pressure, pressure fluctuations (maximum, minimum and total amplitude of swings) and imposed work of breathing.

4.1.2.4 Processing data after collection

Data from the series of experiments were compiled in Excel and exported to SPSS for further analysis. Pressure-volume loops were exported directly from the ASL software.

4.1.2.5 Statistical analysis

Statistical comparisons of means were performed using ANOVA with correction for multiple comparisons. The variability in the measurements was generally low and statistical comparisons identified differences that were small and not likely to be clinically relevant. A p value of less than 0.05 was considered statistically significant.

4.2 RECORDING FLOW (PAPER III)

4.2.1 Introduction and comment

Flow recordings should ideally be performed with systems that have low dead space and low resistance in combination with high signal quality. Resistance can be measured using a mechanical lung model and the in-vitro dead space can be estimated by measuring volumes that contribute to rebreathing.

Determining the quality of the flow signal is more complex since the overall signal quality will depend on several components. Ideally, these components should be optimised for the task. Detailed testing of signal quality would therefore require in-depth knowledge about signal processing and analysis as well as the individual components used in a system. This was beyond the scope of the manuscript. Instead, simple graphical presentations of the raw signals were used to estimate quality. The main problem with this approach is that the signals represent various degrees of post-collection processing and components have not been optimised for the tested flow range

4.2.2 Technical description

4.2.2.1 Experimental set-up

The flow meters were connected to the mechanical lung simulator using the in-line or the flow-through position (Fig. 5). The flow-through position was also tested in combination with an Infant Flow CPAP generator. The lung simulator reproduced a symmetrical sinusoidal flow pattern in the experiments. Resistance was recorded using the mechanical lung simulator described above (4.1).

4.2.2.2 Collecting and presenting flow data

Flow data were collected using provided hardware and software when available. A digital acquisition system (DAQ system) was used for flow meters with an analogue output. The raw flow data recording of a single breath was exported to Excel and presented graphically. There was no statistical analysis performed on the data obtained from the flow meters.

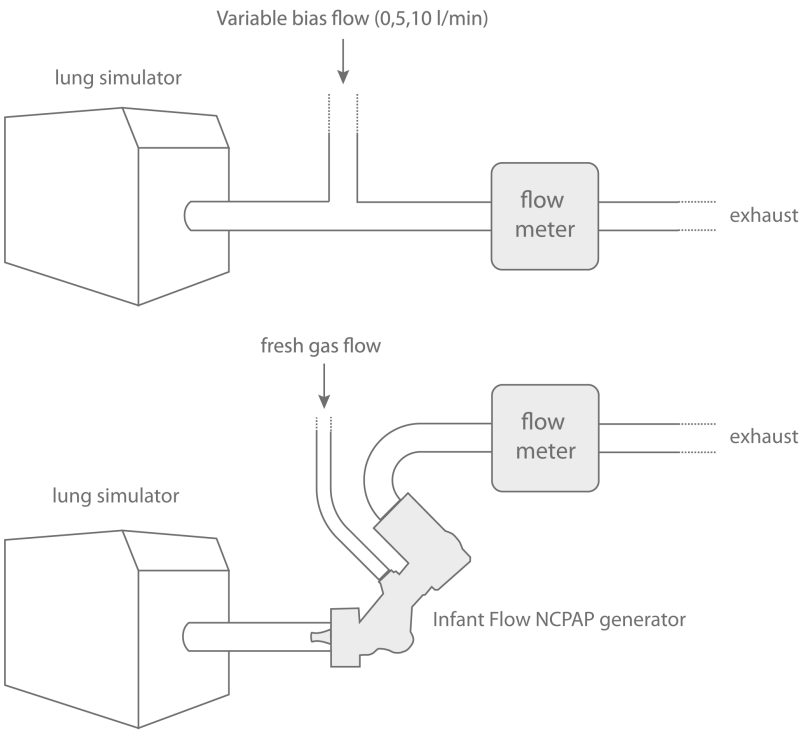

Figure 5: In-line and flow-through position. The bias flow experiments (top) were performed to measure pressure stability and imposed WOB with in-line and flow-through position. A bias flow of 0 L/min is equivalent to in-line positioning. The variable flow CPAP generator experiments (bottom) were performed with an Infant Flow variable flow NCPAP generator. Figure from Paper III.

4.3 DEVELOPING A NEW SYSTEM FOR RESUSCITATION (PAPER IV)

4.3.1 Introduction and comment

The first manuscript (Paper I) identified the Neopuff system as being pressure unstable. This is a general characteristic of CPAP systems that use resistance to generate CPAP. A new system, based on the same principles as the original Infant Flow, was developed. The aim was to allow PPV in a similar way to T-piece systems but also to improve pressure stability during spontaneous breathing. The system should also be possible to use with either face mask or nasal prongs. The designed system was evaluated in-vitro.

The final prototypes were produced by the research group and evaluated in a small clinical feasibility trial on initial stabilisation of preterm infants.

4.3.2 Design, testing and production

4.3.2.1 Design and testing

Prototypes were designed using solid modelling computer-aided design (3D CAD) software and three dimensional (3D) printing. This development and manufacturing technique is often

referred to as rapid prototyping. The prototypes were tested in the mechanical lung model to measure pressure stability during simulated spontaneous breathing. The mechanical lung model testing was described in section 4.1. The design was revised several times to optimise pressure stability and functionality. Figure 6 displays a selection of prototypes and figure 7 gives a description of the new system.

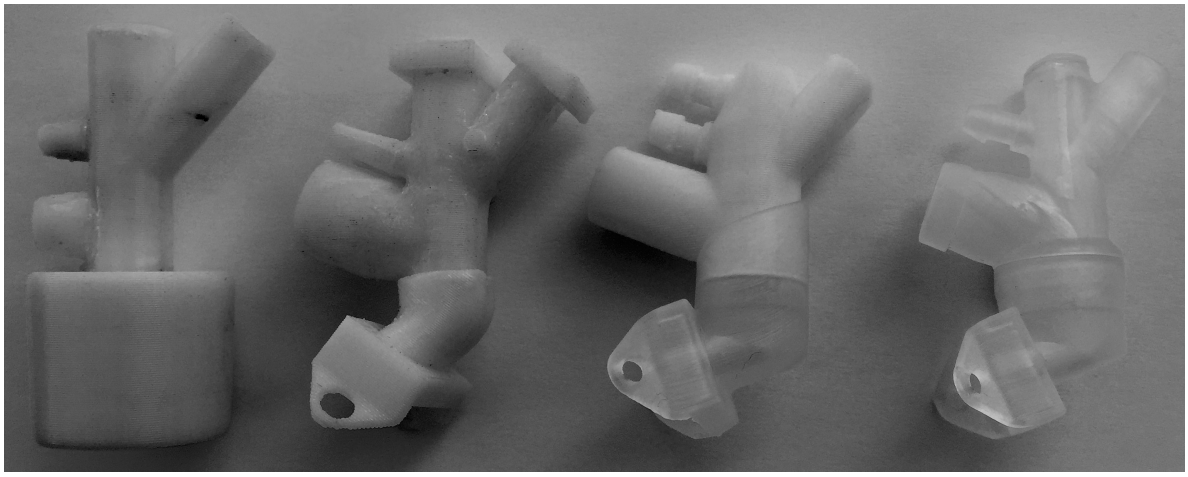

Figure 6: Selected 3D printed prototypes. Far left prototype (2011) represent an early version with a connector intended for face mask interface or endotracheal tube. The next three revisions include a connector for nasal prongs. The last prototype (2014) can be used with nasal prongs or, by changing the connector close to the patient, a face mask (not shown).

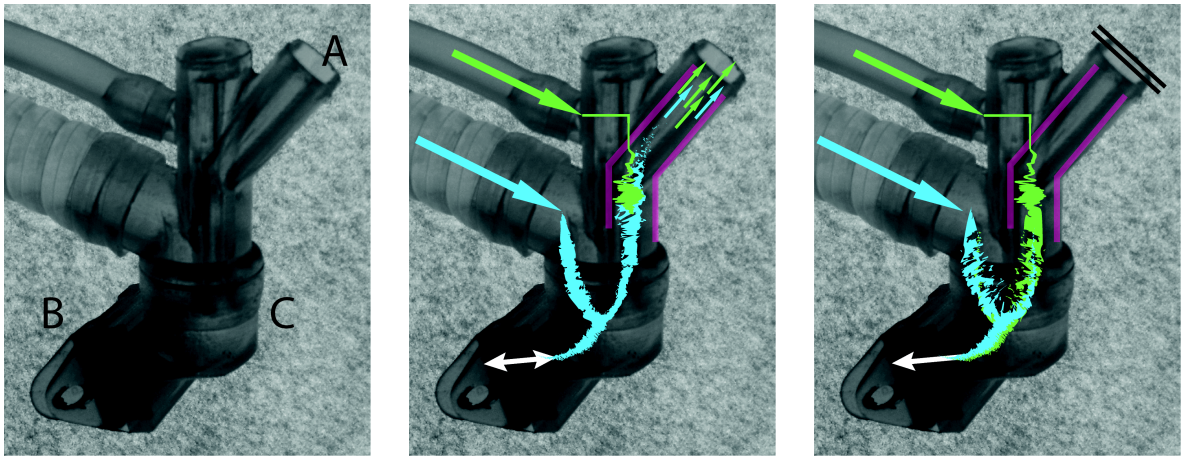

Figure 7: Description of the new system. *Left:* The outlet (A) is open during spontaneous breathing. The patient interface is either short bi-nasal prongs (B) or a face mask (not shown, change of connector (C) required). *Middle:* Continuous positive airway pressure (CPAP) is mainly generated by the flow in the small diameter line (green arrow) by the same method as described by Moa et al. The turbulent flow (green) in the angulated tube (purple) opposes expiration and supports inspiration (white arrow). *Right:* The bias flow (blue) is pressure limited (valve and pressure port positioned upstream) and occlusion of the outlet will generate an inspiratory flow (white arrow). Expiration with positive end expiratory pressure (PEEP) is identical to expiration during CPAP (middle). Figure from Paper IV (in press).

4.3.2.2 Safety

The systems used in the feasibility trial were assembled from standard medical parts and the resuscitation systems were produced in a medical graded material. A risk analysis was performed together with the Medical Technology department at Östersund Hospital, Sweden. The systems were used as in-house produced medical equipment. The use was limited to the Karolinska University Hospital, Sweden and the ethically reviewed feasibility trial.

Producing systems for larger trials is more complex. In Sweden, these trials require a CE-marked product or a clinical trial registered at the Medical Products Agency (both have similar regulatory requirements and standards regarding production and testing). Manufacturing of systems by academic research groups for use in larger trials is generally not feasible (CE-marked or equivalent standard).

4.3.3 Clinical feasibility trial

4.3.3.1 Patient selection and sample size

The patient population represented a convenience selection and the results from the trial were not intended to reflect a defined patient population.

Infants delivered at 27-34 weeks of gestation were selected since they often require respiratory support. A population with term infants would have been difficult to include since they rarely need respiratory support and consent had to be obtained before delivery. A population of smaller infants, for instance extremely premature infants, is generally not suitable for feasibility trials. The patients were recruited from two units of the Neonatal department at the Karolinska University Hospital.

The trial was not intended to detect treatment effects and no power calculations were performed.

4.3.3.2 Inclusion and randomisation

Parents who were admitted for threatening preterm delivery were approached. The inclusion criterion was preterm birth (27-34 weeks of gestation) and exclusion criteria included cardiac or airway malformations, syndromes and neuromuscular disease.

After consent, the infant was randomised by sealed opaque envelopes when birth was imminent. If the infant did not require respiratory support, the envelope was recycled. 36 patients were included with 12 infants in each arm. Randomisation was in one block (12*3) and not stratified.

4.3.3.3 Intervention

After birth, the infant was supported using the randomised system for 10-30 minutes. The three treatment arms were 1) standard T-piece resuscitator, 2) the new system with face mask and 3) the new system with short bi-nasal prongs. Infants who required respiratory support

received 4 cm CPAP and 20 cm H_2O PPV if needed. Treatment was provided according to the ILCOR consensus document [129] and national guidelines[130].

4.3.3.4 Outcomes and variables

The outcomes were related to 1) stabilisation and use of respiratory support in the delivery room, 2) respiratory support and use of surfactant within the first 72 hours and 3) safety. Data from the delivery room were collected after initial stabilisation and the medical records were reviewed after 72 hours. Variables included delivery room intubations, use of PPV, oxygen demand, APGAR, and peripheral capillary oxygen saturation (SpO_2). The 72-hour review of medical records collected data on the use of surfactant, intubation and mechanical ventilation. Safety variables included pneumothorax and problems with equipment or its usage.

4.3.3.5 Statistical analysis

For all variables the distribution of data were tested for normality with Shapiro-Wilk tests and presented as mean (SD) or median (interquartile range). Differences were tested with ANOVA or Kruskal-Wallis tests. Nominal data were tested with Fisher's exact test.

5 RESULTS

5.1 PERFORMANCE OF NCPAP (PAPER I AND II)

5.1.1 Example of differences in pressure stability

The CPAP systems tested in the mechanical lung model showed large variations in pressure stability. An example of the recorded differences imposed work of breathing is presented in figure 8 (including reprocessed data from paper I and II). Statistical comparisons of variables (means generated from consecutive breaths) from simulations in the mechanical lung model were statistically significant at levels below what is likely to be of clinical significance (eg Airlife and Infant Flow LP (figure 8)). Examples of pressure-volume loops for some systems are presented in figure 9 where low-imposed WOB devices (eg Infant Flow) have narrow loops and high-imposed WOB devices have wide loops (eg Medijet and Neopuff).

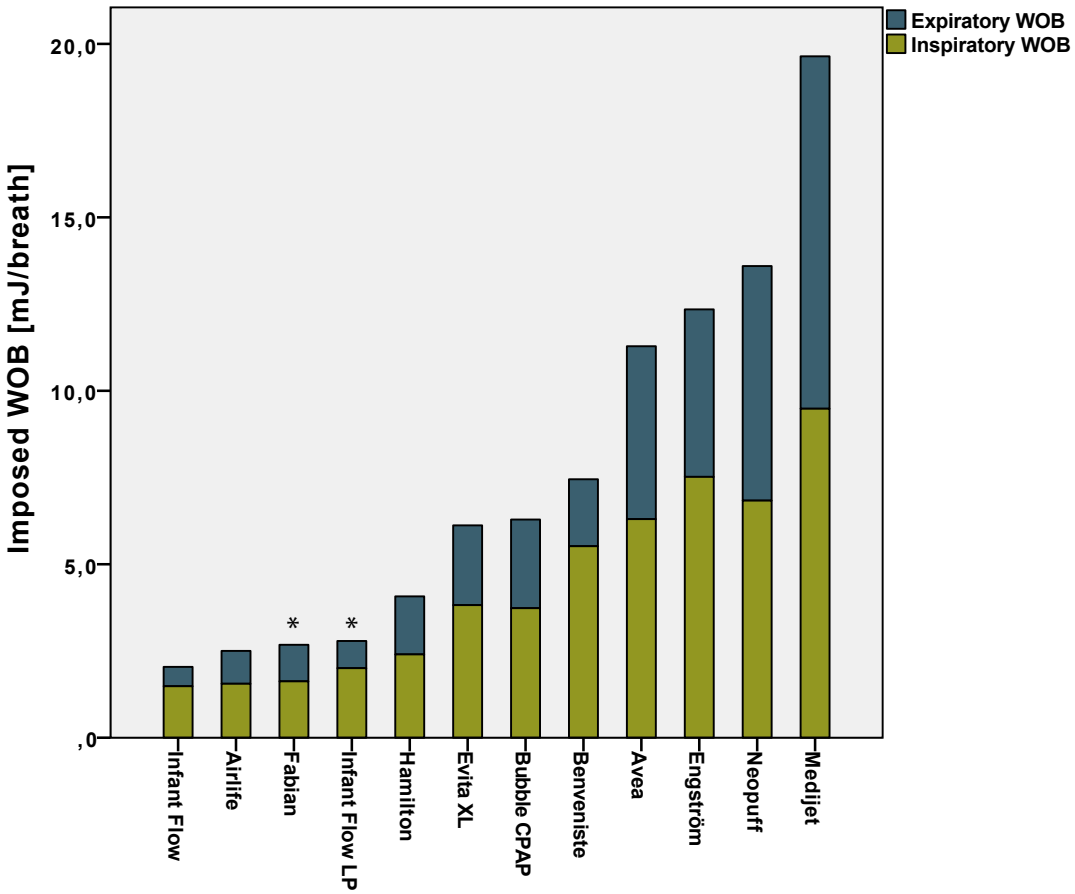

Figure 8: Imposed WOB at 4 cm CPAP for 15 consecutive breaths. Breath profile from a healthy 3,4 kg infant. All systems were tested with large prongs except Neopuff that was tested without prongs. Infant Flow LP has a different design to Infant Flow but almost identical to Airlife. All differences were statistically significant except Fabian and Infant Flow LP (marked *). Data partly presented in Paper I and II.

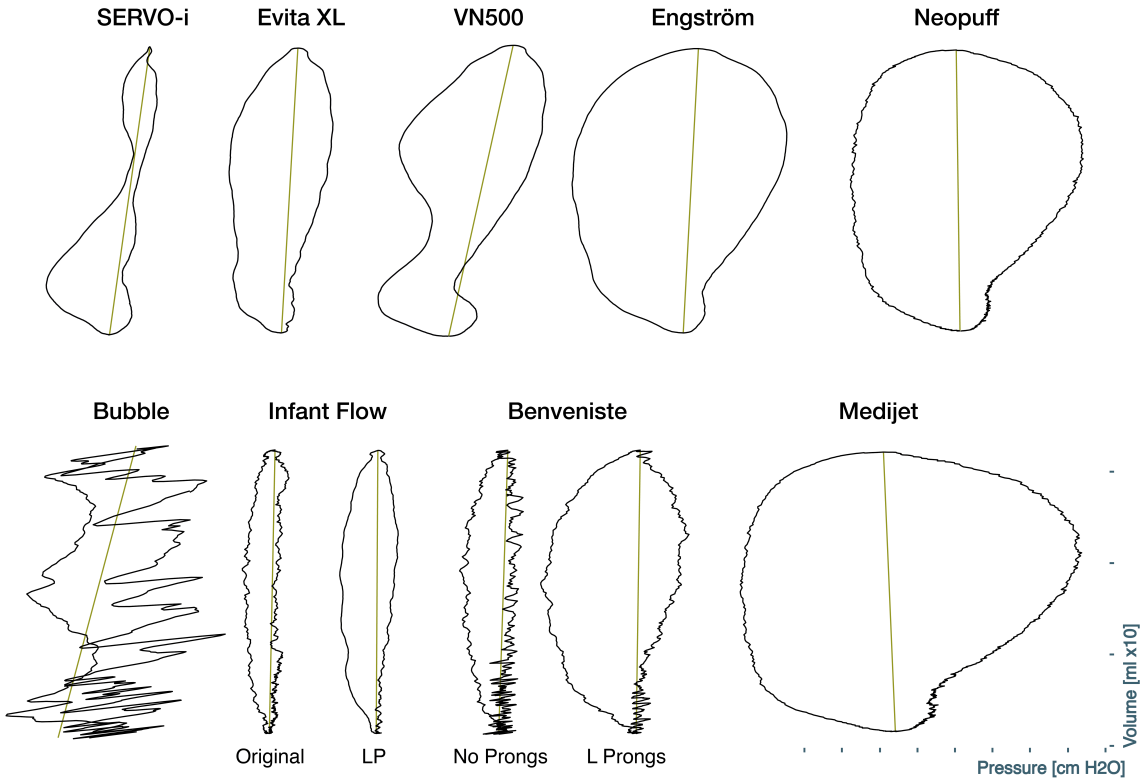

Figure 9: Examples of pressure-volume loops from CPAP systems at 4-5 cm H_2O CPAP. Loops recorded for a single, simulated breath from a 3,4 kg healthy infant and large prongs (Neopuff tested without prongs). The SERVO-i and the VN500 have a small level of pressure support and do not only provide CPAP. The right four loops in top row from Paper II.

5.2 MEASURING FLOW (PAPER III)

The results show the effects of flow meter resistance with the flow meter positioned in the in-line or flow-through position (Fig. 10). With increasing resistance, there is an increased imposed WOB and CPAP generation (in the flow-through experiments). The flow meters intended for neonatal use had higher resistance and larger effects on imposed WOB and CPAP. The flow meters with low resistance showed smaller effects on imposed WOB but instead had large dead space volumes.

In experiments where the flow meter was connected to the exhaust of an Infant Flow CPAP generator the results were similar. Increased imposed WOB was seen in devices with higher resistance (Fig. 11, statistical significant differences for Fleisch 0, FLORIAN and EXHALYZER S in all comparisons).

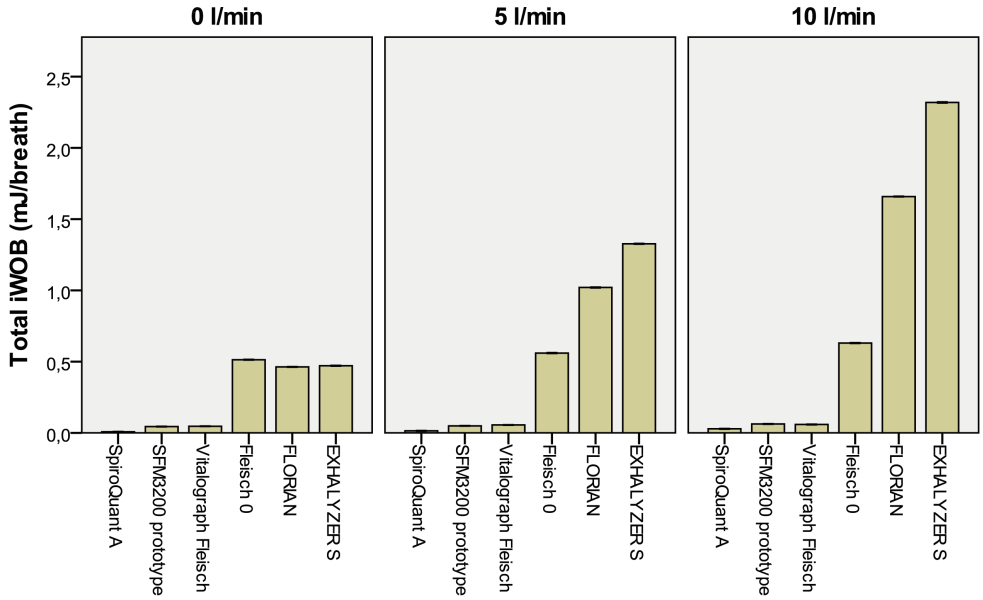

Figure 10: Imposed WOB (Total iWOB) at three levels of bias flow for six flow meters. A bias flow of 0 L/min is equivalent to positioning the flow meter in-line. Bars indicate mean imposed work of breathing (with 95% CI) for 20 consecutive simulated breaths (TV 32 mL, respiratory rate 60 and inspiratory expiratory ratio (I:E) 1:1). All differences between the flow meters were statistically significant except SFM3200 prototype and Vitalograph Fleisch at 10 L/min. Figure from Paper III.

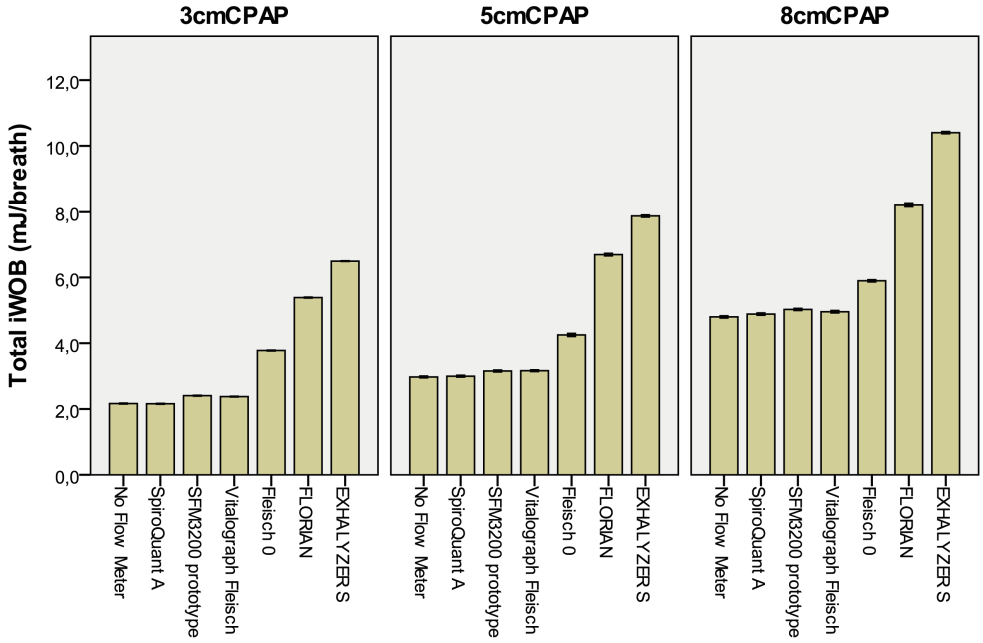

Figure 11: Imposed WOB (Total iWOB) for six flow meters at three levels of CPAP. The flow metes were connected to an Infant Flow CPAP generator using flow through position. Bars indicate mean imposed work of breathing (with 95% CI) for 20 consecutive simulated breaths (TV 32 mL, respiratory rate 60 and I:E 1:1). Statistical significant differences were found in all simulations with Fleisch 0, FLORIAN and EXHALYZER S, but not in all simulations with SpiroQuant A, SFM3200 prototype and Vitalograph Fleisch. Figure from Paper III.

The graphical display of the recorded flow data showed that at least two devices with low resistance may be used with NCPAP systems in combination with flow-through measurements (SFM3200 prototype and Vitalograph Fleisch, figure included in Paper III).

5.3 A NEW RESUSCITATION SYSTEM (PAPER IV)

5.3.1 Design and in-vitro performance

The design and use with prongs on a manikin is shown in figure 12. In simulated neonatal breathing, the new resuscitation device showed a marked reduction in imposed WOB and an increase in pressure stability compared to T-piece resuscitation systems (Fig. 13, statistical significant differences in all comparisons with T-piece systems).

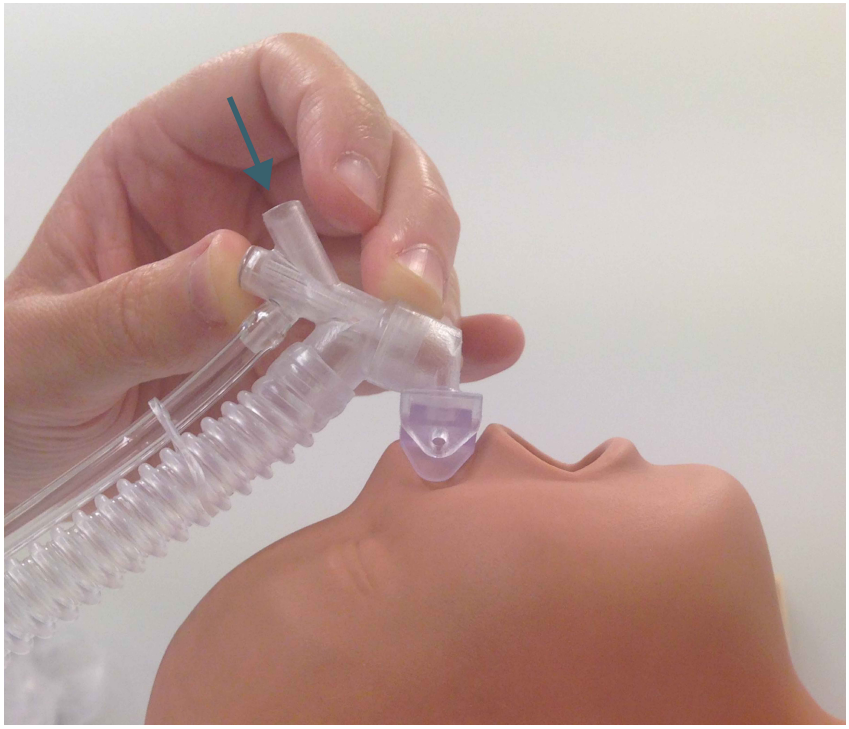

Figure 12: The new system with nasal prongs used on a manikin. Delivery of CPAP and PPV would require minimising leakage by closing the mouth of the manikin. PPV can be obtained by occluding the outlet port (marked with arrow).

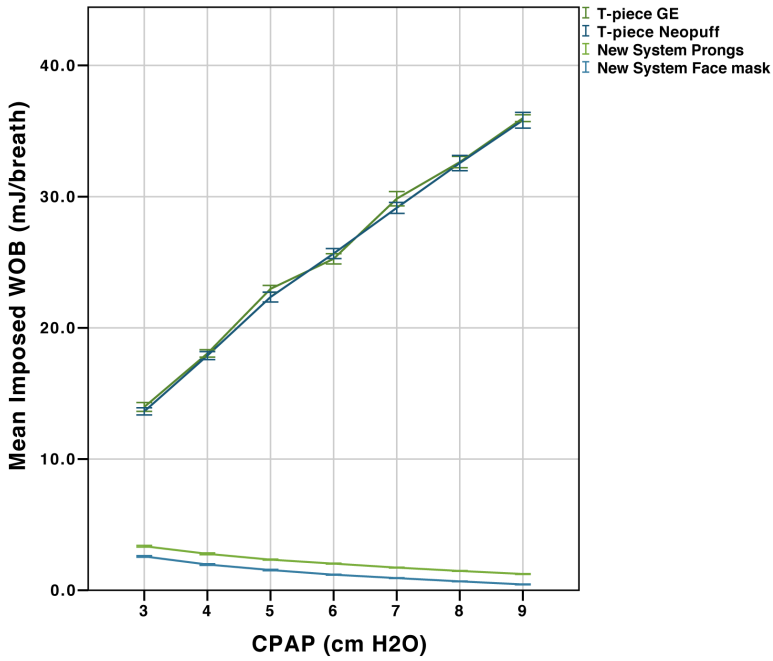

Figure 13: Imposed work of breathing (mean and 95% CI) for T-piece systems and the new system at increasing levels of CPAP in simulated breathing (TV 32 mL, respiratory rate 60 and I:E 1:1). Statistical significant differences at all levels of CPAP for comparisons between new system with face mask, new system with prongs and T-piece systems (no difference between GE and Neopuff at 3, 4, 6, 8 and 9 cm H2O). Figure from Paper IV (in press).

5.3.2 Clinical feasibility trial

Informed consent was obtained for 45 patients out of which 39 were included in the study. Of these, 36 needed respiratory support and were randomised into three arms of equal size. The randomisation resulted in unbalanced groups with significant differences in gestational age. A larger proportion of these more immature infants were treated with surfactant (statistically significant). There were no other statistically significant differences in outcome or treatment between the groups (Table 2).

Two patients treated with the new system (with prongs) developed pneumothoraces in the NICU. They are reported in detail in the manuscript but judged not to be related to resuscitation. One patient could not be ventilated with the new system. Changing to T-piece system did not improve ventilation and the infant had to be intubated. There were no other safety concerns or problems with the equipment.

	T-piece	**New System**		
Interface	Face Mask	Face Mask	Nasal Prongs	
Number of infants	12	12	12	
Gestational Age[a]	33+0 231 (9.9)	32+4 228 (10.7)	30+5 215 (16.9)	0.009
Weight (g)	1828 (1611-2487)	1529 (1308-1829)	1508 (1125-2042)	0.06
Sex (Female/Male)	6/6	6/6	5/7	1.00
Vaginal delivery	5	4	2	0.54
Steroids complete [b]	7	3	7	0.30
Positive Pressure Ventilation	5	6	2	0.34
Intubated in delivery room	0	0	1	1.00
APGAR 1 min	9 (8-9)	9 (6-9)	9.0 (8-9)	0.99
APGAR 5 min	9 (8-9)	10 (8-10)	9.0 (9-10)	0.43
APGAR 10 min	10.0 (9-10)	10.0 (10-10)	10.0 (10-10)	0.15
Time to regular breathing (min)	1.0 (0.0-5.0)	0.5 (0.0-5.0)	0.0 (0.0-1.0)	0.57
Time to SpO2 90%	9.0 (6.0-10.0)	9.0 (5.5-10.0)[c]	6.0 (3.8-6.8)	0.33
Received surfactant <72h	2	0	5	0.046
Pneumothorax	0	0	2	0.31

Table 2: Summary of the three treatment groups. Values as median with interquartile range except Gestational Age (mean).[a] First row mean in weeks+days and second row mean (SD) in days. [b] Two doses with at least 24 h from first dose to delivery and second dose at least 12 h after first dose. [c] Two missing (n=10). Table from Paper IV (in press).

6 GENERAL DISCUSSION

6.1 PERFORMANCE OF NCPAP SYSTEMS

The mechanical lung model allows detailed measurements of performance. Large differences (statistically significant) between CPAP systems were identified. The in-vitro tests show that when discussing pressure stability, it is not possible to make generalised statements on performance of variable flow NCPAP or NCPAP delivered by ventilators. Bubble CPAP and the resistor systems (represented by T-piece) should have a more predictable performance.

The inexpensive bubble CPAP was more pressure stable than some expensive ventilators. Three ventilators were not only providing CPAP but also a low level of pressure support. An example is the SERVO-i ventilator which has a narrow pressure-volume loop indicating high pressure stability but the small pressure support does not allow calculation of imposed WOB.

Resistor systems, represented by the T-piece system, are pressure unstable when used with fresh-gas flow in the same range as inspiratory and expiratory flows. They were used by Gregory but then abandoned for the more pressure stable bubble CPAP.

The Medijet NCPAP system had the highest imposed WOB of all tested systems. It has been presented as an improved Benveniste valve but the high imposed WOB is related to the CPAP being generated by resistance (data not published, manuscript in preparation and not included in the thesis). This gives a performance similar to the T-piece systems.

A limitation of the in-vitro tests is the fixed breathing pattern. In real infants the breathing pattern is likely to adapt to changes in imposed work of breathing, CPAP level and leakage. It is not possible to allow the mechanical lung model to simulate these adaptions since it would give measurements that do not allow comparison of imposed WOB between systems.

The constant leakage used in the simulations is far from the clinical reality. Leakage in patients will vary with prong size, prong design, CPAP level, breathing pattern, level of mouth leakage and the pressure stability of the system being used. Leakage will at the same time also affect the delivered CPAP level and the pressure stability. These multiple interactions will give simulations that are too complex to allow comparisons of different systems. Leakage is probably an important factor in trials of NCPAP and interfaces. For instance, Huckstadt had major problems with leakage and 46 out of 69 recordings had to be excluded.[83]

The in-vitro tests showed large differences in pressure stability between different CPAP systems. The clinical importance of this is not known. If pressure stability is of importance, it raises several questions. It would be difficult to generalise results from a trial that uses a particular system or a mix of systems with varying pressure stability. It would also question conclusions from pooled data from CPAP trails in meta-analyses. This problem with generalisation of results is present in all clinical trials and not unique for NCPAP.

Investigations on effects of increased CPAP is an area where the presented results may be important. Some systems (eg T-piece system) show a steep increase in imposed WOB with higher CPAP. These systems do not permit isolated testing of effects of increasing CPAP since this will increase imposed WOB at the same time. The insufficiently studied clinical effects of differences in pressure stability remain to be investigated.

6.2 MEASURING FLOW

The flow-through technique has been used in several studies. The original study by Rigatto was without CPAP.[103] When the flow-through technique is used in CPAP or respiratory circuits with pressure swings, the effects of tube compliance and gas compression need to be controlled. The flow-through technique is therefore more complicated to use than the in-line technique during positive pressure ventilation (large pressure changes) or pressure unstable CPAP. The CPAP also increases leakage. Huckstadt had to exclude a majority of their included patients because of problems with leakage.[83]

The main disadvantages of positioning a flow meter in-line are the addition of dead space and the added bulk. It has been used for short periods of time and during resuscitation. In resuscitation, the focus has mainly been to identify leakage, airway obstruction and TV during PPV.[131] The added dead-space is a clinical concern in situations with no leakage and with longer duration of use. Rebreathing could affect carbon dioxide levels, breathing patterns and failure rates.

The presented results can be used when evaluating resistance and dead-space for new measurement devices. There are several other aspects of flow measuring techniques that have to be evaluated such as drift, need for calibration, effects of gas composition and temperature. Safety and general suitability for clinical use also have to be assessed.

Another limitation to the study is that optimisation for the intended flow range was not possible. There were also several flow meters that we wanted to test but were unable to get access to.

The initial assessment of signal quality and flow resistance showed that two devices (SFM3200 prototype and Vitalograph Fleisch) had low resistance in combination with an acceptable signal quality. If used in the flow-through position they might allow measurement of flow without adding resistance or dead-space.

6.3 A NEW RESUSCITATION SYSTEM

The new resuscitation device was pressure stable when tested in the mechanical lung model and showed no increase in imposed WOB at higher levels of CPAP.

The clinical feasibility trial showed no problems with safety. The randomisation was not stratified on gestational age and infants in the new device with prongs group were smaller than infants in the other two groups. A larger proportion of these more immature infants were treated with surfactant within 72 hours. The trial was not designed to estimate treatment effects and there were no differences in outcome. The verbal feedback from the users was that stabilisation with the prongs interface was easier than with facemask.

The new resuscitation system has unique features that allow exploration of new and revisit old research questions:

1) It can be used to investigate the importance of high and low pressure stability in infants during initial stabilisation, after extubation and during procedures such as surfactant replacement (by catheters or endotracheal tubes).
2) It can be used to investigate effects of increased CPAP without the marked increase in imposed WOB seen with T-piece systems.
3) It allows comparison of short bi-nasal prongs and facemask during resuscitation.

Clinical trials and investigations in these three areas would give valuable contributions even if the results were not in favour of the new system.

7 CONCLUSIONS

We have shown large differences in performance of the different CPAP systems. The clinical importance of this is not known. If pressure stability is important, it has to be considered when interpreting results or designing trials. The CPAP system (or systems) used in the control or treatment groups could attenuate or augment differences in treatment effects. If pressure stability is important, it is incorrect to draw generalised conclusions regarding CPAP from a trial that has used a particular system or a mix of systems.

Some systems show a marked increase in imposed WOB with higher levels of CPAP (for example Neopuff). Investigating the effects of increasing CPAP with these systems will at the same time investigate the effects of increased imposed WOB.

Flow measurement devices designed for neonatal use have high resistance and imposed work of breathing. Measuring flow without adding dead-space or imposed WOB by using the flow-through technique seems possible.

A new system for neonatal resuscitation has been designed. The new system has low imposed WOB compared to T-piece systems and can be used with either prongs or face mask. A feasibility trial revealed no problems with safety or usage.

8 TOPICS FOR FUTURE RESEARCH

8.1 SUMMARY

The underlying hypothesis driving our research is that non-invasive management is superior to intubation and mechanical ventilation for the majority of patients. This commits us to research aimed at developing and evaluating non-invasive strategies to avoid intubation and mechanical ventilation of preterm infants.

We have identified four topics that we will focus on over the next few years:

- What is the clinical effect of differences in performance of NCPAP systems?
- Can stabilisation using a device with prongs and low imposed WOB during resuscitation reduce intubation rates compared to standard T-piece resusciation?
- Can an updated flow-through system be used as a research or clinical tool?
- What is the relation between static and dynamic investigations of pressure stability for NCPAP systems?

We have worked with two topics that were part of the original research plan before revision:

- Can surfactant in nebulised form be administered to infants at high risk of failing on NCPAP?
- Can the function and flows of the Infant Flow NCPAP geometry be explained using computational fluid dynamics?

In addition, two topics for future research that we would like to engage in are:

- What is the optimal CPAP during resuscitation?
- What is the in-vitro performance of NIPPV and other types of non-invasive support?

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Barn som föds för tidigt har omogna lungor och behöver hjälp med att andas. Det vanligaste hjälpmedlet för barn som kan andas själva heter nasal CPAP. CPAP är en engelsk förkortning för continuous positive airway pressure (kontinuerligt positivt luftvägstryck) och behandling med CPAP innebär att barnet har ett mottryck när det andas. Mottrycket har i vetenskapliga studier visat sig förbättra lungfunktionen och minska behovet av respiratorvård. Målsättningen med denna avhandling är att beskriva kvaliteten hos olika CPAP-system, att utvärdera tekniker för att mäta andning och att ta fram ett nytt system för andningshjälp vid hjärt-lungräddning av nyfödda.

Vi har med hjälp av simuleringar i en mekanisk modell kunnat visa att de CPAP-system som används idag har olika förmåga att bibehålla ett jämnt luftvägstryck. System som inte klarar detta kräver mer arbete av barnet för själva andningen. Förmodligen har detta betydelse vid behandlingen, även om det inte är vetenskapligt bevisat.

Vid forskning och klinisk behandling med CPAP finns ett intresse av att mäta hur barn andas. Ett sätt är att mäta luftflöden men det har varit tekniskt svårt att lösa. Vi har i simulerad andning undersökt andningsmotstånd och bedömt kvaliteten på flödessignaler för två olika mätmetoder. Vi tror att denna teknik kan möjliggöra flödesmätningar utan att belasta barnet med extra andningsarbete och återandning av koldioxid.

När barnet föds måste det själv börja andas och de tidigare vattenfyllda lungorna fyllas med luft. CPAP behandling av förtidigt födda barn direkt efter födseln rekommenderas i flera behandlingsriktlinjer. Det idag vanligaste hjälpmedlet vid stabilisering av nyföddas andning har två egenskaper som skulle kunna vara till nackdel för barnet: Det kräver mycket extra andningsarbete och det används bara med en mask som täcker både mun och näsa (till skillnad från vanlig näs-CPAP som har en näsmask). Vi har tagit fram ett nytt system för hjärt-lungräddning som är lättare för barnet att andas igenom. Det går att använda med både ansiktsmask och näsmask. Det nya andningssystemet har testats i en liten studie och vi såg inga problem med dess användande. Studien var för liten för att kunna dra slutsatser huruvida det nya systemet är bättre eller sämre än det gamla systemet.

Under de närmaste åren kommer vi att arbeta vidare med flera projekt rörande andningshjälp till förtidigt födda barn. Vår målsättning är att undersöka om skillnaderna vi sett mellan olika andningssystem i simulerad andning är viktiga för nyfödda barn i verkligheten. För att kunna undersöka detta vore en förbättrad teknik för flödesmätning värdefull. Det nya systemet för hjärt-lungräddning kommer att testas och jämföras med dagens system i en större studie med slumpvis patienturval. Vår förhoppning är att det kan minska antalet förtidigt födda barn som behöver vårdas i respirator.

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