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Efficacy and safety of non-invasive respiratory support in neonates

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Abbreviation list

AH	absolute humidity
BPD	bronchopulmonary dysplasia
CO_2	carbon dioxide
CPAP	continuous positive airway pressure
eMV	endotracheal mechanical ventilation
GA	gestational age
HFNC	high-flow nasal cannula
HFOV	high-frequency oscillatory ventilation
I:E ratio	inspiratory-to-expiratory ratio
IVH	intraventricular hemorrhage
LISA	less invasive surfactant administration
MIST	minimally invasive surfactant therapy
nBiPAP	nasal bilevel positive airway pressure
nCPAP	nasal continuous positive airway pressure
nHFOV	nasal high-frequency oscillatory ventilation
NICU	neonatal intensive care unit
nIPPV	nasal intermittent positive pressure ventilation
nsBiPAP	nasal synchronized bilevel positive airway pressure
nsIPPV	nasal synchronized intermittent positive pressure ventilation
RCT	randomized controlled trial
RDS	respiratory distress syndrome
RR	respiratory rate
SpO_2	peripheral oxygen saturation

1. Introduction

1.1 Modes of non-invasive respiratory support in neonates

Modern neonatal intensive care offers a broad range of methods to support infants with respiratory failure. Although severely affected patients still require endotracheal mechanical ventilation (eMV) or even adjunctive therapies, such as inhaled nitric oxide or extracorporeal membrane oxygenation,[1] most neonates can nowadays be stabilized by non-invasive modes of respiratory support. Current techniques are listed in Tab. 1, and can be grouped into methods that apply a constant airway pressure and methods that apply a variable airway pressure.[2] In addition, low-flow supplemental oxygen is used as a method to provide oxygen without significant pressure transmission to the airways.

Tab. 1 Current techniques of non-invasive respiratory support.

Type of pressure applied	Mode of non-invasive respiratory support	Clinical status
No significant airway pressure	Low-flow supplemental oxygen	Established method in infants with chronic lung disease
Constant airway pressure	High-flow nasal cannula (HFNC)	Recently established method
	Nasal continuous positive airway pressure (nCPAP)	Standard of care
Variable airway pressure	Nasal bilevel positive airway pressure (nBiPAP)	Established method
	Nasal intermittent positive pressure ventilation (nIPPV)	Established method
	Nasal synchronized bilevel positive airway pressure (nsBiPAP)	Prevalence limited, clinical studies
	Nasal synchronized intermittent positive pressure ventilation (nsIPPV)	Prevalence limited, clinical studies
	Nasal high-frequency oscillatory ventilation (nHFOV)	Prevalence limited, case series, pilot studies

Clinical use of the diverse respiratory support modes may vary considerably from one neonatal intensive care unit (NICU) to another, and there is a multitude of different equipment available.

Apart from various devices that provide the actual mode of non-invasive respiratory support, different tubing systems and heated humidifiers are applied.[3] Moreover, there is a multitude of interfaces, including single and binasal prongs of different lengths and diameters, nasopharyngeal tubes, nasal masks, nasal cannulae, and helmets.[2,4-7] Clinical studies that attempted to prove the superiority of specific devices or interfaces mostly yielded inconsistent results and were focused on short-term outcomes. There is a consensus, though, that short binasal prongs have a lower resistance and are more effective at preventing reintubation than single nasal or nasopharyngeal prongs.[4,8,9]

Surveys that investigated the prevalence of non-invasive respiratory support modes showed that nasal continuous positive airway pressure (nCPAP) is the current standard of care for the treatment of neonatal respiratory disorders. In comparison, nasal bilevel positive airway pressure (nBiPAP) and nasal intermittent positive pressure ventilation (nIPPV) are less frequently applied.[10-12] Moreover, dedicated surveys reflect the rapid increase in the clinical use of heated humidified high-flow nasal cannula (HFNC).[13,14] In addition, nasal synchronized bilevel positive airway pressure (nsBiPAP) and nasal synchronized intermittent positive pressure ventilation (nsIPPV) are being investigated in clinical studies.[15,16] Reports about nasal high-frequency oscillatory ventilation (nHFOV) mostly relate to pilot trials and case series.[17,18]

A recent clinical report by the American Academy of Pediatrics recognized that the newer modalities such as nBiPAP, nsBiPAP, nIPPV, nsIPPV and HFNC may offer some advantages over nCPAP, but warned that efficacy and safety data are still limited.[19]

1.2 Mechanisms of action

All in all, the aforementioned methods of non-invasive respiratory support rely on four basic mechanisms of action:

1. Pressure transmission to airways and lungs (not during low-flow oxygen)
2. Airflow that enters the airways at the level of the interface
3. Oxygen supplementation (possible with all methods)
4. Pressure oscillations

The major feature of continuous positive airway pressure (CPAP) is the application of continuous distending pressure. This pressure splints the upper airways,[20] decreases supraglottic and total pulmonary resistance,[21,22] increases functional residual capacity,[23] and improves the recruitment of the lungs.[24] It is understood that the increased end-expiratory lung volume stabilizes the infant's compliant chest wall and improves thoracoabdominal synchronization.[25,26] The overall effect is a reduced work of breathing.[27] Moreover, the distending pressure reduces obstructive apneas[28] and may preserve stability of oxygenation during central apneas.[29]

There are different devices available to generate the CPAP, which either use continuous flow or variable flow technology. Continuous flow devices deliver a constant background flow to the inspiratory limb of the breathing circuit, while the CPAP is generated by an adjustable resistance to gas flow at the end of the expiratory limb. This adjustable resistance may be the expiratory valve of a neonatal ventilator during ventilator-derived CPAP or an underwater seal during bubble CPAP.[2] By contrast, variable flow devices generate the CPAP pressure close to the nasal orifices via a jet stream passing through an opening in the nosepiece.[30,31] Some of these devices use the Coandă effect to attach the jet stream to different surfaces during inspiration and expiration. This "fluidic flip" technology reduces expiratory resistance and may achieve more stable pressure at the airway with additional reduction in work of breathing.[30,32--35]

During bubble CPAP, the bubbles create pressure oscillations that are transmitted back to the airway opening. This noisy pressure waveform is superimposed on the pressure fluctuations of spontaneous breathing, and may promote airway opening events and lung volume recruitment as a result of stochastic resonance.[36] Moreover,

the pressure oscillations of bubble CPAP may contribute to effective ventilation by unconventional mechanisms of gas exchange, such as facilitated diffusion.[37,38]

Presumably, the flow that enters the airways during CPAP is also important, as it facilitates expiration by a flow-dependent washout effect of carbon dioxide (CO_2) from the pharyngeal dead space.[39]

During HFNC, similar flow-related washout effects exist and are probably the most important mechanism of action.[40] Because the HFNC does not have a snug fit in the nares, additional washout effects may occur at this level.[39] By contrast, transmission of distending pressure is probably less important during HFNC, as bench studies showed that pressures obtained are highly variable and depend on a multitude of factors, such as the flow rate, cannula size and nares diameter.[41,42] Even with less distending pressure, however, HFNC may reduce resistive work of breathing in the upper airways during inspiration by provision of gas flows that match or exceed the patient's peak inspiratory flow.[43] Notably, clinical studies found that the overall work of breathing may be similar during nCPAP and HFNC.[40,44]

As low-flow oxygen lacks the specific action mechanisms of CPAP and HFNC described above, it is nowadays hardly used in the acute phase of neonatal respiratory disease, but matters if the weaning phase is prolonged, particularly if long-term oxygen treatment is required in preterm infants with severe bronchopulmonary dysplasia (BPD), Tab. 1.[45,46]

At the other end of the spectrum, non-invasive respiratory support modes such as nBiPAP, nIPPV, nsBiPAP, nsIPPV and nHFOV attempt to provide "more potent" respiratory support. These techniques combine the provision of continuous distending pressure with variable elevations of the airway pressure to recruit the lungs more efficiently and facilitate CO_2 exhalation.

While BiPAP primarily aims at more effective lung volume recruitment by application of a cyclic shift between a lower and slightly elevated positive airway pressure (generally no more than 11 cm H_2O), nIPPV provides higher inspiratory pressures and shorter inspiratory times to expand the lungs, similar to eMV.[15] Unfortunately, the non-invasive ventilation breaths are rarely transmitted to the chest if they are not synchronized with the infant's respiration.[47] Therefore, triggered methods such as

nsBiPAP and nsIPPV seek to synchronize the non-invasive ventilator breaths with patient breathing. Synchronization may be achieved by a flow trigger[48], a pneumatic capsule taped to the abdomen in the subxiphoid area,[49] neurally adjusted ventilatory assist,[16,50] or transcutaneous electromyography of the diaphragm.[51]

NHFOV is an innovative mode of non-invasive respiratory support that aims to combine the positive effects of CPAP with the additional benefits of high-frequency pressure oscillations superimposed on the patient's tidal breathing. The method has a major advantage in that it does not require patient-ventilator synchronization.[52] Hypothetically, the oscillatory pressure waveform of nHFOV induces unconventional mechanisms of gas exchange similar to those identified in invasive high-frequency oscillatory ventilation (HFOV).[38] The impact of the pressure oscillations on CO_2 clearance is considered greater during nHFOV than bubble CPAP, as nHFOV oscillations are more powerful and have an active expiratory phase.[17] In line with these assumptions, bench studies showed that nHFOV enhances CO_2 elimination.[53,54] Clinical observational studies and a small crossover trial were able to confirm this effect in the clinical setting.[55-57]

1.3 Clinical efficacy

Non-invasive respiratory support may be used in the acute phase of neonatal respiratory disorders, the weaning phase, or both. Appropriate choice of non-invasive treatment depends on several factors, such as the nature and severity of the disease, the maturity and age of the patient, the actual clinical setting, and the effective combination with potent pharmacological agents.

To establish the efficacy of these interventions, clinical studies investigated specific non-invasive treatment strategies in various respiratory conditions. In neonates, probably the largest amount of clinical research was devoted to the investigation of non-invasive respiratory support in the treatment of premature infants with respiratory distress syndrome (RDS). These efforts were mainly undertaken to reduce major complications of RDS, such as mortality and BPD.

BPD has long been recognized as a pulmonary sequela of eMV and oxygen supplementation in surfactant-deficient lungs.[58,59] Subsequently, however, it was acknowledged that BPD is a multifactorial disease of very preterm infants that can also develop without prolonged exposure to oxygen or eMV. This so-called “new BPD” is related to a maturational arrest of the evolving lung. It initially manifests as mild respiratory distress, but leads to increased oxygen requirements and disturbed lung development thereafter.[59,60] Today, BPD is still a common complication of prematurity,[61] and is associated with long-term impairment of lung function, increased risk of asthma, worse neurodevelopmental outcomes, impaired school achievement, and reduced health-related quality of life.[62-64]

In 1987, a cohort study by Avery et al. revealed that the early use of bubble CPAP instead of eMV was associated with a considerably lower incidence of BPD.[65] At the time, however, prospective trials did not investigate this finding further. Quite the opposite, clinical research in the 1990s focused on strategies of early intubation and endotracheal surfactant administration, followed by brief eMV and extubation to nCPAP, as this approach appeared to be associated with the lowest incidence of air leak syndromes and BPD.[66]

After 2000, there was renewed interest in using nCPAP as a primary mode of respiratory support in very premature infants. This had several reasons: First, registry

data revealed that the incidence of BPD remained high in very low birth weight infants ≤28 weeks' gestational age (GA), in spite of widespread use of antenatal steroids and early surfactant administration.[61] Second, animal studies showed that complete avoidance of eMV by nCPAP treatment reduced indicators of acute pulmonary injury in alveolar washes. This suggested that avoiding eMV altogether had the potential to prevent activating the inflammatory cascade in the lung that leads to BPD.[67] Third, several multi-center randomized controlled trials (RCTs) were recruiting patients that compared nCPAP as a primary mode of respiratory support versus prophylactic or early selective surfactant treatment.[68-70] In addition, less invasive ways of surfactant administration during nCPAP were explored[71,72] and tested in RCTs.[73,74] When the present thesis was devised in 2012, data from the aforementioned RCTs were available or upcoming, and some showed trends towards a reduction in BPD. Up until then, however, these results had not been evaluated systematically in a meta-analysis.

Apart from nCPAP, other non-invasive modes of respiratory support are being used in neonates, although there is considerably less evidence from clinical trials to document their efficacy.

HFNC is nowadays recognized as an alternative to nCPAP in many clinical settings. The main advantage of HFNC appears to be its ease of use. Moreover, it allows better access to the infant's face, thus facilitating feeding and bonding with parents.[14] A Cochrane Review in preterm infants analyzed RCTs that compared HFNC with nCPAP after birth (four studies, 439 patients) and for post-extubation support (six studies, 934 patients). The analyses found no difference in the incidence of death, BPD or treatment failure.[75] A recent multi-center RCT, however, compared HFNC with nCPAP after birth in 546 infants ≥28 weeks' GA and showed that treatment failure occurred more frequently in the HFNC group (26% versus 13%).[76] Moreover, concerns have been raised that HFNC may prolong the weaning phase and exposure to supplemental oxygen.[77,78] Further knowledge gaps include the lack of efficacy data about HFNC use in premature infants <28 weeks' GA and its impact on long-term outcomes.

Non-invasive respiratory support modes that apply a variable airway pressure aim to be more efficient at avoiding eMV than nCPAP, and thereby seek for a reduction of BPD rates. To date, however, a beneficial effect of these modalities on the incidence of BPD could not be proven. A recently updated Cochrane review compared RCTs that applied various forms of nIPPV, nsIPPV and nBiPAP versus nCPAP in extubated

preterm infants (10 studies, 1431 patients). In the intervention group, there was a decreased risk of respiratory failure and less need for reintubation, but no difference in death or BPD. Interestingly, a subgroup analysis of nsIPPV versus nCPAP was associated with a reduction in BPD (three studies, 181 patients).[79] Therefore, future RCTs should be devised to investigate nsIPPV as an alternative to nCPAP in preterm infants with RDS, and should consider the use of advanced triggering equipment such as NAVA.[50] Admittedly, the use of NAVA technology may be intricate in VLBW infants. For these patients, nHFOV might be a suitable alternative to augment gas exchange, as patient-ventilator synchronization is not needed during nHFOV.[52] As previously mentioned, however, available cohort studies and pilot trials of nHFOV focused on short-term outcomes such as pCO_2 and were not powered to investigate the effects of nHFOV on long term treatment efficacy.[17,18]

1.4 Adverse effects

There are a number of specific adverse effects associated with the use of non-invasive respiratory support in newborn infants.

At the level of the interface, local adverse effects are a major concern. In particular, the prolonged use of binasal prongs may lead to progressive flaring of the nostrils, circular distortion of nares, and flattening of alar ridges.[80] Studies of nasal prong CPAP reported an incidence of nasal injuries between 20 and 60%.[80-82] Redness, crusting and excoriation typically occurs at the nasal septum.[82] In severe cases, columella necrosis has been reported and may require plastic reconstruction later in childhood.[83] Meticulous nursing care, including appropriate choice of nasal prong size and proper fixation, are paramount to reducing the aforementioned complications.[84] The use of nasal masks has recently been reported to reduce the incidence of severe nasal trauma during CPAP therapy,[85] but nasal masks themselves may cause lesions at the junction between the nasal septum and the philtrum.[82]

Pressure transmission to the airways and lungs is associated with increased risks of pneumothorax and other air leaks.[86] In preterm infants, two multi-center RCTs of nCPAP reported higher pneumothorax rates of 9% in the CPAP-treated groups, in comparison with only 3% in the groups that received earlier intubation and surfactant.[68,87] However, similar multi-center RCTs did not replicate these findings,[69,70] and current guidelines recommend nCPAP with early rescue surfactant administration as a safe alternative to intubation and prophylactic surfactant in the postnatal treatment of premature infants with RDS.[9,88] A more recent RCT even reported lower pneumothorax rates of 4.8% and increased survival without major complications if surfactant was administered via a thin catheter during nCPAP, while the pneumothorax rate was 12.6% in the group that was intubated for surfactant administration.[89]

Benign gaseous distention of the bowel has been reported in preterm infants treated with nCPAP, and may lead to unnecessary contrast studies and surgery.[90] This clinical presentation has been denoted as “benign CPAP belly syndrome,” as it is not associated with abdominal complications. Although there are some concerns that the gaseous distention of the bowel may prolong the duration to achieve full enteral feeds,[91] an ultrasound study in very low birthweight infants even reported faster gastric emptying during nCPAP therapy.[92]

Noise exposure may be substantial during certain modes of respiratory support. Bench studies showed particularly high noise intensities during variable flow CPAP,[93] helmet CPAP,[7] and HFNC.[94] Clinical studies in neonates confirmed that noise levels during variable flow CPAP, bubble CPAP and HFNC often exceeded currently recommended limits, and there are concerns that this may negatively impact preterm infants' hearing.[95-97]

Supplementation of oxygen is often required during non-invasive respiratory support and involves a broad range of risks for neonates. Preterm infants are especially susceptible to oxidative stress,[98] and hyperoxia is a recognized factor in the pathogenesis of developmental diseases of prematurity, such as BPD[58,59,99,100] and retinopathy of prematurity.[101,102] However, the early use of non-invasive respiratory support instead of eMV aims to reduce the cumulative duration of any respiratory support and may also reduce aggregate exposure to supplemental oxygen.

Overall, most data about adverse effects of non-invasive respiratory support relate to nCPAP trials, and there is much less data about other respiratory support modes. In the case of HFNC, specific concerns have been raised about the occurrence of air leaks due to the unpredictable pressure transmission.[103-105] However, bench studies and clinical data indicate that excessive pressure transmission can be avoided by appropriate choice of nasal cannula prong size and the use of a pressure relief valve in the circuit.[41,106] Encouragingly, a recent meta-analysis showed that the rate of air leak during HFNC was comparable to that with nCPAP.[107] With regard to nIPPV, early reports raised concerns about the occurrence of intestinal perforation,[108] but an updated Cochrane review did not substantiate these concerns.[79] For nsIPPV, nsBiPAP, and nHFOV, there is hardly any published information about adverse effects.

Finally, it is important to note that the use of nCPAP and other non-invasive respiratory support modes is only safe if the patient's respiratory effort is sufficient to ensure adequate ventilation. Hypercapnic respiratory failure may evolve unnoticed in preterm infants and has been associated with an increased incidence of severe intraventricular hemorrhage (IVH),[109] especially during the first days of life.[110] Therefore, the aggregate data from RCTs about non-invasive respiratory support should be carefully and systematically analyzed for the incidence of side effects to verify the safety of innovative treatment approaches.

1.5 Significance of leaks

Leaks are a major issue during non-invasive respiratory support of neonates, as they have been shown to affect the efficacy of treatment. Moreover, they may be associated with specific side effects that add to those already mentioned.

Theoretically, leaks can occur at any location between the ventilatory device and the lungs. This may be due to technical problems, such as an improperly connected tubing system or a leakage at the interface's level, such as a nares-prong leak. In this sense, the term "leak" refers to a respiratory support system that is not airtight.[111]

Depending on the interface, leaks may be frequent during non-invasive respiratory support. In neonates, the common use of nasal interfaces allows the continuous loss of air through an open mouth, often denoted as "mouth leak." Moreover, the fit of nasal masks or nasal prongs is often not airtight, nasopharyngeal tube interfaces implicate leaks through the contralateral nostril, and nasal cannulae involve an intentional leak at the nares' level.[2] Surprisingly, quantitative information about the incidence and magnitude of such leaks in infants is scarce.[112,113] In a previous neonatal crossover study, we measured the leak during nasopharyngeal CPAP, with and without nostril occlusion. Spontaneous mouth opening was observed in more than 75% of all measurements. Leaks were almost invariably present and mostly exceeded the given measuring range of >90%, corresponding to leak flows of >1.4 $l \cdot min^{-1}$.[114]

Hypothetically, such leaks impair successful treatment with non-invasive respiratory support in various ways:

First, leaks reduce the efficacy of the pressure transmission to the airways by introducing a discontinuity between the ventilatory device and the lungs.[111] A neonatal bench model of nCPAP demonstrated considerable pressure drops from the prongs to the test lung when nares-prong leaks were simulated.[115] In line with these results, a clinical study in 11 preterm infants on binasal bubble CPAP showed an increase in pharyngeal pressure when the mouth was actively closed.[116] The actual effects of leaks on oxygenation and breathing patterns, however, have never been investigated in infants.

Second, leaks may impede triggering during nsBiPAP or nsIPPV if airway pressure or flow-triggering systems are used for synchronization. However, specially designed flow

triggers exist that are less sensitive to leaks,[48] and other innovative triggering methods such as NAVA or diaphragmatic electromyography may circumvent this problem altogether.[16,51]

Third, continuous bedside monitoring of tidal breathing parameters would be desirable during non-invasive respiratory support to guide treatment, but leaks were shown to interfere with such measurements.[113,114,117]

The presence of leaks may also have positive effects on gas exchange, as leaks facilitate CO_2 exhalation. During HFNC, the intentional leak around the nasal cannula and the high flow rate may prevent expired gas from reentering the nasal prongs, thus eliminating apparatus dead space. In line with this hypothesis, a recent bench study reported considerably lower CO_2 washout times during HFNC than during nCPAP, even when a mouth-closed condition was simulated.[39] In the same study, the quickest CO_2 washout occurred with the mouth-open condition, no matter whether HFNC or nCPAP was applied. This observation can be explained by a unidirectional gas flow in through the nose and out through the mouth.[118,119] Hypothetically, such a continuous leak flow effectively reduces ventilatory dead space by CO_2 washout from the naso- and oropharynx and supersedes CO_2 exhalation via the nasal airway route.[39,53]

Unfortunately, the unidirectional leak flow through the mouth also involves a range of undesired effects. These effects were well documented in adults receiving CPAP treatment, and include sensations of oral and nasal dryness, increases in nasal mucosal blood flux and resistance, and congestion of nasal airways.[118-120] It should be noted that sedated patients and small children are unable to declare such symptoms, and it is likely that similar adverse effects exist in infants. The impact of leaks on upper airway dryness, however, has never been investigated systematically in infants on non-invasive respiratory support.

1.6 Significance of heated humidification

Adequate heating and humidification of breathing gas are crucial to preventing adverse effects associated with heat loss and airway desiccation during non-invasive respiratory support.[121] In preterm infants, it has also been suggested that the provision of warmed and humidified gas increases HFNC's efficacy by minimizing the metabolic work of breathing, and improving respiratory conductance and pulmonary compliance.[6,43,122]

Under normal circumstances, the nose and upper respiratory tract heat and humidify the inspired air in order to achieve constant gas conditions within the lungs.[123] Dery et al. investigated the resulting temperature and humidity gradients along the respiratory tract in adults breathing room air, and found that the gas reached 37°C and 100% relative humidity five cm below the carina.[124] The position of this "isothermic saturation boundary," however, depends on the heat and moisture content of the inspired air, and moves further downward during oral breathing or with increased minute ventilation.[125–127]

During eMV, bypassing the upper airways places a greater burden of gas conditioning on the lower airways. Insufficient heating and humidification of the delivered breathing gas is associated with histological damage and functional impairment of the airway mucosa, including the ciliated epithelium in the tracheobronchial tree.[123] This leads to increased mucous viscosity, depressed cilicary function, and impaired mucociliary clearance of secretions, which increases the risk of airway obstruction and respiratory infection. Moreover, the loss of body water and heat may have important clinical implications in infants, who have a higher minute ventilation-to-body surface area ratio.[128]

During non-invasive respiratory support, inspired gas passes through the upper airways where it is conditioned, but the high flow rates applied may overwhelm the usual airway humidification mechanisms, especially in the presence of leaks.[121] As previously mentioned, the mouth leak is a well-recognized problem in adult patients on CPAP, as the unidirectional leak flow through the mouth causes severe desiccation of the naso- and oropharynx, increased nasal resistance, and increased nasal congestion.[119,120] Interestingly, these adverse effects could be attenuated by heated humidification of the breathing gas.[119,129] In neonates, only a few studies genuinely

investigated gas conditioning during non-invasive respiratory support. A long time ago, a small cohort study in premature infants reported that crusting and clogging of nasopharyngeal CPAP tubes could be prevented by heated humidification.[130] A randomized crossover trial of 12 preterm infants on nCPAP compared two temperature settings of the heated humidifier, but did not detect consistent effects on vital parameters.[131] Recently, a neonatal manikin study systematically assessed the effects of HFNC, low-flow oxygen and various modalities of nCPAP on oropharyngeal gas conditions during heated humidification. The tested devices all achieved oropharyngeal temperature >33°C and relative humidity >80%. This study, however, did not simulate the effects of patient breathing and did not investigate the impact of mouth leaks.[3]

In spite of the limited published evidence about gas conditioning in neonates, heated humidifiers are nowadays a key component of the ventilatory circuit during non-invasive respiratory support. Specifically, there is a consensus that heated humidification is a prerequisite for the use of HFNC, which applies the flow of 2-8 $l \cdot min^{-1}$ to the neonatal nose, which would otherwise cause adverse effects.[6,43] The devices themselves have technologically evolved over the years.[132] In neonatal intensive care, servo controlled pass-over humidifiers are frequently used. These devices apply “single point temperature control” algorithms to target a constant temperature at the chamber outlet.[133] Unfortunately, these devices are strongly influenced by environmental conditions and ventilatory settings.[134] Therefore, the efficacy of heated humidification should be investigated actively whenever novel modes of respiratory support are developed in preterm infants. Notably, a neonatal bench study of invasive HFOV showed larger water losses for low HFOV frequencies and high amplitudes,[135] but gas conditioning has never been explored during nHFOV.

1.7 Aims and objectives

In summary, available evidence about the efficacy and side effects of non-invasive respiratory support justifies the frequent use of these treatments in the NICU. However, clinical studies in infants mostly related to nCPAP, and many open questions remain. Non-invasive strategies that avoid eMV in the primary treatment of RDS are evolving, but the significance of these approaches needs to be assessed, especially with regard to the prevention of BPD and other complications of prematurity. Further knowledge gaps relate to the impact of leaks on the efficacy of non-invasive respiratory support. Moreover, little is known in neonates about leak-related side effects and the impact of heated humidification. Finally, much more research is needed on innovative modes of non-invasive respiratory support, such as nHFOV.

The present habilitation thesis aimed to address these issues in order to extend the knowledge about the efficacy and adverse effects of non-invasive respiratory support in neonates. Specifically, the following research objectives were pursued:

1. To investigate the impact of non-invasive respiratory support strategies on BPD and IVH in a meta-analysis of RCTs, considering published and previously unpublished stratified data for infants <30 weeks' GA.

2. To analyze the effects of nose and mouth leaks on oxygenation and respiratory rate (RR) during neonatal CPAP, using data from a clinical crossover study.

3. To obtain information about the prevalence, clinical practice and side effects of nHFOV in an international survey.

4. To develop a neonatal bench model suitable to investigate the impact of leaks and heated humidification on oropharyngeal temperature and humidity during nCPAP.

5. To investigate the effects of nHFOV on oropharyngeal gas conditions in the previously designed bench model.

2. Original research

2.1 Impact of strategies to avoid endotracheal mechanical ventilation on the incidence of bronchopulmonary dysplasia in preterm infants <30 weeks' gestational age

Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics.* 2013;132(5):e1351-1360

To assess the clinical benefits of avoiding eMV in premature infants at high risk of BPD, we performed a meta-analysis of RCTs in preterm infants <30 weeks' GA. The primary outcome was the incidence of death or BPD, defined as oxygen treatment at 36 weeks' GA.[59] As preterm infants are particularly vulnerable to IVH during the first days of life,[109,110] severe IVH (Papile grade three or four) was investigated as a secondary outcome.[136] RCTs were eligible for meta-analysis if they compared a strategy that aimed at avoidance of eMV with a control group in which eMV was performed at an earlier stage. Data search, extraction and analysis followed the standard methodology of the Cochrane Neonatal Review Group.[137] After completing the literature search, we requested previously unpublished stratified data from the corresponding authors of two RCTs.[74,87] Thanks to their cooperation, we were able to meta-analyze seven RCTs comprising a total of 3289 patients.

All included studies either used nCPAP alone or nCPAP combined with surfactant administration via a thin catheter to avoid eMV. The meta-analysis showed that applying these strategies in preterm infants <30 weeks' GA reduced the overall incidence of death or BPD from 42.4% to 39.6% (p=0.01, number needed to treat=35), without increasing the incidence of IVH.[138]

The relatively small benefit of the "non-invasive approach" on the outcome death or BPD and the high percentage of preterm infants who eventually required intubation and eMV in the nCPAP groups (31-83% in the included RCTs) suggested that further studies are needed to improve the efficacy of non-invasive respiratory support.

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2.2 Influence of nose and mouth leaks on peripheral oxygen saturation during continuous positive airway pressure in neonates

Fischer HS, Roehr CC, Proquitté H, Schmalisch G. Influence of nose and mouth leaks on peripheral oxygen saturation during continuous positive airway pressure in neonates. *World J Pediatr.* 2013;9(4):318-322

The presence of leaks at the nasal interface or through the open mouth may have been one reason why nCPAP was less effective to avoid eMV in neonatal RCTs. In preterm infants with RDS, increasing levels of nCPAP (0, 2, 4, 6, and 8 cm H_2O) were shown to result in higher tidal volumes, higher end-expiratory lung volumes and better thoracoabdominal synchronization.[26] By contrast, nCPAP failure is often the consequence of a gradual clinical deterioration, which is heralded by increased CPAP- and oxygen requirements.[139] Hypothetically, the presence of leaks could have a role in this process, as they impair pressure transmission to the airways[116] and may therefore allow derecruitment of the lungs. To our knowledge, however, the impact of leaks on oxygenation and breathing pattern has never been investigated during neonatal CPAP.

To assess the influence of leaks on oxygenation and RR in the clinical setting, we analyzed monitoring data from a previous randomized crossover trial of 32 newborns on nasopharyngeal CPAP.[114] In this trial, peripheral oxygen saturation (SpO_2) and RR measurements were taken with and without occlusion of the contralateral nostril, and were recorded in one-minute intervals over a 10-minute period during each condition. Mouth position was documented as “open” or “closed.”

The study results showed no significant impact of nostril occlusion or mouth opening on SpO_2. However, in a subgroup analysis of 17 infants with a SpO_2 ≤93% during open nostril, active nostril occlusion resulted in a higher SpO_2 [median(range) 91(80-96)% versus 89.5(78.5-93)%, p=0.036]. In the whole study group, RR was slightly lower during nostril occlusion [median(range) 48(32-85) min^{-1} versus 50.5(26-82) min^{-1}, p=0.027].[140]

Fischer HS, Roehr CC, Proquitté H, Schmalisch G. *World J Pediatr.* 2013;9(4):318-322 https://doi.org/10.1007/s12519-013-0435-z

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Fischer HS, Roehr CC, Proquitté H, Schmalisch G. *World J Pediatr.* 2013;9(4):318-322 https://doi.org/10.1007/s12519-013-0435-z

2.3 Exploring the prevalence, clinical application and side effects of nasal high-frequency oscillatory ventilation in neonatal intensive care units

Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C. Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. *Eur J Pediatr.* 2015;174(4):465-471

Hypercapnic respiratory failure is another reason why neonates may fail nCPAP therapy. This may occur due to poor respiratory drive or due to respiratory fatigue of the infant. NHFOV is a promising mode of non-invasive ventilation that combines the application of a continuous distending pressure with high-frequency oscillations to facilitate CO_2 exhalation.[17,18] To date, however, there is little evidence to support its efficiency and safety.

To obtain information about the current clinical use and experience with nHFOV in neonates, we conducted a survey in five European countries (Austria, Switzerland, Germany, the Netherlands and Sweden). Clinical directors of NICUs who provide the highest level of care in their country were requested to provide data about their use of nHFOV. The 26-item questionnaire inquired about indications for nHFOV, equipment used, ventilator settings and side effects.

Altogether, 172/186 (92%) of all contacted neonatologists took part in the survey, and 30/172 (17%) of the participants affirmed the use of nHFOV. NICUs who used nHFOV differed substantially with regard to their nHFOV equipment, indications and settings. Interestingly, thick, almost solid secretions in 7/30 (23%) and upper airway obstruction due to secretions in 8/30 (27%) were reported as specific nHFOV side effects.[141]

These observations suggested that nHFOV reduces air humidity in the upper airways, and may lead to the desiccation of secretions. The particular factors that caused this problem, however, were not known and required further research.

Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C.
Eur J Pediatr. 2015;174(4):465-471
https://doi.org/10.1007/s00431-014-2419-y

Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C.
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Fischer HS, Bohlin K, Bührer C, Schmalisch G, Cremer M, Reiss I, Czernik C.
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https://doi.org/10.1007/s00431-014-2419-y

2.4 Influence of mouth opening on oropharyngeal humidification and temperature during neonatal continuous positive airway pressure

Fischer HS, Ullrich TL, Bührer C, Czernik C, Schmalisch G. Influence of mouth opening on oropharyngeal humidification and temperature in a bench model of neonatal continuous positive airway pressure. *Med Eng Phys.* 2017;40:87-94

This bench model was designed to investigate factors that could negatively impact oropharyngeal humidity and temperature during non-invasive respiratory support of neonates. Because the unilateral leak flow through an open mouth was hypothesized to be one cause of upper airway desiccation, we placed importance on the simulation of open and closed mouth conditions.

As shown in Fig. 1, an active lung model with adjustable RR was used to simulate infant breathing, and a modified rubber ball served as a model oropharynx. An interposed pass-over humidifier simulated the exhalation of heated and humidified air to the oropharynx. Oropharyngeal temperature and humidity were measured by a digital thermo-hygro sensor. An occludable opening in the model oropharynx allowed the simulation of mouth leaks.

In the first set of measurements, the model was tested during unsupported breathing. It was shown that near-physiological gas conditions could be obtained in the model oropharynx and mouth opening had no significant effect. In the second set of measurements, the influence of mouth opening was investigated during nCPAP using three different scenarios: 1) no conditioning in the CPAP circuit, 2) heating only, and 3) heated humidification. In all scenarios, mouth opening significantly reduced the mean absolute humidity (AH) in the model oropharynx ($p<0.001$, respectively), which fell to an AH of 3.0 ±0.3 g m^{-3} without conditioning. During heated humidification, however, temperature and AH remained within clinically acceptable limits, regardless of whether the mouth was closed (AH 42.6 ±0.9 g m^{-3} with an occluded model mouth versus 35.7 ±1.9 g m^{-3} with an open mouth, $p < 0.001$).[142]

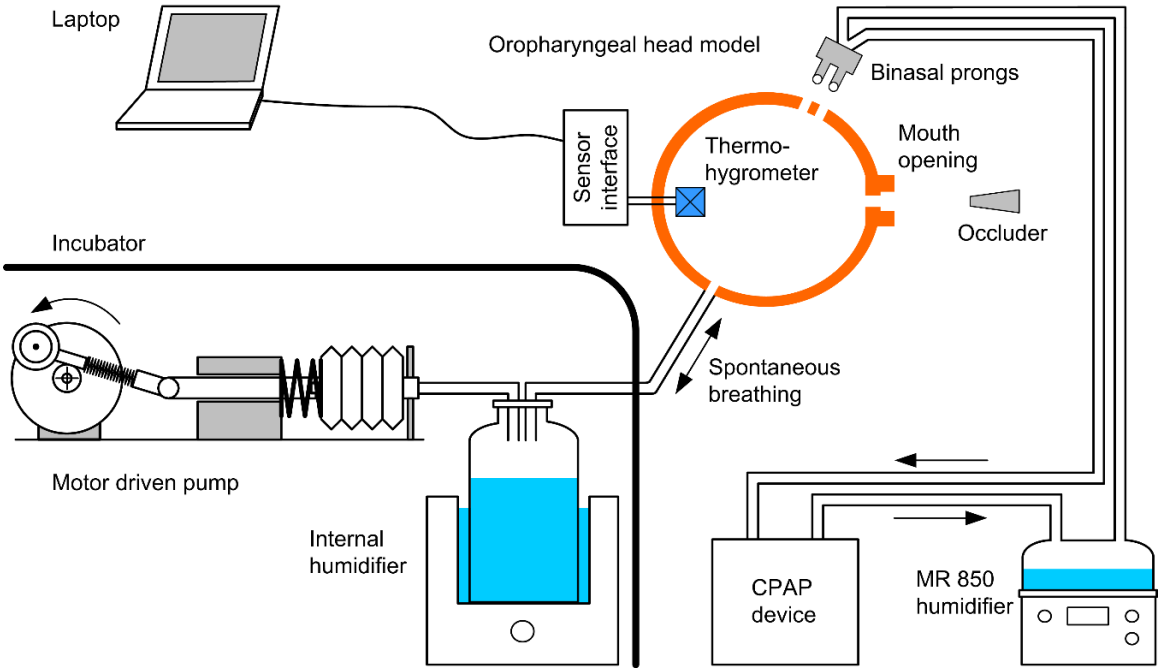

Fig. 1 Experimental set-up used to investigate the influence of mouth opening on temperature and humidity in the model oropharynx. The model mouth was occluded with a cone-shaped silicone stopper as needed. Binasal prongs and the CPAP circuit were used in the second series of experiments. (Fischer et al., *Med Eng Phys* 2017; open access article under the CC BY-NC-ND license)[142]

Fischer HS, Ullrich TL, Bührer C, Czernik C, Schmalisch G.
Med Eng Phys. 2017;40:87-94
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Med Eng Phys. 2017;40:87-94
https://doi.org/10.1016/j.medengphy.2016.12.005

2.5 Impact of nasal high-frequency oscillatory ventilation on oropharyngeal humidification and temperature

Ullrich TL, Czernik C, Bührer C, Schmalisch G, **Fischer HS**. Nasal high-frequency oscillatory ventilation impairs heated humidification: a neonatal bench study. *Pediatr Pulmonol.* 2017;52(11):1455-1460

The nHFOV survey indicated that upper airway obstruction due to highly viscous secretions is an adverse effect that occurred more frequently during nHFOV than during nCPAP (publication 2.3).[141] Hypothetically, this may be due to a direct impact of nHFOV on oropharyngeal gas conditioning. We therefore investigated the effects of the nHFOV pressure oscillations on oropharyngeal T and AH, using the bench model described in publication 2.4 (Fig 1).[142]

To differentiate the influence of different ventilatory settings, oropharyngeal temperature and humidity were measured at various nHFOV frequencies (7, 10, 13 Hz), amplitudes (10, 20, 30 cm H_2O), and inspiratory-to-expiratory ratios (I:E ratios) (25:75, 33:66, 50:50), and also during nCPAP. All experiments were conducted with an open model mouth.

The use of nHFOV led to a lower temperature and AH in the model oropharynx in comparison with nCPAP ($p<0.001$, respectively). During nHFOV, decreasing frequency and increasing amplitude both impacted negatively on temperature and AH ($p<0.001$, respectively). Mean temperature and AH decreased from a maximum during nCPAP (T 34.8±0.6°C, AH 39.3±1.3 $g \cdot m^{-3}$) to a minimum when nHFOV with a frequency of 7 Hz and an amplitude of 30 cm H_2O was used (T 32.4 ± 0.3°C, AH 34.7 ± 0.5 $g \cdot m^{-3}$). Increasing the I:E ratio also resulted in a reduction of oropharyngeal temperature and AH ($p = 0.03$).[143]

In summary, the bench data showed that nHFOV negatively impacted gas conditioning in the model oropharynx. In particular, intensified nHFOV settings with low frequencies, high amplitudes, and high I:E ratios may be associated with an increased risk of adverse effects due to upper airway desiccation in the clinical setting.

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Pediatr Pulmonol. 2017;52(11):1455-1460
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3. Discussion

The present habilitation thesis relied on different methodologies to investigate the efficacy and safety of non-invasive respiratory support in neonates. Specifically, it included a meta-analysis, a clinical study, a survey and two in vitro studies using a newly-devised mechanical bench model.

The meta-analysis explored the efficacy and safety of approaches aimed at avoiding eMV in the treatment of very premature infants with respiratory distress. It was shown that the use of non-invasive respiratory support strategies to avoid eMV reduced the incidence of death or BPD without increasing the risk of IVH.[138] At the time, this was the largest meta-analysis investigating non-invasive respiratory support as an alternative to earlier intubation and surfactant, and the first to also include RCTs of surfactant administration via a thin catheter during nCPAP.[73,74] Particular strengths of this meta-analysis were the strict adherence to Cochrane methodology in a predetermined study protocol,[137] and the use of previously unpublished stratified data for infants <30 weeks' GA. The latter allowed us to target those infants at the highest risk of BPD and IVH. The main limitation of our study was the restricted focus on only two outcomes (BPD and IVH). In spite of this, the meta-analysis supported the view that avoiding eMV by using nCPAP is beneficial and safe in preterm infants <30 weeks' GA, and represents a viable alternative to early intubation and surfactant therapy.

Since the completion of our meta-analysis, a considerable number of new RCTs and meta-analyses have been published that investigated specific strategies of non-invasive respiratory support in very preterm infants. A meta-analysis of four RCTs by Schmölzer et al., published immediately prior to ours, evaluated the effect of nCPAP compared with intubation in preterm infants born at <32 weeks' GA. They reported a similar reduction in death or BPD at 36 weeks' corrected GA, with a number needed to treat of 25, and found no differences in pneumothorax, severe IVH, and other adverse outcomes of prematurity.[144] Similarly, an updated Cochrane review found that prophylactic nCPAP after birth in comparison with eMV reduced both the need for surfactant and the incidence of death or BPD in preterm infants born at <32 weeks' GA.[145] Isayama et al. meta-analyzed RCTs that compared early INSURE with NCPAP in preterm infants of up to 35 weeks' corrected GA and detected no difference in seven main outcomes, including BPD.[146] More recently, surfactant application during nCPAP

has attracted particular attention, as these techniques appear to combine the benefits of surfactant with the benefits of a CPAP-only approach.[147] The idea of surfactant administration by using a thin catheter during spontaneous breathing was first described by Verder et al. in 1992.[148] Interestingly, this method of "less invasive surfactant administration" (LISA) was only developed further by Kribs et al. after the year 2000.[71] It has since been adopted by many European NICUs,[149,150] and was tested in a number of RCTs.[73,74,89,151] Notably, the NINSAPP multi-center RCT compared LISA versus conventional surfactant application during eMV in extremely preterm infants of <27 weeks' GA. Although LISA did not increase survival without BPD, LISA was associated with increased survival without major complications.[89] Apart from LISA, other methods of less invasive surfactant delivery are emerging.[147,152] Most importantly, Dargaville et al. devised a technique of surfactant application via orotracheal catheterization using a semi-rigid, narrow-bore vascular catheter. This method was termed "minimally invasive surfactant therapy" (MIST) and does not require the use of a Magill forceps.[72] To date, it has only been tested in cohort studies and a pilot RCT,[153-155] but in 2018, the first multi-center data of the "OPTIMIST-A" trial is awaited, which aims to assess the impact of MIST on survival without BPD in preterm infants of 25-28 weeks' GA.[156] For now, several conventional meta-analyses and a Bayesian random-effects network meta-analysis indicate that nCPAP in combination with LISA or MIST is currently the most efficient strategy of non-invasive respiratory support to reduce the combined outcome of death or BPD in preterm infants.[157-160]

With regard to IVH, our meta-analysis confirmed that non-invasive respiratory support is a safe approach in the primary treatment of preterm infants with RDS. It implies that concerns about hypercapnia with consequential IVH during nCPAP treatment are unsubstantiated if appropriate thresholds for "rescue" intubation and surfactant are set. This finding is in accordance with recent results of a multi-center RCT and a meta-analysis in mechanically-ventilated preterm infants, which showed that the incidence of severe IVH did not increase if higher than normal pCO_2 values of up to 65 mmHg were accepted on days one to three.[161,162]

While a lot of research activities were dedicated to the investigation of surfactant and specific non-invasive respiratory support strategies in very preterm infants, there is only limited knowledge about the significance of leaks during neonatal CPAP. In a clinical crossover study of experimental nostril occlusion in 32 neonates on

nasopharyngeal CPAP, we assessed the influence of nose leaks and spontaneous mouth opening on SpO_2 and RR. Nostril occlusion resulted in a marginal reduction of RR, but had no effect on SpO_2. Only in a subgroup of 17 infants with a SpO_2 ≤93% during open nostril, median SpO_2 increased from 89.5 to 91% during nostril occlusion. No effects of mouth opening could be shown.[140] To our knowledge, this was the first clinical study that investigated the impact of leaks on SpO_2 and RR during neonatal CPAP. It is reasonable to assume that the positive effect of nostril occlusion on SpO_2 was due to improved CPAP transmission,[116] as CPAP is known to stabilize functional residual capacity and oxygenation.[23,29] If leak reduction improves oxygenation during neonatal CPAP therapy, this finding might be clinically relevant, as intermittent hypoxemic episodes were associated with severe retinopathy of prematurity in infants of <28 weeks' gestation.[163] The present study results, however, need to be interpreted with caution. First, the effects on SpO_2 were only evident in a subgroup analysis, and the effect size was small. Second, the study only assessed short-term effects on two monitoring parameters, whereas the long-term outcomes of leak reduction remain unknown. Third, too few study patients opened and closed their mouths during the measurement period to assess the true impact of mouth leaks.

From a clinical point of view, nose leaks are nowadays easily minimized by the use of a closely-fitting binasal prong interface, whereas mouth leaks remain a significant problem. To date, it is unknown whether deliberate mouth occlusion would result in better long-term outcomes, and our study did not address this question. Interestingly, chin straps and pacifiers have recently been recommended to reduce mouth leaks and maintain airway pressure during nCPAP.[84] The efficacy and safety of these measures, however, remains to be proven. A recent crossover trial by Ahmadpour-Kacho investigated the introduction of a pacifier to elicit non-nutritive sucking in 25 preterm infants treated with nCPAP. The intervention resulted in a small but statistically significant increase of SpO_2 from 96.3 to 98.4%.[164] Overall, the limited data available suggests that measures to reduce leaks during neonatal CPAP may have small beneficial effects and warrant further clinical studies.

The use of nHFOV is another approach to enhance the beneficial effects of nCPAP. Due to the paucity of clinical data about nHFOV, we decided to conduct a survey in the tertiary NICUs of five European countries. Surprisingly, nHFOV was already being used by 30/172 (17%) of the responders. The substantial differences in nHFOV

equipment, indications and settings reported by the survey participants underlined the urgent need for clinical trials about nHFOV. Notably, for the first time, “thick secretions” and “upper airway obstruction due to secretions” were reported as specific nHFOV side effects that occurred more frequently during nHFOV than during nCPAP.[141] This was the very first survey dedicated to nHFOV, and the first study that inquired into its side effects. The results can be considered representative due to the 92% response rate and the detailed responses of all nHFOV users. The main limitation was the obvious fact that the survey data was merely based on individual experiences and preferences. As these may have been subjective or biased, the efficacy of nHFOV still needs to be proven. Another limitation was the restricted focus on European countries.

In the meantime, Mukerji et al. have conducted a survey of non-invasive respiratory support practices in Canada. With a response rate of 93%, a reported nHFOV use of 5/28 (18%) in tertiary NICUs and a wide variation of clinical practices, their results were similar to the European survey.[165] A number of clinical reports, a crossover trial and two pilot RCTs have since enhanced our knowledge about nHFOV’s clinical efficacy: Aktas et al. presented a small case series of nHFOV application via a new binasal cannula interface in extremely low birthweight infants. They successfully used nHFOV to avoid reintubation in three patients.[166] In the abstract of a cohort study published in Chinese language by Wang et al., they confirmed previous reports that nHFOV in very low birthweight infants was associated with a reduction of apneas, oxygen desaturations and pCO_2.[167] For the first time, De Luca et al. tested nHFOV in four older infants/toddlers of about one year old. They documented an effective pressure transmission by a face mask, but also observed a considerable dampening effect of the pressure oscillations between the ventilator and the mask.[168] Mukerji et al. reported a pilot RCT of nHFOV versus nBiPAP in 39 infants with a birthweight of <1250 g who failed nCPAP therapy. They could not show statistically significant effects, but there was a trend towards less treatment failure in the nHFOV group (38% versus 65%, p=0.09).[169] In a clinical crossover trial, Klotz et al. compared nHFOV with nCPAP in 26 preterm infants <32 weeks’ GA following LISA or extubation. They found that the pCO_2 after four hours of nHFOV compared with four hours of nCPAP was not different.[170] In a pilot RCT of nHFOV versus nCPAP in preterm infants with moderate to severe RDS, Zhu et al. showed a reduced need for eMV in the nHFOV group (24% versus 56%, p<0.01).[171]

In spite of the aforementioned reports, the overall data about the efficacy of nHFOV is still limited. The available evidence from recent trials suggests some clinical benefits for nHFOV, but also indicates that pilot studies from single centers will be insufficient for examining long-term outcomes. Future RCTs should therefore employ a multi-center approach, focusing on those infants with a high risk of BPD and other complications of prematurity. In particular, it might be promising to conduct a multi-center RCT to investigate nHFOV in the primary treatment of more severe RDS in preterm infants of 24-28 weeks' GA.[172]

With regard to adverse effects, only the cohort study by Wang et al. reported nasal septum injury in 4/36 (11%) of all nHFOV cases,[167] but this could have happened likewise during nCPAP. Overall, it is encouraging that side effects seemed to be extremely rare in all clinical reports of nHFOV. The aforementioned studies, however, were neither designed nor powered to detect specific adverse events. Importantly, further research was needed to clarify the apparent nHFOV-related side effects of upper airway obstruction due to highly viscous secretions reported in the European survey. As previously mentioned, similar symptoms of crusting secretions and tube blockage were observed during nasopharyngeal CPAP prior to the era of heated humidification.[130] We therefore hypothesized that nHFOV negatively impacts heated humidification and thus allows desiccation of the upper airways. Because temperature and humidity measurements in the upper airways would be extremely intricate in neonates, we decided to design a neonatal bench model suitable for simulating oropharyngeal gas conditions during non-invasive respiratory support.

The neonatal bench model was first devised to investigate the impact of mouth opening on oropharyngeal temperature and AH during nCPAP. Initial experiments during unsupported breathing confirmed that the model was suitable for simulating stable and near-physiological temperature and humidity in the model oropharynx. During nCPAP, the mouth leak had a considerable negative impact on temperature and AH during three different scenarios of gas conditioning. With heating only or without gas conditioning, the AH reductions were extreme and resulted in AH values of $<4.5\ g \cdot m^{-3}$, respectively. Even during heated humidification, mouth opening considerably impaired oropharyngeal gas conditions, with a decrease in AH from $42.6\ g \cdot m^{-3}$ to $35.7\ g \cdot m^{-3}$.[142] To our knowledge, this was the first study to specifically investigate the impact of mouth leaks on upper airway temperature and AH during neonatal CPAP. The new bench

model combined several well-established features, such as a thermo-stable incubator environment,[3,173] a miniaturized thermo-hygro sensor[133] and the intentional simulation of a mouth leak.[41] Furthermore, an extra heated humidifier was interposed between the active model lung and the oropharynx to simulate the recurrent expiration of heated and humidified air (Fig. 1). In spite of these efforts to create realistic gas conditions in the model oropharynx, the study results need to be interpreted cautiously. It is obvious that the mechanical bench model greatly simplified the pharyngeal anatomy, and was not designed to simulate the complex physiology of heat and moisture exchange in the upper airways.[125,126,174] Moreover, the accuracy of the capacitive humidity sensor may have been limited during high humidity levels.[175] On the other hand, the bench study yielded reproducible results that were entirely plausible. Mouth leaks are recognized contributors to oropharyngeal gas conditions during non-invasive respiratory support,[121] and the findings of reduced oropharyngeal temperature and AH during mouth leaks are consistent with clinical studies in adults.[119,129]

In the future, the present bench model could assist in shedding light on the factors that influence oropharyngeal gas conditions during non-invasive respiratory support in neonates. In particular, the model would be suited for investigating the impact of mouth leaks during different non-invasive respiratory support modes and to assess the impact of different ventilatory settings. It could also be applied to compare different equipment, such as various ventilatory devices, interfaces or heated humidifiers. Recently, we used the model to conduct a bench study of neonatal HFNC. During occluded mouth, oropharyngeal temperature and AH increased with increasing flow. In the presence of an open mouth, however, temperature and AH plateaued if flows of >6 $L \cdot min^{-1}$ were applied.[176] To answer the original question of whether nHFOV influences heated humidification, another bench study was performed.

The bench study of nHFOV aimed to investigate the impact of the nasal high-frequency oscillations on oropharyngeal temperature and AH. For this purpose, measurements were conducted during nHFOV using different ventilatory parameters, and during nCPAP. As the previous study during nCPAP had shown that the open mouth condition represents the greatest challenge for heated humidification, all measurements were taken during open mouth. In comparison with nCPAP, nHFOV impaired the oropharyngeal gas conditions, with a resultant decrease in AH from a maximum of 39.3 $g \cdot m^{-3}$ to a minimum of 34.7 $g \cdot m^{-3}$. Specifically, lower nHFOV frequencies, higher

amplitudes, and higher I:E ratios reduced temperature and AH in the model oropharynx.[143] As these are results of a bench study, they should ideally be confirmed in a clinical trial. In particular, it is difficult to say which decreases of temperature and AH would be clinically relevant to avoid side effects during nHFOV. In spite of this, the present study clearly showed that nHFOV negatively impacted oropharyngeal gas conditions, and thus indicated that previously reported adverse events of highly viscous secretions and consecutive upper airway obstruction can be related directly with the use of nHFOV.

Interestingly, the decreased efficiency of heated humidification was associated with ventilatory settings of nHFOV that are known to enhance nHFOV tidal volume and CO_2 elimination.[54,177] Although the exact mechanisms of heat and moisture exchange during nHFOV still need to be elucidated, these findings are of immediate clinical relevance. Clinicians should be aware that intensifying ventilatory settings of nHFOV puts their patients at increased risk of upper airway desiccation and potentially dangerous airway obstruction. Hypothetically, even partial airway obstruction could increase airway resistance and may represent an under-recognized reason for nHFOV failure. Preemptive measures to avoid these problems are needed but have never been explored. According to our previous study about the impact of mouth leaks during nCPAP, leak reduction by a chin strap or a pacifier could theoretically be an option for improving oropharyngeal gas conditioning.[142] However, a recent bench study by Klotz et al. showed that moderate leakage is necessary to achieve the most effective CO_2 elimination during nHFOV.[53] Future bench studies and clinical trials should therefore be dedicated to investigating strategies to optimize heated humidification during neonatal nHFOV.

4. Summary

Non-invasive respiratory support is nowadays a mainstay of treatment in neonates with respiratory failure. Established treatment options such as nCPAP have been refined over the years. Innovative strategies of non-invasive respiratory support are evolving, but quite often there is a paucity of evidence to support their use. The present habilitation thesis applied different methodologies to address specific research questions relating to the efficacy and safety of these new approaches.

In a meta-analysis of RCTs, we showed that non-invasive respiratory support strategies to avoid eMV reduced the incidence of death or BPD without increasing IVH in preterm infants of <30 weeks' GA. In a clinical crossover study, we investigated the impact of experimental leak reduction in 32 neonates on nasopharyngeal CPAP but detected only minor beneficial effects on oxygenation. In an international survey, we gained insights about the current clinical use of nHFOV in tertiary NICUs. We encountered a great variety of clinical practices and identified upper airway obstruction due to highly viscous secretions as a specific adverse effect of nHFOV. In a dedicated neonatal bench model, we further investigated the determinants of oropharyngeal gas conditions during non-invasive respiratory support. A bench study during nCPAP showed that mouth opening reduced oropharyngeal temperature and AH, even during heated humidification. A second bench study showed that nHFOV additionally impaired oropharyngeal gas conditions and that the magnitude of this effect depended on the ventilatory settings of nHFOV.

From a clinical point of view, the meta-analysis results approved the use of non-invasive respiratory support in the primary treatment of preterm infants with RDS, but the large number needed to treat to prevent one case of death or BPD clarified that a comprehensive approach of different measures is required to effectively reduce BPD in very preterm infants. The nHFOV survey provided information about the clinical experiences with this novel mode, but as evidence about its efficacy and safety is still limited, its clinical application should be confined to individual patients and RCTs. Importantly, the survey and the bench studies suggest that nHFOV patients are at risk of upper airway obstruction due to thick secretions, especially when intensified ventilatory settings (low nHFOV frequency, high amplitude, high I:E ratio) are applied in the presence of mouth leaks.

According to the results of this thesis, the following four areas will require additional research:

1) Innovative ways of surfactant administration should be advanced as a means to avoid eMV in preterm infants, as early surfactant administration during nCPAP currently appears to be the most effective respiratory intervention to avoid BPD.

2) Adjunctive measures to improve pressure transmission during nCPAP, such as chin straps or pacifiers, should be investigated in clinical trials.

3) Bench studies are warranted to optimize heated humidification during nHFOV.

4) Appropriately powered multi-center RCTs will be needed to investigate the efficacy and safety of nHFOV, and should focus on preterm infants at high risk of BPD.

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Statutory declaration

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