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Non-invasive respiratory support for preterm neonates requiring resuscitation

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“Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.”

Albert Einstein

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List of abbreviations

AHA = American Heart Association

BPD = bronchopulmonary dysplasia

COIN = CPAP or Intubation of Neonates (COIN)

CPAP = continuous positive airway pressure

DR = delivery room

ERC = European Resuscitation Council

ET = endotracheal tube

FIB = flow-inflating bag

FiO_2 = fraction of inspired oxygen

FRC = functional residual capacity

GA = gestational age

ILCOR = International Liaison Committee on Resuscitation

INSURE = intubate, surfactant, extubation

MV = mechanical ventilation

NICU = neonatal intensive care unit

O_2 = Oxygen

OR = odds ratio

PEEP = positive end expiratory pressure

PIP = peak inspiratory pressure

PPV = positive pressure ventilation

RCT = randomized controlled trial

RDS = respiratory distress syndrome

SIB = self-inflating bag

SpO_2 = peripheral oxygen saturation

SUPPORT = Surfactant Positive Pressure and Oxygen Randomized Trial

T-piece = T-piece resuscitation device

VLBW = very low birth weight (< 1500 g birth weight)

V_t = tidal volume

1. Introduction

1.1. Perinatal transition: From breathing liquid to air

The fetus breathes. Pulmonary epithelial cells secrete fluid, which the fetus moves with breath like motions from the lungs to the amniotic cavity[1,2]. The presence of intra-pulmonary fluid is an essential physiologic stimulus for normal fetal lung development[3,4,5,6], and the breathing movements are necessary to condition the pulmonary tissue and the respiratory musculature for their functions after birth[7,8,9,10].

1.1.1. Pulmonary aeration - The significance of establishing the functional residual capacity and tidal volume at birth

Once born, the infant needs to rapidly clear its airways. Pulmonary expansion is achieved by creating sub-atmospheric inspiratory pressures during the first diaphragmatic contractions[11]. The amount of air breathed in and out of the lungs defines the tidal volume (V_t). With each new breath, more air enters than leaves the lungs, thus creating the functional residual capacity (FRC), which describes the amount of air remaining in the lung at the end of passive expiration[12,13]. Luminal sodium channels create an osmotic gradient by which alveolar fluid follows into the interstitial space[14]. A steady V_t and an adequate FRC are mandatory for efficient gas exchange, as oxygenation is proportional to the open alveolar surface area[15,16]. Term infants generate an FRC of approx. 30ml/kg and a V_t of approx. 5ml/kg within minutes of birth[11,17]. However, the whole physiological process of pulmonary aeration takes several hours to complete[12,18]. Failure to establish lung clearance results in a functional reduction of alveolar surface area, insufficient gas exchange, and respiratory distress[19,20,21].

The preterm infant's respiratory system differs from that of the term infant: the chest wall and larger airways are cartilaginous, providing less resistance against atmospheric pressure, the pulmonary architecture remains at an immature, saccular developmental stage, luminal sodium channels are under expressed, and the surfactant system is not fully functional[18,22,23,24,25]. Their respiratory drive is poorly controlled by the immature respiratory centre, which is less sensitive to carbon dioxide and provides a less coordinated respiratory pattern[26,27]. These factors predispose preterm infants to insufficient generation of V_t and FRC (table 1)[28,29]. Thus, premature birth is associated with an increased risk for respiratory distress[30,31].

Table 1: Morphological and functional disadvantages of the premature infant's airways

Cause	Consequence	Signs
Morphological factors		
developmental immaturity (saccular stage) decreased blood-air surface area with insufficient vascularization immature (saccular) vascularization of alveolar structure	- decreased alveolar surface area for gas exchange (pulmonary side) - decreased alveolar vascular bed for gas exchange (vascular side / blood saturation) - increased diffusion distance	Hypoxia
reduced number of lymphatic vessels	decreased fluid clearance	Crepitations
immature, saccular aleveoli decreased numbers of elastic fibres in alveolar tissue	decreased tolerance for alveolar stretch	alveolar damage, hyaline membranes
cartilaginous rib cage	reduced resistance against atmospheric pressure and pulmonary recoil	recessions, atelectasis
small airways	increased resistance	laboured breathing
Biochemical factors		
small and insufficient alveolar surfactant pool and slow surfactant metabolism	alveolar collapse	respiratory distress, hypoxia
imbalance of pro- and anti-inflammatory enzymes decreased intracellular anti-oxidative capacity	pulmonary inflammation, destruction of alveolar and pulmonary structures	hyaline membranes
Functional factors		
delayed absorption of fetal lung fluid / lung clearance	delayed FRC / V_t establishment	transient and persistent tachypnae
immature respiratory muscles	Apnoea	Apnoea
high dead space / FRC ratio	persisting dead space ventilation	hypoxia, hypercarbia
extra-cardiac shunting (PDA)	pulmonary overflow, persisting pulmonary circulation	hypoxia, hypercarbia

Adapted from Wauer R. Surfactant in der Neonatologie. Ligatur Verlag Stuttgart 2010, page 45 (Reference 29).

1.2. Supporting the preterm neonate with respiratory distress

1.2.1. The concept of postnatal iatrogenic lung injury

Despite many improvements in perinatal medicine, respiratory distress remains a common problem of preterm infants[32,33,]. Respiratory distress together with surfactant deficiency is defined as the respiratory distress syndrome (RDS)[34]. More than 50% of preterm infants with very low birth weight (VLBW, birth weight < 1500g) suffer from RDS, and the risk increases to almost 90% for preterm infants born below 750g[35,36,37]. Until recently, endotracheal intubation and mechanical ventilation (MV) was the standard treatment for RDS. It is recognised that MV is an independent risk factor for bronchopulmonary dysplasia (BPD), a chronic pulmonary illness which affects approx. 20% of VLBW infants[38,39,40,41]. The delicate lung tissue of the preterm infant is particularly vulnerable to baro-, volu-, and atelectotraumata, which are all too easily inflicted by medical professionals and are known to lead to long-term respiratory complications[42,43,44,45,46,47,48,49]. Björklund and colleagues were among the first to describe the noxious effects of excessive peak inspiratory pressures (PIP) and high V_t on the lung tissue as a consequence of vigorous neonatal resuscitation[42,43]. Dreyfuss and co-workers have illustrated the harmful impact of a high volume stretch on the neonatal lung through excessively PIP and high positive end expiratory pressure (PEEP) during manual ventilation[44]. Tidal volumes above 8 ml/kg and PIPs in excess of 25 cmH_2O are believed to be particularly noxious to preterm human lungs, however until today, the dynamic process of lung aeration is not appropriately accounted for during manual positive pressure ventilation (PPV)[22,50,51,52].

1.2.2. Lung protective management from birth

The incidence of BPD continues to rise and the pathophysiology of BPD has changed with the increasing number of VLBW infants that now survive the neonatal period[41,53]. Intratracheal surfactant-replacement therapy has helped to markedly reduce neonatal mortality, but not BPD[23,54]. Presently, BPD is thought to be due to surfactant deficiency and secondary to structural pulmonary immaturity, which promotes a maldevelopment sequence that results in reduced pulmonary alveolarisation[40,41,48,54,55].

The growing awareness of the mechanisms of early neonatal lung injury has led to calls for a lung protective management from birth[48,56,57]. As reviewed by the author in a recent synopsis, this concept includes improved prenatal care, maternal antenatal antibiotic and corticosteroid treatment, improved postnatal care including the avoidance of excessive pressure or volume ventilation, the use of non-invasive respiratory support, and permissive hypercarbia[58,59,60,61,62,63].

1.2.3. "To tube or not to tube": Non-invasive respiratory support or intubation and mechanical ventilation for premature neonates

Avery was the first to identify that the avoidance of intubation and MV by an early and consequent application of nasal continuous positive airway pressure (CPAP) was protective of BPD[64]. Today, a growing body of evidence is evolving, which supports a minimal-invasive approach to RDS in the delivery room (DR)[65,66,67,68,69,70,71]. These very recent clinical trials have clearly shown that in breathing VLBW infants early CPAP is effective and results in more favourable pulmonary outcomes with no difference in extra-pulmonary outcomes, compared to routine intubation and MV.

1.2.4. Neonatal resuscitation guidelines and current knowledge gaps

Preterm birth is a major risk factor for neonatal death[72]. Sufficient airway management is the cornerstone of successful neonatal resuscitation[73]. The American Academy of Pediatrics, the international liaison committee on resuscitation (ILCOR) and the European Resuscitation Council (ERC) advise on the techniques of, and on the equipment for neonatal resuscitation[74,75,76]. Until recently, these guidelines favoured intubation of preterm infants with signs of respiratory distress over non-invasive methods of resuscitation, and self-inflating bags (SIBs) were advised as primary tools for delivering manual ventilation[73,76]. Following the 2005 guidelines, the ILCOR panel summarised the most significant knowledge gaps and research priorities regarding neonatal resuscitation: i) "the optimal ventilatory strategy for neonatal resuscitation in the delivery room", ii) "airway pressures, inspiratory times, devices, timing, and volumes in relation to gestational age", and iii) "options for providing feedback to rescuers to ensure correct ventilation rates and tidal volumes" were considered top research priorities[77].

In accordance to ILCOR, the SIB is still the most commonly used device for manual ventilation of neonates[78,79]. SIBs are predominantly handled without pressure manometers or other appropriate pressure control[80,81]. In 2001, Finer and colleagues published on inaccurately high and very variable PIPs provided by SIBs during neonatal ventilation[82]. In 2002, a novel device for providing manual PPV was introduced in Europe: The Neopuff® (Fisher & Paykel Healthcare, Auckland, New Zealand). This flow dependent device permits control over PIP and PEEP during manual ventilation. Due to its characteristic mask/ or tube interface, it is also referred to as a T-piece resuscitator or T-piece device. Alarmed by the studies from Prof. Finer's group[82,83], we speculated that T-piece devices could be promising alternatives to SIBs, and might successfully be integrated into the concept of lung protective management of neonates from birth.

1.3. Aims of the thesis

Aiming to understand variables that influence the provision of PIP, PEEP and V_t during neonatal resuscitation, and the clinical consequences of a less invasive concept of respiratory support, we sought to investigate the following questions:

1) Are there device specific and operator specific characteristics that influence the delivery of PIP and V_t in the circumstances of simulated neonatal resuscitation?
2) What is the impact of an operator's individual resuscitation training on the delivery of PPV?
3) Are there device specific properties that influence the delivery of PEEP during simulated neonatal resuscitation?
4) Are there measureable differences in pulmonary outcomes between VLBW preterm infants treated with non-invasive respiratory support (CPAP) or intubation and MV?
5) Whether the practice of neonatal resuscitation in German, Austrian and Swiss NICUs was in line with current international recommendations, with a particular focus on the devices used for respiratory support of VLBW preterm infants?

2. Results

2.1. Investigating the provision of tidal volume and peak inspiratory pressure during respiratory support of very low birth weight neonates

Roehr CC, Kelm M, Fischer HS, Bührer C, Schmalisch G, Proquitté H. Manual ventilation devices in neonatal resuscitation: tidal volume and positive pressure-provision. Resuscitation. 2010; 81: 202-5.

To investigate our first question regarding the device and operator specific characteristics influences on manual PPV provision, we investigated 120 medical professionals (doctors, nurses and midwives), using a standard scenario and experimental set up. Briefly, an intubated manikin resembling a 1 kg neonate, which had been prepared for manual ventilation was ventilated by the participants by using either a SIB or a T-piece resuscitator. We investigated the adherence to a given set of respiratory parameters and measured PIP, PEEP, and V_t by using a respiratory monitor (RFM). We studied the inter subject variability of PIP, PEEP and V_t provision, and compared the participants of our study as far as their ventilation performance with both devices was concerned.

2.2. Comparison of operator skills and use of equipment on tidal volume and peak inspiratory pressure provision during simulated neonatal resuscitation

Roehr CC, Kelm M, Proquitté H, Schmalisch G. Equipment and operator training denote manual ventilation performance in neonatal resuscitation. Am J Perinatol. 2010; 27: 753-8.

The first study showed that when handling SIBs, mere “hands on” experience had no significant influence on the provided PIP, PEEP and V_t. In the following study we speculated that not clinical experience per se, but rather the quality of professional training would influence pressure and volume control. Therefore, we set out to investigate the operator’s specific ventilation skills. Skills are defined as the combination of practical experience in neonatal resuscitation, plus formal teaching in the principles of lung protective manual ventilation of preterm infants, as offered in various courses on neonatal resuscitation[84]. Our hypothesis was that the more specific the training, the less often would excessive PIPs and V_t occur during manual ventilation. Hence, we assessed the provision of PIP and V_t in accordance to skill level, and by the ventilation device used. We could show that when using SIBs, operator training significantly affected provision of PIP ($p<0.001$), and V_t ($p<0.001$). Using a T-piece, PIP and V_t provision was independent of operator training ($p<0.55$ and $p<0.66$, respectively). Previous ventilation experience with T-piece devices correlated significantly with lower PIP and lower V_t provision ($p<0.001$ for PIP and V_t). Operator training level and device-specific experience had a significant impact on PIP and V_t provision when using SI-bags for manual ventilation. For operators with no specific training in manual ventilation, use of T-piece devices is advised to control for excessive PIP and VT application.

2.3. Critical observations on the reliability of commonly used ventilation equipment

Kelm M, Proquitté H, Schmalisch G, **Roehr CC**. Reliability of two common PEEP-generating devices used in neonatal resuscitation.
Klin Padiatr. 2009; 221: 415-8.

The use of PEEP during neonatal resuscitation is advised in the 2005 and 2010 ILCOR and ERC guidelines[76,77,85,86,87]. A PEEP of 4-8 cmH_2O is thought to be adequate to stabilize the airways and is said to improve both the FRC and lung compliance[59,60,88,89] In our studies on ventilation performance of the afore mentioned groups of participants, we observed differences in the delivered PEEP when using standard PEEP valves. It appeared that regular Ambu® 10-PEEP valves, as used in daily routine on the neonatal intensive care unit (NICU), produced a highly variable PEEP. In the following study, we systematically studied a SIB with various Ambu® 10-PEEP valves that were taken from daily ward routine, and T-piece resuscitators (Neopuff®) regarding their reliability of PEEP provision.

2.4. Investigating the effect of early non-invasive respiratory support in very low birth weight neonates on pulmonary function at term

Roehr CC, Proquitté H, Hammer H, Wauer RR, Morley CJ, Schmalisch G. Positive effects of early continuous positive airway pressure on pulmonary function in extremely premature infants: results of a subgroup analysis of the COIN trial. Arch Dis Child Fetal Neonatal Ed. 2010.

In a comprehensive review, Davis et al. recently pointed out that the avoidance of MV through means of non-invasive respiratory support, either with or without surfactant administration, may be the most effective way to reduce the risk of chronic lung disease[61]. Regarding the early use of CPAP, the first large scale randomized controlled trial (RCT) to compare early CPAP to early MV as initial mode of respiratory support in extremely premature infants (25-28+6 weeks) was the so called COIN trial (CPAP or Intubation for Neonates)[68]. The trial showed that early use of CPAP was associated with less need for mechanical ventilation, fewer doses of surfactant, shorter duration of ventilation, less need for oxygen at day 28 of life, and no difference in extra-pulmonary outcomes between the two groups[68].

The Department of Neonatology at the Charité Berlin contributed to the COIN study. Owing to the concept of reduced local and systemic inflammatory response through the avoidance of MV, we assumed that use of early CPAP would reduce pulmonary injury[47,90,91,92]. Following this, we hypothesized that less lung damage would lead to a reduced need for and a lower intensity of MV. The effect of this should result in improved pulmonary function at term compared to infants who were initially managed with MV. We compared the lung function of VLBW infants treated according the COIN protocol.

2.5. Current management of very low birth weight neonates in the delivery room

Roehr CC, Gröbe S, Rüdiger M, Hummler H, Nelle M, Proquitté H, Hammer H, Schmalisch G. Delivery room management of very low birth weight infants in Germany, Austria and Switzerland - a comparison of protocols. Eur J Med Res. 2010; 15: 493-503.

The above investigations were carried out between 2003 and 2009. The then up-to-date advice on how to proceed with neonatal airway management during resuscitation was formulated by the ILCOR and the ERC[75,76]. But, despite efforts to standardize DR management of VLBW preterm infants, surveys from Australia, the USA, Italy and Spain had shown wide inter-institutional variations in DR management of VLBW preterm infants, as well as significant discrepancies from the recommendations given in the ILCOR/ ERC guidelines[78,79,80,93]. To characterise the practice of DR management in Germany, Austria and Switzerland, we surveyed NICUs from these countries with regards to their protocols and equipment used for the DR management of preterm infants, and compared them with the above guidelines.

3. Discussion

In our studies, we considered three particular aspects of non-invasive airway management during the postnatal stabilization of VLBW infants: i) bench studies of equipment and operator specific characteristics of manual positive pressure provision, ii) clinical outcomes of VLBW infants randomly assigned to different strategies of respiratory support, and iii) epidemiological data on the practice of neonatal resuscitation and adherence to international resuscitation guidelines.

With respect to the bench studies, our results were in keeping with those of other investigators who have recently published on the reliability of manual ventilation devices[94,95,96,97,98]. However, our investigations are distinguished by their particular focus on V_t delivery, the comparison of operator and device specific characteristics, as well as of the effect of training. Concerning our results of PIP, PEEP and V_t provision by various ventilation devices and operators, we could show that even in the presence of an intact pressure relief valve, even skilled operators would regularly provide PIPs in excess of 40 cmH_2O and high V_ts, thus potentially inflicting severe baro- and volutrauma. Our studies, together with those of other investigators have helped to sharpen the awareness towards potential dangers, which arise during uncontrolled manual neonatal ventilation, particularly when using the SIB. T-piece resuscitators protect the lungs of preterm infants from the application of uncontrolled high PIPs and V_ts. We suggest that uninstructed medical personnel should not handle SIBs, but rather resort to handling pressure-limited devices, like the T-piece resuscitator. However noteworthy, Hawkes C et al. and Finer N et al. have recently shown that these devices may also not be entirely safe. For instance, erroneously high incoming flow to the Neopuff® (>15 l/min) resulted in excessively high PEEP or PIPs[99,100]. Likewise, incorrectly assembled equipment may also hamper PIP/ PEEP provision with the T-piece devices, as well as with SIBs[101]. Further, T-piece devices are so far dependent on constant flow of medical air, which greatly impedes their use in the ambulant setting or in low resource areas[102]. Additional findings of our work, like the inaccuracy of PEEP provision by our cot side PEEP-valves, have sparked off discussions and further work in this field[103,104]. In summary, specific training and careful instructions are mandatory for any equipment that is applied to VLBW infants. The most recent 2010 ILCOR and ERC guidelines now recognise T-piece resuscitators as equally suitable for neonatal resuscitation as the SIBs[86,87]. Further, the ILCOR guidelines contain a note of caution regarding the use of PEEP-valves, and they are now hopefully being used with greater caution[86].

Notwithstanding, our bench studies suffer from several limitations, and it will be a matter of further study to investigate whether our results can be directly applied to the clinical setting: Firstly, we worked with a neonatal manikin in a laboratory setting. The artificial lungs and manikin were carefully designed to simulate a living infant, however, they cannot simulate the dynamic changes in lung compliance that can be observed during neonatal resuscitation. It needs to be studied whether subjectively felt changes in lung compliance do actually influence the operators' ventilation performance. Kattwinkel and co-workers recently reported on the successful use of a dynamic lung model for training controlled PIP provision[105]. Secondly, our manikin we have used was free of leak. To have a leak free model is important when measuring respiratory parameters, which are easily affected by small changes in gas volume. Other groups have recently looked into the extent of leak in neonatal ventilation. Wood and colleagues have shown that during simulated manual ventilation leak around face-masks was above 50%, irrespective of the operator's experience[106,107]. A leak of such magnitude would have made most of our recordings impossible to analyse. The aim of the above studies was not to investigate the effect of leak size during manual ventilation, but this has been only recently been undertaken by our group (Hartung J et al. 2011, under review). Thirdly, although we completed three independent measurement cycles to check the reliability of the equipment and to control for the repeatability of the results, this may not fully exclude the possibility of measurement errors. Lastly, the data were analysed together with an independent statistician who was not involved in the experiments. This does, however, not preclude from errors in the interpretation of our results.

Despite the limitations of our laboratory studies, and that of other investigators in the field of simulated neonatal resuscitation, a marked change can be observed by the latest 2010 ILCOR and ERC guidelines: T-piece devices are now regarded as equivalent alternatives to SIBs[86,87,108]. As an outlook, we speculate that the use of T-piece devices will surpass that of SIBs. Future developments of T-piece devices should focus on making them independent of stationary compressed gas, and include means to quantify V_t [109,110,111]. The use of modern monitoring equipment has greatly improved neonatal management[112,113,114,115]. Coming studies will provide evidence to persuade caretaker and policy makers towards the wide spread use of RFMs during neonatal resuscitation and training (Kelm M et al. 2011, under review).

Regarding our clinical investigations, we managed to report on medium term pulmonary outcomes of VLBW preterm infants that were allocated to different respiratory support strategies from birth. Our investigations were performed in a subgroup of the COIN trial, the by then largest RCT comparing intubation and MV to CPAP from birth in VLBW infants[68]. Few other investigators have studied preterm infant's lung function at term[117,118,120]. Investigating a cohort of non-intubated premature infants by lung function tests (LFTs) three weeks after birth and then at term, Hoo and co-workers could show that airway function varied considerably during the first year of life[118]. Thomas et al. compared LFTs from VLBW infants that were either supported by conventional MV or high-frequency oscillatory ventilation. They found no significant difference with respect to pulmonary outcomes and lung function between the two groups[117]. Friedrich et al. studied 62 preterm infants who had only mild respiratory support. They found prematurity to be independently associated with reduced lung function at one month of age. Male sex, lower gestational age, and weight were identified as predictors for reduced LFTs[116].

To the best of our knowledge, our study was the first to demonstrate that a non-invasive approach to respiratory support of VLBW neonates in the DR resulted in improved LFTs at or near term[120]. The superiority of a lung protective concept with reduced pulmonary trauma, less inflammation and hence fewer fibrous remodelling is supported by the improved pulmonary compliance and exemplified in the significantly higher compliance and lower work of breathing and respiratory rate of the VLBW infants treated with non-invasive respiratory support[42-52,56,57,120]. According to Gappa et al., proof of concept on the favourable impact of one intervention on the developing lung cannot be made on the basis of a single improved LFT parameter[121]. Accordingly, we saw improvements in the measures of respiratory mechanics (respiratory rate and compliance, work of breathing) and also airway function, as shown by a reduced need for oxygen at 28 days of life[120]. Thus, although only a relatively small group of 39 patients from the total COIN population of 610 infants were studied, our analysis of the trial's lung function data was internationally recognised as a first step towards proving the benefits of non-invasive respiratory support on lung function at term. Appreciatively, for this study the 2011 clinical fellow's research prize of the Society of Paediatric Research was awarded to our group. As a future direction the individuals from this study need to be followed up in order to characterise their following clinical morbidity and regarding the differences between the groups. Further large scale RCTs of long-term pulmonary and extra-pulmonary outcome of preterm birth in the light of non-invasive respiratory support should be conducted. For instance, follow-up data of the respiratory outcome from the recently completed SUPPORT trial is expected to be available in 2014 (Prof. N. Finer, personal communication).

In summary, we believe that by the early avoidance of baro-, volu- and atelecto-trauma, BPD rates can be significantly reduced[122]. Bearing in mind that BPD has a devastating effect on a child's global development, including increased respiratory morbidity, poor neurodevelopmental outcome and repeated hospitalisation as an additional social and financial burden on both family and healthcare system, all means to avoid this disease should be pursued[41,123,124].

As for the epidemiological study, our investigation was performed in 2008, which lay in the interim of the 2005 and 2010 ILCOR and ERC statements. At the time of survey, several fundamental aspects of neonatal resuscitation (invasive vs. non-invasive respiratory support, oxygen supplementation, oro-tracheal suctioning, PPV provision, etc.) were questioned and tested by many groups of investigators (Kamlin et al. 2008, Dawson et al. 2009, O'Donnell et al. 2003, Te Pas et al. 2007, Hascoet et al. 2008, Wang et al. 2008, to name but a few)[112,113,125,126,127]. We were therefore particularly impressed to find that most German NICUs had already applied the concept of non-invasive positive pressure respiratory support as their primary support strategy for breathing VLBW preterm infants. This implies that the majority of the heads of German, Austrian and Swiss NICUs followed these discussions and were ready to integrate the most recent evidence from RCT into daily practice, albeit without uniform protocols.

Despite past and present efforts to increased DR research, many areas of neonatal respiratory support still warrant urgent investigation. For instance, and in line with other authors, we have provided data to prove that the concept of the so-called "educated hand" does not hold against objective testing. Our findings show that despite clinical experience, even the most experienced clinicians have provided excessive PIP and V_t during simulated neonatal resuscitation[82,83,128,129]. We performed our studies with the help of an RFM. Preliminary data on the use of RFMs during resuscitation training suggests that such devices in combination with SIBs will allow closer adherence to targeted pressures and V_t. Therefore, and considering or bench studies' results, we suggest that a) the monitoring for PIP during resuscitation be mandatory, and b) monitoring for V_t should also become an integrated part of neonatal resuscitation and of resuscitation training[110,111,130]. This should be a primary goal for the near future, and manufacturers of modern resuscitation devices should swiftly include this technology in their latest developments. Of equal importance are clinical studies, which need to be performed to investigate the effect of such measures on neonatal outcome in RCTs. As a first step towards standardisation of care, future prospective studies need to include short and long term outcome data, such as morbidity and mortality of infants given various means of non-invasive respiratory support. Use of LFTs could again be used to help objectify the physiological response to this, more controlled, means of resuscitation.

Further research should also focus on the distribution and acceptance of evaluated research findings throughout the neonatal community and to formulate unbiased standards of care. International organizations like ILCOR and the ERC should strive further to come up with one unanimous recommendation on neonatal resuscitation[131]. This, as well as any high-quality research should be made available to all through the internet, and free of charge. Building up on the work by Gazmuri et al., and as the quintessence of international research seminars on non-invasive ventilation and DR management of VLBW infants, which were organized through our group, we published a summary of the most pressing knowledge gaps and outlined possible means to meet them[132]. It is hoped that the recently founded international cooperation of Neonatologists and Physiologists, the European Scientific Collaboration on Neonatal Resuscitation Research (ESCNR, established in Copenhagen 2010) will strive to generate important and desperately needed evidence regarding the many open questions surrounding the issue of neonatal resuscitation.

4. Summary

This thesis contributes to three areas of neonatal resuscitation research. We provide data on: 1) strengths and weaknesses of equipment used for providing respiratory support, 2) the clinical effect of non-invasive respiratory support of VLBW infants at birth, and 3) epidemiologic data of delivery room practice in Europe. Concerning our studies on resuscitation equipment, the most significant discoveries were that device- and operator specific characteristics influence the quality of PIP, PEEP and V_t provision during manual respiratory support of VLBW infants. Using SIBs, operators from all professions (original study 1) and from all grades of professional training (original study 2) produced highly variable and at times excessive PIP and V_t. Conversely, the use of the pressure limited T-piece device protected against the application of too high PIP and also V_ts. An important secondary finding of our investigations was the lack of accuracy of the commonly used PEEP-valves (original study 3). Our prospective study of the clinical effect of a non-invasive approach to resuscitation of VLBW preterm infants proved that infants supported with CPAP had improved lung function at term, compared to those treated with early MV (original study 4). Surveying the NICUs of German speaking countries in 2008, we found that such an approach had already been widely applied, albeit without uniform protocols (original study 5).

Non-invasive respiratory support from birth, if consistently and cautiously provided to VLBW preterm infants has the potential of minimising neonatal lung injury and minimise the risk of BPD. Referring to the current discussion on whether invasive (MV) or non-invasive respiratory support (CPAP) should be the first line treatment for neonatal RDS, we believe that in a situation of equipoise the least invasive method of support should be chosen. Thanks to many high quality studies in this field and possibly including the ones presented in this thesis, the paradigm of neonatal resuscitation has already swayed away from early invasive MV and PPV to a more individualized, patient centred approach with the primary aim to provide non-invasive respiratory support. Thus, early non-invasive respiratory support should now be considered as the recommended ventilatory support preterm infants, leaving the burden of proving superiority to those still advocating primary intubation and MV.

5. Literature

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7. Declaration instead of oath

Eidesstattliche Erklärung

§ 4 Abs. 3 (k) der HabMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wird bzw. wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/ Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden und
- mir die geltende Habilitationsordnung bekannt ist.

Dr. Charles Christoph Röhr, unterschrieben
Berlin, den 20.10.2011