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Unraveling the Links Between the Initiation of Ventilation and Brain Injury in Preterm Infants

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The initiation of ventilation in the delivery room is one of the most important but least controlled interventions a preterm infant will face. Tidal volumes (V_T) used in the neonatal intensive care unit are carefully measured and adjusted. However, the V_T s that an infant receives during resuscitation are usually unmonitored and highly variable. Inappropriate V_T s delivered to preterm infants during respiratory support substantially increase the risk of injury and inflammation to the lungs and brain. These may cause cerebral blood flow instability and initiate a cerebral inflammatory cascade. The two pathways increase the risk of brain injury and potential life-long adverse neurodevelopmental outcomes. The employment of new technologies, including respiratory function monitors, can improve and guide the optimal delivery of V_T s and reduce confounders, such as leak. Better respiratory support in the delivery room has the potential to improve both respiratory and neurological outcomes in this vulnerable population.

Keywords: resuscitation, tidal volume, cerebral palsy, brain injury, premature, respiratory support, lungs

PRETERM BIRTH, BRAIN INJURY, AND VENTILATION REQUIREMENT

Preterm birth, defined as birth prior to 37 completed weeks of gestation, affects 7–12% of births worldwide (1). Preterm babies have underdeveloped lungs, characterized by fewer alveoli, less surfactant, and a thicker blood–gas barrier that reduces oxygen and carbon dioxide diffusion into the bloodstream (2, 3). Many of these babies have impaired lung function, rendering them unable to survive without assistance. In Australia, 28% of all infants required some form of respiratory support in the delivery room, with suction and oxygen support encompassing the majority of this support. However, 7.5% required intermittent positive pressure ventilation (IPPV); the requirement for IPPV increases with decreasing gestational age (4). Respiratory support is the cornerstone of successful neonatal resuscitation (5); it allows appropriate transition from fetal to neonatal circulation

Abbreviations: BPD, bronchopulmonary dysplasia; CBF, cerebral blood flow; IL, interleukin; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; VILI, ventilation-induced lung injury; V_T , tidal volume; WM, white matter.

as well as aiding in lung liquid clearance and functional residual capacity establishment. However, it is now well established that assisted ventilation increases inflammation and injury to the preterm lungs (6).

The effect of respiratory support at birth on other organ systems, especially the brain, remains relatively unexplored. This is of particular importance given that preterm infants have a significantly increased risk of acute and chronic brain injury compared to term infants. Children born preterm have higher rates of sensory deficits, learning disabilities, and cerebral palsy than children born at term (7). Compared to term infants, babies born extremely preterm have a greater incidence of moderate–severe disability (20.3 vs. 2.5%), moderate–severe developmental delay (16 vs. 2%) and cerebral palsy (9.8 vs. 0%) at 2 years of age (8). Given the higher incidence of poor neurodevelopmental outcomes in preterm infants, reducing the incidence and severity of brain injury in this population is essential to enhance the long-term health and welfare of individuals born preterm.

There is increasing evidence from animal studies that ventilation-induced lung injury (VILI) leads to systemic (9–11) and brain (12, 13) inflammation and injury. Furthermore, inflammatory and hemodynamic pathways play a critical role in the pathogenesis of brain injury in preterm infants (14–16). Thus, given the underlying risk of brain injury in preterm babies, the requirement for ventilation further exacerbates the probability of acute injury and chronic disability suggesting injurious ventilation to be an important contributor to brain damage in the preterm infant. It is therefore imperative that a baby born preterm receives the safest possible respiratory support in the delivery room.

INITIATION OF VENTILATION IN THE DELIVERY ROOM

Neonatologists are familiar with the concept of VILI and are increasingly careful in the neonatal intensive care unit (NICU) to apply mechanical ventilation strategies that are gentle and minimize trauma to the lungs (17, 18). Although ventilation and supplemental oxygen therapy are two of the most common interventions used in the NICU, neonatologists appear less aware that the same gentle approach should be applied to reduce VILI in the delivery room (17, 18). All modern ventilators allow adequate monitoring followed by continuous adjustment of setting (19) to achieve gentle ventilation, yet the same strategies have not been employed in the delivery room (20–23). The lack of adequate monitoring in the delivery room may influence the development of respiratory distress syndrome and bronchopulmonary dysplasia (BPD).

Devices for Respiratory Support in the Delivery Room – Accuracy and Efficacy

The International Liaison Committee on Resuscitation (ILCOR) advises on the techniques and the equipment used for neonatal resuscitation (24). Acknowledging the scant evidence available regarding the optimal initial airway management of preterm infants, ILCOR has summarized the most significant knowledge

gaps and research priorities regarding neonatal resuscitation as (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” (25). The application of safe and effective manual ventilation in the delivery room relies on several components – the safety and reliability of the equipment and the operator’s skills and clinical expertise when handling it.

According to recent surveys, the most commonly used devices for the initial respiratory support of newborn infants are self-inflating bags, flow-inflating (anesthetic) bags, and T-piece resuscitators (26–29). The delivered peak inspiratory pressure (PIP) and V_T are highly device dependent (30–32). A fundamental difference between T-piece resuscitators and self-inflating bags is that the T-piece resuscitators have pressure-limiting valves for PIP and positive-end expiratory pressure (PEEP), whereas self-inflating bags do not. Pressure manometers for self-inflating bags are available but rely on the operator to watch the manometer and adjust their technique to achieve the desired pressure. PEEP valves are an optional addition of doubtful clinical effectiveness (33). Therefore, self-inflating bags are often used without pressure manometers (26), despite evidence showing a pressure manometer significantly reduces the median applied PIP (34). T-piece resuscitators provide accurate, reliable, well-controlled PIP and PEEP compared to self-inflating bags (34, 35).

Pressure and volume delivery depends on a secure patient–device interface. Initial positive pressure ventilation is generally applied via a face mask. However, mask leaks are frequently encountered due to an inadequate mask seal around the infants’ nose and mouth. This can inadvertently lead to variable V_T delivery (36, 37). Fluctuating mask leak may lead to either inadequate ventilation or dangerously high V_T s being delivered. Furthermore, airway obstruction is also a significant problem in the initial respiratory support, and also results in inadequate ventilation. The problems of leak and airway obstruction highlight the need for monitoring of both PIP and V_T during ventilation in the delivery room; this would aid clinicians in accurate placement of the face mask to minimize mask leak, and the repositioning of the head and neck in the case of airway obstruction, thus optimizing ventilation and preventing delivery of excessive V_T s. Training of the correct mask hold technique and of manual ventilation has been shown to improve the ventilation of neonates (38).

Significant improvements in the consistency of V_T , rate, and rhythm of neonatal resuscitation have been demonstrated by the use of respiratory function monitors and auditory prompts (29, 39–41). The use of respiratory function monitors in clinical practice is not standard, but studies investigating their use during neonatal resuscitation are underway. Measuring exhaled CO_2 also shows promise as an indicator of adequate lung aeration with correlations drawn between exhaled CO_2 and end lung volume in animal models (42); this could be beneficial in the delivery room by representing an established functional residual capacity. Mian et al. found that the use of a flow sensor during ventilation within the delivery room allowed the monitoring of V_T and exhaled CO_2 , though the study was limited to babies receiving continuous

positive airway pressure (CPAP) (43). The implementation of respiratory function monitors and/or flow sensors may, therefore, provide additional technical support for clinicians in ensuring correct ventilation of neonates within the delivery room. This is particularly relevant given that the younger and sicker preterm babies, that are more inclined to require respiratory support, are also more likely to be delivered in tertiary centers that are able to employ such devices.

In summary, the ability of any resuscitation device to deliver accurate pressures and V_T s is dependent on both the device and the ability of the operator to use it skillfully. It is pertinent to note that none of the currently available devices provide clinicians with any feedback of the V_T delivered, a critical omission given the potential for significant lung injury.

High Tidal Volume Ventilation in the Delivery Room: Lung and Systemic Consequences

The V_T delivered during neonatal resuscitation is not well controlled; given that volume distension of the lungs rather than pressure or oxygen toxicity is the important factor causing the initiation of injury (17, 44–49), better V_T monitoring may improve neonatal outcomes. Devices used in the delivery room allow for the delivery of consistent PIP, but the V_T achieved will vary not only due variable leak, but also according to the changing compliance and resistance of the lung, the stiffness of the chest wall, and the volume of lung liquid retained within the airways (50). Trials at the Royal Women's Hospital, Melbourne, Australia found the V_T delivered to preterm infants varied from 0 to >30 mL/kg when the PIP was set at 30 cmH₂O (50). Importantly, 85% of these infants inadvertently received a V_T higher than recommended (45, 51), which is likely to be injurious. This study also demonstrated the difficulty clinicians face in assessing V_T in the absence of appropriate feedback from the devices; five resuscitators in the delivery room could not estimate the V_T , one over-estimated and 14 under-estimated the actual V_T delivered (50). These studies clearly illustrate that preterm infants are inadvertently receiving high V_T in the delivery room.

The links between high V_T ventilation and VILI are well established. Studies in preterm lambs highlighted that ventilation, regardless of the strategy used, triggers an inflammatory response in the lung (6). However, lung inflammation and injury are amplified when lambs received a high V_T (10 mL/kg) compared to a normal V_T (5 mL/kg) (52). Indeed, as few as three large V_T breaths is sufficient to initiate an inflammatory response in the lungs (53, 54), resulting in lung inflammation and injury leading to BPD. The maintenance of high V_T for up to 15 min leads to profound lung inflammation and injury (55, 56). Further, VILI can trigger a systemic inflammatory response (9, 10), which can cause inflammation in multiple organs (10, 57). Term and late preterm infants have an acute systemic inflammatory response after 2 h of ventilation evidenced by increased plasma pro-inflammatory cytokines interleukin (IL)-8 (2.5-fold), IL-1 β (7.5-fold), and TNF- α (10-fold) and a decrease in the anti-inflammatory cytokine IL-10 (by 90%) (58). The initiation of a systemic inflammatory cascade is a known mechanism of cerebral white matter inflammation and injury (59). Strong associations have been made between VILI

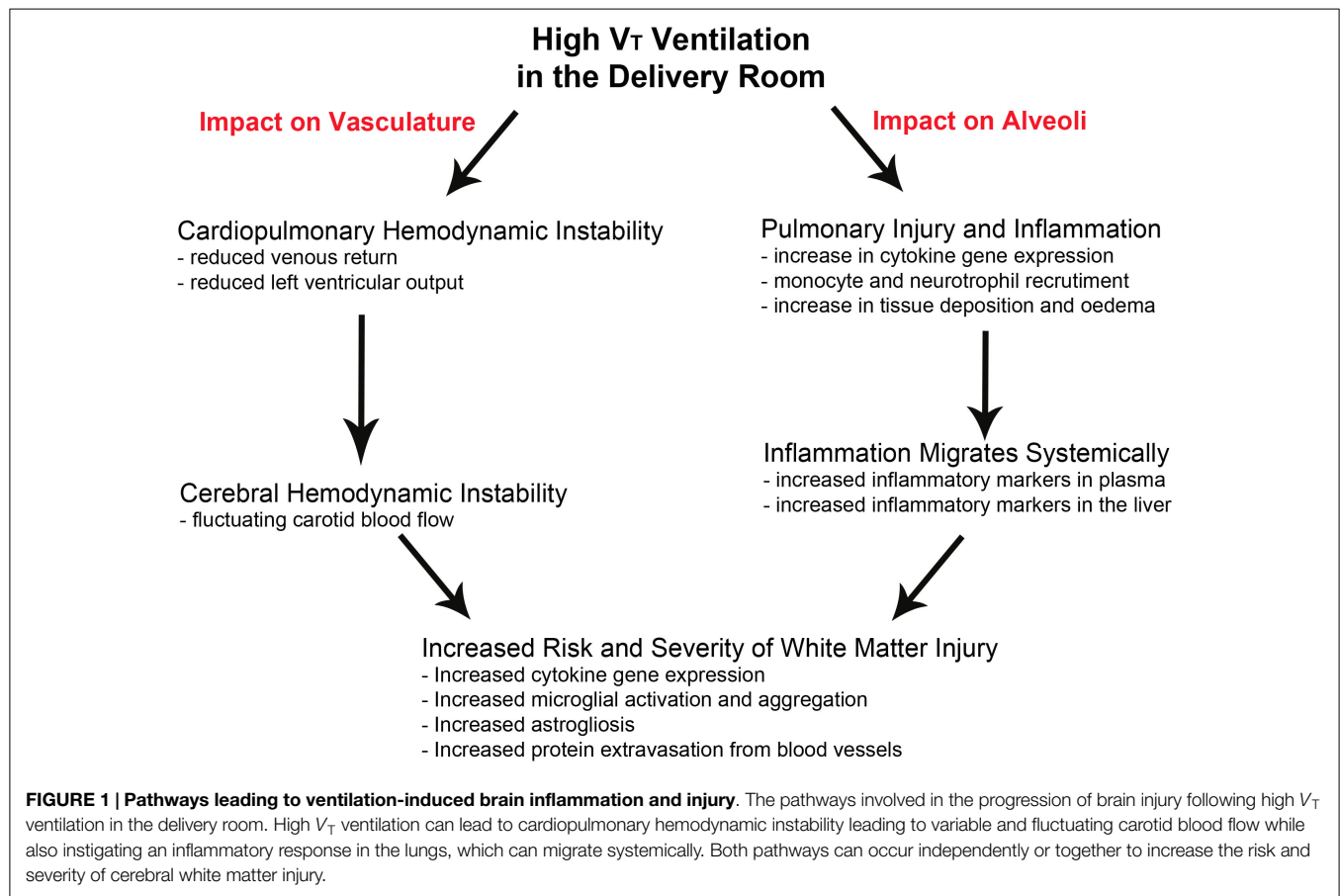
and BPD (60), and BPD and cerebral palsy (61), and the duration of ventilation increases the risk of white matter pathology (62). Together these studies suggest a causal link between ventilation, an inflammatory cascade and brain pathology. However, until recently, the effects of the initial resuscitation in the delivery room on the preterm brain were unknown.

High Tidal Volume Ventilation in the Delivery Room: Consequences for the Preterm Brain

Recent studies in preterm lambs (13, 63), coupled with studies in preterm infants (64), have demonstrated that the initiation of ventilation causes brain pathology through the same two mechanistic pathways key to perinatal brain injury, hemodynamic instability, and a localized cerebral inflammatory response (13, 14) (Figure 1).

Over-distension of the preterm lungs as a result of high V_T or end-expiratory lung volume within the first minutes to hours after birth, compresses the alveolar capillaries leading to pulmonary hemodynamic instability. This, in turn, alters pulmonary venous return and cardiac output and results in large swings in cerebral blood flow (CBF) (13, 65–67). Similarly, the application of IPPV and PEEP induces variability in intrathoracic pressure, which can independently alter cardiac function by affecting preload, afterload, heart rate, and myocardial contractility (68), which will also influence cerebral hemodynamics. This is not usually a problem in normal term infants, as they have the ability to maintain near-constant blood flow in the face of changing perfusion pressures by altering cerebral vasculature resistance (autoregulation) (69). However, it is now clear that preterm infants <30 weeks have episodes of impaired autoregulation, primarily due to their cerebral immaturity (70). Episodes of impaired autoregulation are reported to occur as much as 50% of the time during the first 5 days of life (71). Without intact autoregulation, abnormal CBF can cause hypoxia/ischemia (if CBF is low) or cerebral hemorrhage (if CBF is high or rapidly fluctuating between low and high flows).

Over-distension of the alveoli also initiates a pulmonary inflammatory response, which migrates systemically to the brain before crossing the blood–brain barrier (72) and activating a localized inflammatory response (13). This results in a profound increase in pro-inflammatory cytokine gene expression in the brains of ventilated preterm lambs (73). The underlying mechanism of perinatal white matter injury is upregulation of proinflammatory cytokines and diffuse activation of microglia within the immature white matter (59). The microglia mediate the local response by generating free radicals and amplifying cytokine production, which are important causes of brain injury. Increased pro-inflammatory cytokines (IL-1 β , IL-6, and TNF- α) can also compromise the cerebral vasculature reducing its ability to protect against abnormal CBF, as well as reducing the integrity of the blood–brain barrier making it more prone to hemorrhage (74, 75). Thus, the inflammatory cascade may injure the preterm brain via direct gliosis-induced toxicity or through increased blood–brain barrier permeability, as well as via perturbation of the cerebral vasculature leading to abnormal CBF.

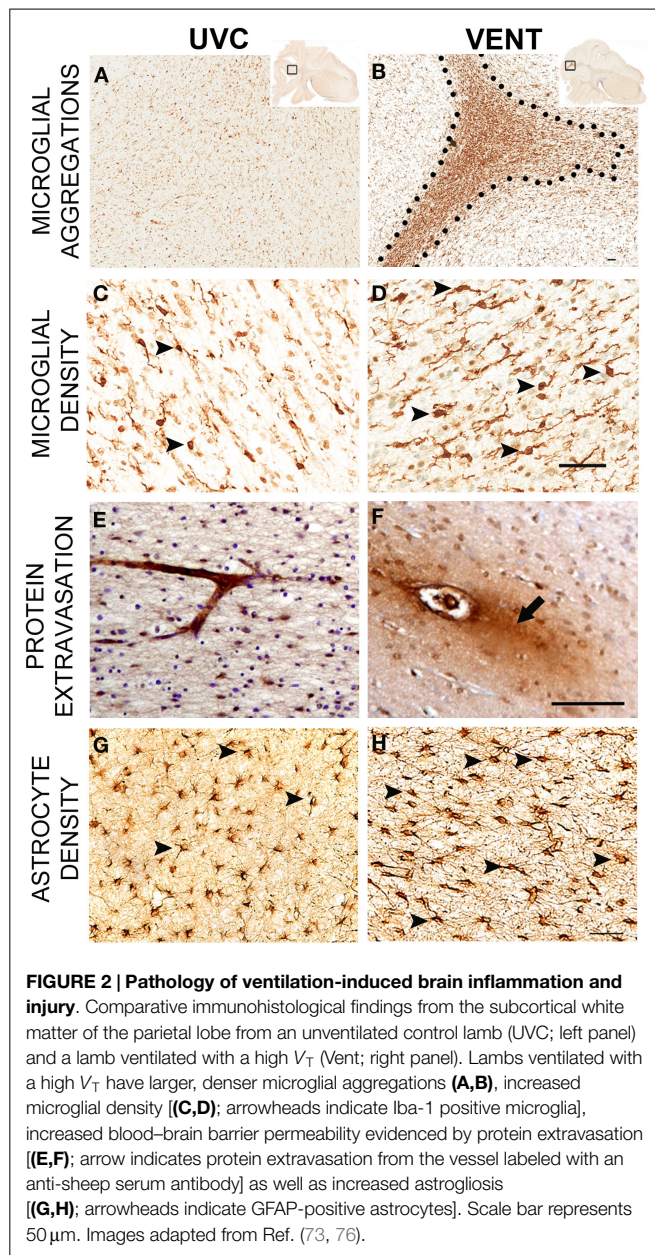


High V_T ventilation produces a distinct pattern of pathology within the white matter (**Figure 2**). At a histological level, the inflammatory response is evident within the brain parenchyma with an increase in size and density of microglial aggregations; importantly these can be observed after only 2 h of ventilation (73, 76). Subsequent increases in markers of astrogliosis, oxidative stress, and cell death are also characteristics (13, 73, 76). Indicators of brain inflammation and injury are also evident using clinical tools. Using magnetic resonance spectroscopy (MRS), Skiöld et al. found higher concentrations of markers of neuronal damage and cell membrane turnover in lambs that received high V_T for the first 15 min compared to lambs that received a normal V_T (12). Using near-infrared spectroscopy (NIRS), Polglase et al. found highly variable cerebral oxygenation in preterm lambs ventilated with high V_T , compared to lambs ventilated with a protective strategy (13). This has been mirrored clinically with low cerebral oxygenation in the delivery room during neonatal transition, measured using NIRS, being associated with IVH development (77). Permeability of the blood–brain barrier is also increased by high V_T ventilation (13, 76), this can have devastating consequences for the preterm infant as it allows passage of inflammatory mediators into the parenchyma (78).

The impact of high V_T ventilation in the delivery room on the preterm brain has now been assessed. Two groups of preterm infants ventilated with a $V_T < 5.8$ mL/kg and > 5.8 mL/kg were assessed; 48% of the cohort analyzed were not intubated in the

delivery room and of this proportion of babies, mask leak was monitored (with a mask leak $> 30\%$ excluded from analysis). It was found that 51% (25/49) of infants receiving high V_T in the delivery room were diagnosed with IVH compared to only 13% (2/16) of infants receiving the lower V_T . Furthermore, of the 25 infants who received the high V_T and developed IVH, 36% had the severest grade IV IVH (64). It is worth highlighting that, given the trial design, the babies requiring high V_T ventilation could have been more compromised than their low V_T ventilation counterparts rendering them more susceptible to lung and brain injury. Yet, despite this being a preliminary study, and groups being non-randomized, it highlights the requirement for further investigation into the critical relationship between high V_T ventilation in the delivery room and the potential for IVH in preterm babies.

Taken together, these studies highlight the intimate association between the lungs, heart, and brain during the initial resuscitation, and the critical need to consider the potential downstream consequences. Given that the pathways leading to brain damage can be activated as early as the first breaths delivered to a preterm infant in the delivery room, it is imperative that careful ventilation strategies, including V_T monitoring (18), as already practiced in most NICUs, are used in the delivery room. Indeed, studies have demonstrated that a lower V_T improves cerebral hemodynamic stability and reduces the inflammatory response. Polglase et al. demonstrated that a protective ventilation strategy, encompassing prophylactic surfactant, a sustained inflation (SI)



and low V_T , largely prevented molecular and histological brain injury compared to a high V_T (13) and also reduced signs of brain injury using MRS (12). Mian et al. supported this contention in a study of human preterm infants whereby neonates receiving $V_T < 5.8$ mL/kg had reduced rates of IVH than neonates receiving $V_T > 5.8$ mL/kg (64). These studies highlight the importance of controlling the V_T in the delivery room.

The Delivery Room and Beyond: Strategies for a Continuum of Non-Invasive Respiratory Support

We have so far focused on the importance of monitoring respiratory parameters within the delivery room, with the most emphasis placed on V_T , yet we must also highlight the increasing popularity

of non-invasive respiratory support both in the delivery room and the NICU. The two most common forms of non-invasive respiratory support in the NICU are CPAP and nasal high flow therapy (nasal HFT). Non-invasive respiratory support is preferable over intubation and mechanical ventilation, given the prevention of adverse effects that can result from intubation (79). While CPAP is now routinely used in the delivery room, nasal HFT remains limited to the NICU.

A recent survey of delivery room stabilization practice of very preterm infants showed 77% of tertiary units used CPAP (80). While Singh and Oddie highlight the increased use of non-invasive respiratory support in the delivery room, they also acknowledge that there is a marked variation in practice between units (80). Further, the optimal timing of CPAP, as well as ways to deliver surfactant, remains elusive. The COIN trial randomized 610 extremely preterm infants to either CPAP in the delivery room, or intubation and mechanical ventilation, and found CPAP resulted in reduced need for supplementary oxygen at 28 days as well as reduced median days requiring ventilatory support (81), although CPAP was associated with a higher rate of pneumothoraces. Similar findings were demonstrated in the SUPPORT trial. Infants who received CPAP treatment less frequently required intubation, postnatal corticosteroids, required fewer days of mechanical ventilation and had better outcomes at 7 days (82) compared to infants that received mechanical ventilation and early surfactant therapy. There appears to be an apparent respiratory benefit at least in the short term, and this is well documented (83–85), maintaining respiratory benefits in the long term (86). However, despite these initial improvements, the use of CPAP in the delivery room has not translated into improved long-term neurological outcomes of preterm infants (87) with death or neurodevelopmental impairment at 18–22 months corrected age occurring in ~30% of infants in both groups. In animal models: CPAP did not reduce lung or systemic markers of inflammation after 3 h compared to preterm lambs receiving conventional mechanical ventilation (9). Given the pathways of ventilation-induced brain injury, these data can be extrapolated to allow the assumption that CPAP would not have protected the brains of these lambs from ventilation-induced inflammation. In the preterm brain, the advantages of early CPAP over delayed CPAP have been shown in a preterm baboon model (88), albeit “early CPAP” in this model commenced 24 h after delivery. A lamb model of early CPAP allowing prolonged ventilation has now been developed which successfully transitioned to nCPAP from nasal intermittent positive pressure ventilation (NIPPV) at 28 ± 11 min (89); further progress with a similar model will hopefully allow more in-depth assessment of the impact of early CPAP on the preterm brain.

It is worth also addressing the use of SIs in the delivery room, particularly their combination with CPAP, given their rapid introduction into conventional respiratory care. Extensive animal models have demonstrated the physiological advantages of SI in improving the cardiovascular transition at birth, establishing a functional residual capacity as well as assisting in uniform lung aeration (90, 91). Yet, the use of an SI does not correlate to reduced lung inflammation and injury (92). Furthermore, there is concern about the rapid increase in cardiopulmonary and cerebral

hemodynamics after an SI. A recent study in term asphyxial lambs demonstrated that the more rapid increase in CBF after a 30-s SI resulted in increased vascular extravasation; a surrogate for IVH (93). The translation to human studies has to date demonstrated variable results. An SI has been associated with increased incidence of patent ductus arteriosus and a trend for increased incidence of IVH (94, 95). The use of an SI prior to nCPAP in the delivery room appears to improve ventilation parameters and reduce the time on mechanical ventilation but there was also a trend towards higher rates of pneumothoraces (96, 97). The observed differences between the animal and clinical studies may be due to the actual delivery of the SI – the animal studies were all conducted in intubated animals while clinical trials are delivering the SI largely using facemasks. Therefore, the difference in the interface may alter the efficacy of the delivery of the SI. More studies are required to determine the efficacy of a SI for use in the DR before this becomes standard care.

Nasal HFT is becoming increasingly common as an alternative for CPAP, but to date is mainly limited to use in the NICU. It allows the delivery of humidified blended air and oxygen via high flow nasal cannulae (HFNC) and can deliver a PEEP, such as CPAP (98). To date, studies have demonstrated similar effectiveness of CPAP and HFNC as post-extubation therapy, although HFNC was not quite as effective as CPAP in preventing extubation failure (99–101). Thus, HFNC appears a potential alternative mode of non-invasive ventilation for many preterm infants. Its ease of use, popularity with nurses and parents, and reduced rates of nasal trauma (102, 103) have resulted in rapid uptake of HFNC in neonatal units worldwide. Furthermore, a recent pilot study suggests that HFNC may be as effective as NIPPV in preventing endotracheal ventilation in the primary treatment of respiratory distress syndrome in premature infants <35 weeks (104). However, to date, no studies have determined the safety or efficacy of using HFNC in the delivery room as an alternative to CPAP or IPPV, nor have any long-term neurological outcomes of the trials been presented. Thus, HFNC remains a relatively untested, but potentially promising, future therapy for preterm respiratory support in the delivery room.

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SUMMARY

Many preterm infants require IPPV in the delivery room. Due to the lack of sophistication of devices used to provide respiratory support to preterm infants in the delivery room, many of these babies receive inadvertently high V_T , which can injure their immature lungs and brain. The safety and effectiveness of mask ventilation may be improved if respiratory function monitoring is used to help clinicians deliver appropriate V_T s. Non-invasive respiratory support in the delivery room reduces the risks associated with endotracheal intubation. However, increased use of CPAP has not translated into improved long-term neurological outcomes for preterm infants. Many infants initially managed with CPAP eventually require intubation and mechanical ventilation increasing the potential for lung and brain injury. There is a critical need to improve respiratory care in the delivery room and minimize the number of babies receiving inadvertently injurious ventilation, thus reducing the risk and severity of adverse pulmonary and neurological outcomes.

AUTHOR CONTRIBUTIONS

SB, CR, GS, and GP all contributed to the conception and design of the review and SB, CR, GS, GP, MT, SM, PD, TM, DL and SH all contributed to the drafting, revising, and final approval of the version to be published.

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