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The contribution of ovine models to perinatal respiratory physiology

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1. ABSTRACT

The dramatic transition to air breathing at birth represents a true challenge for the newborn infant mammal, a period in which neonatal respiratory diseases are common. Since the 1930s, fetal and newborn lambs have been the model of choice for whole-animal studies on neonatal respiration. The present review aims to illustrate the relevance of ovine models in studying the establishment of successful breathing at birth and its maintenance in the early postnatal period, as well as a number of abnormal conditions that can interfere with these processes.

2. INTRODUCTION

Animal models have vastly contributed to our understanding of both human physiology and the pathophysiology of diseases. The majority of animal studies have been and are still conducted in rodents. The use of larger animal species often appears necessary, however, due to the overall recognition that experimental observations in large animals may be more representative of human conditions. Accordingly, lambs represent a model of choice for studying normal and abnormal neonatal respiration. As a result, studies conducted in fetal, premature and term lambs have provided a better understanding of neonatal respiration and thus better care of newborn infants with respiratory disorders. Due to its comparable size to the human neonate as well as its robustness, the entire therapeutic arsenal used in the intensive care setting can be easily adapted to the lamb, making it an ideal translational research model. This review constitutes an attempt at summarizing the contribution of the ovine model to our knowledge of the normal establishment of successful breathing at birth and its maintenance in the early postnatal period, as well as to a number of abnormal conditions that can interfere with these processes.

3. ESTABLISHMENT OF SUCCESSFUL AIR BREATHING AT BIRTH

At birth, the newborn must immediately adapt to air breathing. This adaptation includes lung aeration as well as maintenance of regular and efficient respiratory efforts (reviewed in (1-3)).

3.1. Transition from a liquid-filled lung to air breathing at birth

3.1.1. Normal lung aeration at birth in newborn infants

Rapid aeration of liquid-filled lungs at birth is mandatory for a successful transition from the fetal to the newborn state. Forceful inspiratory efforts (in which intrathoracic pressure as high as -90 cmH_2O is generated by the newborn during the first respirations) create a pressure gradient within the airways, which moves air into the lungs. This in turn opens the alveoli and moves the liquid across the alveolar epithelium into the parenchyma. In addition, repetitive active expiratory laryngeal closure contributes to air-stacking in the lungs, ultimately maintaining a sufficient amount of air into the lung at the end of expiration, *i.e.* functional residual capacity. The presence of surfactant is crucial in this process; by decreasing the surface tension of the distal airways, the surfactant decreases the elastic recoil of the lung, hence decreasing expiratory emptying of the lung. At the same time, lung inflation and ventilation are responsible for an increase in pulmonary blood flow and the release of two potent pulmonary vasodilators, nitric oxide (NO) and prostacyclin, by the pulmonary endothelium (1), creating an optimal situation for alveolar-capillary gas exchange.

3.1.2. Lung aeration at birth in the premature newborn

It is estimated that 7.5.% of infants are born prematurely in developed countries (4). In addition, the rate of survivors among extremely premature infants (22-27 weeks gestational age) is steadily increasing (5), representing a demanding challenge in the transition to air breathing at birth. While this transition occurs smoothly in the vast majority of full-term newborns, a number of premature neonates, especially the very low birth weight newborns, are unable to successfully initiate air breathing at birth. Immaturity of the central respiratory drive, weak and fatigue-prone inspiratory muscles, absence of functional surfactant, extremely pliable rib cage and persistence of a high pulmonary vascular resistance are among the factors that negatively impact respiration onset at birth.

Hence, at birth, many very preterm infants require the use of some form of positive pressure respiratory support, such as mechanical ventilation, positive end-expiratory pressure (PEEP) and/or sustained lung inflation. This, however, can have highly deleterious effects on the immature lungs. For instance, studies in preterm lambs have shown that the use of large tidal volumes (35 ml/kg) for only 6 breaths in order to aerate the lungs at birth is sufficient to induce lung inflammation and initiate ventilator-induced lung injury, thereby setting the stage for chronic lung disease of infancy (6). Convincing evidence of the proinflammatory effect of positive pressure ventilation at the onset of breathing at birth has now been demonstrated in a number of preclinical studies, using the preterm lamb model (7-10). Long lasting consequences of this ventilator-induced lung inflammation will be further reviewed in the section on bronchopulmonary dysplasia.

3.1.3. The quest for the optimal ventilator strategy to support lung aeration at birth in very preterm newborns

Given the deleterious effects of positive pressure ventilation at birth in preterm lungs, a number of studies have been conducted in preterm lambs (gestational ages between 129 to 137 days; normal term of 147 days) to establish which ventilatory support modality would minimize ventilator-induced lung injury and ultimately reduce the occurrence and severity of bronchopulmonary dysplasia. Although much progress has been made in recent years, the optimal respiratory support to offer during neonatal transition in the extreme preterm newborn remains a matter of active research, for which the lamb represents the model of choice.

3.1.3.1. Endotracheal ventilation

The optimal means to provide endotracheal mechanical ventilation at birth in preterm newborns has been the subject of numerous studies in preterm lambs. Antenatal corticosteroid treatment (11) and surfactant treatment prior to endotracheal ventilation at birth (8, 12) have been shown to decrease the pulmonary inflammatory response in preterm lambs, with these measures being successfully translated to the clinical setting. The use of various levels of PEEP has been especially investigated in preterm lambs (127 to 133 days gestation). Studies have shown that using PEEP to maintain a higher end-expiratory lung volume improved oxygenation after antenatal glucocorticoids and/or postnatal surfactant (13) while lessening ventilator-induced pulmonary inflammation (8, 14, 15). The latter was not prevented however by using a low tidal volume (8 ml/kg) and PEEP in other studies (16). Although increasing PEEP from 4 to 12 cmH_2O improved oxygenation, it heightened pulmonary vascular resistance and diverted the blood flow through the ductus arteriosus, which adversely decreased pulmonary blood flow and favored the persistence of fetal circulation (17). While the use of a sustained inflation with a fixed duration (most often during 15-30 seconds) was initially reported not to prevent lung inflammation in preterm lambs (18, 19), it was later suggested that a sustained inflation with an individualized duration represents a better approach (10). Sustained inflation also appears to improve lung function without adverse circulatory effects as well as to stabilize neonatal cerebral oxygen delivery and potentially prevent cerebral hyperoxia in preterm lambs (127 days of gestation) (20). Results of the above studies have paved the way for clinical trials, some of which are currently ongoing (21-24).

Moreover, variable ventilation settings using the same breath-to-breath minute volume but variable tidal volume and respiratory rate have been reported to improve ventilation efficiency and lung compliance without increasing lung inflammation (15, 25). Conversely, an incremental tidal volume strategy at birth was found to result in worse oxygenation and gravity-dependent heterogeneity in aeration in preterm lambs (26).

3.1.3.2. Non-invasive respiratory support

Given the negative effects of aerating the lungs at birth using endotracheal mechanical ventilation, non-invasive respiratory support has become an attractive modality for very low birth weight infants. Studies using preterm lambs, among others, have revealed that the early use of non-invasive respiratory support leads to better respiratory outcomes (27-31). The nebulization of humidified surfactant with nasal CPAP applied from birth has been shown to improve oxygenation and lung function in preterm lambs (135 – 137 days gestation) at 3 hours of life (32). In another study, preterm lambs (131 – 133 days of gestation) were successfully transitioned from nasal intermittent positive pressure ventilation + respiratory stimulants to nasal CPAP soon after birth (28). However, premature lambs (130 – 132 days of gestation) with significant respiratory distress showed a progressive deterioration of respiratory gas exchange after a few hours when supported with bubble CPAP through nasal prongs or a nasopharyngeal tube (30).

The above evidence in lambs, in addition to the demonstration that delaying umbilical cord clamping positively impacts oxygenation and hemodynamics (33-40), has opened the door for numerous clinical studies on the best approach with regard to the care of the preterm newborn at birth. The current clinical management of the preterm infant in the delivery room is hence aimed at delaying umbilical cord clamping, avoiding tracheal intubation by the systematic use of non-invasive continuous positive pressure support and the use of minimally invasive surfactant administration techniques (41-43). Unfortunately, with the current approaches, mechanical ventilation nonetheless appears unavoidable for most infants born at the limits of viability (*i.e.* 22-24 weeks gestational age). For such patients, exogenous surfactant administration, gentle ventilation strategies and early extubation are used. Volume-targeted ventilation aimed at low tidal volume (*i.e.* amount of gas administered at each inspiration) (44) with a permissive hypercapnia strategy (*i.e.* tolerating high partial CO_2 pressure) is suggested (45). This field of study is still very active and bold approaches, such as artificial placenta and total liquid ventilation (see section 4.3.2.3.), are being investigated in lambs in an effort to further prevent early ventilator-induced lung injury.

3.2. Maintenance of efficient and continuous breathing at birth

In addition to successful lung aeration at birth, the maintenance of efficient breathing movements

is a vital necessity for the newborn. Studies in ovine models have shown the presence of fetal breathing movements and allowed a better understanding of the normal perinatal control of breathing and its alterations in disease states.

3.2.1. Fetal breathing movements

While fetal breathing movements were first observed in humans using kymography in 1888 (46, 47), it is during the 1970s that their occurrence was confirmed by recordings *in utero* in chronically-instrumented lambs (48, 49). Numerous experiments have since shown the presence of fetal breathing movements, which can be observed as early as 40 days in the fetal lamb (*vs.* 110 days in the human fetus). While continuous in early gestation, their occurrence evolves with cerebral maturation, ultimately becoming linked to a REM sleep-like state in the third trimester (50). Beyond providing evidence of the early maturation of respiratory control, fetal breathing movements are crucial for prenatal lung growth (reviewed in 50, 51). During fetal breathing movements, diaphragmatic contractions are already well coordinated with contraction of the upper airway muscles, such that laryngeal constrictor muscles are tonically active when phasic diaphragm activity is absent, while remaining silent when the diaphragm contracts (52). Together with continuous lung liquid secretion, this tonic closure of the larynx allows the building of positive pressure in the lung, thereby promoting lung growth. Fetal breathing movements have been shown to be the major stimulus for lung growth and maturation *via* mechanical stretch of the lung (53) and, at least partly, *via* stimulation of the epidermal growth factor receptor (54). Mechanical stretch of the lung occurs both with fetal breathing movements, which change the shape of the thorax, as well as during the prolonged phases without fetal breathing movements, when active tonic closure of the larynx prevents the egress of lung liquid into the amniotic cavity, resulting in continuous distention of the lungs. In addition, pulmonary vascular resistance is decreased and pulmonary blood flood increased during accentuated episodes of fetal breathing movements in lambs, possibly as a result of phasic reductions in intrapulmonary pressure (55).

3.2.2. Perinatal control of breathing

3.2.2.1. Establishment of continuous breathing at birth

The process underlying the dramatic change from intermittent breathing in the fetus to continuous breathing in the newborn is far from being completely understood. Again, much of the information has been derived from studies in the fetal and newborn lamb. A number of stimuli are likely involved in this process, including alterations in arterial CO_2 ($PaCO_2$) and O_2 (PaO_2) pressure (for instance, severe hypoxia will inhibit breathing) (56, 57), a surge in catecholamines, wakefulness, body cooling and sensorial stimulations (1). In addition, controversial results have been reported on the crucial importance of a breathing inhibitory factor from placental origin, namely prostaglandin E2, whose effect is suddenly halted at birth with section of the umbilical cord (56, 58).

3.2.2.2. Neonatal maturation of the hypoxic ventilatory response

Numerous experiments have been conducted in lambs to study, among others, the hypoxic ventilatory response in the perinatal period (see reviews in 50, 59). Prenatally, hypoxia is responsible for a decrease in fetal breathing movements in the fetal lamb, which is likely due to stimulation of the upper pons (reviewed in 50). Postnatally, the hypoxic ventilatory response is biphasic in mammals. Following a rapid increase in ventilation for 1-2 min due to carotid body stimulation, various central mechanisms such as adenosine, GABA and endogenous opioids as well as decreased metabolism are responsible for a roll-off of the hypoxic ventilatory response (50, 59). In addition, in the preterm lamb, this response to hypoxia is decreased compared to the full-term lamb, due to the absence of the normal increase in tidal volume (as well as in heart rate) (60).

Postnatal maturation of the carotid body response to hypoxia has also been widely studied (61). Studies in lambs have established that following birth, carotid body sensitivity to O_2 is reset within the first 3 days (reviewed in 62). This resetting is due to the increase in PaO_2 occurring with the transition to air breathing at birth (PaO_2 rapidly increases from 25 to 80 mmHg), as shown by the fact that rising PaO_2 in the fetal lamb *in utero* by mechanical ventilation is responsible for increased carotid body sensitivity at birth, meaning that carotid body resetting had occurred prenatally (63).

Moreover, studies in lambs have shown that hypoxia can disturb heart rate variability (64, 65). Accordingly, both long- and short-term variabilities progressively decrease during hypoxia in 2- to 3-week old lambs, as opposed to an initial and transient increase in both long- and short-term variabilities in the early period of hypoxia in older animals (64). Our studies have furthermore shown that hypoxia enhances REM sleep-related sympathovagal co-activation in full-term lambs (65).

3.2.2.3. Ventilatory response to CO_2 in the newborn

Contrary to hypoxia, hypercapnia already stimulates fetal breathing movements in lambs (51). Postnatal studies in lambs have complemented experiments in other species showing that, overall, a

ventilatory response to CO_2 is present at birth, at times as vigorous as in adult life (reviewed in 66). CO_2 drive has been shown to be a major factor for maintaining breathing rhythmicity in lambs in the first hours of life (57). The importance of peripheral chemoreceptors for the rapid ventilatory and arousal response to CO_2 in early postnatal life has been highlighted in several studies (61, 67, 68). In addition, hypercapnia has been shown to abolish periodic breathing (69). Finally, ventilatory hypercapnia (increased alveolar PCO_2) but not perfusion hypercapnia (increased blood PCO_2), increases pulmonary vascular resistance via arteriolar constriction (70).

3.2.2.4. Importance of vagal afferents for neonatal breathing

By monitoring the mechanical status of the lungs throughout the breathing cycle, continuous vagal afferent information originating from several types of bronchopulmonary receptors exerts a major influence on respiratory center output. Among other roles, slowly-adapting receptors are responsible for the Hering-Breuer reflex that tightly controls tidal volume in newborn mammals, while rapidly-adapting receptors induce augmented breaths (= sighs), whereas C fibers participate with slowly-adapting receptors in maintaining a dynamic high end-expiratory lung volume (71). The vital importance of such information in the immediate postnatal period has been demonstrated in vagotomized newborn lambs, which die from respiratory failure within a few hours, likely from atelectasis and hypoxia secondary to the loss of both the active maintenance of a high end-expiratory lung volume and augmented breaths (72). Although not as crucial in the few days after birth, vagal afferent information nonetheless remains of major importance for normal breathing in the first months of life. Indeed, the role of the Hering-Breuer reflex in exerting a tight control at this period is well established in newborn mammals (73), underlying the key role of slowly-adapting bronchopulmonary receptors. Experiments in lambs have shown that preterm birth does not alter maturation of the Hering-Breuer reflex. In addition, reflexes originating from C fibers are also present at birth in preterm lambs, although less potent than after full-term birth (74).

3.2.3. Apnea of prematurity

Apnea of prematurity is usually defined in preterm infants as a cessation of breathing lasting more than 20 s or shorter if associated with oxygen desaturation (SpO_2 < 80 to 85%) and/or bradycardia (heart rate < 80 bpm or < 2/3 of baseline). Such cardiorespiratory events are present in virtually all newborns before 28 weeks of gestation. Various mechanisms are involved in the pathogenesis of cardiorespiratory events in preterm infants (75). This primarily includes immaturity of the brainstem centers as well as peripheral reflexes, such as from arterial chemoreceptors, laryngeal chemoreceptors and bronchopulmonary receptors. In addition, immaturity of the respiratory system control is superimposed on immature lung development and respiratory thoraco-abdominal pump. A number of studies on apnea of prematurity have been conducted in ovine models, especially when there was a need for either invasive instrumentation (*e.g.* in studies on upper airway muscle activity) or for experimental conditions unacceptable in human infants (*e.g.* repeated stimulation of the laryngeal mucosa). The following paragraphs summarize some of the studies performed in this area, beginning with the description of the preterm lamb model.

3.2.3.1. The preterm lamb model to study cardio-respiratory events of prematurity

Studies on spontaneous breathing in unanesthetized preterm animals have been mainly performed in lambs (76-80), which allow extensive chronic instrumentation and prolonged polysomnographic recordings. We have been studying preterm lambs born at 131 ± 2 days (normal gestation 147 days) for the past two decades. Following years of improvement (74, 81-84) and without using positive pressure ventilatory support, our current protocol ensures a survival rate of ~ 75% at 5-7 days of life, when lambs are ready for surgical instrumentation followed by polysomnographic recordings. Lambs are born by vaginal delivery after antenatal lung maturation by betamethasone and premature labor induction by mifepristone. No other medication, *e.g.* medroxyprogesterone acetate, is used antenatally. Lambs require continuous care during the first 48h of life to prevent and treat hypothermia, hypoxia and hypoglycemia. In addition, high-flow nasal cannula is occasionally used in lambs with mild to moderate respiratory distress syndrome (85). Overall, our preterm lambs constitute a model of late preterm infant born at about 34 weeks of gestation.

3.2.3.2. Active laryngeal closure during neonatal central apneas

Current knowledge ascribes an essential role to the larynx in perinatal respiration. Accordingly, the larynx helps the newborn in its transition from intrauterine to extra uterine environment by promotion of fetal lung growth, establishment of functional residual capacity, reabsorption of lung water (86) and maintenance of a high functional residual capacity in early postnatal life (87). Moreover, several studies suggest an important role of the larynx in neonatal central apneas. In 1980, Milner observed that laryngeal closure was frequently present during central apneas in preterm newborns (88), a finding since

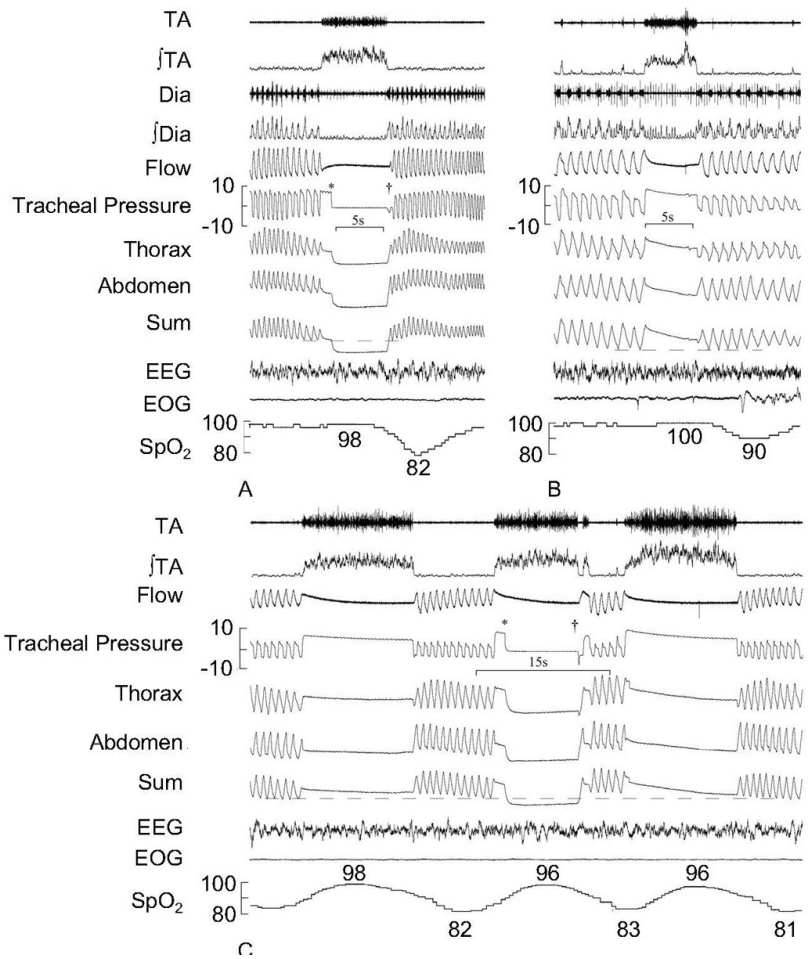

Figure 1. Recordings obtained in a tracheostomized preterm lamb during quiet sleep. The importance of active laryngeal closure during central apnea for maintaining the apneic volume over the preceding functional residual capacity (dotted line) is shown in panel B (tracheostomy is closed) vs. panel A (tracheostomy is opened). A similar demonstration is shown in panel C during periodic breathing. TA and ∫ TA: raw and integrated thyroarytenoid muscle (laryngeal constrictor) electrical activity; Dia and ∫ Dia: raw and integrated diaphragmatic electrical activity; F: nasal airflow; Sub-P: subglottal pressure; Sum: lung volume variations measured by respiratory inductance plethysmography; EEG: electroencephalogram; EOG: electrooculogram; SpO2: pulse oximetry. Adapted with permission from (83).

confirmed by several observations in the newborn lamb (reviewed in 89). In a first series of experiments on artificially-induced central apneas, continuous electrical activity of the thyroarytenoid muscle (a glottal constrictor muscle) was observed throughout central apneas, irrespective of the level of PaO_2 and $PaCO_2$ (90-92). Direct endoscopic observation further showed complete glottal closure, associated with positive subglottal and translaryngeal pressure along with a high apneic lung volume well above the end expiratory volume (93, 94). Overall, central apneas in full-term lambs were similar to inspiratory breath-holdings due to active laryngeal closure. This active laryngeal closure was also present between gasps observed during anoxic gasping in lambs, which was interpreted as a strategy to maintain a greater volume of air within the lungs in order to promote a more efficient oxygenation between the low-frequency gasps (95).

Laryngeal dynamics have also been subsequently assessed during spontaneously occurring apneas in preterm lambs (83). Results from preterm lambs born between 129 and 132 days of gestation showed that continuous electrical activity of the thyroarytenoid muscle was observed throughout 88% of all apneas, including periodic breathing epochs, regardless of sleep state (71). This glottal constrictor activity was also associated with positive subglottal pressure and maintenance of a high apneic lung volume well over the passive functional residual capacity, consequently limiting the decrease in hemoglobin desaturation secondary to the central apnea (see Figure 1) (82).

3.2.3.3. Cardiorespiratory events originating from the laryngeal chemoreceptors

Laryngeal chemoreflexes (LCR) are a group of reflexes triggered by the contact between a liquid

(especially if acidic or of low chloride content) and the laryngeal mucosa. In immature mammals, LCR are characterized by a vagal component consisting in laryngospasm, central or mixed/obstructive apneas, oxygen desaturation and bradycardia and can be life-threatening (96). In preterm infants, LCR can be triggered by laryngopharyngeal refluxes or oral feeding and even by upper airway secretions (96). In addition, LCR can be responsible for apparent life-threatening events in some infants, even when born after full-term gestation, as well as for certain cases of sudden infant death syndrome (96, 97).

Following the first observations of apnea and bradycardia in response to water on the epiglottis in anesthetized lambs by Tchobroutzky in 1969 (98), several studies in lambs (in parallel to studies in piglets, puppies and rat pups) have assessed the LCR response to various liquids (78, 84, 99-101). In full-term lambs, LCR during non-REM sleep are mainly characterized by lower airway protective responses such as swallowing, cough and arousal, with mild cardiorespiratory responses (99). In addition, a long-lasting increase in heart rate variability due to sympathovagal co-activation has been reported following LCR in full-term lambs (102). Conversely, our studies in the preterm lamb (132 days of gestation) have shown fetal-type LCR, with prominent apnea, bradycardia and hemoglobin desaturation (84). This enhanced LCR-related cardiorespiratory inhibition in preterm lambs largely decreased with postnatal maturation (84), whereas the autonomic activity following LCR decreased (103). In addition, while application of nasal continuous positive airway pressure was found to consistently blunt the LCR-related cardiorespiratory inhibition in preterm lambs, the overall effect of caffeine was found to be non-significant (85).

In addition to preterm birth, other neonatal conditions have been reported to enhance cardiorespiratory inhibition observed during LCR in newborn lambs, including artificially-induced reflux laryngitis (104), respiratory syncytial virus infection (105, 106), hypoxia (107) and postnatal exposure to nicotine (108) or cigarette smoke (109). On the contrary, terbutaline has been reported to blunt the LCR response in lambs aged 2-4 weeks, following postnatal carotid body maturation (110).

3.2.3.4. Cardiorespiratory events related to oral feeding in preterm newborns

Many preterm newborns still require some respiratory support in the form of nasal CPAP or high-flow nasal cannula at the time when oral feeding initiation is being considered. Introduction of oral feeding under nasal respiratory support is a much-debated topic among neonatologists, prompted by fear that nCPAP could disrupt sucking, swallowing and breathing coordination and in turn promote cardiorespiratory events. While some teams have claimed success with initiation of oral feeding in immature infants with nCPAP (111-113), many others advocate waiting for weaning of nCPAP or high-flow nasal cannula before any attempt at oral feeding (114, 115). Studies in full-term newborn lambs have shown that nCPAP up to 10 cmH_2O had no deleterious effects on both bottle-feeding efficiency and safety and did not alter nutritive swallowing-breathing coordination in full-term lambs (116). In addition, recent results have revealed that a nCPAP of 6 cmH_2O increased feeding efficiency while maintaining higher oxygenation without deleterious cardiorespiratory events in preterm lambs (132 days of gestation) feeding for the first time under nCPAP (117).

3.2.3.5. Apneas triggered by the stimulation of esophageal receptors

The involvement of gastroesophageal refluxes in apnea-bradycardia of prematurity remains controversial (118), although a few physiological studies have shown that the stimulation of esophageal receptors leads to cardiorespiratory reflexes (119-121). Recent results have revealed that esophageal stimulations (balloon distension and/or HCl injection) can induce forceful, clinically-relevant cardiorespiratory events in non-sedated preterm lambs (132 days of gestation), especially when mimicking a proximal gastro-esophageal reflux (122). Ongoing studies in lambs specifically aim to assess whether certain neonatal conditions (*e.g.* sepsis) or interventions (*e.g.* CPAP) alter the intensity of the cardiorespiratory events reflexly triggered by esophageal stimulation.

3.2.3.6. Sepsis-related neonatal apneas

Late-onset sepsis in the preterm newborn is a life-threatening condition, occurring in approximately 35% of preterms born before 28 weeks of gestation in the neonatal intensive care unit, with mortality reaching as high as 15% (123). The first sign of sepsis is often severe repetitive bouts of apneas and/or bradycardias (124). Studies in newborn rats have shown that apneas are at least partly related to systemic inflammation *via* the inhibiting action of prostaglandin E2 on the respiratory centers (125). While this hypothesis has received some confirmation in preterm humans, the severe bradycardias that are often prominent in late onset sepsis do not appear to be fully explained by the action of PGE2 (126). Using intravenous injection of lipopolysaccharides or polyinosinic:polycytidylic acid, we recently designed neonatal ovine models of bacterial or viral sepsis (127). Studies aiming to gain further knowledge on sepsis-related cardiorespiratory events in newborns are ongoing.

4. NEONATAL LUNG DISEASES

4.1. Congenital diaphragmatic hernia

Congenital diaphragmatic hernia is an anatomical defect of the diaphragm, whose prevalence is between 1,000 and 4,000 live births. It is secondary to various genetic mutations as well as poorly known environmental factors. When isolated, congenital diaphragmatic hernia is lethal in about 30% of cases treated in tertiary centers (128). To date, attempts at surgical closure of the hernia *in utero* have failed to demonstrate an advantage over postnatal management. Current management at birth consists in “gentle” ventilation with permissive hypercapnia and minimal sedation to prevent ventilator-induced lung injury, while the surgical closure of the diaphragmatic defect is delayed until clinical stabilization. Nitric oxide inhalation, high-frequency ventilation and extracorporeal membrane oxygenation can be used during the first days of life (129). Since postnatal care is not sufficient in the most severe cases with major lung hypoplasia and persistent pulmonary hypertension of the newborn, a prenatal approach to the treatment of lung hypoplasia is hence of major appeal.

Congenital diaphragmatic hernia can be surgically induced at the pseudoglandular stage of lung development in the fetal lamb (130). The ovine model has greatly contributed to the understanding of the pathogenesis and to the design of *in utero* surgical procedures in order to alleviate prenatal lung hypoplasia in human infants, such as tracheal occlusion (131, 132). Accordingly, fetal endoscopic tracheal occlusion has been shown to prevent the efflux of lung fluid and to promote lung growth *via* pulmonary stretch in fetal lambs (128). Human studies however on Fetoscopic EndoTracheal Occlusion are sparse and have led to mixed results, with an increase in survival, albeit with higher rates of prematurity. This technique is thus still under investigation (133).

Medical treatment, consisting mainly of vitamins (A, C or E) and corticoids (betamethasone, dexamethasone or prednisolone) given either to the ewe or directly into the amniotic cavity or the trachea, has shown some positive effect in preventing lung hypoplasia, although the overall current conclusion is that no medical treatment is currently considered effective for use in humans (reviewed in 134).

4.2. Meconium aspiration syndrome

Meconium aspiration is defined as inhalation of the meconium present in the amniotic fluid during or before delivery, secondary to anoxic gasping. Meconium aspiration syndrome induces: 1) mechanical obstruction of airways; 2) chemical alveolitis and epithelial damage; 3) inhibition of surfactant and 4) pulmonary artery hypertension (135-138). A number of treatment options have been tested in a variety of animal models, including promising results with lung lavage using diluted surfactant (139) or liquid ventilation (139-141) in full-term newborn lambs.

4.3. Bronchopulmonary dysplasia, a complication of premature birth

Bronchopulmonary dysplasia (BDP) is defined by the need for oxygen supplementation at 28 days of life, its severity being further characterized by the level of inspiratory oxygen fraction needed at 36 weeks corrected age (142). BPD, a chronic lung disease of the preterm newborn, is due to both genetic and environmental factors. The latter include mechanical ventilation and oxygen exposure as well as pre- and postnatal infections, among others. Altogether, they are responsible for an important inflammatory response of the lung that ultimately leads to a decrease in alveolarization and pulmonary microvascular development, which is characteristic of the BPD observed in very preterm infants. Other factors such as nutrition, fluid restriction, diuretics and corticosteroid treatment also impact postnatal lung growth (143). Currently, bronchopulmonary dysplasia is diagnosed in 30,000 infants every year in North America. It increases the risk of respiratory problems in the first years of life (144) and has long-term consequences including, among others, an increase in the incidence of asthma and chronic obstructive pulmonary disease at adult age (145, 146).

Numerous studies conducted in ovine models have attempted to gain a better understanding of the pathogenesis as well as to prevent this disease.

4.3.1. Pathogenesis of bronchopulmonary dysplasia

4.3.1.1. Effect of chorioamnionitis on the neonatal lung

Although still controversial (147), the relationship between chorioamnionitis (defined as an inflammation of the fetal membranes) and lung disease in preterm infants has been extensively studied in lambs. Chorioamnionitis has been induced by intra-amniotic injection of pro-inflammatory mediators such as IL-1beta (148, 149), IL-1alpha (149), Escherichia coli lipopolysaccharides (150) or Ureaplasma parvum (151, 152). Two recent reviews elegantly summarized the results obtained in these ovine models of chorioamnionitis (147, 153). Overall, chorioamnionitis can cause acute lung inflammation/injury (154, 155) and/or maturation of the fetal lung (149, 152, 156, 157), all of which are capable of modifying neonatal lung diseases.

4.3.1.2. Effects of hyperoxia on the newborn lung

Hyperoxia is undoubtedly involved in the pathogenesis of bronchopulmonary dysplasia (reviewed in 158). At birth, the transition from the intra-uterine environment (PaO_2 ~ 25 mmHg) to ambient air constitutes a hyperoxic stress in itself. The latter is particularly deleterious in the very preterm newborn, which lacks efficient anti-oxidant defenses and is often given a high oxygen fraction for treating a severe respiratory distress syndrome.

Reactive oxygen and nitrogen species released by alveolar epithelial cells and inflammatory cells subsequently promote both endothelial and epithelial cell death. Ultimately, hyperoxia largely contributes to decreased alveolarization and microvascular pulmonary development.

4.3.1.3. Effect of mechanical ventilation on the preterm lung

Ventilator-induced lung injury, which can occur with the very first positive pressure ventilations necessary at birth to aerate the lungs, is a major factor in the pathogenesis of bronchopulmonary dysplasia. Hence, “volutrauma” and “atelectrauma” during mechanical ventilation are responsible for shear stress and stretch lesions of lung cells (reviewed in 159). Extensive inflammation and death of resident lung cells ensue and in turn augment alveolar-capillary permeability within a few minutes. The consequent influx of neutrophils and macrophages induces the release of proinflammatory cytokines and chemokines, which amplify the inflammatory response initiated by resident lung cells. Consequences of extensive ventilator-induced lung injury include decreased alveolarization and microvascular pulmonary development *via* alterations of normal extracellular matrix remodeling and elastin deposition in the developing secondary septae, as well as a decrease in vascular endothelial growth factor.

The preterm lamb has been frequently used to characterize the effects of mechanical ventilation on lung injury (160-162). While much of the data has been collected during experiments on respiratory distress syndrome lasting only a few hours, one team has studied preterm lambs born at the saccular stage of lung development along with immature surfactant and anti-oxidant lung systems during several weeks under mechanical ventilation (163).

4.3.2. Prevention and treatment of bronchopulmonary dysplasia

4.3.2.1. Antenatal glucocorticoid administration

It is well established that glucocorticoids accelerate alveolar formation in the fetus as well as the rate of fluid clearance at birth. In addition, cortisol infusion significantly increases type II alveolar epithelial cell proportion (164), surfactant synthesis and secretion (165, 166). Beginning with the seminal study of Liggins and Howie, antenatal glucocorticoid administration has become a standard of care in preventing respiratory distress syndrome in the event of imminent preterm delivery (167). Studies in the preterm lamb (168, 169) have clearly shown that antenatal corticosteroid exposure induces fetal lung maturation and greatly decreases the frequency and severity of respiratory distress syndrome in the newborn. Such improvement in lung function is most likely mediated by surfactant production (170, 171), structural lung modifications (168, 172, 173) and alveolar fluid clearance (174). Antenatal glucocorticoids have also been shown to be beneficial in a sheep model of intrauterine growth restriction. The high clinical relevance of this observation stems from the frequent association of the latter with prematurity (175). On the other hand, recent studies in sheep suggest that antenatal glucocorticoid administration is not effective at the late canalicular phase of lung development, which corresponds to the extreme premature newborns increasingly present nowadays in neonatal intensive care units (176).

4.3.2.2. Non-invasive ventilatory support

Avoidance of invasive mechanical ventilation through the judicious use of non-invasive respiratory support immediately after birth and onward represents the cornerstone of the current clinical approach to prevent BPD. In particular, the use of nasal high frequency oscillation ventilation over several weeks after birth in preterm lambs has been compared to endotracheal intermittent mandatory ventilation. Results showed that nasal high frequency oscillation ventilation provided adequate gas exchange at lower inspired O_2 levels and respiratory pressures while promoting alveolarization (29, 30). A major difference between nasal and endotracheal ventilation however is the interposition of the larynx between the ventilator and the lungs in the former modality. Our studies in full-term newborn lambs have shown that certain modes of non-invasive ventilation, such as nasal pressure support, elicit an active inspiratory laryngeal closure (see Figure 2), which opposes ventilator insufflations and limits lung ventilation in proportion to the inspiratory positive pressure (177). On the contrary, nasal neurally-adjusted ventilatory assist (178) and nasal high-frequency oscillatory ventilation (179) do not induce active inspiratory laryngeal narrowing. The reflex inspiratory closure of the larynx in nasal pressure support ventilation has been shown to originate from bronchopulmonary mechanoreceptors (180, 181), and to be prevented by permitting moderate hypercapnia (182).

In addition to limiting lung ventilation, inspiratory closure of the larynx could in theory be

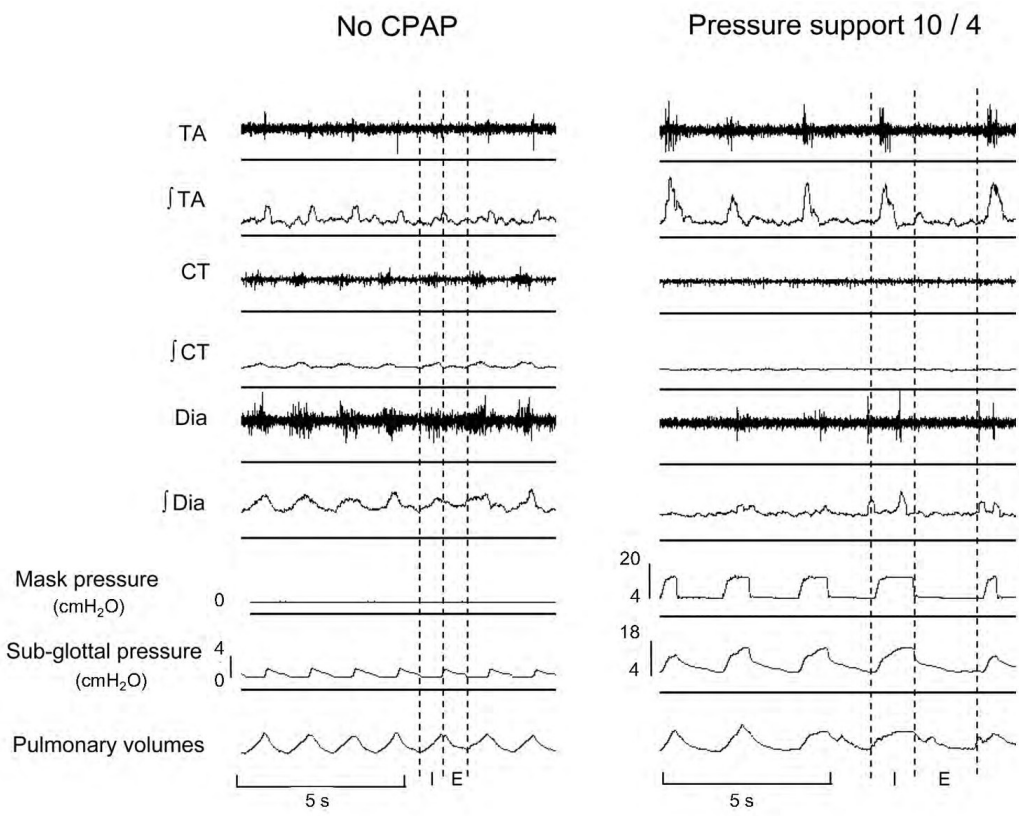

Figure 2. Recordings showing active laryngeal closure during pressure support ventilation in a lamb during quiet sleep. During pressure support (10/4 cmH2O), active laryngeal closure is shown by the presence of an inspiratory burst of thyroarytenoid muscle electrical activity (see first top traces TA and ∫ TA). TA and ∫ TA: raw and integrated thyroarytenoid muscle (laryngeal constrictor) electrical activity; CT and ∫ CT: raw and integrated cricothyroid muscle (laryngeal dilator) electrical activity; Dia and ∫ Dia: raw and integrated diaphragmatic electrical activity; I: inspiration; E: expiration. Adapted with permission from (178).

responsible for the deviation of insufflated gas into the digestive system, leading in turn to gastric distension and gastroesophageal refluxes (183-185). Our recent experiments in the newborn lamb however have shown that both nasal pressure support and neurally-adjusted ventilatory assist inhibit gastroesophageal refluxes at positive pressures of 15/4 cmH_2O (186). We have also previously shown a virtual abolition of gastroesophageal refluxes with the application of nCPAP at 6 cmH_2O, the mechanism being seemingly related to the decrease in the duration and depth of transient relaxations of the lower esophageal sphincter (187).

4.3.2.3. Thinking outside the box: bold approaches to BPD prevention

Despite an effort to avoid invasive mechanical ventilation by providing immediate non-invasive pressure support from birth, the majority of newborns between 22 and 26 weeks gestational age will develop respiratory failure and require endotracheal intubation. Although some improvements have been made in gaseous ventilation techniques in order to reduce lung injury, including volume-targeted approaches (44), BPD remains a highly significant health concern. Bold strategies have thus been suggested to avoid ventilator-induced lung injury in preterm babies. Total liquid ventilation, artificial placenta and stem cell therapy are currently under investigation. After unsuccessful attempts at partial liquid ventilation (188), where a perfluorocarbon is injected into the lungs while a conventional ventilator administers standard gaseous ventilation, total liquid ventilation (TLV) is now generating renewed interest. During TLV, the lung is filled with a perfluorocarbon and the fluid is cycled through a dedicated ventilator (*i.e.* tidal liquid ventilation), thereby eliminating the air-liquid interface. TLV has first been successfully used to ventilate term (189) and slightly preterm lambs (190). Subsequently, Degraeuwe and colleagues demonstrated that very premature lambs (124-126 days of gestation) could also be successfully maintained on TLV, with less evidence of lung injury compared to gas ventilation (191). Of significance for very preterm newborns, perfluorocarbons have also been shown to stimulate lung growth (192). Our INOLIVENT (for InNovative LIquid VENTilation) team at the University of Sherbrooke has used the lamb model to develop a dedicated liquid ventilator technology (193) and a

commercially available TLV ventilator is expected to be available for clinical trials within the next few years. Our team is currently using a lamb model to investigate the potential of TLV as an initial ventilation strategy in extreme preterm newborns for prevention of bronchopulmonary dysplasia. While proof of concept of TLV in the management of preterm lambs remains to be performed, refinement of TLV techniques is still necessary before planning for a clinical trial.

Among other approaches, the concept of the artificial placenta was first tested some 50 years ago (194). Several groups of researchers from around the world have since developed an enhanced extrauterine artificial placenta, using extracorporeal membranous oxygenation *via* the umbilical vessels in very preterm lambs (195-200). If successful, this method, alone or in combination with gentle ventilation approaches, could represent a major breakthrough for ventilator-induced lung injury and BPD prevention in extreme preterm infants. Stem cells also represent a promising treatment for the prevention and treatment of bronchopulmonary dysplasia. The newborn ovine model has been used to demonstrate the beneficial effects of human amnion epithelial cells on ventilation- or inflammation-induced lung injury (201-203).

4.4. Respiratory complications of intrauterine growth restriction

Chronic hypoxemia has been identified as a key regulator of lung maturation in fetuses with intrauterine growth restriction (IUGR) (204). Although the respiratory consequences of IUGR are variable in terms of extent, some studies suggest that IUGR may have worse adverse effects for the developing lung than extreme prematurity (205-207). Respiratory complications of IUGR can be present not only at birth and during the neonatal period (208), but can also have long-term consequences into adult life.

As reviewed in several publications (209-211), sheep models of IUGR have been extensively used in an attempt to understand the altered molecular pathways that contribute to abnormal lung development. A series of studies have been conducted in the ewe to induce IUGR by pre-mating carunclectomy (212-215), umbilicoplacental embolization (216, 217), maternal hyperthermia (218), single umbilical artery ligation (175) or isobaric hypoxia (209). Collectively, these studies have shown that during periods of chronic hypoxemia, the enhanced degradation of the hypoxia inducible factor-alpha subunit (HIF-α) by overactivation of prolyl hydroxylase domain-containing proteins leads to alterations in hypoxia signaling (214). This is turn delays surfactant maturation. Of note, intratracheal administration of vascular endothelial growth factor, a key hypoxia-signaling factor, promotes structural lung maturation in sheep fetuses with chronic hypoxemia; the resulting increased proportion of type 2 alveolar epithelial cells may bear some therapeutic potential (215).

Chronic hypoxemia during fetal life is also associated with decreased pulmonary vessel growth, pulmonary artery endothelial cell dysfunction (218) and pulmonary vascular remodeling. The latter can in turn be responsible for pulmonary arterial hypertension, which persists after birth. Studies conducted in ovine models have revealed that the platelet-activating factor and the epidermal growth factor receptor are both involved in the remodeling of pulmonary arteries (219, 220). Consequently, both factors could represent valuable pharmaceutical targets in women exposed to chronic hypoxia during pregnancy, such as women living at high altitude.

One important conclusion of studies in sheep is that alterations in fetal lung development following chronic hypoxemia can be markedly different if hypoxemia is present in early *vs.* late gestation, despite the same level of IUGR (165, 204, 221). Indeed, in fetuses with chronic hypoxemia throughout gestation (following carunclectomy), a decrease in lung surfactant protein was observed (165, 212, 213). Conversely, following late gestation hypoxemia (induced by umbilicoplacental embolization (216, 217) or isobaric hypoxia (204, 209)), surfactant protein expression was unaffected or increased. In addition, with late gestation hypoxemia, expression of the genes regulating sodium movement, and hence fetal lung liquid reabsorption at birth, was increased. Responses to late gestation hypoxemia were suggested to represent an adaptive response to anticipated preterm birth in order to maximize postnatal survival (204, 209). Overall, studies in sheep models of IUGR have highlighted that the various respiratory problems of the IUGR newborn depend on the timing, severity and duration of chronic hypoxemia experienced during pregnancy.

In addition to lung development, IUGR has been shown to affect the perinatal development of the control of breathing, marked by a blunting of the physiological postnatal increase in the ventilatory sensitivity to hypoxia. In contrast, no effect was observed on the sensitivity to hypercapnia (222).

5. CONCLUSION

Studies in fetal, premature and term ovine models have provided a better understanding of the physiology and pathophysiology of neonatal respiration. Studies in ovine have also been successfully translated to clinical practices in human infants. Characteristic examples include the administration of antenatal glucocorticoids in case of preterm labor, delaying umbilical cord clamping and optimization of the

immediate respiratory support of the preterm newborn at birth, as well as fetal endoscopic tracheal occlusion for treating congenital diaphragmatic hernia *in utero*.

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