Paediatric Respiratory Reviews 16 (2015) 147–150

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-symposium: Alveolar and Vascular Transition at Birth

Cardiopulmonary changes with aeration of the newborn lung

Stuart Brian Hooper [a,b,*], Graeme Roger Polglase [a,b], Charles Christoph Roehr [a,c,d]

[a] The Ritchie Centre, MIMR-PHI Institute of Medical Research, Melbourne, Australia
[b] Department of Obstetrics and Gynaecology, Monash University, Melbourne, Australia
[c] Newborn Services, John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom
[d] Department Neonatology, Charité University Medical Centre, Berlin, Germany

EDUCATIONAL AIMS

The reader will be able to better appreciate that:

- The transition to newborn life is triggered by lung aeration and airway liquid clearance.
- The primary mechanism for airway liquid clearance at birth is the increased transpulmonary pressure generated by inspiration.
- Aeration of the lung triggers the increase in pulmonary blood flow.
- The increase in pulmonary blood flow facilitates efficient pulmonary gas exchange and provides venous return and preload for the left heart.
- Delaying umbilical cord clamping until breathing has commenced allows time for pulmonary blood flow to increase, provides preload for the left heart and stabilizes the newborn circulation at birth, as shown in animal experiments.

ARTICLE INFO

Keywords:
Newborn
Cardiovascular
Pulmonary
Transition
Umbilical
PDA

SUMMARY

The newborn's transition from fetal to neonatal life includes aeration of the lungs, establishment of pulmonary gas exchange and changing the fetal circulation into the adult phenotype. This review summarizes the latest research findings, which show that lung aeration, airway liquid clearance and cardiovascular changes are directly interconnected at birth. The mechanisms of airway liquid clearance at birth are reviewed and the particular importance of the transpulmonary pressure gradient during lung aeration is discussed. Further, we summarize research findings which prove that lung aeration triggers the increase in pulmonary blood flow (PBF) at birth, and how the increase in PBF secures the preload for left ventricular output. Consequently, we review animal experiments which suggest that delaying umbilical cord clamping until breathing commences facilitates hemodynamic stability during transition. These data are reviewed with respect to the clinical applicability: As lung aeration is the key to successful transition to newborn life, providing adequate respiratory support at birth must be the primary objective of neonatal staff attending to the newborn infant. Clinical studies are needed to demonstrate whether the obvious benefits of delaying cord clamping until breathing commences hold true in human babies.

INTRODUCTION

The transition from fetal to newborn life can occur within minutes of birth and involves major physiological changes including aeration of the lungs, establishment of pulmonary gas exchange and changing the fetal circulation into the adult phenotype. Considering the complexity of these vital physiological processes it is surprising that most infants undergo this transition without difficulty. However, some infants, particularly infants born very premature, require assistance in making this transition. While the aim of this assistance is to stabilize the preterm infant, it is still unclear whether it is doing more harm than good. Indeed, to help these infants transition effectively without causing organ damage, we need to have a comprehensive understanding of the factors underpinning the physiological changes during normal transition at birth. In this paper, we present the latest evidence from physiological and human studies regarding the cardiovascular changes at birth.

* Corresponding author.
E-mail address: stuart.hooper@monash.edu (S.B. Hooper).

http://dx.doi.org/10.1016/j.prrv.2015.03.003
1526-0542/

Lung aeration and airway liquid clearance

In utero, the future airways are filled with a liquid that is secreted by the lung and leaves the lungs via the trachea. The resistance created by the glottis and upper airways, particularly during apnea, causes liquid to accumulate within the airways, which provides a trans-pulmonary pressure gradient between the airways and amniotic sac. The resulting high degree of fetal lung distension is a major stimulus for lung growth and airway development [1,2]. At birth, the newborn needs to clear this liquid rapidly to allow air entry and the onset of pulmonary gas exchange. As it also triggers the increase in pulmonary blood flow (PBF) at birth, lung aeration is the central determining event for the successful transition to newborn life.

The mechanisms that drive airway liquid clearance at birth have been subject of much debate, with the predominant paradigm focusing on the role of adrenaline driven sodium (Na^+) channels. According to this paradigm, adrenaline released during labour activates Na^+ channels (ENaCs) within the luminal surface of pulmonary epithelial cells, which subsequently increases Na^+ flux (and Cl^- flux) across the epithelium, away from the lumen of the distal airways [3]. This is thought to reverse the osmotic gradient across the pulmonary epithelium, which drove lung liquid secretion during fetal life, and was thought to be the primary mechanism for liquid reabsorption postnatally. While there now is considerable evidence to support the existence of this mechanism for airway liquid clearance, recent animal studies indicate that it is unlikely to be the most important mechanism of lung liquid clearance at birth [4].

Three different mechanisms are believed to be responsible for airway liquid clearance at birth and their relative contribution will likely depend on the mode and timing of delivery. Firstly, small increases in pressure across the highly compliant fetal respiratory system (transpulmonary pressure) can cause large losses of fetal lung liquid via the trachea. Such increases will occur with uterine contractions during labor and will be particularly forceful in the absence of amniotic fluid [5]. This leads to an increase in abdominal pressure that increases the transpulmonary pressure gradient by forcing the diaphragm up into the chest. This results in an increase in airway pressure and liquid loss via the trachea. This mechanism, rather than a "vaginal squeeze" of the thorax, likely explains the expulsion of liquid from the infant's nose and mouth following delivery of the fetal head, as has been numerously reported in the literature for vaginal deliveries.

Secondly, the stress response elicited by the passage of the fetal head through the cervix and vagina results in a large increase in fetal adrenaline concentrations. As explained above, adrenaline is thought to stimulate the Na^+ reabsorption mechanism via activation of ENaCs. The observation that infants born without active labor by caesarean section are at higher risk of "wet lung" is consistent with this proposal. This could be because the infants were not "stressed" at birth and so the catecholamine induced stimulation of Na^+ reabsorption was not activated. However, this mechanism matures relatively late in gestation and is thought to be absent in immature, preterm infants [5]. Although insufficient ENaCs in preterm infants could contribute to their inability to effectively clear airway liquid at birth, many are able to clear their lungs of liquid. Furthermore, many infants born at term by caesarean section would presumably have missed the large increase in catecholamine levels, but are still able to aerate their lungs after birth. In any event, it is now evident that additional mechanisms make a major (predominant) contribution to airway liquid clearance at birth.

The third mechanism of lung aeration and airway liquid clearance was studied using a recently developed imaging technique, phase contrast (PC) X-ray imaging [6]. PC X-ray imaging is particularly useful for visualizing air entry and airway liquid clearance at birth, as it uses the refractive index difference between air and water to produce contrast between these two media. Our studies have clearly demonstrated that in both spontaneously breathing and mechanically ventilated newborn rabbits, airway liquid clearance and lung aeration happen simultaneously and only occur during inspiration or lung inflation. The rates of airway liquid clearance measured during inspiration (35 L/hr/kg) are 3 orders of magnitude greater than the maximum liquid reabsorption rates that can be stimulated in late gestation fetuses using pharmacological doses of adrenaline. This high rate of pressure driven liquid clearance explains why complete airway liquid clearance can occur within minutes of birth in spontaneously breathing newborns. We also have shown that during mechanical ventilation without use of positive end-expiratory pressure (PEEP), liquid re-enters the airways during expiration, resulting in a reduction in functional residual capacity (FRC) [7].

The most likely and unifying explanation for the finding that lung inflation drives airway liquid clearance is that the increase in transpulmonary (i.e. across the airway wall) pressure generated during inspiration or lung inflation provides a hydrostatic pressure gradient that drives liquid movement from the airways and into the surrounding tissue. Whether or not lung inflation results from a spontaneous breath or from a positive pressure inflation applied mechanically using a ventilator, airway pressures are higher than the surrounding interstitial tissue pressures, which increases the pressure gradient for liquid to move out of the airways. As the liquid moves into the interstitial tissue space at a faster rate than it is cleared from the tissue it accumulates in the tissue, forming perivascular cuffs, which increases interstitial tissue pressure. As a result, the chest wall expands to accommodate the increase in air volume with little or no loss in liquid volume as the liquid has moved into the tissue, but still resides in the chest [8]. *In vivo* measurements indicate that interstitial tissue pressures transiently increase to $\sim$6 cmH_2O following lung aeration and then gradually decline, but remain above atmospheric pressure for at least 4 hours after birth [9]. This gradual reduction in pressure probably reflects the rate of liquid clearance from the tissue by the circulation or lymphatics. Eventually, tissue pressure becomes sub-atmospheric, like intrapleural pressures, where they remain for the remainder of the infant's life.

The high interstitial tissue pressures during the immediate newborn period likely explain the re-entry of liquid into the airways. As a consequence, fluctuations in FRC can be observed during expiration in both spontaneously breathing term newborns and ventilated preterm newborns in the absence of PEEP. It also explains why the application of PEEP assists in maintaining FRC, as PEEP provides an opposing pressure within the airspaces which counterbalances the high interstitial tissue pressure [7]. Therefore, the more liquid that resides in the infant's lung following delivery the larger the accumulated volumes within the interstitial tissue space and the larger increase in interstitial tissue pressure will occur. This will increase the likelihood of liquid re-entering the airways during expiration, leading to the requirement for greater inflation pressures for clearing the liquid again during the subsequent inflation. This rationale provides an additional explanation for why infants born by caesarean section suffer a higher risk of "wet lung". In the absence of an increase in transpulmonary pressure and adrenaline induced Na^+ reabsorption (see above) that would normally accompany vaginal delivery, infants born by caesarean section without labor have to cope with larger volumes of liquid within the interstitial tissue following lung aeration. As a result, interstitial tissue pressures are higher and so liquid is more likely to re-enter the airways. This is consistent with the finding that the application of a continuous positive airway pressure (CPAP) can effectively treat infants with "wet lung".