Cardiopulmonary changes with aeration of the newborn lung

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Abstract

The newborns transition from fetal to neonatal life includes aeration of the lungs, establishment of pulmonary gas exchange and a 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 increased 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.

Keywords

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

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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.

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 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 (Harding et al 1990) {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, but many are able to clear their lungs from 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 ~6 cmH$_2$O 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".

Based on the concept that lung liquid moves distally through the airways and is cleared from the terminal airsacs (alveoli) due to pressure gradients generated by inspiration, new approaches can be developed that facilitate this process in infants requiring respiratory assistance at birth. For instance, as liquid has a much higher viscosity than air, the movement of liquid though the airways has a much higher resistance (by ~100 fold) than the movement of air. As a result, to move the same volume of liquid as air through the airways requires either higher pressures gradients or longer inflation times. For this reason, clinicians and researchers have advocated the use of prolonged inflation times, or sustained inflations, (SI) during neonatal resuscitation when the lung is still mostly liquid-filled {10, 11}. By sustaining the inflation pressure, the movement of liquid through the airways is facilitated over the course of a single inflation, resulting in more rapid recruitment of tidal volume and FRC and a more uniform distribution of ventilation {12, 13}. Alternatively, the application of PEEP between inflations maintains a sustained pressure on the airways throughout the respiratory cycle, however, at a different pressure. This may not be sufficient to maintain the movement of liquid down the airways, but it appears that PEEP prevents liquid from refilling the airways between inflations {7}.

Lung aeration and the cardiovascular transition at birth

The majority of physiological processes that characterize the transition to newborn life are triggered by lung aeration. The penetration of air into the distal gas exchange units of the lung allows pulmonary gas exchange to commence and triggers a significant increase in pulmonary blood flow (PBF). It's the increase in PBF at birth that not only underpins the infant's transition from placental to pulmonary gas exchange, but also triggers the transition of the circulation into the adult phenotype.

The fetal circulation is very different to that of the adult. The ventricles of the fetal heart pump in parallel as the right and left ventricle both contribute predominantly to systemic circulation. Pulmonary blood flow in the fetus accounts for only about 10% of right ventricular output, due to increased pulmonary vasoconstriction leading to high pulmonary vascular resistance (PVR). Most blood exiting the right ventricle (~90%) flows from the main pulmonary artery through the ductus arteriosus (DA) into the aorta, contributing to systemic arterial flow. Shunting across the DA is entirely right-to-left because PVR is markedly higher compared to systemic vascular resistance. As a result, PBF only receives 10-20% of right ventricular output, whereas the placental circulation receives 30-50% of total cardiac output (CO). It follows therefore, that 30-50% of venous return comes from the placental circulation. Unlike in the adult, the low PBF of the fetus is incapable of providing adequate preload for the left ventricle, which instead primarily comes from umbilical, i.e. placental, venous return. A large (~50%) proportion of oxygenated umbilical venous blood flows through the ductus venosus, passes up the inferior vena cava and through the foramen ovale to directly enter the left atrium. This results in higher oxygen concentration in the preductal arteries (arteries originating from the aorta prior to the junction with the DA), compared with the postductal arteries.

In view of the role of umbilical venous return in supplying preload for the left ventricle in the fetus, clamping the umbilical cord immediately after birth represents a dramatic challenge to the infant's freshly establishing circulatory system. In particular, the infant has to compensate for the loss of placental venous return. This primarily occurs due to a decrease in PVR and an increase in the percentage of cardiac output (CO) that flows through the lungs, so that the increase in PBF will eventually replace umbilical venous return as the source of preload for the left ventricle. Initially, clamping the umbilical cord at birth causes an instantaneous increase in systemic vascular resistance (SVR), leading to a large increase (~30%) in systemic arterial pressure over the first 4 heart beats after clamping {14}. Despite the increase in systemic arterial pressure, blood flow through the DA remains right-to-left as downstream resistances in the placental vascular bed remains higher than SVR, despite the loss of the low resistance placental vascular bed. With clamping of the umbilical cord, the venous return to the heart is markedly diminished and as a result preload and afterload are increase (indicated by the higher arterial pressure) leading to a reduction in CO. Importantly, CO remains reduced until PBF increases in response to lung aeration, at which point PBF becomes the primary source of preload for the left ventricle. Consequently, the increase in PBF immediately after birth is a major determinant of left ventricular output {15}.

After the onset of ventilation, PVR falls and resistance within the pulmonary circulation drops below that of the systemic circulation. As a result, net flow through the DA reverses, becoming predominantly left-to-right within 10-20 mins after birth {16, 17}. However, over a single heartbeat, the flow is bidirectional. This is due to the shorter distance between the pulmonary valve and pulmonary artery/DA junction than between the aortic valve and DA/aorta junction. Assuming that the pressure waves travel at approximately the same speed, during systole the pressure waves exiting the ventricles will therefore reach either end of the DA at different times. Given this, the pressure waves will reach the pulmonary artery/DA junction first, causing right-to-left flow but this is quickly reversed when the pressure wave emanating from the left ventricle hits the DA/aortic junction. At this point, the net flow

through the DA is predominantly left-to-right, providing up to 50% to PBF and, therefore, also contributing to pulmonary venous return and preload for the left ventricle. Hence, in essence, for a brief period after birth, the left ventricle provides output for PBF and contributes to its own preload, forming a left heart - lung - left heart short circuit (16). As all preductal arteries lie within the short circuit, the organs supplied by these arteries (eg the brain) will benefit from the resulting improved left ventricular output, which to a certain extent can occur irrespective of right ventricular output.

Implications for clinical practice

At birth, the marked reduction in CO caused by immediate cord clamping, due to a reduction in preload, can be avoided by aerating the lung and increasing PBF before the umbilical cord is clamped {18}. This is because decreasing PVR and increasing PBF before the cord is clamped, allows pulmonary venous return to immediately replace umbilical venous return as the primary source of left ventricular preload, without any diminution in supply. Furthermore, as UCC increases SVR, if the reduction in PVR caused by lung aeration precedes UCC, as soon as the cord is clamped, net flow through the DA reverses. As a result blood predominantly flows from the aorta back into the pulmonary circulation (left-to-right), which as indicated above, contributes to PBF during the immediate newborn period and enhances venous return and preload for the left ventricle. Although the benefits of delayed UCC are often thought of in terms of increasing the transfer of blood from the placenta to the infant, clearly preserving preload and CO during the transition at birth is also a major benefit. More importantly, it indicates that the timing of UCC should be linked to a physiological outcome, such as breathing onset, rather than an arbitrary period of time after birth that bears no relationship to the underlying physiological changes that are occurring in the infant.

Lung aeration and the increase in pulmonary blood flow at birth

Although it is well established that lung aeration triggers the increase in PBF after birth, which in turn initiates the cardiovascular changes that underpin the transition to newborn life, the mechanisms involved are unclear. In general, the decrease in PVR is thought to be an integrated response to a number of physiological stimuli, particularly as a result of an increase in oxygenation. For instance, with the entry of air into the distal gas exchange units of the lung, the associated exposure of the vascular endothelium to increased oxygen levels is thought to trigger an increase in nitric oxide (NO) mediated vasodilation. The entry of air into the distal gas exchange units of the lung is also thought to decrease PVR due to the formation of an air/liquid interface and an associated increase in lung recoil. That is following lung aeration, surface tension forms within the lung for the first time, which markedly increases lung recoil despite the presence of surfactant. The increase in lung recoil plays a vital role in normal lung function by providing ~2/3 (1/3 is due to the inherent elasticity of lung tissue) of the lung recoil that drives normal (unforced) expiration. In addition, as the basement membranes underlying the alveolar epithelium and capillary endothelium are fused for ~50% of the surface area of the lung, the alveoli and capillary walls are mechanically coupled {19}. As such, forces applied in one compartment will be transmitted into the other compartment. For instance, an increase in alveolar recoil causes capillary distension and a decrease in PVR, whereas increases in alveolar pressure cause

capillary compression and an increase in PVR; the latter is thought to be the primary mechanism by which high PEEP levels increase PVR and decrease PBF {20}.

Although the suggested mechanisms for the decrease in PVR at birth are relatively diverse, the one thing they have in common is that lung aeration and the increase in PBF should be spatially related. That is, PBF should increase preferentially in aerated regions of the lung, which would be consistent with the well-established ventilation/perfusion relationships that have been described in the adult lung. However, recent evidence indicates that lung aeration is not spatially related with the increase in PBF, as partial lung aeration causes a global increase in PBF (21). This indicates that additional mechanisms may be involved. Considering the important role that the increase in PBF has in maintaining CO in the newborn, from a teleological perspective, it would appear preferable to not spatially link the increase in PBF with lung aeration. Indeed, as lung aeration is notoriously heterogeneous, making the optimal increase in PBF dependent upon complete lung aeration would appear to be a much less robust approach, placing the infant at considerable risk of suffering poor cardiac function after birth if the lungs do not aerate fully.

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Learning objectives

The reader will be able to better appreciate that:

1. The transition to newborn life is triggered by lung aeration and airway liquid clearance.

2. The primary mechanism for airway liquid clearance at birth is the increased transpulmonary pressure generated by inspiration.

3. Aeration of the lung triggers the increase in pulmonary blood flow.

4. The increase in pulmonary blood flow facilitates efficient pulmonary gas exchange and provides venous return and preload for the left heart.

5. 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.

Key Major recommendations

The transition to newborn life is triggered by lung aeration and airway liquid clearance. Recent evidence indicates that the primary mechanism for airway liquid clearance at birth is the result of increased transpulmonary pressures (across the airway wall) generated by inspiration. These pressure gradients facilitate the movement of liquid from the airways into the surrounding tissue from where it is cleared, but at a much slower rate. As a result, the lung is relatively "edematous" during the first few hours after birth, increasing the likelihood of liquid re-entering the airways. Lung aeration not only allows air to penetrate into the distal gas exchange regions of the lung, so that pulmonary gas exchange can commence, but it also triggers the increase in PBF. The increase in PBF is necessary to facilitate efficient pulmonary gas exchange and also provides venous return and preload for the left ventricle that is lost following UCC. In view of the vital role that lung aeration plays in the transition to newborn life, providing adequate respiratory support should be the top priority in infants requiring assistance to make this transition. Furthermore, as the increase in PBF after birth is vital for providing preload for the left ventricle, umbilical cord clamping should be delayed until after the infant initiates ventilation onset. This gives time for PBF to increase and immediately take over the role of providing preload for the left ventricle as soon as the cord is clamped.