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Issues in cardiopulmonary transition at birth

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ABSTRACT

The transition from fetal to newborn life involves a complex series of physiological events that commences with lung aeration, which is thought to involve 3 mechanisms. Two mechanisms occur during labour, Na^+ re-absorption and fetal postural changes, and one occurs after birth due to pressure gradients generated by inspiration. However, only one of these mechanisms, fetal postural changes, involves the loss of liquid from the respiratory system. Both other mechanisms involve liquid being reabsorbed from the airways into lung tissue. While this stimulates an increase in pulmonary blood flow (PBF), in large quantities this liquid can adversely affect postnatal respiratory function. The increase in PBF (i) facilitates the onset of pulmonary gas exchange and (ii) allows pulmonary venous return to take over the role of providing preload for the left ventricle, a role played by umbilical venous return during fetal life. Thus, aerating the lung and increasing PBF before umbilical cord clamping (known as physiological based cord clamping), can avoid the loss of preload and reduction in cardiac output that normally accompanies immediate cord clamping.

1. Introduction

At birth, the remarkable ease at which most infants transition to newborn life belies the complexity of the physiological changes that are needed to survive after birth. Before birth, the lungs are liquid-filled and gas exchange occurs across the placenta. Pulmonary blood flow (PBF) is low and the majority of right ventricular output bypasses the lungs and flows through the ductus arteriosus (DA) to enter the descending aorta [1,2]. As much of this blood is then directed through the placenta, the right ventricle supplies the majority of blood flowing through the fetal gas exchange organ (placenta), just like it does in adults. Similarly, in the fetus, a large proportion of the blood returning from the placenta to the heart is shunted (through the ductus venosus and foramen ovale) directly into the left side of the heart, bypassing the right side and the lungs. As such, in the fetus, blood returning from the fetal gas exchange organ (placenta), provides much of the preload for the left ventricle, just like in the adult, which receives blood returning from the lungs [3].

Switching the site of gas exchange from the placenta to the lungs at birth, necessitates that the airways are cleared of liquid, to allow the entry of air, and that pulmonary vascular resistance (PVR) substantially decreases. The latter is necessary so that: (i) the entire output from the right ventricle can be redirected through the lungs to facilitate gas exchange and (ii) PBF substantially increases (~30 fold) so that it can replace umbilical venous return as the source of preload for the left ventricle [2]. These major physiological changes are critical for survival after birth and are triggered by the one event that cannot occur before birth, aeration of the lungs. Indeed, lung aeration at birth is not just important for allowing the onset of pulmonary gas exchange. It also triggers a sequence of inter-dependent physiological events, beginning with the increase in PBF, that initiates a major reorganisation of the fetal circulation into the adult phenotype, allowing the two circulations to separate [2].

2. The respiratory transition at birth

Before birth, airway liquid is secreted by the lung and plays a vital role in fetal lung growth and development by maintaining the lung in a distended state [4,5]. Increasing the degree of lung distension is a potent stimulus for fetal lung growth whereas a reduction in lung expansion causes fetal lung growth and development to cease [4,5]. However, at birth this liquid must be cleared from the airways to allow the entry of air and the onset of pulmonary gas exchange. To understand how airway liquid clearance can affect respiratory function after birth, it helps to recognise that the lung passes through two distinct phases before it starts to function like an adult lung [1]. During the first

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phase, the airways are liquid-filled which precludes pulmonary gas exchange and greatly increases airway resistance. During the second phase, the airways are cleared of liquid, allowing pulmonary gas exchange, but the liquid has shifted into lung tissue. This causes a form of pulmonary oedema, which likely plays a critical role of stimulating the increase in PBF (see below), but can also reduce respiratory function. While the first phase is usually quite short (30–60 s), the second phase is markedly longer (4–6hrs) and can potentially influence respiratory function well into the newborn period [1].

3. Phase 1: Airway liquid clearance and lung aeration at birth

The timing and mechanisms of airway liquid clearance are generally not well understood, with many still believing that airway liquid clearance simply results from Na^+ reabsorption induced by the stress of labour. However, up to three mechanisms are involved, with the primary mechanism in any one infant depending upon the timing and mode of delivery [1]. Two of these mechanisms are active during labour and the third is active after birth (see below). Some have argued that liquid clearance begins days to weeks before labour onset [6]. However, the evidence supporting this concept was obtained from animal experiments performed before the relationship between reduced amniotic fluid volumes and reduced lung liquid volumes was fully recognised [7,8]. Indeed, a common side effect of fetal surgery in sheep is amniotic fluid leakage, which may have interfered with the findings. We now know that the volume of fetal lung liquid present in the airways before birth varies considerably between individuals and largely depends on the available intra-uterine space [5]. Reducing this space, as occurs with reduced amniotic fluid volumes, reduces lung liquid volumes [7] and it is possible that other factors, such as the presence of a twin, may have a similar effect.

3.1. Airway liquid clearance before birth

Na^+ reabsorption can result from increased circulating fetal adrenaline levels, induced by the stress of labour (particularly during vaginal delivery of the head), which act on alveolar epithelial cells to stimulate Na^+ uptake from the lung lumen [6,9]. This reverses the osmotic gradient across the lung epithelium leading to liquid reabsorption from the airways. While this mechanism has been demonstrated experimentally, it is only present late in gestation and pharmacological doses of adrenaline are required [10–12]. As such, this mechanism is not active in preterm infants. Furthermore, despite the requirement for very high adrenaline levels, maximum re-absorption rates are ~3 orders of magnitude less than airway liquid clearance rates after birth [10–12] (see below). Thus, if airway liquid clearance occurred by Na^+ reabsorption alone, it would take hours before gas exchange could occur, adrenaline levels would have to be elevated throughout this time and preterm infants would not be able to aerate their lungs [1]. There is also much confusion over whether adrenaline levels are consistently increased during delivery and whether the mode of delivery influences adrenaline levels. While no difference in cord blood adrenaline levels were found between infants delivered vaginally or by caesarean section (CS), this reference [13] is commonly cited (incorrectly) as demonstrating that adrenaline levels are increased in vaginally delivered, compared to CS delivered, infants. In contrast, asphyxic and breech delivered infants had markedly elevated adrenaline levels [13]. The concept that airway liquid clearance is not dependent upon Na^+ reabsorption is consistent with the finding that Na^+ channel blockade (with amiloride) does not affect the extent or the spatial and temporal pattern of airway liquid clearance after birth [14].

Forces imposed on the infant during uterine contractions can also cause large volumes of liquid to exit the lungs via the nose and mouth [7]. Indeed, gushes of liquid from the nose and mouth can be observed upon delivery of the head, which likely results from increased dorsoventral flexion of the fetal abdomen during uterine contractions [15]. Increased spinal flexion, increases abdominal pressure and elevates the diaphragm causing an increase in transpulmonary pressure and the loss of lung liquid via the trachea [7]. As the fetal respiratory system is highly compliant, only small increases in transpulmonary pressure are needed to lose large volumes of liquid [16]. However, the contribution of this mechanism to airway liquid clearance at birth, likely varies considerably between individuals. For instance, infants delivered vaginally and exposed to strong uterine contractions during a protracted labour, will likely lose large volumes of lung liquid via this mechanism [1]. On the other hand, infants delivered by elective CS without labour will lose little or no liquid via this mechanism. It is important to note that this mechanism of airway liquid loss, is the only mechanism whereby liquid is completely lost from the respiratory system following its clearance. Both other mechanisms (Na^+ reabsorption and inspiratory efforts, see below) involve the clearance of liquid into lung tissue, before it is eventually cleared from the tissue hours after birth [1]. As described below, the presence of this liquid in lung tissue has significant implications for respiratory function after birth.

3.2. Airway liquid clearance after birth

Phase contrast X-ray imaging studies Fig. 1 have demonstrated that, after birth, the pressure gradients generated by inspiration rapidly and efficiently clear the airways of liquid, resulting in full aeration within 3–5 breaths (< 30secs) in term newborns [17,18]. Indeed, the calculated rates of liquid clearance during inspiration are astonishingly large (~32 L/hr/kg) and explain why infants can rapidly initiate pulmonary gas exchange after birth, even in infants born by CS without labour [17,18]. The images show that the air/liquid interface moves distally through the airways in a stepwise manner with each inspiration, with little or no distal movement between breaths Fig. 1. Some proximal movement can occur between breaths, which likely results from liquid re-entry into the airways [17,18].

The pressure gradients driving liquid movement distally through the airways and across the distal airway wall are derived from inspiration, which reduces interstitial tissue pressures [17,18]. This results in a large hydrostatic pressure gradient between the tissue and airways causing liquid to move out of the airways into the surrounding lung tissue. Similar pressure gradients can be applied using positive pressure ventilation, producing a similar effect [14,19,20]. The initial resistance to moving air into the lung after birth is governed by the resistance to moving liquid through the airways and across the distal airway wall. As lung liquid has a viscosity that is ~100x greater than air, the initial resistance to moving air into the lung is ~100x greater than it is following lung aeration and rapidly decreases as the lung aerates [21] Fig. 2. Preterm infants have smaller airways and as the resistance increases exponentially (4th power) as the airway radius decreases, the initial resistance to moving liquid through the airways at the start of lung aeration should be significantly greater in preterm compared to term infants [21] Fig. 2. Similarly, as the surface area of the distal airways increases exponentially with increasing gestational age, preterm infants have a markedly reduced distal airway surface area, which must also increase the resistance for liquid movement into lung tissue. Despite this, it is recommended that at birth preterm infants are ventilated with starting pressures that are much lower than term infants [22].

The reduction in airway resistance during lung aeration follows an exponential function that is difficult to predict, resulting in large changes in respiratory mechanics on a breath-by-breath basis [21]. Thus, using intermittent positive pressure ventilation (iPPV) with a single set inflation pressure during lung aeration may initially produce small tidal volume changes, but result in very large tidal volumes following lung aeration. As such, it is difficult to understand why highly sophisticated ventilators that can monitor and respond to breath-by-breath changes in respiratory mechanics are commonly used in the NICU, but not in the delivery room. Indeed, respiratory mechanics have

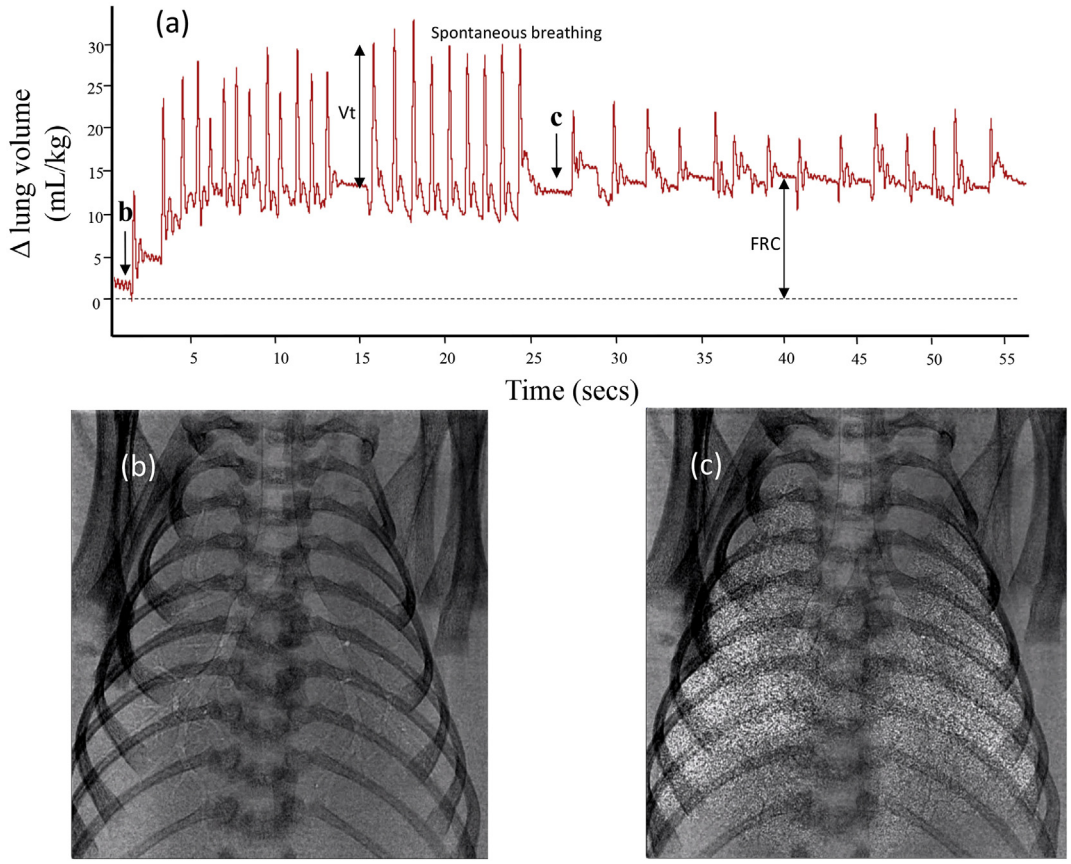

Fig. 1. (a) Lung gas volumes, measured by plethysmography, in spontaneously breathing near term newborn rabbits from birth. The increase in baseline volume represents the formation of a functional residual capacity (FRC), which rapidly increases with each breath. Initially, the tidal volumes are large (10–15 mL/kg), but decrease (to 7–8 mL/kg) following lung aeration. This newborn rabbit took ~15 s to generate an FRC of ~15 mL/kg (b) and (c) are phase contrast X-ray images, acquired at the time points indicated by (b) and (c) in the plethysmography recording (a), showing the degree of lung aeration at each time point. Data obtained from Ref. [17].

usually stabilised by the time the infant reaches the NICU, whereas in the delivery room, the changes in respiratory mechanics are rapid and complex. Despite this, ventilation in the delivery room most commonly involves the use of rudimentary devices (T-piece devices or resuscitation bags) that are incapable of automatically adjusting ventilation parameters to take into account rapidly changing respiratory mechanics. This likely greatly contributes to the large variation in tidal volumes measured in preterm infants at birth [23].

4. Phase 2: effect of airway liquid within lung tissue

As the lung's interstitial tissue compartment has a fixed volume, the entry of airway liquid into this compartment increases interstitial tissues pressures, causing a form of oedema that persists for 4–6 h while the liquid is gradually cleared from the tissue [24,25]. The presence of this liquid in lung tissue potentially has major implications for respiratory function after birth. For instance, as airway liquid is replaced with air when it moves into lung tissue, it still remains within the chest. As a result, the chest wall must expand to accommodate both the liquid and the volume of air that resides in the lung at end-expiration (functional residual capacity; FRC) [17] Fig. 3. The increase in interstitial tissue pressure also increases the pressure gradient for liquid to re-enter the airways at end-expiration, which is subsequently cleared during the next breath/inflation [18]. While the presence of this liquid in lung tissue also reduces lung compliance [26], making the lungs stiffer and more difficult to inflate, there is very little understanding for how this consequence of airway liquid clearance may contribute to respiratory morbidity in the new born.

4.1. Transient tachypnea of the newborn

Increased spinal flexion and airway liquid loss from the nose and mouth is the only mechanism of airway liquid clearance that results in the complete loss of liquid from the respiratory system [1]. Thus, if this mechanism is not activated, all liquid present in the airways at birth must be cleared (either by Na reabsorption or inspiration) across the distal airway wall into lung tissue. For example, in all infants born by elective CS without labour, the majority of airway liquid must be cleared by the pressures generated during inspiration and all of this liquid must enter lung tissue [1]. In contrast, infants delivered vaginally will have lost significant volumes of liquid via the nose and mouth during delivery [15]. As a result, after birth, the volume of liquid that must be cleared into lung tissue is considerably less. There is now mounting evidence to suggest that transient tachypnoea of the newborn (TTN) does not result from a failure to clear fetal lung liquid, but results from having larger volumes of airway liquid at the onset of breathing [1,26]. As a result, larger volumes must be cleared into lung tissue, which increases the degree of lung “oedema” following lung aeration [24,25]. This is consistent with the findings of multiple RCTs, targeting the stimulation of Na reabsorption mechanisms (eg β-agonists such as salbutamol), that have failed to show any benefit with regard to reducing the incidence or severity of TTN [27].

Recent experimental studies have simulated the influence of labour (reduced lung liquid) and absence of labour (increased lung liquid) on respiratory function and mechanics immediately after birth [26]. Increasing lung liquid volumes at birth, reduces lung compliance and FRC and causes the chest wall to expand further and the diaphragm to

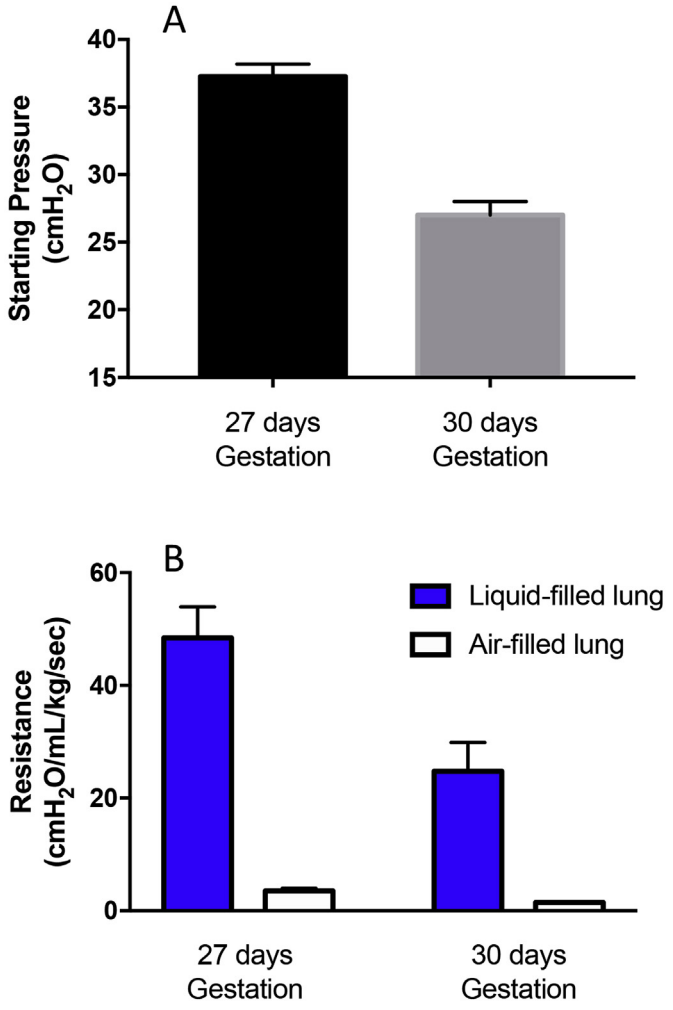

Fig. 2. (A) Inflation pressures required before gas first starts to move into the liquid-filled lung immediately after birth in either very premature (27 days gestational; black bar) or near-term (30 days gestation; grey bar) rabbits. The starting pressure is considerably less ($p < 0.001$) in older more mature newborn rabbits. (B) Airway resistance measured in a liquid-filled lung (blue bars) and moments later after lung aeration (open bar) in very premature (27 days gestation) and near-term (30 days gestion) newborn rabbits. Note that aeration of the lung markedly reduces airway resistance at both ages and that airway resistances are always less in older, more mature newborns. Data reploted from Ref. [21].

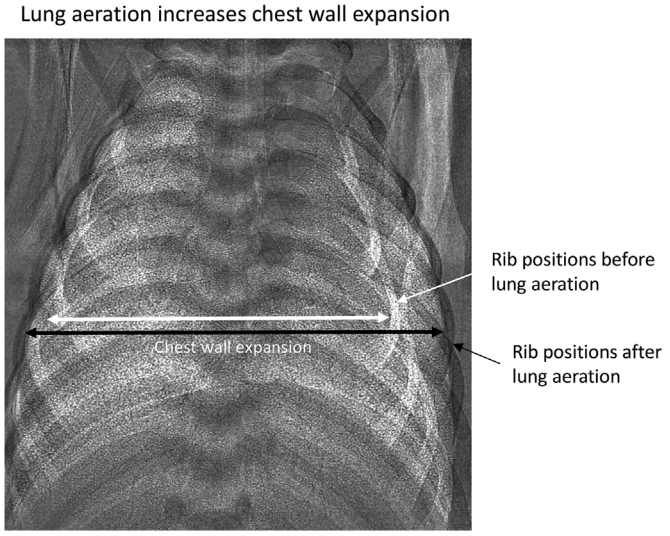

Fig. 3. Two superimposed phase contract X-ray images acquired from the same newborn rabbit before (inverted image, ribs displayed in white) and following (ribs displayed in black) lung aeration; both images were acquired at functional residual capacity. Note that, based on rib position, the chest wall has considerably expanded following lung aeration.

flatten [26]. These changes readily explain the respiratory symptoms characterised by infants diagnosed with TTN. The reduction in FRC explains the expiratory grunting, which is caused by closure of the glottis during expiration and is commonly used by newborns to preserve lung volumes (FRC) after birth. On the other hand, chest wall expansion and flattening of the diaphragm reduces inspiratory reserve volumes and when combined with a lower lung compliance, restricts tidal volumes. Thus, to sustain alveolar ventilation, respiratory rates must increase, which explains the tachypnea and laboured breathing.

With regard to understanding the causes and full significance of TTN, how it should be treated and whether it can be avoided in at risk infants, it is important to recognise that the diagnosis of TTN is imprecise, subjective and often occurs in retrospect after the infant has recovered [28]. As such, infants diagnosed with TTN are commonly regarded as a subgroup of near term infants with respiratory morbidity that is usually mild and self-limiting. Indeed, the latter characteristic is a significant contributing factor to the diagnosis, but it is highly questionable whether it has any clinical value with regard to treatment. It may also artificially divide infants into subgroups despite having the same underlying problem. Indeed, how should infants, who initially show similar TTN-like symptoms, but then develop more severe and protracted respiratory distress, be diagnosed? It is possible that the underlying morbidity is multifactorial that can progress from a mild respiratory disease into a major respiratory pathology (eg severe respiratory distress or pulmonary hypertension). The progression towards more severe disease may depend on factors such as the volume of airway liquid at the onset of breathing and the availability and timely use of treatments like continuous positive airway pressure (CPAP; see below) [29]. Indeed, accommodating large volumes of liquid in lung tissue may cause lung injury and respiratory distress due to a continuous cycle of airway liquid clearance and then re-entry with each breath [18]. As CPAP provides a positive pressure gradient that opposes liquid re-entry into the airways during expiration, this explains why CPAP may be an effective treatment for TTN [19,20]. However, prevention is better than treatment and so fully understanding the mechanism of TTN may help to develop delivery techniques at CS that simulate the liquid loss during vaginal delivery. Nevertheless, as language is important, it may be prudent to change the name or at the very least, remove the word “transient” as it is potentially misleading and necessitates that the diagnosis be made retrospectively.

5. The cardiovascular transition at birth

As described above, the fetal cardiovascular system is considerably more complex than the adult, containing multiple shunts that interconnect the pulmonary and systemic circulations [3] Fig. 4. However, while the fetal and adult circulations are anatomically distinct, functionally they are quite similar, differing only because the placenta, rather than the lung, is the fetal organ of gas exchange. That is, due to the presence of the ductus arteriosus, which shunts blood from the pulmonary artery into the aorta, the right ventricle provides the majority of blood flow to the organ of gas exchange (placenta) in the fetus [3], just like it does in the adult. Similarly, due to the presence of the ductus venosus and foramen ovale, which shunts umbilical venous return directly into the left atrium, blood returning from the gas exchange organ in the fetus, provides the majority of preload for the left ventricle, just like it does in the adult [3,30] Fig. 4. However, as the lungs must take over the role of gas exchange at birth, the circulation has to undergo a massive re-organisation so that the lungs can: (i) become the sole

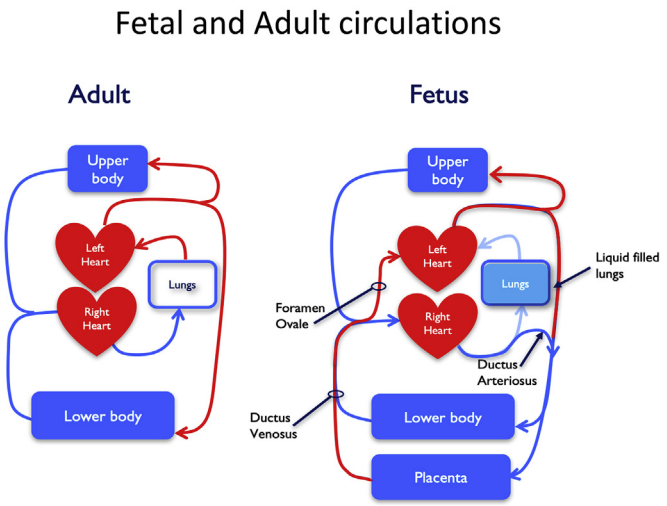

Fig. 4. Functional structure of the adult and fetal circulations. In the adult, all venous return from the upper and lower body returns to the right side of the heart, providing the right ventricle with preload. As all of right ventricular output flows through the lungs, pulmonary venous return provides all preload for the left ventricle. In the fetus, pulmonary blood flow (PBF) is low as the majority of right ventricular output flows through the ductus arteriosus into the descending aorta, with much of this blood flowing through the placenta. As such, PBF provides little preload for the left ventricle, which instead comes from umbilical venous return via the ductus venosus and foramen ovale. While the fetal circulation is anatomically quite distinct from the adult circulation, functionally it is quite similar in that the right ventricle provides all or most of the flow to the organ of gas exchange (lung and placenta). Similarly, the left ventricle receives its preload predominantly from venous blood returning from the organ of gas exchange.

recipient of blood flow exiting the right ventricle and (ii) provide sufficient venous return to sustain left ventricular output. The primary factor that underlies these changes is a very large decrease in pulmonary vascular resistance (PVR), which in turn is triggered by the one event that cannot occur before birth, lung aeration [2].

6. Increase in PBF at birth

Increased vasodilator release, particularly nitric oxide (NO), in response to an increase in oxygenation, is thought to be the primary mechanism that stimulates an increase in PBF in response to lung aeration [31]. Indeed, oxygenation is an important regulator of PBF in adults, being largely responsible for ventilation/perfusion matching in the lung. However, while, increasing oxygen levels can increase fetal PBF, the effect of oxygen is not sustained [31] and ventilation of the lung with a gas devoid of oxygen (ie 100% nitrogen) or with low oxygen levels, can stimulate a large increase in PBF [32,33]. Thus, other mechanisms are also involved, which include, an increase in lung recoil caused by the formation of an air/liquid interface and the creation of surface tension within the lung following aeration [34]. However, while deflating the fetal lung increases PBF, the increase is considerably smaller than the increase in PBF at birth [34].

Recent imaging experiments have discovered a previously unknown mechanism for the increase in PBF at birth while investigating the spatial relationship between lung aeration and the increase in PBF [35–37] Fig. 5. In view of the effects of oxygenation and lung recoil on PBF, it was hypothesized that, at birth, the increase in PBF would be restricted to aerated lung regions [37]. However, partial lung aeration was found to cause a global increase in PBF (Fig. 2), which occurred equally and simultaneously in all parts of the lung, irrespective of their aerated state Fig. 5. Similarly, partial aeration of the lung with a gas devoid of oxygen (100% nitrogen) also caused a global increase in PBF [35]. As such, the global response cannot be due to increased oxygenation following recirculation of oxygenated blood from aerated into unaerated lung regions. On the other hand, as partial lung aeration with 100% oxygen caused a larger PBF increase in aerated regions, compared to unaerated regions [35], increased oxygenation likely contributes to the increase in PBF at birth, but the effect is localised to aerated lung regions.

Realisation that partial lung aeration causes rapid vasodilation simultaneously in aerated and unaerated regions, led to the hypothesis that a neural reflex mediates the lung aeration induced increase in PBF [36]. In the adult lung, the juxta-capillary receptor (J-receptor), is thought to be sensitive to lung oedema and when activated triggers an increase in breathing rate (tachypnoea) [38]. The receptors are thought to be located within juxta-capillary tissue between adjacent alveoli and to signal via afferent C-fibres passing within the vagal nerve trunk. As lung aeration at birth involves lung liquid leaving the distal airways and entering the peri-alveolar tissue, the accumulation of liquid within lung tissue simulates lung oedema and may activate these J-receptors. The receptors signal the brain via the vagus which then initiates global pulmonary vasodilation, presumably via efferent parasympathetic nerves. This hypothesis is consistent with the finding that bilateral *trans*-section of the vagus nerves [36] blocked the global increase in PBF caused by partial lung aeration. Interestingly, partial lung aeration with 100% oxygen increased PBF only in aerated lung regions, indicating that the oxygen mediated increase in PBF was not affected. As such, the increase in PBF at birth in response to lung aeration may result from a hierarchy of mechanisms that either have global or localised effects. That is, the initial movement of liquid out of the airways into lung tissue activates receptors (possibly J-receptors) to initiate a global increase in PBF via a neural reflex. However, this increase in PBF is modulated at the local level by increased oxygenation, which is likely to be mediated by NO release.

7. Why should lung aeration initiate a global increase in PBF?

In the healthy adult lung, ventilation of lung regions is closely "matched" with the level of blood flow (perfusion) through those lung regions, which is known as "ventilation/perfusion matching" [39]. This is largely regulated by changing oxygenation levels within localised lung regions and plays an important role in optimising the lung's gas exchange potential. This is achieved by ensuring that when ventilation within lung regions change, affected regions receive a matching change in blood flow. In the diseased lung, a ventilation/perfusion "mismatch" can occur whereby lung regions with little or no ventilation receive large amounts of blood flow. This is commonly referred to as a pulmonary shunt and can greatly reduce the gas exchange efficiency of the lung.

While a ventilation/perfusion "mismatch" is thought to be problematic in adults, the presence of a large pulmonary shunt in newborns at birth can be viewed in a very different context [37]. Indeed, while survival at birth is not dependent upon the entire lung being ventilated, good cardiac output is essential for preventing hypoxic/ischemic brain injury during periods of reduced oxygenation, which is relatively common at birth. Thus, as a high PBF is essential to maintain left ventricular output, it is important that the increase in PBF is not limited by whether or not the lung is fully aerated. As lung aeration can be delayed in some infants, particularly very preterm infants, it makes good teleological sense that cardiac output is not limited by the degree of lung aeration.

8. Cardiovascular effects of umbilical cord clamping at birth

As discussed above, during fetal life, PBF is low and contributes little to the supply of preload for the left ventricle, which instead primarily comes from umbilical venous return [3,30]. Thus, after birth the supply of preload for the left ventricle must switch from umbilical venous return to pulmonary venous return, but before this can happen,

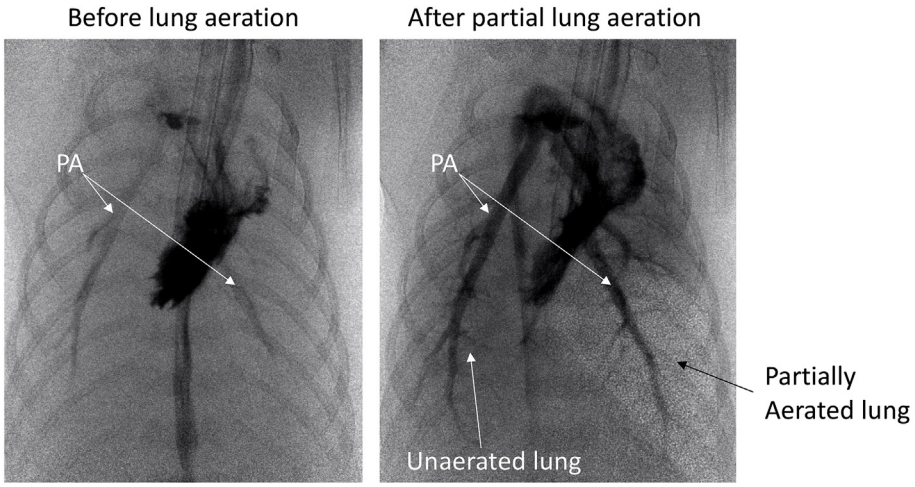

Fig. 5. Simultaneous angiographic and phase contrast X-ray images of a newborn rabbit before and after lung aeration. Very little iodine contrast flows into the pulmonary arteries (PA) before lung aeration, which is indicative of low PBF. Following partial aeration of the lung, PBF markedly increases in both PAs, increasing equally in both arteries irrespective of whether they are perfusing aerated or unaerated regions of the lung.

the lungs must aerate so that PBF can increase [40,41]. As such, when umbilical cord clamping occurs immediately after birth, before the lungs have had an opportunity to aerate, the loss of umbilical venous return causes a loss of preload and a sudden reduction in cardiac output [40]. Cardiac output remains low until the lungs aerate and PBF increases to restore venous return to the left ventricle [40]. In addition, the loss of the low resistance placental circulation upon cord clamping causes a large rapid increase in systemic vascular resistance, resulting in a rapid rise in arterial pressure (30% increase in 4 heart beats) [40]. As a result, umbilical cord clamping before lung aeration not only causes a loss in ventricular preload, but also causes a large increase in after load, which likely contributes to the reduction in cardiac output [40].

The question of whether immediate cord clamping before lung aeration could impact on cardiac output at birth was first raised by the study detailing the nomograms for heart rate changes from birth in normal healthy well oxygenated infants [42]. Up to 50% of normal healthy infants were found to be bradycardic (heart rate < 100) within the first minute of birth, which was difficult to explain simply in terms of a hypoxia-mediated bradycardia [42]. Instead it was suggested that the loss of umbilical venous return due to cord clamping caused a large reduction in cardiac output, which was reflected by a decrease in heart rate [42]. This suggestion was subsequently confirmed in animal studies, which also demonstrated that if lung aeration and the increase in PBF occurs before umbilical cord clamping, the reduction in cardiac output is avoided [40]. This is now referred to as physiological based cord clamping (PBCC) and provides an additional or alternative explanation for the benefits of delayed umbilical cord clamping [2,43,44].

9. Delayed umbilical cord clamping

Until recently, the benefits of delaying or deferring umbilical cord clamping (DCC) immediately after birth has entirely centred around the concept of placental transfusion [45,46]. This is thought to result from a net shift of blood volume out of the placenta into the infant in a time-dependent manner after birth [47]. Compared with immediate cord clamping, the infant body weight gains associated with placental transfusion during DCC [45] are consistent with the reduction in birth weight found in the meta-analysis comparing active vs expectant management of the third stage of labour [48]; immediate cord clamping is one of three components of the active management strategy. As such, the evidence for “placental transfusion” is compelling [49], but as yet there is still no scientific data explaining how this occurs and it is possible that the word “transfusion” is misleading. It is not gravity related [50,51], it is not due to uterine contractions “squeezing” blood out of the placenta (unpublished observations), it is not due to the increase in PBF causing a reduction in umbilical artery flow [52] and it is not due to intrathoracic pressure reductions caused by inspiration [53]. It could result from a shift in blood volume out of the infant and into the placenta during vaginal birth, which then shifts back to to "rebalance" the circulations after delivery. But this needs verification. Nevertheless, the focus on “placental transfusion” has meant that the vast majority of clinical trials on DCC have used a time-based approach, because placental transfusion is thought to be time-dependent [45,46]. However, we now know that a time-based approach makes little biological sense and is less than ideal, particularly for infants requiring respiratory support at birth [2,43]. Indeed, those infants will either receive immediate cord clamping or have their respiratory support delayed so that they can receive a “placental transfusion”. As indicated above and below, the science is very clear and predicts that both strategies are far from ideal, particularly the latter.

10. Physiological based cord clamping (PBCC)

The concept underpinning PBCC is quite simple. That is, at birth, if the lung aerates and PBF increases before the cord is clamped, then PBF is able to immediately take over the role of providing preload for the left ventricle following cord clamping [2,43]. This avoids the reduction in cardiac output caused by the loss of umbilical venous return upon cord clamping [40]. In addition, cord clamping after lung aeration greatly mitigates the increase in arterial pressure caused by cord clamping, because the lung becomes an alternate low resistance pathway for blood flow for both left and right ventricles [40,41]. As a result, left-to-right shunting through the ductus arteriosus increases, leading to a further increase in PBF and venous return to the left ventricle [41]. On the other hand, clamping the umbilical cord immediately after birth causes a reduction in cardiac output that is sustained until after the lungs aerate and PBF increases [40]. As such, if lung aeration is delayed, cardiac output will remain reduced throughout this period. Then, after lung aeration, cardiac output is rapidly restored, causing a rebound in arterial pressure and a large increase in cerebral blood flow [40]. It is not surprising therefore, that one of the noted benefits of DCC is a reduction in IVH [49].

While PBCC can sustain cardiac output immediately after birth and may protect the brain from vascular damage, the logistics of helping infants, particularly very preterm infants, aerate their lungs with an intact umbilical cord was, until recently, thought to be unfeasible. However, recent feasibility studies have demonstrated that the logistical issues are not insurmountable [54]. One study (Baby-directed umbilical cord clamping study; Baby-DUCC), assessed the feasibility of stabilising preterm infants (> 32 weeks) with the cord intact by placing the baby on the mum's legs [55]. They found that stabilising infants, as indicated by regular stable breathing, with the cord intact, prevented the bradycardia evident in normal healthy infants immediately after

birth. Another study (ABC) has used a purpose-built resuscitation table (Concord table, Concord Neonatal, the Netherlands) that allows for more extensive resuscitation and monitoring of the infant while the umbilical cord remains intact [54,56]. Recent safety and feasibility studies in very preterm infants (< 30 weeks) have shown that all necessary interventions for cardiopulmonary stabilization can be performed while the infant remains attached to the umbilical cord [57]. They also observed less bradycardia and hypoxia at birth, supporting the concept of a more stable haemodynamic transition. As the average cord clamping time was over 4 min [57], this approach also allows preterm infants to maximally benefit from placental transfusion, while not delaying the onset of resuscitation. A number of trials are now in progress that are focussed on PBCC, rather than a time-based approach, and the sub-group of infants that may benefit is being expanded to include other infants likely to experience a long delay between birth and lung aeration. These include infants with a congenital diaphragmatic hernia [58,59].

10.1. Umbilical cord milking

It has been suggested that the "placental transfusion" associated with DCC can be replicated, over a much shorter time period, simply by milking the umbilical cord [60]. Cord milking involves squeezing the cord between thumb and finger and then "miking" the cord towards the infant, forcing any blood in the cord to move into the infant. This milking procedure can occur once or several times along a segment of cord (up to 20 cm long) [60]. It has been suggested that cord milking may be an alternative to DCC and may benefit infants needing resuscitation at birth, allowing them to get a "transfusion" without the delay [60]. However, this assumes that the only benefit of DCC is placental transfusion, which we know is incorrect [2,43]. Furthermore, recent scientific evidence indicates that cord milking is potentially worse than immediate cord clamping, particularly if it is done several times [52]. That is, consecutive milks result in large fluctuations in blood pressure and cerebral blood flow that are potentially injurious [52], particularly if the infant is hypoxic at birth and has a vasodilated cerebral vascular bed. Furthermore, whether or not milking results in a net "transfusion" of blood into the infant depends on the milking procedure, because retrograde flow can occur out of the infant between milks [52].

Some have argued that umbilical cord milking is safe because numerous trials have not detected any harmful effects in infants [60], in apparent contradiction to what would be predicted based on the scientific evidence [52]. However, a recent trial (PREMOD2) in very preterm infants was stopped early due to an increase in IVH rates in milked infants (22% vs 6%) [61]. This finding may provide a clue as to why it is safe in some infants, but increases the risk of cerebral vascular damage in others. Indeed, the scientific studies on PBCC have shown that the impact of cord clamping on arterial blood pressure is greatly mitigated when cord clamping follows breathing onset and the increase in PBF [40]. As such, if cord milking occurs following breathing onset (and the increase in PBF), it will likely have little impact on arterial blood pressure, whereas if it occurs before breathing onset it should cause large fluctuations in pressure. Until recently, most trials examining the effects of cord milking have occurred in healthy near-term infants, who are likely to have commenced breathing immediately after birth [60]. This would be expected to greatly mitigate the pressure fluctuations caused by milking. In contrast, those infants requiring immediate resuscitation at birth were mostly excluded from these trials and, therefore, did not receive milking. However, as very preterm infants have difficulty in aerating their lungs at birth, most will not have aerated their lungs before cord milking. As such, these infants are at high risk of being exposed to the large arterial pressure surges associated with cord milking [52]. Nevertheless, until the science has been thoroughly investigated, it seems prudent to avoid cord milking, particularly in infants requiring resuscitation at birth.

11. Conclusion

In recent years we have learnt much about the cardiorespiratory changes that occur at birth and, in particular, the role of lung aeration in driving these changes. This reinforces the neonatologist's mantra that lung aeration is the key to neonatal resuscitation at birth. While airway liquid clearance can commence during labour, the liquid remaining in the airways after birth and following the first breath is cleared into lung tissue due to the transpulmonary pressures created during inspiration. While this allows the onset of gas exchange, the presence of this liquid in lung tissue can have consequences for respiratory function after birth. In particular, if large volumes of liquid must be cleared into lung tissue, respiratory function can be compromised. This likely explains much of the respiratory distress that can occur in near term infants, particularly TTN. Indeed, as infants born by elective CS without labour will lose little liquid from the nose and mouth, which may explain why these infants are at higher risk of TTN.

Lung aeration also triggers the increase in PBF at birth which is not only important for increasing the efficiency of pulmonary gas exchange, but is also important for providing preload for the left ventricle. During fetal life, preload for the left ventricle is primarily derived from the umbilical vein, but this is lost upon clamping of the umbilical cord at birth. To avoid this, it is logical to aerate the lung and increase PBF before the cord is clamped to avoid the loss in preload and the associated reduction in cardiac output. This is known as PBCC and cannot be replicated by manoeuvres such as cord milking.

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