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Measuring Physiological Changes during the Transition to Life after Birth

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Abstract
The transition to life after birth is characterized by major physiological changes in respiratory and hemodynamic function, which are predominantly initiated by breathing at birth and clamping of the umbilical cord. Lung aeration leads to the establishment of functional residual capacity, allowing pulmonary gas exchange to commence. This triggers a significant decrease in pulmonary vascular resistance, consequently increasing pulmonary blood flow and cardiac venous return. Clamping the umbilical cord also contributes to these hemodynamic changes by altering the cardiac preload and increasing peripheral systemic vascular resistance. The resulting changes in systemic and pulmonary circulation influence blood flow through both the oval foramen and ductus arteriosus. This eventually leads to closure of these structures and the separation of the pulmonary and systemic circulations. Most of our knowledge on human neonatal transition is based on human (fetal) data from the 1970s and extrapolation from animal studies. However, there is renewed interest in performing measurements directly at birth. By using less cumbersome techniques (and probably more accurate), our previous understanding of the physiological transition at birth is challenged, as well as the causes and consequences for when this transition fails to progress. This review will provide an overview of physiological measurements of the respiratory and hemodynamic transition at birth. Also, it will give a perspective on some of the upcoming technological advances in physiological measurements of neonatal transition in infants who are unable to make the transition without support.

Introduction

The fetal to neonatal transition at birth starts when the newborn takes the first breaths, initiating major physiological respiratory and hemodynamic changes [1]. During the initial breaths lung liquid is cleared and air remains in the lung at the end of expiration, providing a functional residual capacity (FRC) [2]. Aeration of the lungs decreases pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) is increased by clamping of the umbilical cord after birth [3]. These events trigger major changes in the newborn's circulatory system [3]. Uniform lung aeration, establishing FRC

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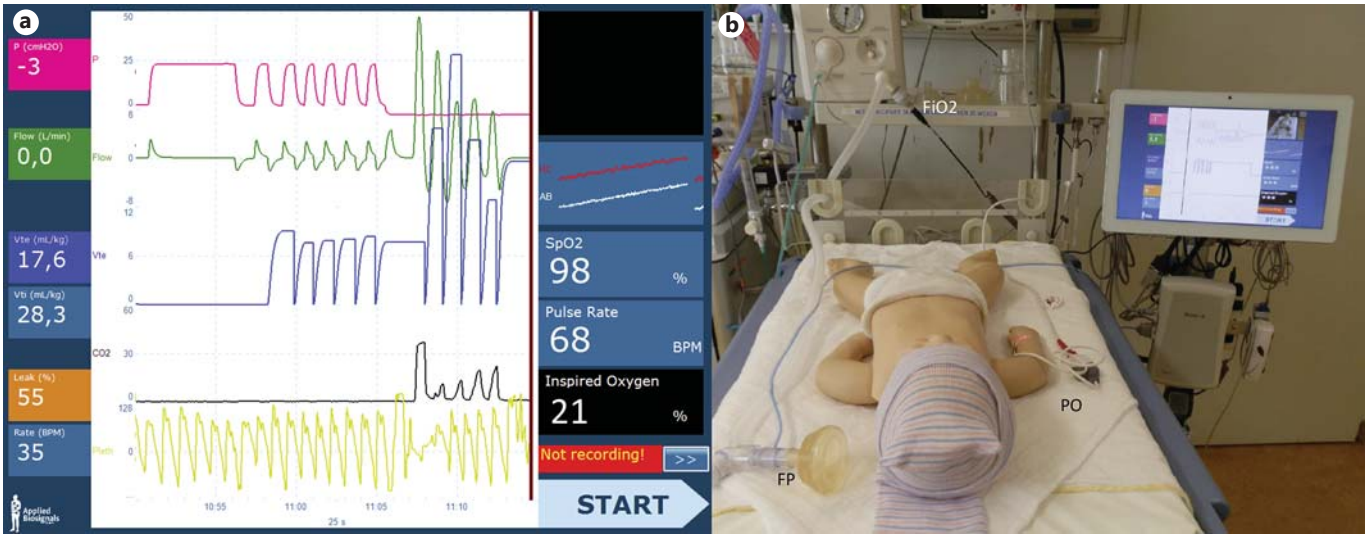

Fig. 1. a Respiratory tracing showing pressure (red), flow (green), expiratory volume (blue), capnography (black) and HR plethysmography (yellow) in waveforms. It also provides HR, So_2, FiO_2, inspiratory volume, expiratory volume and leak in numerals. **b** Respiratory function monitor (Applied Biosignals, Weener, Germany) and set-up as currently used for physiological research of the newborn infant. The flow probe (FP) is connected to the face mask. Also, an oxygen analyzer (FiO_2) and pulse oximeter (PO) can be added to monitor supplied oxygen as well as So_2 and HR.

and decreasing PVR are required to commence effective pulmonary gas exchange, which in turn improves the infant's heart rate (HR), cardiac output (CO) and oxygenation.

Although many observations have been made in humans [2], most of the understanding of the fetal to neonatal transition originates from animal studies [4]. Investigating this major life event in the delivery room is difficult as the neonatal transition can be very rapid and as a result time pressure is high. In addition, most of the techniques used for physiological measurements performed in the 1960–1980s would currently be considered unethical (X-rays, esophageal balloons, reverse plethysmography, umbilical catheterization, and angiocardiography) [1, 5]. However, less cumbersome and noninvasive techniques are currently used to gather observational data in the delivery room [6, 7], challenging our understanding of transition and resuscitative practices (fig. 1). In addition, more sophisticated techniques and approaches are now used in animal models to investigate the transition.

In this review, we will give an overview of the information obtained from current experimental and human physiological studies, which are designed to better understand the pulmonary and hemodynamic transition at birth [8]. Equipped with this new information we will also offer some future insights on how neonatal transition could be facilitated in infants who are unable to make this transition without support.

Pulmonary Transition

Breathing at Birth

Fetal breathing movements (FBM), needed for lung growth and development, are very similar to breathing activity after birth. Fetal respiratory drive is controlled by similar stimuli (hypoxia and hypercapnia), which arises from the respiratory center and mainly causes activation of the diaphragm via the phrenic nerve [6]. However, as FBM are restricted to levels of fetal activity, they are discontinuous, occurring <50% of the time. Further, although most FBM generate transpulmonary pressures of <20 cm H_2O, fetuses commonly can make large inspiratory efforts (>30 cm H_2O) [9, 10], demonstrating that they are capable of generating transpulmonary pressures needed to aerate the lungs after birth [7]. The mechanisms controlling the switch to continuous breathing after birth are currently unknown. There is a general belief that activation of chemoreceptors (particularly an increase in arterial CO_2, $PaCO_2$) and physical stimuli (light, temperature and handling) trigger the onset of large in-

spiratory efforts. Data on this matter are scarce, although animal studies have shown that cooling lambs at birth elicits normal quiet breathing, but no large initial gasps [8]. In contrast, painful stimuli elicit gasps in unanesthetized lambs with an intact umbilical cord, but not sustained respiratory movements [9].

Although hypoxia is considered to be a stimulus for respiratory drive, it remains questionable if this also accounts for the increased respiratory drive at birth [10, 11]. Hypoxia is known to inhibit breathing movements in the fetus and the hypoxic sensitivity is relatively low shortly after birth [10]. After birth, hypoxia increasingly stimulates respiratory drive in the newborn due a temporal change in O_2 sensitivity, which increases days/weeks after birth [10]. Although most preterm infants breathe at birth [12, 13], it is not known when the switch from respiratory suppression to a stimulation occurs in response to hypoxia. It is possible that hypoxia immediately after birth will produce a weakened or even absent respiratory drive, particularly in preterm infants. Indeed, maturation of the hypoxic sensitivity increase is delayed in preterm lambs [10]. In contrast, hyperoxia has been shown to delay the onset of breathing in asphyxiated rats, but it is difficult to extrapolate this finding as the rats were more than a week old [14]. Also, a delay of the first breath was observed in asphyxiated term infants at birth when 100% oxygen with no titration was given during resuscitation [15]. However, the first breath was observed and not measured and it is very difficult to identify the first breath, especially when the infant is ventilated [16].

As shown in animals, resuscitation with 100% oxygen compared to room air could also delay the onset of breathing via a mechanism that may involve both hyperoxemic and hypocapnic inhibition of chemoreceptors [14], although these animals were more than a week old at the time of the study. Antenatally, FBM are inhibited by hypoxia, but hypoxic sensitivity is relatively low shortly after birth and gradually increases days/weeks after birth [10]. Hypercapnia is a powerful stimulant for respiratory drive both before and after birth and could induce the large respiratory efforts observed. However, not all infants will be hypercapnic immediately after birth.

Lung Liquid Clearance and Aeration

Experimental studies have predicted that the stress of labor starts fetal lung liquid clearance due to the release of adrenaline, which stimulates pulmonary epithelial cells to activate luminal surface sodium channels. This reverses both the Na^+ flux and the osmotic gradient across the epithelium, causing reabsorption of lung liquid [17]. However, the dominant role of sodium channel activation for lung liquid reabsorption after birth has been challenged by recent studies [18]. These studies used phase-contrast X-ray imaging to image air entry into the lungs during the first breaths in newborn rabbits. They demonstrated that liquid clearance exactly coincides with inspiration and occurs very rapidly (3 ml/kg over the first 5 breaths, at 35 l/kg/h). They concluded that airway liquid clearance cannot solely be explained by activation of sodium channels, and probably involves transpulmonary pressures generated by the inspiratory effort [18]. Cell membrane water channels (aquaporins, AQPs) could play an essential role in this process. During pregnancy different types of AQPs are expressed [19] and at birth the expression of pulmonary AQPs changes. Through these channels water can be absorbed into the interstitium in the first days after birth [20, 21]. In preterm infants the expression of AQPs differs compared to term infants, possibly increasing the incidence of neonatal respiratory distress syndrome and bronchopulmonary dysplasia [20].

Lung liquid clearance by 'vaginal squeeze' is an old theory some authors still consider as an important mechanism [22]. This theory originates from studies [5, 23] performed in 1917 and repeated in 1962 using X-ray imaging showing compression of the fetal chest of term infants passing through the birth canal. In later studies intrathoracic pressures of 70 cm H_2O were measured and oral expulsion of lung liquid was observed during delivery [24–26].

However, the little resistance that the chest offers when following the head in the birth canal makes it unlikely that 'vaginal squeeze' per se significantly influences liquid clearance [27, 28]. In contrast, as postural changes during labor can cause lung liquid loss [29], flexion of the fetal trunk, which increases abdominal pressure and elevates the diaphragm, are more likely to cause liquid expulsion [22, 23].

Another theory, observed in 1891 in excised lungs, suggested the increase in pulmonary circulation would be responsible for lung aeration ('capillary erection') [30–32]. However, this theory has been abandoned since experimental studies [33, 34] have shown that pulmonary vasodilation occurs in response to lung aeration, leading to a gradual reduction in pulmonary arterial pressure.

Thoracic recoil after passage through the birth canal is also described to explain lung aeration, as suggested in 1901 [35]. In 1962 Karlberg et al. [1, 36] used reverse plethysmography for lung volume measurements in human infants and reported that elastic recoil of the chest

after expulsion from the birth canal caused air entering the lung [1, 23, 36]. The measurements were repeated later, but elastic recoil forcing air into the lung could not be confirmed [25].

Karlberg et al. [36] and Saunders and Milner [25] have also measured transesophageal pressures using an esophageal balloon catheter. Karlberg et al. [36] observed that relatively large subatmospheric pressures (20–40 cm H_2O) were necessary before air started entering the lung, which was considered to be the 'opening pressure' needed to overcome resistance and newly formed surface tension [37]. However, Saunders and Milner [25] could not confirm this and stated that the balloon in Karlberg's study was probably misplaced. Although 'opening pressure' is a misnomer, as the lungs are not collapsed at birth, it is still used as rationale for initially providing higher ventilation pressures during neonatal resuscitation [32].

More recently, phase-contrast X-ray imaging in a newborn rabbit model demonstrated that lung liquid clearance almost exclusively occurs (>95%) during inspiration [4]. The transpulmonary pressure gradients generated during inspiration are likely to be primarily responsible for the rapid clearance of airway liquid immediately after birth [4]. That is, the inspiratory effort reduces (becomes more subatmospheric) in both the intrapleural space and the interstitial tissue surrounding alveoli, which forces liquid to move across the alveoli's epithelium into the interstitium. This causes liquid to accumulate in the interstitial space, forming perivascular fluid cuffs [38], resulting in an increase in resting interstitial tissue pressure [4, 39, 40]. End expiratory pressures generated during braking of the expiration (breath holds, crying), surfactant and probably activated epithelial sodium channels are likely to be important in preventing liquid moving back into the alveoli [41]. The sum of lung liquid moving into the interstitium and being replaced by air that occupies the airways explains the increase in thorax circumference and shape before and after lung aeration was made visible in radiographs from both humans [42] and newborn rabbits [43]. This has been indirectly confirmed by Miserocchi and Agostoni [44] who found a larger pressure in the interstitium at the end of inspiration, showing that both FRC and pleural liquid pressure increased simultaneously. The movement of liquid from the airways into the surrounding lung tissue has also been visualized in ventilated preterm rabbit pups [4]. Eventually, liquid in the interstitium is cleared in approximately 6 h via the blood and lymph vessels [4, 39, 40].

Creating and Maintaining FRC

From the start of research in respiration during neonatal transition several theories have been suggested describing FRC creation and maintenance right after birth, which are necessary for adequate gas exchange. One theory described that alveoli were splinted open by 'air trapping', i.e. more air is inspired than exhaled [45]. 'Air-trapping' could occur due to braking of expiration, which was described previously as 'frog breathing' [46–48]. Karlberg and Koch [47], using chest X-rays and reverse plethysmography, described the first breath as a deeper and slower breath than subsequent breaths, composed of a large inspiration followed by a braked, slow expiration. As a result, large changes in esophageal pressures were found to be related to both changes in inspiratory volume and the subsequent braking of expiration [17, 41]. During expiratory braking the infant builds up a large intrathoracic pressure by simultaneously closing the glottis and contracting the abdominal muscles. The physiological consequences of this are unclear, although an increase in airway liquid clearance is unlikely because pressure within the interstitial tissue will also increase simultaneously, resulting in little or no change in transpulmonary pressure [40].

Several breathing patterns have recently been described in infants at birth using a hot-wire anemometer attached to a mask [41, 48]. Patterns that slow expiration (expiratory hold, slow expiration, crying and grunting) and shorten expiratory time (panting) were thought to be important for maintaining FRC in the newborn period [41]. Preterm infants were more commonly found to use breath-holds and cause a complete cessation of expiratory flow, whereas term infants most commonly slowed expiration during crying [48]. Imaging experiments in spontaneously breathing newborn rabbits have confirmed the role of expiratory braking in preventing liquid moving back into the airways and maintaining FRC [18].

Using reversed plethysmography, Karlberg and Koch [47] found that in the first minutes after birth an infant's FRC can reach levels of 20–40 ml. Mortola et al. [49], using a face mask with a pneumotachograph attached, measured an average FRC of 42 ± 26 ml in term infants. However, mask leak could have been a confounding factor. Recent animal studies confirmed that large amounts of FRC are established during the first breaths (3 ml/kg over the first 5 breaths) [18]. However, the speed at which FRC is established and maintained is variable [7, 18]. This is due to the variable effect of the inspiratory efforts, the reentry of liquid into the airways and the mechanisms such as expiratory holds [18].

Surfactant also plays an important role in creating and maintaining FRC at birth, by reducing the surface tension, lung recoil and the transpulmonary pressure gradient for lung liquid moving back to the alveolar space [50, 51]. In addition, surfactant greatly increases the uniformity of lung aeration, which indicates that surface tension determines whether the air/liquid interface progresses down both airways at each airway branch [51].

Hemodynamic Transition

As with the respiratory system, the cardiovascular system undergoes a major transformation after birth. The major components of these transformations occur within minutes of commencing pulmonary ventilation (fig. 2, 3) However, the cardiovascular transition requires hours to days to complete. The immediate consequence of the neonatal transition is the direct reversal of vascular shunts of the foramen ovale (FO) and ductus arteriosus (DA). Due to the continued patency of the FO and DA, transition is prolonged. After birth the increasing afterload will increase the likelihood of left-to-right shunt through the DA in the first days after birth. However, DA constriction will cause shunting through the DA to decrease [52]. Changes in SVR and the decrease in PVR resistance that occur during transition will cause blood pressure (BP) and flows in the pulmonary and systemic circulations to change. This promotes functional closure of the FO, thus completing transition. The ductus venosus (DV) will remain patent up to days after birth [53]. However, it will not be of further influence to the cardiovascular system.

In fetal sheep, depending upon the gestational age, approximately 30–50% of combined CO (right and left ventricle) flows to the placenta [54] and therefore 30–50% of cardiac venous return must come from the placenta. Approximately 50% of umbilical venous blood flow in sheep fetuses [55] and 30% of blood flow in the human fetuses [56] passes through the DV, bypassing the liver. A large proportion of this oxygenated placental blood passes through the FO and enters the left atrium [57]. The remainder of the venous return, which mostly consists of poorly oxygenated blood from the superior and inferior vena cava, enters the right atrium and is directed into the right ventricle. However, as PVR is high in the fetus, most of the right ventricular output (RVO, 90%) bypasses the lungs and is shunted through the DA into the aorta [54, 58]. A large portion of this deoxygenated blood will flow back to the placenta as this organ's vascular resistance is lower than the vascular resistance of the fetus' lower body [34].

The Effect of Breathing on Hemodynamic Transition

The decrease in PVR, which is necessary for adequate pulmonary gas exchange after birth, is triggered by the onset of pulmonary ventilation. This emphasizes that establishing adequate breathing at birth is important for a proper hemodynamic transition as this has significant influence on the pulmonary blood flow [3, 34, 54, 59]. Lind and Wegelius [60] visualized the large blood flow through the pulmonary artery in term infants using angiocardiography with Umbradil injected in the umbilical vein directly after birth. Up to 50% of the increase in pulmonary blood flow was supplied by a left-to-right shunt through the DA [54], caused by the differential pressures between pulmonary and systemic circulation. As a consequence, particularly the timing in the reversal of blood flow shunting through the DA (from right-to-left to left-to-right) is unclear. The change in shunting direction will create disturbance of the blood flow. This is likely to promote and contribute to anatomical closure of the vascular shunts (DA and FO) separating pulmonary and systemic circulations [54, 58].

Effect of Umbilical Cord Clamping on Hemodynamic Transition

Clamping the umbilical cord at birth has a large impact on the fetal circulation and plays an integral role in the transition. The acute loss of the high-flow and low-resistance placental vascular bed has two implications: (1) SVR instantly increases and (2) venous return to the heart is decreased by 30–50% [54]. Both have the potential to compromise the infant's CO.

The timing of cord clamping in relation to lung aeration could influence transition extensively. While before birth the left ventricular preload is mostly dependent on umbilical venous blood flow, after cord clamping the left ventricular output (LVO) becomes largely dependent on pulmonary blood flow and pulmonary venous return. A recent study in preterm lambs hypothesized that breathing before cord clamping would improve cardiovascular stability. It was shown that cord clamping before ventilation reduced HR by 40%, and decreased RVO and blood flow in the carotid artery. It was observed that carotid blood flow remained stable and the decrease in HR and RVO associated with cord clamping were greatly reduced when ventilation was commenced before cord clamping [61]. It is likely that this cardiovascular stability plays an important part in the benefits of delayed cord clamping such as improved tissue perfusion, lower incidence of necrotizing enterocolitis and intraventricular hemorrhage [62].

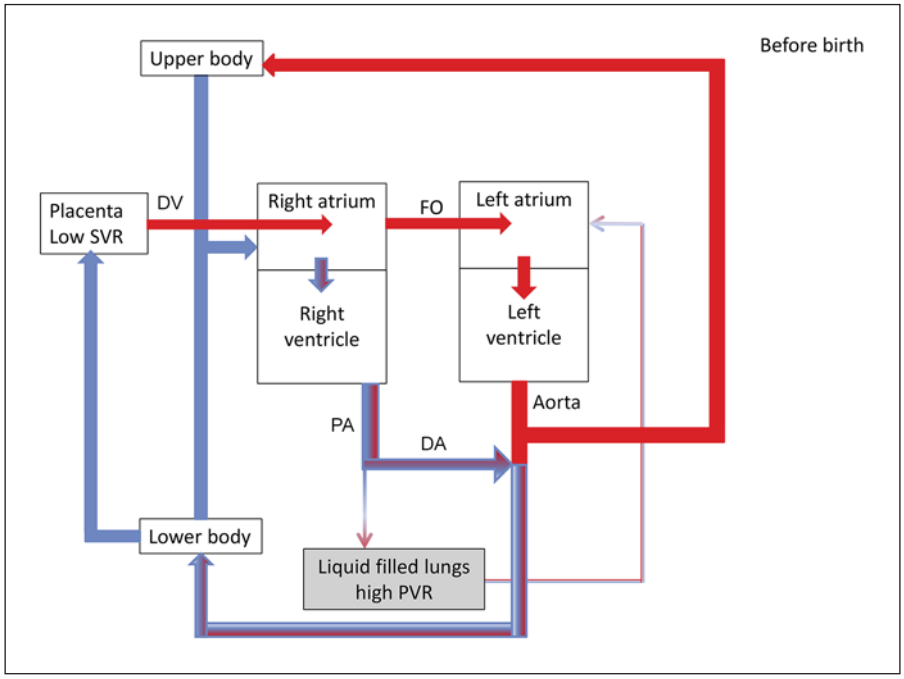

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Fig. 2. Schematic drawing of the fetal circulation. Red indicates blood with a high SO_2 and blue indicates blood with a low SO_2. Before birth blood from the placenta enters the infant through the DV and passes into the right atrium. 2/3 of the blood shunts through the open FO and 1/3 passes through to the right ventricle and into the pulmonary artery (PA). 90% of the blood shunts through the DA and only 10% enters the lungs due to the high PVR.

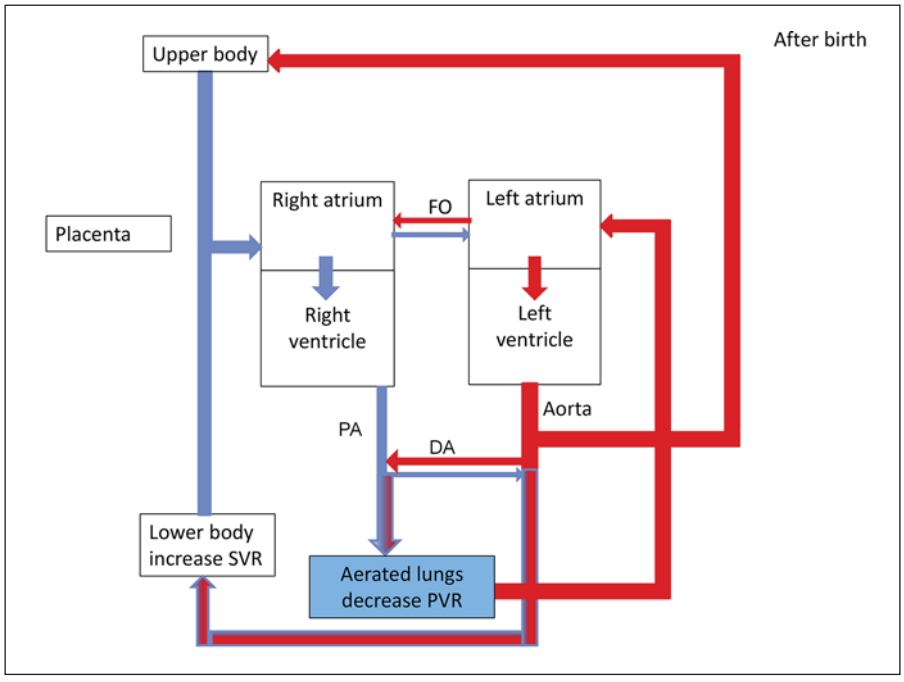

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Fig. 3. Schematic drawing of the neonatal circulation just after birth. Red indicates blood with a high SO_2 and blue indicates blood with a low SO_2. After birth the umbilicus is clamped and there is loss of 30–50% of total venous return. Pulmonary resistance decreases due to aeration of the lungs causing increased pulmonary blood flow through the pulmonary artery (PA). Blood flow through the DA and FO becomes bidirectional. Up to 50% of the pulmonary blood flow arises from the DA through via a left-to-right shunt.

There are little physiological human data available measuring the quantity and characteristics of fetoplacental transfusion between birth and cord clamping [63–65]. Mechanisms have been suggested that could influence fetoplacental transfusion (e.g. uterine contractions and breathing), but these still need to be investigated [61, 66].

Measurements for Evaluating Transition

Heart Rate

Currently the only parameter used clinically to evaluate the hemodynamic transition is HR, which is believed to be the primary measure of adequate transition [67]. A cut-off value of HR of 100 beats per minute was suggested

by Virginia Apgar to characterize adequate transition. Nonetheless, a HR of <100 beats per minute is commonly observed in healthy term infants in the first minutes after birth, followed by a fast and significant increase [68]. The relatively low HR in the first minutes after birth is assumed to be caused by a hypoxia-stimulated bradycardia that involves a parasympathetic-activated vagal reflex [69]. However, the transient bradycardia after birth could also be caused by immediate umbilical cord clamping before the lungs are aerated, which decreases both LVO and RVO [61]. Early cord clamping causes the SVR to increase before PVR is reduced and pulmonary blood flow can increase. As a consequence of the low pulmonary vascular return, together with the sudden decrease in right-to-left shunting through the FO, left ventricular preload is low and therefore a baroreflex-provoked bradycardia could arise [61].

Oxygen Saturation

Several experimental and human studies [70–73] show that fetal oxygen saturation (So_2) is low (45–65%) and can be even lower during labor. However, directly after birth it was found that there is no significant difference in oxygen uptake between term infants born by cesarean section or infants born vaginally (6.58 ml/min/kg) [74]. So_2 measured peripherally is, however, not necessarily related to central oxygen uptake. Until recently pink color was seen as a sign of a proper transition. It was found that there is a large variation in So_2 when clinicians stated an infant to be pink [75]. So_2 should preferably be measured preductally using pulse oximetry [76]. In 2010 a lower and slowly rising So_2 was considered acceptable during the transitory phase according to the normograms presented by Dawson et al. [77]. Infants delivered by cesarean section have a significantly lower So_2 and require a longer time period to reach So_2 ≥85% [77–79]. This could lead to a delayed or compromised transition. Also, infants born with a gestational age <37 weeks without medical intervention required a longer time to reach So_2 (87 vs. 90% at 5 min after birth) [77].

CO and Stroke Volume

CO is determined by both HR and stroke volume (SV; CO = HR·SV). It is sometimes still assumed that SV cannot be altered in the neonate because the contractility of the myocardium characteristically functions high on the Frank-Starling curve and is unable to increase further, as well as the fetal myocardium [80]. This would imply that a change in end diastolic volume cannot be accompanied by a large change in CO. However, it has been shown in sheep fetuses that SV can be adapted [81]. Echocardiography has been used to monitor CO during the neonatal transition [82–84]. However, this data was collected in the hours to days after birth when the major changes of neonatal transition already occurred. Recently, Noori et al. [85] were the first to use echocardiography shortly after birth and observed that as a consequence of rising SV, LVO non-significantly increased from 168 ± 42 ml/kg/min at 3–7 min to 186 ± 26 ml/kg/min at 9–14 min after birth. HR decreased and SV increased between the two measurement periods. It is possible that the increase in LVO was missed in the first minutes as the first measurements were conducted between 3 and 7 min. However, Noori et al. [85] have shown that increasing SV is important for CO during the first minutes after birth as it is later during transition [52].

Blood Pressure

BP is determined by SVR and CO and although it is not well correlated to systemic blood flow, it is considered an important value for hemodynamic monitoring of critically ill infants [86]. However, while HR is considered important for decision making in the delivery room, BP is rarely used for evaluating the neonatal transition or the need for resuscitation at birth.

There is very little data of BP at birth and reference values are lacking. Although the exact time points of measurements are unknown, in 1938 Woodbury et al. [87] inserted an umbilical arterial line in term infants directly after birth and observed a mean systolic artery pressure of 80.1 ± 8.1 mm Hg and diastolic pressure of 46.3 ± 8.2 mm Hg. BP was markedly influenced by crying, administration of fluids [87] and increasing gestational age [88]. Interestingly, small undulations in the BP concomitant with breathing were seen [87]. Ashworth and Neligan [89] (using a sphygmomanometer on the right arm, preductally) observed lower systolic BPs (±10 mm Hg difference) in the hours following birth when the cord was clamped during delivery, compared to when the cord was clamped after birth. This could infer that when the cord is clamped before pulmonary blood flow has increased there will be less circulating volume. In a more recent study in term infants a mean BP of 42 ± 11 mm Hg at 5 min after birth was measured [90]. It could be helpful to measure BP preductally during transition to evaluate the hemodynamic transition and assess the CO.

Gas Exchange Measurements

Palme-Kilander and Tunell [91] and Tunell et al. [92] measured carbon dioxide production (Vco_2), using a face

Table 1. Respiratory parameters for different breathing patterns for infants who did not require respiratory support with a gestational age of 29 ± 1.9 weeks and mean birth weight of 1,220 ± 412 g [41, 48]

	VTE, ml/kg	Respiratory rate, min^{-1}	Inspiratory time, s	Expiratory time, s
Preterm infants (<32 weeks; CPAP)				
Braked expiration	7.2 ± 3.8	60 ± 30	0.32 ± 0.14	1.03 ± 0.84
Unbraked expiration	3.7 ± 2.2	90 ± 26	0.30 ± 0.09	0.41 ± 0.16
Term infants				
Braked expiration	6.8 ± 4.2	50 ± 23	0.33 ± 0.16	1.33 ± 1.02
Unbraked expiration	5.5 ± 3.4	91 ± 31	0.30 ± 0.13	0.43 ± 0.26
All infants				
Expiratory hold	5.8 ± 4.1	32 ± 11	0.36 ± 0.10	1.85 ± 1.14
Slow expiration	3.5 ± 2.3	48 ± 16	0.34 ± 0.15	1.10 ± 0.90
Crying/grunting	7.5 ± 4.2	42 ± 18	0.38 ± 0.14	1.30 ± 0.75
Normal expiration/ respiratory rate	4.2 ± 1.5	54 ± 4	0.40 ± 0.08	0.65 ± 0.11
Panting	3.1 ± 1.7	88 ± 18	0.34 ± 0.07	0.41 ± 0.14

VTE = Expiratory tidal volume.

mask and collection system, directly after birth in both breathing and ventilated infants. Asphyxiated preterm and term infants needing assisted ventilation at birth had similar V_{CO_2} in the first minutes after birth [91, 92]. However, breathing infants had higher V_{CO_2} values than ventilated infants (5–7 vs. 2–4 ml/kg/min), which probably reflects a lower temporal increase in FRC in ventilated infants, indicating that ventilation was not as effective as breathing [74, 93]. However, a higher energy cost associated with spontaneous breathing cannot be discounted [94].

A similar phenomenon was observed in a recent trial testing the use of end-tidal carbon dioxide levels (ET_{CO_2}) to keep Pa_{CO_2} levels within range [95]. Although the number of out-of-range Pa_{CO_2} values was not reduced, ET_{CO_2} was lower during ventilation than during breathing [95]. While studies in the neonatal intensive care unit have found that ET_{CO_2} closely correlates with Pa_{CO_2} [96–98], it is important not to extrapolate these findings to the situation in the delivery room, when the lung is partially liquid filled. The assumption that ET_{CO_2} will approximate Pa_{CO_2} levels relies on the fact that CO_2 exchange in the lung is not diffusion limited. However, a recent study demonstrated that during the early transition period, ET_{CO_2} values are primarily determined by inspiratory lung volumes [99].

Tidal Volume

Although extrapolated from studies performed later in life, during ventilation at birth, tidal volumes between 4 and 8 ml/kg are considered adequate. However, at birth, term infants use significantly larger tidal volumes for their first breaths (11 ± 5 ml/kg) [1, 49]. Similarly, Milner and Saunders [100] measured a mean tidal volume of 44.6 ml (range 13.4–90 ml) for the first breath. te Pas et al. [48], who measured tidal volumes in preterm infants breathing on CPAP at birth and during different breathing patterns, found a range of volumes between 3.1 ± 1.7 ml/kg and 7.5 ± 4.2 ml/kg (table 1). In infants without support at birth, tidal volumes of more mature preterm infants were comparable to term infants (6.7 ± 3.9 vs. 6.5 ± 4.1 ml/kg; NS) [41].

Tissue Perfusion

For determination of the tissue perfusion two methods can be used: the perfusion index (PI) and near infrared spectroscopy (NIRS). PI is the ratio of pulsatile blood flow/nonpulsatile static blood flow and is deducted from the strength of the photo-plethysmographic signal emitted during pulse oximetry [101]. At birth, a consistent PI was observed in healthy term infants and values were higher when compared to infants with sepsis (PI at 1 min 4.50 ± 0.83 vs. 1.74 ± 0.32 and at 5 min 4.42 ± 2.10 vs. 2.18 ± 1.02) [102]. However, since various factors can influence PI, e.g. changing temperature and local skin vasoconstriction, its value for evaluating transition remains questionable.

NIRS is a technique developed for monitoring perfusion of brain tissue. In term infants at birth regional S_{O_2} of the brain (rS_{O_2}brain) rapidly adapts to extrauterine life with 44% at 3 min to 76% at 7 min, after which it remained stable [90]. rS_{O_2}brain was not affected by manner of birth,

Table 2. Tidal volumes and pressures in infants just after birth during resuscitation measured using a respiratory function monitor

	VTE of spontaneous breaths, ml/kg	VTE of prolonged inflation, ml/kg	VTE of inflations (PPV), ml/kg	Breaths between inflations (CPAP), ml/kg	Breaths coinciding with inflations, ml/kg
Preterm infants (<32 weeks)					
Schilleman et al. [16], 2012		0.8 (0–5.6)	3.7 (1.4–6.7)	3.3 (2.1–6.6)	4.6 (2.1–7.8)
Schmölzer et al. [108], 2010			8.0 (5.2–11.2)		
Term infants					
Milner et al. [100], 1977 (face mask)			4.1 (1.7–6.4)		
Milner et al. [100], 1977 (intubated)			7.8 (0.4–11.7)		
Mortola et al. [49], 1982	11.7 ± 5.5				
Karlberg et al. [1], 1962	10.6 ± 4.4				
Hull et al. [112], 1969 (asphyxiated intubated)					10.8 ± 1.4

VTE = Expiratory tidal volume; PPV = positive pressure ventilation.

indicating that blood flow to the brain is possibly determined by auto regulation independently from the mode of delivery [103]. Also, fractional oxygen extraction [$(SO_2 - rSO_{2brain})/SO_2$] can be determined using NIRS, which is a measure for the amount of oxygen consumed by the tissue. In the first 5 min after birth fractional oxygen extraction rises significantly and thereafter it levels [90]. When assuming that cerebral metabolism remains stable, fractional oxygen extraction could also be used as an indirect parameter for cerebral blood flow.

Physiological Measurements during Resuscitation

Until recently, accurate physiological recordings were not used to evaluate neonatal resuscitation, but instead subjective and inaccurate clinical observations were used [67, 75, 104–107]. Several recent studies have now addressed the importance of monitoring neonatal resuscitation by measuring HR, SO_2 and respiratory function in the immediate newborn period [16, 108–110].

Observations in the early 70s by Milner et al. [111] showed that ventilation during neonatal resuscitation of asphyxiated term infants was often inadequate, only small tidal volumes were administered and substantial FRC was only created when spontaneous breathing started. Recently, Schilleman et al. [16] also observed much lower tidal volumes during mask ventilation of preterm infants at birth compared to the volumes inhaled during spontaneous breathing (table 2). Spontaneous breathing occurred more often in between and during inflations than clinicians were aware, which might have contributed to the effect of resuscitation [16]. Schmölzer et al. [108] measured higher tidal volumes during ventilation, probably as a result of spontaneous breaths in between and during inflations, as these were not separately identified and could have been mistaken for inflations during analysis.

Asphyxiated infants often do not breathe at birth. Nevertheless, in intubated asphyxiated infants, tidal volumes of 10.8 (1.4) ml/kg were measured during resuscitation shortly after birth [112]. The pressure signals [112] show a pressure drop during inflation. This might implicate a spontaneous inspiration which could explain the high tidal volumes measured.

The observed breaths in asphyxiated infants could be caused by a reflex induced by ventilation [113]. Certain reflexes such as the Head's paradoxical reflex could be triggered by alveolar distention during positive pressure ventilation causing spontaneous breaths [114]. Furthermore, the reflex was found to be very important for the formation of FRC, resulting in volumes of up to 10 ml and negative endotracheal pressures of up to 30 cm H_2O in

asphyxiated infants [115]. Other reflexes have also been observed, triggering spontaneous expiration after the first manual inflation in newborn infants [112]. This could possibly be caused by the Hering-Breuer reflex [116], acting as a mechanism to prevent overdistension of the airways.

Conclusion and Future Perspectives

It has been shown that it is feasible and not cumbersome to perform noninvasive physiological measurements to evaluate the success or failure of transition and resuscitation if needed. However, more data is needed to develop a full understanding of the physiological mechanisms involved in adaptation to extrauterine life. This will help us to identify normal or delayed transition. It is of vital importance to improve our resuscitation strategies as the patients that need intervention will keep presenting at lower gestational ages with more complicated (pulmonary and hemodynamic) problems.

Currently, it is assumed that proper tidal volumes are in the range of 4–8 ml/kg. However, a larger range in tidal volumes was measured in mask-ventilated healthy term and preterm infants [49, 117]. Therefore, the safe range of adequate tidal volumes still needs to be determined. The use of a respiratory function monitor could improve our care during the neonatal transition by informing on spontaneous breathing, the amount of tidal volumes of inspired volumes and mask leak [16]. Furthermore, the use of a monitor guiding the resuscitation could also improve the outcome of infants needing resuscitation due to reducing lung injury and as a consequence reducing chronic lung disease and bronchopulmonary dysplasia.

Imaging techniques such as MRI could prove promising in improving our understanding of the mechanism of labor and its implications for the physiological changes taking place during birth [118]. Gas exchange measurements during transition, using capnography, could assist in defining adequate tidal volumes [96–98] and the total amount of proper gas exchange. However, this technique can be influenced by other variables such as mask leak and the dead space of the mask and sensor. Therefore, the value of capnography still needs to be determined. Capnography can immediately provide data on the effectivity of gas exchange, but does not provide information on the total amount of FRC. Measurement of the changes in FRC will be helpful in improving our ventilation strategies. This will however be challenging. FRC could be determined using noninvasive techniques such as respiratory inductance plethysmography, which could prove helpful in providing information on relative FRC changes and the work of breathing [119, 120]. However, FRC measurements gathered with respiratory inductance plethysmography should be collected simultaneously with leak-free volume measurements in order to calculate the absolute changes in FRC. Furthermore, this will provide insight into the effectivity of mask ventilation and the effect of changing interventions. BP and PI measurements could help us to evaluate the hemodynamic transition. However, more data is needed to define reference values and temporal changes after birth. Both parameters are advisory on the physiological changes during transition in terms of circulation and perfusion and could be used to intervene if the transition is not taking place as it should. Echocardiography and NIRS have been shown to be valuable research tools for investigating transition. In particular, NIRS is useful to monitor the effect of transition on the most important organ of the human body (the brain) and may help to predict prognosis of the neurological outcome. In conclusion, these noninvasive physiological measurements will help us to translate concepts derived from current experimental studies to human infants and increase our knowledge of human physiology.

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