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Spontaneous breathing and respiratory support of preterm infants at birth

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Citation

Pas, A. B. de. (2009, March 5). *Spontaneous breathing and respiratory support of preterm infants at birth*. Retrieved from <https://hdl.handle.net/1887/13595>

Version: Corrected Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

CHAPTER 2

From liquid to air: breathing after birth

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Abstract

Studying the transition from placental to pulmonary gas exchange has always been an intriguing and difficult challenge. Lung liquid is partly cleared before and during labour, but residual liquid must be cleared after birth. Where the liquid goes at the moment air is drawn into the lungs is unclear, but recent evidence indicates that it is transiently retained within the interstitial tissue causing chest wall expansion. Studies on the breathing pattern of infants immediately after birth indicate that "gas trapping" is important. The first breaths of air after birth are characterized by a quick inspiration, followed by constriction of the larynx which holds gas within the lungs with a positive intrathoracic pressure. This is followed by a short active expiration through a narrowed larynx with an immediate inspiration. To overcome frictional resistance of the airway liquid and surface tension at the air-liquid interface, a trans-pulmonary "opening" pressure is required during manual inflation. This appears to be less when infants breathe spontaneously than during a manual inflation. How very preterm infants with poor respiratory muscle strength, surfactant deficiency, compliant chest walls and impaired lung liquid clearance, defend their lung gas volumes immediately after birth is poorly understood. This review discusses the available knowledge about the first breath of air and the breathing pattern adopted by infants at birth.

Introduction

The first breaths following birth are characterized by a rapid transition from liquid to air-filled lungs. Air is drawn into the lung during inspiration and some remains at end expiration to establish an end-expiratory gas volume or functional residual capacity (FRC). This is usually marked by a cry, often misinterpreted as a protest from the baby. Some infants, especially those born preterm, require respiratory support during this transitional phase. To do this effectively, we need to understand the normal physiological processes occurring at this time.

Sometimes it can be difficult to aerate the lungs of preterm infants with intermittent positive pressure ventilation (IPPV) using pressures recommended in international guidelines, particularly when the infant does not breathe and aeration is completely dependent on the inflation pressures. Studies have shown that IPPV should be performed without high tidal volumes to avoid damaging the lung whilst establishing the FRC (1;2). However, since the use of antenatal steroids, more very preterm infants breathe spontaneously at birth, only requiring support from nasal continuous positive airway pressure (NCPAP).

Understanding the normal spontaneous breathing pattern after birth is essential for developing safe, efficient ventilatory strategies when breathing is inadequate. Numerous physiological studies of spontaneously breathing infants, immediately after birth, were published between 1960 and 1986 (3-10). However, little new data are currently available on this topic, reflecting the difficulties of performing these studies at birth. This review will discuss what happens during the first breaths of air with the emphasis on where the liquid goes and the current knowledge about the spontaneous breathing pattern adopted by infants immediately after birth.

Clearing Lung Liquid

In utero the lungs are filled with a liquid that is secreted by the lung epithelium. The volume of liquid in the lung before birth is controversial, but the available evidence indicates that it is greater than the FRC measured soon after birth (11). The high prenatal lung volume is due to adduction of the glottis restricting lung liquid efflux promoting its accumulation within the airways and increasing lung expansion. The high degree of lung expansion provides an essential physiological stimulus for fetal lung development (12).

Although the precise mechanisms for airway liquid clearance at birth are unclear, the process starts just before or with the onset of labour (13). It is well established that limited intra-uterine space (as occurs during labour), impose changes in fetal posture that alter fetal chest wall configuration, increase transpulmonary pressure and lead to the loss of large volumes of liquid from the lung (14). In addition, a large release of fetal adrenaline

occurs late in labor, which stimulates pulmonary epithelial cells to stop secreting and start reabsorbing lung liquid due to the activation of luminal surface sodium channels (15;16). Many studies have focused on the role of epithelial sodium channels in lung liquid reabsorption and they have been the subject of several reviews (16-19). At birth the pulmonary epithelium switches from facilitated Cl^- secretion to active Na^+ reabsorption with the opening of amiloride-sensitive Na^+ channels on the apical surface. This is thought to reverse liquid movement across the pulmonary epithelium, promoting liquid uptake from the airways into the interstitium (20). Diminished activity or immaturity of this process may reduce the adaptation of the newborn lung to air breathing contributing to wet lung syndrome and hyaline membrane disease (17;18). However, the specific role of Na channel activation in lung liquid reabsorption at birth is still unclear. In animal studies the blockade of epithelial Na^+ channels with amiloride and selective inhibition of β adrenergic receptors (proposed mechanism for Na^+ channel activation) reduces or delays, but does not prevent lung liquid clearance at birth (21). Similarly, although deletion of the gene encoding αENaC (but not βENaC or γENaC) impairs lung liquid clearance, as indicated by high lung water contents, the $\alpha\text{ENaC}^{-/-}$ neonates must establish some pulmonary gas exchange as they survive for up to 40 h after birth (22). Recent commentaries have highlighted the considerable evidence supporting a role for Na^+ uptake in alveolar fluid clearance, particularly under stimulated conditions, and the role of glucocorticoids, catecholamines and oxygen in regulating the activity of this uptake.(18) But it has also been noted that additional mechanisms, that are independent of amiloride sensitive Na^+ uptake, are likely to be involved (18).

Mechanical forces aid lung liquid clearance during labour. In 1917, Warnekros used x-rays to show that the thorax is compressed and stretched as the fetus is forced through the distal part of the birth canal (23). In 1962, Borell and Fernstrom concluded that compression of the thorax and abdomen during birth must reduce lung volume and cause lung liquid expulsion (24). Between 1935 and 1956 German textbooks stated that as the respiratory tract is suddenly exposed at birth to the lower pressure outside the uterus, a jet of liquid is forced from the nose and mouth (25). Measurements during delivery indicated that 25-33% of lung liquid could be expelled in this way (26;27). Vyas et al, measured intra-thoracic pressures during birth and found the maximum pressure averaged 145 cm H_2O (range 88 to 265 cm H_2O), but failed to show any loss of lung liquid. However, they reported liquid escaped from the mouth before they could place a mask on the infant's face (9). They also compared infants born by elective caesarean section and vaginal delivery and found the esophageal pressure changes were halved during caesarean section. Furthermore, although the initial inspiratory volumes recorded in the two groups were similar, significantly fewer infants born by caesarean section retained air at the end of their first breath. This may reflect greater liquid retention within a lung of an infant born by caesarean section that had not been exposed to labour, thereby limiting the entry of air into the lower airways (7).

Most early studies suggested that “vaginal squeeze” during the progression of the chest through the birth canal was the predominant mechanical factor influencing lung liquid loss at birth. However, uterine contractions during labour impose fetal postural changes, leading to compression of the thorax, that could account for the high intra-thoracic pressures measured previously (9), causing expulsion of lung liquid early in labour. Indeed, large volumes of lung liquid can be lost shortly after the first signs of labor, before the onset of second stage (13).

Whatever the mechanism for removal of liquid from the airways before birth, liquid still fills the airways after birth until the infant takes its first breath. A recent study used phase contrast X-ray imaging to observe the rate and spatial pattern of lung aeration at birth in rabbit pups delivered by caesarean section (28). They demonstrated that the distal movement of the air/liquid interface only occurred during inspiration, indicating that the transpulmonary pressure generated by inspiratory efforts also plays a critical role in airway liquid clearance. They also noted that thoracic volume increased during lung aeration indicating that the gas volume of the lung increased faster than the liquid could be cleared from the thorax. They concluded that the transpulmonary pressure gradient during inspiration promoted the movement of liquid into the interstitial tissue compartment from which it was gradually cleared, probably by the pulmonary circulation and lymphatics. This suggestion is consistent with the finding that interstitial tissue pressures transiently increase at birth (29) and accounts for the increase in thoracic lymph flow observed in immature and term fetal sheep after the initiation of ventilation (30;31).

Creating and sustaining an end-expiratory gas volume (FRC)

The normal FRC of about 30 ml/kg body weight is usually achieved within hours of birth (32), taking 2-3 hours in vaginally delivered term infants and 5-6 hours in infants delivered by caesarean section (33;34). Many explanations of how air enters the lungs at birth have been suggested. In 1901, Olshausen suggested that thoracic recoil, caused by passive expansion of the chest at delivery, drew air into the lungs (35). This was supported by Warnekros (23) and Karlberg (26) who measured inspiratory volumes of up to 29 mL before the first obvious spontaneous breath. However, Saunders suggested these observed volume changes may have been the initial breaths that were missed within seconds of delivery (27). Other proposed mechanisms include erection of the pulmonary capillaries leading to lung expansion and active inflation through contraction of pharyngeal muscles (glossopharyngeal respiration, “frog breathing”) (36-39). However, the capillary erection theory was disproved by the finding of an immediate and dramatic decrease in pulmonary vascular resistance with inflation (40). In addition, although glossopharyngeal breathing has never been formally rejected as a potential mechanism, it is too slow and inefficient to make a substantial contribution to lung gas volumes.

To understand the mechanics of creating and maintaining end-expiratory gas volumes in the lung, cineradiography (38;41) and recordings of breathing patterns (4;10;42) were performed in full term infants. Fawcitt et al, showed that the first inspiration of air resulted from contraction of the diaphragm which was associated with dilation of the intra-thoracic trachea and the movement of air into the posterior portions of the lung (41). During expiration, some air remained in the lung and some closure of the pharynx-larynx was observed (38;41). These studies and the more recent phase-contrast X-ray imaging of the lung (28) have demonstrated that the entry of air into the lung is dependent upon the generation of a transpulmonary pressure created by inspiratory efforts; this mainly results from contraction of the diaphragm.

Measurements of respiratory activity in healthy term infants at birth indicate that it can take up to 30 seconds before the infant takes its first breath (4;9;10;42). The first breaths tend to be deeper and longer than subsequent breaths and are characterized by a short deep inspiration followed by a prolonged expiratory phase. Commonly, expiratory flow is interrupted by a period of low or zero flow, ending in a short expiratory flow peak or multiple expiratory flow peaks. This is known as expiratory braking and can result in high positive airway pressure when accompanied by abdominal muscle contraction, pressurizing the gas in the lungs. This respiratory pattern is similar between vaginal and caesarean delivered infants (4;10) and has also been observed in spontaneous breathing infants later in life (43-47). Two braking mechanisms contribute to the maintenance of an elevated end-expiratory gas volume. The first, seen in both preterm and term infants, is post-inspiratory activity of the inspiratory muscles, mainly the diaphragm, which slows the rate of lung deflation by counteracting its passive recoil (44;46-48). The second is adduction of the glottis during expiration which increases the resistance to expiratory airflow (32;43;47). This suggestion has been confirmed in studies showing that airflow is controlled throughout the breathing cycle by vagal reflex mediated activation of diaphragmatic and laryngeal muscles (49-53). These vagal reflexes are present at birth in term and preterm infants and are thought to have a crucial role in the control of breathing and lung gas volumes at this time. For a comprehensive review see Frappell and MacFarlane (54).

Transpulmonary pressures required for lung aeration

Several studies have demonstrated an "opening pressure" which must be exceeded to aerate the lungs. Theoretically, the "opening pressure" is analogous to the transpulmonary pressure required to overcome the frictional resistance of liquid movement through the airways, as well as the lung recoil associated with the newly formed surface tension, and drive the air/liquid interface into the distal airways (28;55;56). Experiments in animals and stillborn or deceased newborn infants indicate that the "opening pressure" ranges between 20 and 55 cmH₂O, depending upon whether it was a healthy or diseased lung (55-57). As less pressure was needed to open the lungs when they were inflated with fluid compared

with air, the surface tension at the air liquid interface associated with lung aeration is a major contributing factor to the need for an opening pressure (56-59).

Near term, alveolar type-II epithelial cells secrete surfactant into the lung fluid which reduces the "opening pressure" needed to aerate the lungs (60). As air enters the alveoli the recruitment of surfactant to the air/liquid interface reduces the surface tension, facilitating further alveolar expansion and preventing their collapse (61). Studies measuring inspiratory pressures and tidal volumes of spontaneously breathing infants at birth, showed that sub-atmospheric intrathoracic pressures of 30 cm H₂O produce an average inspired volume of 40 ml (4;5;7;27). At the end of inspiration there is a positive intra-thoracic pressure of about 35 cm H₂O, but there is no loss of gas from the lungs due to a closed glottis. This positive intra-thoracic pressure facilitates the distribution of air within the lung and probably promotes liquid clearance. However, these studies were not able to detect a positive "opening pressure" per se (4;5;7;27) which led Milner to repeat them with more accurate pressure transducers. He observed that infants can generate very high inspiratory pressures (mean 52 cm H₂O; range 28-105 cm H₂O) and positive expiratory pressures (mean 71 cm H₂O; range 18-115 cm H₂O) during the first breath to achieve similar inspired volumes as previously measured, but still no positive "opening pressures" were noted (9). Clearly, the pressure gradient between the mouth opening and the alveolus, rather than a positive "opening pressure" per se, determines gas entry into the lung.

In contrast, positive "opening pressures" required for gas entry into the lungs have been examined in ventilated apneic infants. Boon studied 20 asphyxiated babies born by caesarean section and showed that an inflation pressure of >20 cm H₂O (mean 27 cm H₂O) was required for gas entry into the lungs (62). Inflations of 30 cm H₂O produced an initial tidal volume of 15 ml, which is low compared to the 40 ml measured in spontaneous breathing infants (62;63). In most instances, a significant FRC was not achieved until the baby began its own respiratory efforts, probably in response to a Head's paradoxical reflex (62). This reflex promotes continued inspiration after a sudden inflation and is important in the initial aeration of the lung after birth (62;64;65).

Boon also noted that during the first inspirations, gas was still entering the lung after one second (62), which prompted them to examine the effect of sustained inflations. When an inflation of 30 cm H₂O was prolonged for 5 seconds, the inspired volume was similar to that achieved by spontaneously breathing infants. Thus, it is possible that a prolonged inflation, at this pressure, overcomes the long time constant of a fluid-filled lung, allows more air to enter the alveoli and also helps to clear airway liquid. When the inflation pressure was increased slowly over three to five seconds, lower opening pressures were required compared with standard inflations (10 to 25 cm H₂O) (66).

Lung aeration in very preterm infants

There are several reasons why very preterm infants may have difficulty aerating their lungs and keeping them open. Because of weak respiratory muscles and inadequate surfactant, insufficient inspiratory pressures are generated to overcome the high surface tension and frictional forces to achieve effective lung aeration. Because the neonatal chest wall is very compliant, it deforms during diaphragmatic contraction, thereby reducing the inspired tidal volume, and is unable to resist lung recoil which reduces resting lung gas volumes at end expiration (67;68). In addition, the lungs of preterm infants are less responsive to mechanisms such as sodium reabsorption and so are less efficient at clearing lung liquid (16;69;70). Retention of lung liquid in the air spaces reduces lung gas volume, promotes non-uniform aeration and impairs the changes in cardio-pulmonary physiology that are essential for postnatal survival (16;69;70). Most very preterm infants now receive antenatal corticosteroids which greatly improve postnatal lung function. Glucocorticoids stimulate surfactant production, accelerate development of the distal airway structure and mature liquid clearance mechanisms thereby enhancing lung aeration at birth (18;71). Thus, following glucocorticoid treatment, many very preterm infants can breathe more easily and establish an FRC with only nasal continuous positive airway pressure (NCPAP) as support (72;73).

Most studies investigating the first breaths of extra-uterine life have focused on healthy or asphyxiated term infants, not very preterm infants. Signs such as grunting expiration, chest retraction and tachypnea in very preterm infants suggest that they have similar lung volume defense mechanisms to mature infants. However, it cannot be assumed that results of studies of term infants apply to preterm infants.

The lungs of very preterm infants are vulnerable and inappropriate ventilatory support can cause injury which is closely associated with the development of bronchopulmonary dysplasia (1;2). A more detailed examination of the breathing patterns adopted by very preterm infants that successfully establish and maintain an FRC after birth may help us understand the most appropriate ways to ventilate those infants requiring respiratory support. It is possible that, instead of using higher pressures to open the lung, an initial sustained inflation should be given to overcome the long time constant of the fluid-filled lung (66;74). There are also compelling data emerging to indicate that the creation and maintenance of an FRC during resuscitation is dependent upon PEEP which prevents airway collapse at end expiration (75). NCPAP immediately after birth versus intubation and prophylactic surfactant is a controversial topic. Administration of prophylactic surfactant in preterm infants has been shown to reduce mortality and the incidence of pneumothoraces, (76) most probably by improving lung compliance and facilitating lung aeration. However, there is limited data concerning the immediate effect of surfactant during resuscitation directly after birth (77;78). The advantages of NCPAP are that it is relatively non-invasive, it conserves surfactant and supports and stimulates spontaneous breathing, avoiding

possible damage caused by intubation and ventilation. It is likely that the sub-atmospheric pressure generated during spontaneous inspiration is more efficient than positive pressure applied via the airways (62;63); and may promote faster and more uniform liquid clearance from the airways and lung tissue. A recent RCT in very preterm infants combined the strategies of a prolonged initial inspiration with early CPAP and showed a reduction in intubations in the delivery room and within 72 hours of age (74).

Conclusion

A good understanding of the strategies used by an infant to breathe and create and sustain a FRC at birth should be the basis of respiratory support in the delivery room when breathing is inadequate. The spontaneous breathing pattern is very different from that imposed during mechanical ventilation. The lung expands more easily with spontaneous inspirations than inflations, most probably because artificially applied inflations do not adequately duplicate the first spontaneous breaths. Important questions remain unanswered. 1) How do very preterm infants aerate their lungs spontaneously and develop an FRC and how can this be stimulated and supported? 2) Would it be better to use ventilation techniques that mimic spontaneous breathing at birth to aerate the lung in apneic very preterm infants? To learn more about spontaneous breathing patterns and artificial inflations in the delivery room, more studies of both term and preterm infants using advanced techniques are needed. Studies using animal models will remain an important complement to human studies.

Reference List

1. Bjorklund LJ, Ingimarsson J, Curstedt T, John J, Robertson B, Werner O, et al. Manual ventilation with a few large breaths at birth compromises the therapeutic effect of subsequent surfactant replacement in immature lambs. *Pediatr Res* 1997 Sep;42(3):348-55.
2. Wada K, Jobe AH, Ikegami M. Tidal volume effects on surfactant treatment responses with the initiation of ventilation in preterm lambs. *J Appl Physiol* 1997 Oct;83(4):1054-61.
3. Karlberg P. The adaptive changes in the immediate postnatal period, with particular reference to respiration. *J Pediatr* 1960 May;56:585-604.
4. Karlberg P, Cherry RB, Escardo FE, Koch G. pulmonary ventilation and mechanics of breathing in the first minutes of life, including the onset of respiration. *Acta Paediatr Scand* 1962;51:121-36.
5. Milner AD, Saunders RA. Pressure and volume changes during the first breath of human neonates. *Arch Dis Child* 1977 Dec;52(12):918-24.
6. Saunders RA, Milner AD. Pulmonary pressure/volume relationships during the last phase of delivery and the first postnatal breaths in human subjects. *J Pediatr* 1978 Oct;93(4):667-73.
7. Vyas H, Milner AD, Hopkins IE. Intrathoracic pressure and volume changes during the spontaneous onset of respiration in babies born by cesarean section and by vaginal delivery. *J Pediatr* 1981 Nov;99(5):787-91.

8. Vyas H, Milner AD, Hopkin IE, Falconer AD. Role of labour in the establishment of functional residual capacity at birth. *Arch Dis Child* 1983 Jul;58(7):512-7.
9. Vyas H, Field D, Milner AD, Hopkin IE. Determinants of the first inspiratory volume and functional residual capacity at birth. *Pediatr Pulmonol* 1986 Jul;2(4):189-93.
10. Mortola JP, Fisher JT, Smith JB, Fox GS, Weeks S, Willis D. Onset of respiration in infants delivered by cesarean section. *J Appl Physiol* 1982 Mar;52(3):716-24.
11. Harding R, Hooper SB. Regulation of lung expansion and lung growth before birth. *J Appl Physiol* 1996 Jul;81(1):209-24.
12. Hooper SB, Wallace MJ. Role of the physicochemical environment in lung development. *Clin Exp Pharmacol Physiol* 2006 Mar;33(3):273-9.
13. Lines A, Hooper SB, Harding R. Lung liquid production rates and volumes do not decrease before labor in healthy fetal sheep. *J Appl Physiol* 1997 Mar;82(3):927-32.
14. Harding R, Hooper SB, Dickson KA. A mechanism leading to reduced lung expansion and lung hypoplasia in fetal sheep during oligohydramnios. *Am J Obstet Gynecol* 1990 Dec;163(6 Pt 1):1904-13.
15. Brown MJ, Olver RE, Ramsden CA, Strang LB, Walters DV. Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. *J Physiol* 1983 Nov;344:137-52.
16. Barker PM, Olver RE. Invited review: Clearance of lung liquid during the perinatal period. *J Appl Physiol* 2002 Oct;93(4):1542-8.
17. Jain L, Dudell GG. Respiratory transition in infants delivered by cesarean section. *Semin Perinatol* 2006 Oct;30(5):296-304.
18. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. *Semin Perinatol* 2006 Feb;30(1):34-43.
19. Bland RD. Loss of liquid from the lung lumen in labor: more than a simple "squeeze". *Am J Physiol Lung Cell Mol Physiol* 2001 Apr;280(4):L602-L605.
20. Olver RE, Ramsden CA, Strang LB, Walters DV. The role of amiloride-blockable sodium transport in adrenaline-induced lung liquid reabsorption in the fetal lamb. *J Physiol* 1986 Jul;376:321-40.
21. O'Brodovich H, Hannam V, Seear M, Mullen JB. Amiloride impairs lung water clearance in newborn guinea pigs. *J Appl Physiol* 1990 Apr;68(4):1758-62.
22. Hummler E, Barker P, Gatz J, Beermann F, Verdumo C, Schmidt A, et al. Early death due to defective neonatal lung liquid clearance in alpha-ENaC-deficient mice. *Nat Genet* 1996 Mar;12(3):325-8.
23. Warnekros K. Schwangerschaft und Geburt im Röntgenbilde. Wiesbaden: JF Bergman; 1917.
24. Borell U, Fernstrom I. The shape of the foetal chest during its passage through the birth canal. A radio-graphic study. *Acta Obstet Gynecol Scand* 1962;41:213-22.
25. Martius H, Bickenbach W. *Lehrbuch der Geburtshilfe*. 3th ed. Stuttgart: George Thieme Verlag; 1956.
26. Karlberg P, Adams FH, Geubelle F, Wallgren G. Alteration of the infant's thorax during vaginal delivery. *Acta Obstet Gynecol Scand* 1962;41:223-9.
27. Saunders RA, Milner AD. Pulmonary pressure/volume relationships during the last phase of delivery and the first postnatal breaths in human subjects. *J Pediatr* 1978 Oct;93(4):667-73.
28. Hooper SB, Kitchen MJ, Wallace MJ, Yagi N, Uesugi K, Morgan MJ, et al. Imaging lung aeration and lung liquid clearance at birth. *FASEB J* 2007; 21(12):3329-37.
29. Miserocchi G, Poskurica BH, Del Fabbro M. Pulmonary interstitial pressure in anesthetized paralyzed newborn rabbits. *J Appl Physiol* 1994 Nov;77(5):2260-8.
30. Boston RW, Humphreys PW, Reynolds EO, Strang LB. Lymph-flow and clearance of liquid from the lungs of the foetal lamb. *Lancet* 1965 Sep 4;10:473-4.
31. Humphreys PW, Normand IC, Reynolds EO, Strang LB. Pulmonary lymph flow and the uptake of liquid from the lungs of the lamb at the start of breathing. *J Physiol* 1967 Nov;193(1):1-29.
32. Milner AD, Saunders RA, Hopkin IE. Is air trapping important in the maintenance of the functional residual capacity in the hours after birth? *Early Hum Dev* 1978 Jul;2(2):97-105.

33. Chu JS, Dawson P, Klaus M, Sweet AY. Lung compliance and lung volume measured concurrently in normal full-term and premature infants. *Pediatrics* 1964 Oct;34:525-32.
34. Milner AD, Saunders RA, Hopkin IE. Effects of delivery by caesarean section on lung mechanics and lung volume in the human neonate. *Arch Dis Child* 1978 Jul;53(7):545-8.
35. Olshausen R. Beitrag zur Lehre vom Mechanismus der Geburt. Stuttgart: Ferdinand Enke; 1901.
36. Jaykka S. Capillary erection and lung expansion; an experimental study of the effect of liquid pressure applied to the capillary network of excised fetal lungs. *Acta Paediatr Suppl* 1957 Jan;46(suppl 112):1-91.
37. Adams FH, Karlberg P, Lind J. possible role of capillary erection as a cause for lung expansion. *Clin Res* 1958;6:111.
38. Bosma JF, Lind J, Gentz N. Motions of the pharynx associated with initial aeration of the lungs of the newborn infant. *Acta Paediatr Suppl* 1959 Apr 11;48(Suppl 117):117-22.
39. Bosma JE, Truby HM, Lind J. Studies of neo-natal transition: correlated cineradiographic and visual-acoustic observations. *Acta Paediatr Scand* 1965; Suppl 163:93+.
40. Dawes GS, Mott JC, Widdicombe JG, Wyatt DG. Changes in the lungs of the new-born lamb. *J Physiol* 1953 Jul;121(1):141-62.
41. Fawcitt J, Lind J, Wegelius C. The first breath: a preliminary communication describing some methods of investigation of the first breath of a baby and the results obtained from them. *Acta Paediatr Suppl* 1960 Mar;49(Suppl 123):5-17.
42. Engstrom L, Karlberg P, Rooth G, Tunell R. The onset of respiration, a study of respiration and changes in blood gases and acid-base balance. New York: Association for the aid of crippled children; 1966.
43. Fisher JT, Mortola JP, Smith JB, Fox GS, Weeks S. Respiration in newborns: development of the control of breathing. *Am Rev Respir Dis* 1982 Jun;125(6):650-7.
44. Kosch PC, Stark AR. Dynamic maintenance of end-expiratory lung volume in full-term infants. *J Appl Physiol* 1984 Oct;57(4):1126-33.
45. Lindroth M, Johnson B, Ahlstrom H, Svenningsen NW. Pulmonary mechanics in early infancy. Subclinical grunting in low-birth-weight infants. *Pediatr Res* 1981 Jul;15(7):979-84.
46. Mortola JP, Milic-Emili J, Noworaj A, Smith B, Fox G, Weeks S. Muscle pressure and flow during expiration in infants. *Am Rev Respir Dis* 1984 Jan;129(1):49-53.
47. Radvanyi-Bouvet MF, Monset-Couchard M, Morel-Kahn F, Vicente G, Dreyfus-Brisac C. Expiratory patterns during sleep in normal full-term and premature neonates. *Biol Neonate* 1982;41(1-2):74-84.
48. Stark AR, Cohlman BA, Waggner TB, Frantz ID, III, Kosch PC. Regulation of end-expiratory lung volume during sleep in premature infants. *J Appl Physiol* 1987 Mar;62(3):1117-23.
49. Kosch PC, Hutchinson AA, Wozniak JA, Carlo WA, Stark AR. Posterior cricoarytenoid and diaphragm activities during tidal breathing in neonates. *J Appl Physiol* 1988 May;64(5):1968-78.
50. Kosch PC, Davenport PW, Wozniak JA, Stark AR. Reflex control of expiratory duration in newborn infants. *J Appl Physiol* 1985 Feb;58(2):575-81.
51. England SJ, Kent G, Stogryn HA. Laryngeal muscle and diaphragmatic activities in conscious dog pups. *Respir Physiol* 1985 Apr;60(1):95-108.
52. Harding R, Johnson P, McClelland ME. Respiratory function of the larynx in developing sheep and the influence of sleep state. *Respir Physiol* 1980 May;40(2):165-79.
53. Henderson-Smart DJ, Johnson P, McClelland ME. Asynchronous respiratory activity of the diaphragm during spontaneous breathing in the lamb. *J Physiol* 1982 Jun;327:377-91.
54. Frappell PB, MacFarlane PM. Development of mechanics and pulmonary reflexes. *Respir Physiol Neurobiol* 2005 Nov 15;149(1-3):143-54.
55. Mead J, Whittenberger JL, Radford EP, Jr. Surface tension as a factor in pulmonary volume-pressure hysteresis. *J Appl Physiol* 1957 Mar;10(2):191-6.
56. Avery ME, Frank NR, Gribetz I. The inflationary force produced by pulmonary vascular distention in excised lungs; the possible relation of this force to that needed to inflate the lungs at birth. *J Clin Invest* 1959 Mar;38(3):456-62.

57. Gruenwald P. surface tension as a factor in the resistance of neonatal lungs to aeration. *Am J Obstet Gynecol* 1947;1947(53):996.
58. Agostoni E, Taglietti A, Agostoni AF, Setnikar I. Mechanical aspects of the first breath. *J Appl Physiol* 1958 Nov;13(3):344-8.
59. Gruenwald P. Normal and abnormal expansion of the lungs of newborn infants obtained at autopsy. I. Expansion of lungs by liquid media. *Anat Rec* 1961 Apr;139:471-81.
60. Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *AMA J Dis Child* 1959 May;97(5, Part 1):517-23.
61. Hildebran JN, Goerke J, Clements JA. Surfactant release in excised rat lung is stimulated by air inflation. *J Appl Physiol* 1981 Oct;51(4):905-10.
62. Boon AW, Milner AD, Hopkin IE. Lung expansion, tidal exchange, and formation of the functional residual capacity during resuscitation of asphyxiated neonates. *J Pediatr* 1979 Dec;95(6):1031-6.
63. Boon AW, Milner AD, Hopkin IE. Physiological responses of the newborn infant to resuscitation. *Arch Dis Child* 1979 Jul;54(7):492-8.
64. Cross KW. Head's paradoxical reflex. *Brain* 1961 Dec;84:529-34.
65. Hull D. Lung expansion and ventilation during resuscitation of asphyxiated newborn infants. *J Pediatr* 1969 Jul;75(1):47-58.
66. Vyas H, Milner AD, Hopkin IE, Boon AW. Physiologic responses to prolonged and slow-rise inflation in the resuscitation of the asphyxiated newborn infant. *J Pediatr* 1981 Oct;99(4):635-9.
67. Gerhardt T, Bancalari E. Chestwall compliance in full-term and premature infants. *Acta Paediatr Scand* 1980 May;69(3):359-64.
68. Heldt GP, McIlroy MB. Dynamics of chest wall in preterm infants. *J Appl Physiol* 1987 Jan;62(1):170-4.
69. Barker PM, Gowen CW, Lawson EE, Knowles MR. Decreased sodium ion absorption across nasal epithelium of very premature infants with respiratory distress syndrome. *J Pediatr* 1997 Mar;130(3):373-7.
70. Zelenina M, Zelenin S, Aperia A. Water channels (aquaporins) and their role for postnatal adaptation. *Pediatr Res* 2005 May;57(5 Pt 2):47R-53R.
71. Bolt RJ, van Weissenbruch MM, Lafeber HN, Delemarre-van de Waal HA. Glucocorticoids and lung development in the fetus and preterm infant. *Pediatr Pulmonol* 2001 Jul;32(1):76-91.
72. Aly H, Massaro AN, Patel K, El Mohandes AA. Is it safer to intubate premature infants in the delivery room? *Pediatrics* 2005 Jun;115(6):1660-5.
73. Thomson MA. Continuous positive airway pressure and surfactant; combined data from animal experiments and clinical trials. *Biol Neonate* 2002;81 Suppl 1:16-9.
74. te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. *Pediatrics* 2007 Aug;120(2):322-9.
75. Hooper SB, Wallace MJ, Kitchen M, Siew M, Yagi N, Uesugi K, et al. Lung aeration at birth: spontaneous breathing versus mechanical ventilation. *Pediatric Academic Societies. Toronto, Canada Abstract* 7155.10. 2007.
76. Soll RF. Prophylactic synthetic surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000;(2):CD001079.
77. Lachmann B, Berggren P, Curstedt T, Grossmann G, Robertson B. Combined effects of surfactant substitution and prolongation of inspiration phase in artificially ventilated premature newborn rabbits. *Pediatr Res* 1982 Nov;16(11):921-7.
78. Song GW, Sun B, Curstedt T, Grossmann G, Robertson B. Effect of amiloride and surfactant on lung liquid clearance in newborn rabbits. *Respir Physiol* 1992 Apr;88(1-2):233-46.