ASSESSING RESUSCITATION RESPONSES IN PREMATURELY BORN INFANTS

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Abstract

Background: Infants born prematurely may need cardio pulmonary resuscitation soon after birth. The infant's responses to resuscitation have rarely been monitored in real time, yet can influence the effectiveness of resuscitation.

Aim: Using a respiratory function monitor to assess physiological responses during the resuscitation of prematurely born infants

Methods: A series of studies were undertaken and the main objectives were

- To evaluate current resuscitation techniques and the physiological responses of prematurely born infants
- To determine the efficacy of current resuscitation methods
- To evaluate the use of respiratory function monitoring during the resuscitation of prematurely born infants

Results: During the first five inflations delivered by a face mask, clinicians rarely maintained the inflations beyond two seconds. The median tidal volume was low with mechanical lung inflations but significantly increased when combined with the infant's respiratory efforts (median 2.1 vs 5.6 ml/kg; p=0.007). Similarly, expired carbon dioxide levels were significantly higher with a combination of inflation and inspiratory effort (median 0.3 vs 2.3 kpa; $p< 0.01$). Similar findings were demonstrated when resuscitation was performed though an endotracheal tube. A survey of clinicians who used respiratory function monitoring (RFM) during preterm resuscitation, demonstrated that they thought that the RPM was useful, but their interventions were not evidence based

Conclusions: Respiratory function monitoring demonstrated variability in the initial resuscitation of preterm infants and highlighted the importance of the infants' respiratory efforts contributing to the efficacy of resuscitation

Acknowledgments

I would never have been able to complete my dissertation without the guidance of Professor Anne Greenough, Professor Milner and support from my family and wife, Priya.

I would like to express my deepest gratitude to my supervisors (Professors Greenough and Milner) who trusted me and made me believe that this project can be done and importantly, providing me with an excellent atmosphere for conducting research. I am grateful to them for their excellent guidance, patience, sympathy and above all being the driving force to present and publish my work and complete my thesis.

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Published work arising from this thesis

1. **Murthy V**, D'Costa W, Shah R, Fox GF, Campbell ME, Milner AD, Greenough A. Prematurely born infants' response to resuscitation via an endotracheal tube or a face mask. Early human development. 2015 Mar;91(3):235-8.

2. Milner A**, Murthy V**, Bhat P, Fox G, Campbell ME, Milner AD, Greenough A. Evaluation of respiratory function monitoring at the resuscitation of prematurely born infants. European journal of Pediatrics. 2015 Feb;174(2):205-8.

3. **Murthy V**, O'Rourke-Potocki A, Dattani N, Fox GF, Campbell ME, Milner AD, Greenough A. End tidal carbon dioxide levels during the resuscitation of prematurely born infants. Early human development.2012 Oct;88(10):783-7.

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With the help of my supervisors Professor Greenough and Milner, I contributed to the published studies by conceptualising the study, data collection, interpretation and analysis. I drafted the manuscript, critically reviewed the article prior to final approval for publication.

Chapter 1 : Introduction

1.1 Background

The immediate postnatal period is the most challenging and hazardous time for a newborn infant. Rapid adaptation to extra-uterine life is crucial for survival. Worldwide approximately 135 million infants are born each year and 12.9 million are born prematurely (1). A large proportion of prematurely born infants require respiratory support to assist in the transition and rapid cardio- pulmonary adaptation is needed for survival (2). The need for support is inversely related to the gestational age at birth, that is extremely premature infants are more likely to require support than those born at greater gestational age.

Resuscitation of the newborn infant is one of the most cost effective, lifesaving interventions in medical care, yet resuscitation of prematurely born infant is one of the least studied interventions in newborn medicine.(3) The current resuscitation practices used to help support the breathing and circulation of premature infants are based largely upon evidence from infants born at term. In preterm infants, the lungs are immature and vulnerable to damage, this is further complicated by the need for higher pressures and oxygen supplementation in infants having severe surfactant deficiency. The estimated airway opening pressure needed during resuscitation of term born infant is estimated to be 30 cm H_2O (4) however in preterm born infants this must be variable across gestational, hence using evidence from the resuscitation of term born infants may potentially be damaging to the immature lungs.

1.2 Historical perspectives

Newborn death due to respiratory failure and asphyxia has been recognised for many centuries. The Chinese emperor and philosopher Huang Ti in the 2600 BC observed respiratory failure was more common in prematurely born infants. Subsequently, in the 16th Century BC Papyrus Ebers (5)commented on the prognosis of a baby immediately after birth, “If it cries nee, it will live, if it moans “ba”, it will die”, likely suggesting respiratory distress in the newborn infant. Inflating the lung and artificial breathing has been described in newborn lambs and in humans in the “The Babylonian Talmud”(6) and by Hippocrates. “Reviving” newborn babies by numerous resuscitation techniques has been documented since the 1600s, however current approaches to resuscitation of a newborn has its origin since the eighteenth century.

In the 1750s, initially Smellie and later Pugh, described their experiences in resuscitating asphyxiated infants by blowing into the lung through a straight endotracheal tube inserted in to the trachea. With concerns regarding the use of exhaled air, Hunter, an influential obstetrician at the time, devised a bellow system to inflate the lungs. Nevertheless, mouth to tube inflation continued to be favoured. François Chaussier, an obstetrician in Paris, and James Blundell, an obstetrician at Guy’s Hospital, both described their techniques of manual intubation with straight endotracheal tubes and lung inflation to resuscitate newborn infants. During this period, numerous other techniques were also described by Cangiamila(7). The techniques include insufflation of warm human breath through a tube into the infant’s mouth, sucking the infant’s nipples, tickling its soles, giving it a warm bath, burning the umbilical cord, rectal insufflation of tobacco smoke and placing the infant in a chicken carcass.

Francis Chaussier in 1780 first initiated oxygen use in clinical medicine when he invented a pressure – limited ventilator device that was used for newborn resuscitation, subsequently the use of oxygen became popular throughout Europe(8).

In 1827, Leroy d'Etiolles described the association between lung inflation and pneumothoraces. During the next one hundred years, there was significant interests and developments in respiratory support with better understanding of fetal and neonatal lung physiology. Lung inflation techniques were modified and newer equipment designed for clinical application. The first mechanical ventilators were introduced in the 1870s, but due to their size they were not available to use in the labour ward.

Since the 1870s alternative methods were also used and included techniques such as swinging the infant upside down (the Schultze method), squeezing the chest (Prochownich method), moving the arms up and down while the assistant compressed the chest (the Sylvester method), tickling the chest, yelling, slapping, pinching, and rhythmic traction of the tongue.

A commercial automatic mask ventilator "Pulmotor" was developed in 1907 and subsequently "Baby Pulmotor" was developed and used in most delivery rooms across Europe until the 1950s.

The current practices evolved rapidly since Yandell Henderson(9) published his use of a face mask, carbon dioxide and oxygen flow and a t-piece for intermittent obstruction with a blow off pressure measuring system during newborn resuscitation. Flagg believed that Henderson's method of administration could be improved and described the straight tube, neonatal

laryngoscope technique(10). Mathieu and Holman instead advocated the use of the operator's finger as a guide to perform "blind intubation" with an endotracheal tube and the operator's own breath, which they argued could deliver appropriate amounts of oxygen and carbon dioxide. Although they advocated the use of carbon dioxide gas during resuscitation arguing that it stimulated the respiratory centre, the efficacy of this approach was not described.

In the 1930s Nicholson J Eastman studied the effects of hypoxia and hypercarbia levels and its association with the initiation of respiration. He published a series of five articles on foetal blood studies and concluded that:

> *"There seems to be only one urgent indication in the treatment of asphyxia neonatorum, and that is to introduce oxygen into the circulating blood of the infant. Whether this is effected by manual artificial respiration, by mouth to mouth breathing, or by some form of apparatus such as the Drinker respirator, seems to us of minor importance, so long as the air passages have been carefully cleared of mucus and a constant supply of oxygen (or air) is maintained into the pulmonary alveoli"*(11).

Eastman's research findings influenced the work done by JB Blaikley and GF Gibberd (12)who were obstetricians based at the Guy's Hospital, London. In March 1935, they published their method of tracheal intubation using a modified laryngoscope followed by lung inflation with up to pressures of 35cm H_2O, calculating that an inflation pressure of only 15cm H_2O was generated as there was leak around the tube. This was maintained until the infants commenced breathing, effectively maintaining a positive end expiratory pressure (PEEP). Numerous novel newborn resuscitation techniques were introduced for the

treatment of asphyxia neonatorum, including Henderson's inhalatory method and Pauluel Flagg's intubation with positive pressure insufflation. Henderson was influenced by his research on adults suffering from asphyxia, and using applied physiology, he argued that asphyxia should be treated with inhalation of carbon dioxide mixed in oxygen(13). Henderson believed that the respiratory centre should be stimulated chemically by carbon dioxide, and recommended the use of a mask inhalator, which was attached to the gas cylinder via a manometer which controlled the gas pressure. His inhalatory method involved placing a mask over the infant's nose and mouth and supplying a mixture of carbon dioxide and oxygen as a steady stream(9) (Figure 1-1). Pauluel agreed with Henderson that a resuscitation technique should supply a mixture of carbon dioxide and oxygen to the newborn, but felt that Henderson's method of administration could be improved by use of a laryngoscope and endotracheal tube (Figure 1-2)(10) Those two techniques came to be viewed as representative of a 'modern' and 'scientific' approach to newborn resuscitation at a time when newborn care was accused of lacking a scientific basis and of being empirical in nature.

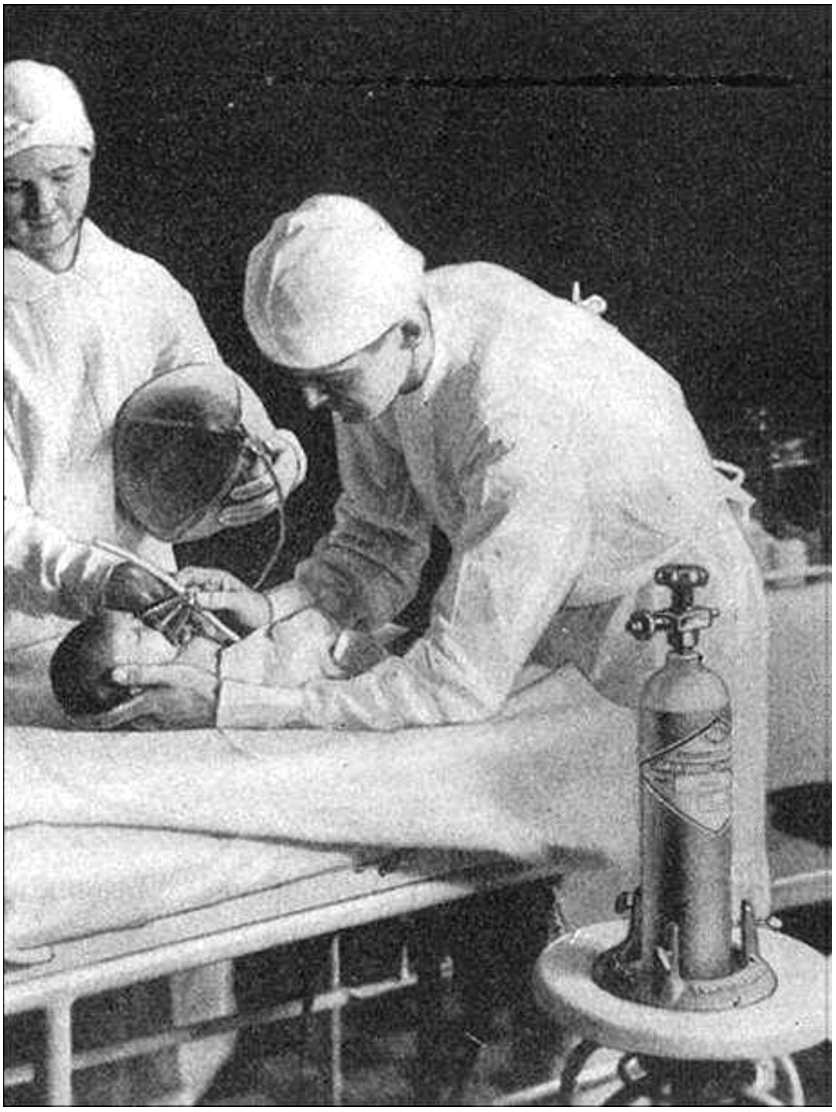

Figure 1-1: Henderson's Inhalatory Method.

Image taken from Henderson (1938) Adventures in Respiration. [Appendix III for copyright status].

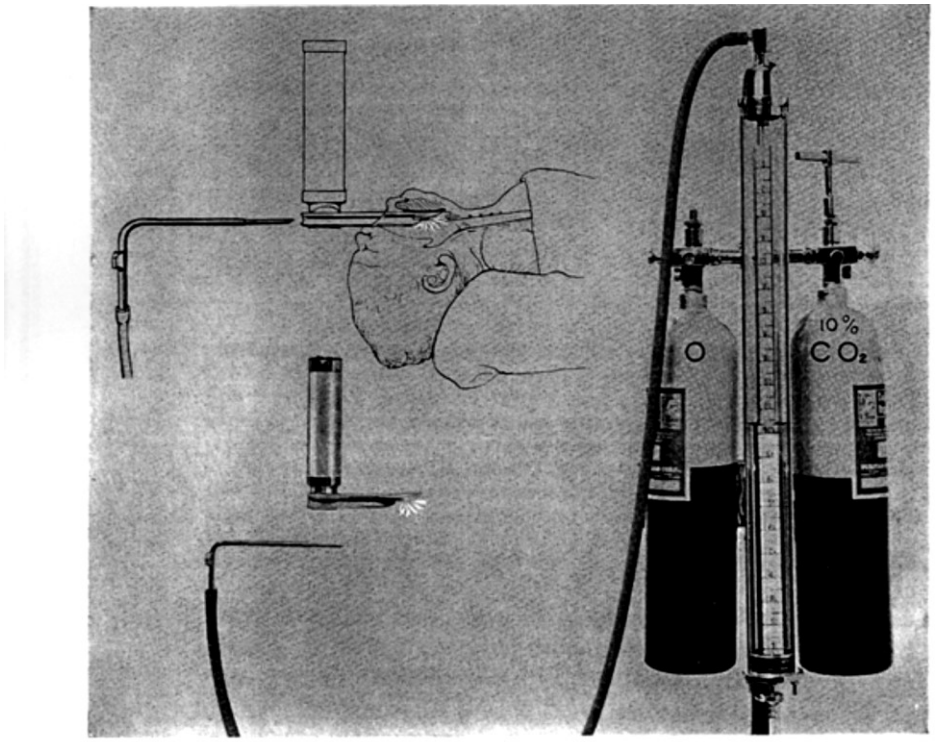

FIG. 648.—FLAGG'S APPARATUS.

Left—visualization of the larynx, removal of mucus, and direct insufflation of air. Right—the water gauge indicates the pressure of the gases and "blows off" when it passes 10" of water.

Figure 1-2: Flagg's method of endotracheal intubation and positive pressure insufflation.
Image taken from DeLee & Grennhill (1943) The Principles and Practice of Obstetrics [Appendix III for copyright status].

Since Eastman's conclusions on the benefits of using oxygen during newborn resuscitation, one approach described was the Bloxon positive pressure oxygen-air lock(14). Infants with asphyxia were placed in a metal chamber and humidified and warmed oxygen was introduced, the oxygen level was raised to 60%. The pressure in the chamber was then increased to three pounds of pressure for 30-40 seconds, then reduced to one pound pressure for 15 seconds before the cycle was repeated. This apparently reduced the mortality of infants treated by 25% compared to historical controls. An alternative method was to deliver oxygen to the gastrointestinal tract on the assumption that oxygen would then be absorbed into the blood(15). James et al (16) reported

that the technique did not add any benefit during resuscitation of newborn infants. James Hutchinson and colleagues reported their experience in using hyperbaric oxygen in asphyxia neonatorum. They raised the ambient oxygen to up to three atmospheres for 30 minutes after placing the asphyxiated infant in a compression chamber. They reported that this technique was beneficial but needed further investigation. Subsequently, the same group conducted a randomised controlled trial of hyperbaric oxygen versus tracheal intubation and intermittent positive-pressure with oxygen as methods of neonatal resuscitation was conducted in two maternity hospitals. Two hundred and eighteen infants were recruited into the trial over a 16-month period. There were no significant differences in mortality between the two groups, with 15 deaths in the intubated infants and 19 in the hyperbaric group. The authors claimed that the main benefit of hyperbaric oxygen therapy was that less skill was required than tracheal intubation (17). Some of these methods continued until 1950s despite growing evidence on the efficacy of lung inflation techniques.

In 1960's, Saling (18-21) published his findings of comparisons on the value of different methods of treating asphyxia as assessed by measuring the umbilical artery and venous blood oxygen content. He found that thorax compression, mouth to mouth breathing and intragastric oxygen were ineffective, but intubation and ventilation using 100% oxygen led to a more rapid response in the blood gas parameters and was similar to that of spontaneously breathing infants. He also recommended that the cord should be left uncut for as long as possible and that there should be no delay in commencing resuscitation after the delivery of asphyxiated infants.

1.2.1 Lung inflation technique and devices

In the 1930s, Yandell Henderson popularised the use of a face-mask to supply positive pressure during resuscitation of an asphyxiated newborn infant. He argued that it was only the flaccid infant who required active resuscitation and with the introduction of an endotracheal tube and resuscitative gas reached the lungs much more efficiently via an endotracheal tube if the infant was intubated. Flagg stressed that the use of a face-mask could not guarantee a patent airway and was therefore not as effective as an endotracheal tube. In March 1935, Blaikley and Gibberd published an important paper describing their method of tracheal intubation using a modified laryngoscope(12).Blaikley and Gibberd shared Flagg's concerns that a face-mask was not the most effective means of supplying positive pressure ventilation in a severely asphyxiated baby. They believed that in the majority of cases simple methods of clearing airways and supplying oxygen and carbon dioxide would be enough to help the newborn to initiate spontaneous respiration.

In 1952 Roberts published the results of a trial conducted on severely asphyxiated newborns treated with intubation and insufflation(22). She had treated sixty-six 'severely asphyxiated' infants using endotracheal insufflation with oxygen. Intermittent positive pressure at 20 cm H_2O of water at 10-15 lung inflations per minute was administered with oxygen, she reported only 14 deaths(22). Blaikely and Gibberd, by this time had been practicing this technique for 17 years and reported that they did not have any adverse event with this technique(23).

Furthermore, in a bid to address the concerns over the use and safety of positive pressure resuscitation, Day et al. began to investigate pressure-time relations needed to inflate atelectatic lungs in animals.(24). He made comparisons of animals to the newborn human lung and hypothesized that in asphyxiated infants, high positive pressures of up to 40 cm H_2O, over short intervals of 0.15 seconds would be needed.

Goddard and Bennet conducted post-mortem studies on the human infant lung. They concluded that when a positive pressure of 30 cm H_2O was applied over a 0.2 second interval there was patchy lung aeration and pressures up to 50 cm H_2O at short intervals was needed for more uniform lung expansion(25). Based on the physiological principles and scientific observations from published studies they developed the Goddard-Bennett-Lovelace (GBL) infant hand resuscitator, which used a face mask attached to a reservoir bag, which could be used to employ intermittent positive pressure ventilation by the bed side (Figure 1-3).

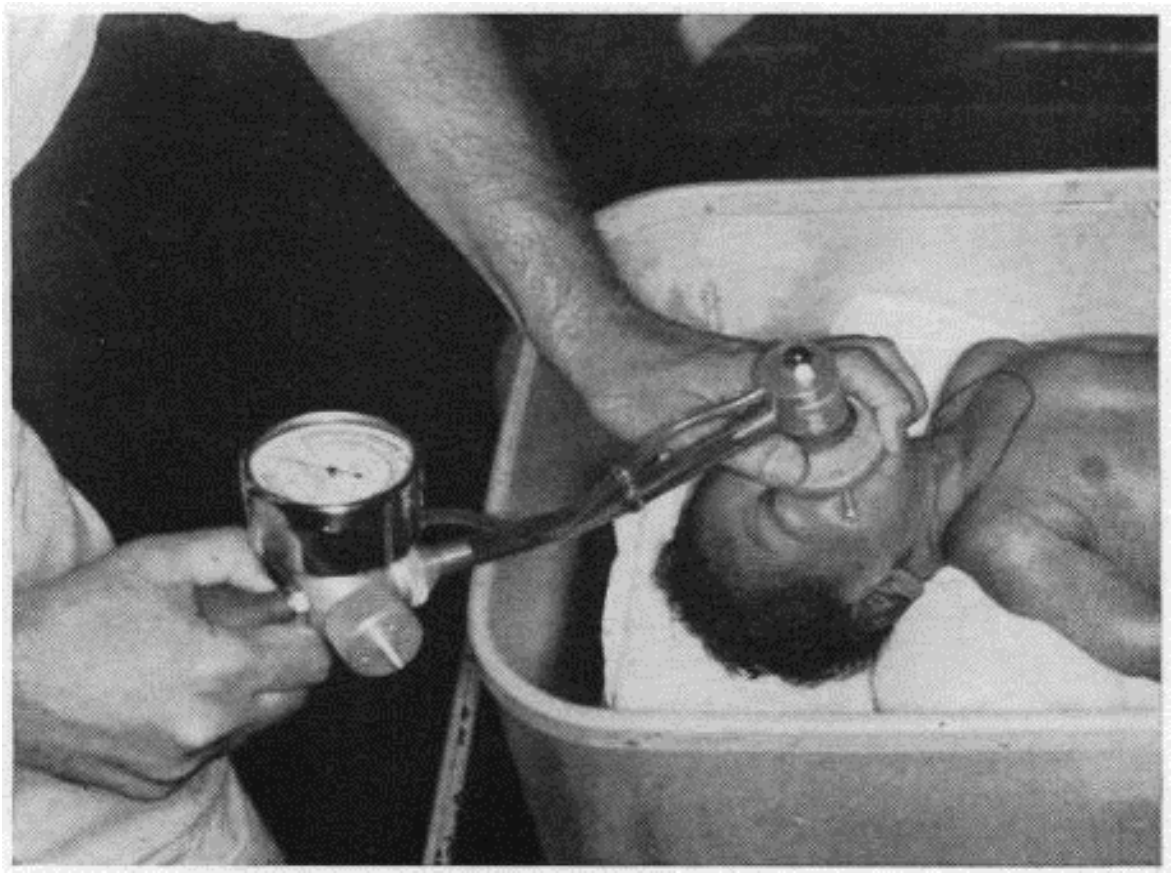

Figure 1-3: Goddard-Bennett-Lovelace (GBL) infant hand resuscitator in clinical use.
[Appendix III for copyright status].

The introduction of the anaesthetic bag in 1958(26) in combination with the face mask and pressure vales, made it more simper to administer positive pressure ventilation by the bedside. The optimum pressure to inflate the newborn lung still remained a mystery as it had not been possible to measure the airway opening pressure of the first breaths of a newborn infant. Then Karlberg et al (27)in 1954 demonstrated that many term born infants generated pressures greater than 20cm H_2O in their first breath. Further studies by Hull et al(28), however, reported that the inflation pressures needed during newborn resuscitation were variable and often exceeded 30 cm H_2O. The peak inflation pressures needed for newborn resuscitation is still currently being debated. In

preterm birth, due to the severity of lung disease across gestational ages, it had caused more difficulty in understating the airway opening pressure needed for resuscitation in prematurely born infant.

1.3 Pulmonary adaptation in a newborn born infant

Immediately after birth, the newborn infant lung has to achieve adequate exchange of oxygen (O_2) and carbon dioxide (CO_2) to cope with high metabolic demands of the body. For newborn infants to survive after birth, they must be able to match alveolar ventilation in proportion to metabolic demand such that blood gas (carbon dioxide and oxygen) tensions and pH in tissue can be maintained within a relatively narrow range. In order to achieve adequate gas exchange, lung fluid must be cleared from the alveolar spaces and air introduced into the lungs, establishing a functional residual capacity (FRC).

Pulmonary blood flow must increase to match ventilation. An air/liquid interface needs be maintained to achieve adequate ventilation, this is facilitated by surfactant which minimises the surface tension at the air/liquid interface, thus facilitating alveolar expansion and preventing the collapse of small alveoli.

1.4 Fetal Breathing movements

Fetal breathing movements are irregular and can be episodic with intermittent periods of apnea during early pregnancy (29). In humans, they become detectable as early as at 10-11 weeks gestation by ultrasound (30, 31). Fetal breathing movements become more regular and uniform as gestational age increases(32).In the 1970s Merlet et al(33) and Dawes et al(29) published their work on fetal lambs demonstrating that irregular breathing movements increased with increasing gestation age. Wiggelsworth et al(34) and Nagai et

al(35) demonstrated that eliminating fetal breathing movements by cervical cord transection resulted in immature and underdeveloped lungs.

Mechanical stretch, promotes differentiation (36) and proliferation of respiratory epithelial cells, including type II pneumocytes(37, 38). It is evident from animal studies that draining of the lung fluid (39) or abolition of fetal breathing movements (34, 40) leads to lung hypoplasia. The tonic hydrostatic distention and cyclical mechanical deformation of the lung provides crucial physical signals for normal fetal lung growth. While the importance of fetal breathing movements is now widely accepted as a mechanism of lung development, their role in establishing spontaneous respiratory activity and gas exchanged is still under investigation.

1.5 Fetal Lung fluid

Fluid is present in the lung lumen as early as the sixth week of gestation (41). Fetal lung fluid, amniotic fluid and plasma differ in their constituents (42) with the lung fluid having significantly higher levels of chloride. In the fetal lamb lung, transport of chloride ions takes place against the existing electrochemical gradient (43). The main force driving fluid in to the lumen is the active transport of chloride into the lumen from the interstitial space (44). In animal models, the lung is filled with approximately 4-6ml/kg of fluid for body weight and at mid gestation to about 20ml/kg of fluid for body weight by term. The rate of lung fluid production increases from 2ml/kg/hr to 5ml/kg/hr by term, contributing to about one half of amniotic fluid production per day.

Secretion of fluid into the lung lumen results in increased intrapulmonary pressure by approximately one cm H_2O greater than the amniotic fluid.

Additionally, during the periods of apnoea the closed vocal cords and larynx and nasopharynx constriction prevent the outflow of lung fluid (45, 46) , thus raising the intrathoracic pressure higher than the amniotic fluid. Vilos et al (47)studied the intrathoracic pressures of fetal lamb and observed that during the period of apnoea, the pressure in the trachea exceeded the intra-pleural space by at least 2.9 cm H_2O. It was postulated that the positive pressure was generated by the continuous production of lung fluid and maintained by an increased resistance to the outflow. This is essential for lung development and pathological states where there is chronic drainage of amniotic fluid results in hypoplastic lungs(48). This can also be due to other congenital abnormalities such as congenital diaphragmatic hernia, skeletal dysplasia or diaphragmatic paralysis (49, 50), where the intrapulmonary pressure is lower than in the normal healthy fetus.

1.6 Lung fluid absorption

Although lung fluid is critical for lung growth, this needs to be expelled or reabsorbed immediately after birth and be replaced by air. There is a better understanding of the mechanisms associated with clearance of fetal lung fluid soon after birth It has been demonstrated that lung fluid remains fairly constant at 90-95% of the total lung weight up to the third trimester suggesting that lung fluid is not reabsorbed during this period(51). Kitterman(52) and others(53, 54) demonstrated that lung fluid production starts to decrease a few days before spontaneous vaginal delivery and the alveolar fluid volume decreases from approximately 25 to 18 ml/kg. Bland et al (55-57) demonstrated that preterm delivery and surgical delivery without the onset of labour results in retention of lung fluid in preterm rabbits, and in fetal lambs. More recently, Berger et al (58)

evaluated the effect of postnatal lung liquid volume on respiratory performance following caesarean section in lamb fetuses.

Using chronically catheterized fetal lambs, the investigators found that lambs born with reduced lung liquid volume improved their arterial blood gas and acid base status quicker than those lambs born without a prenatal decrease in their lung liquid volume. The investigators concluded that postnatal gas exchange is enhanced by a reduction in the volume of liquid remaining in the lungs when breathing starts.

Amongst many, three main factors contributing to lung fluid clearance is thought be due to the (i) sodium channels (ii) hormones and (iii) trans pulmonary pressures, due to their effect on fetal lung fluid clearance in animal models.

1.6.1 Role of Sodium channels in lung fluid absorption

Nearing the end of gestation, the direction of ion and fluid flow across the alveolar epithelium rapidly changes from secretion to absorption. In fluid-absorbing fetal lungs, Na^+ reabsorption is a two-step process. The first step is passive movement of Na^+ from lumen across the apical membrane into the cell through Na^+ permeable ion channels. The second step is active transport of Na^+ from the cell across the basolateral membrane into the serosal space. Several investigators have demonstrated that the initial entry step involves amiloride-sensitive Na^+ channels. Amiloride-sensitive sodium transport by lung epithelia through epithelial sodium channels (ENaC) is a key event in the trans epithelial movement of alveolar fluid(59-65).The lung epithelial sodium channel (ENaC) has at least three sub types(α, β, and γ). Hummler et al(66) have demonstrated

that genetically knocking out the α-subunit of the epithelial Na^+ channel leads to defective lung liquid clearance and premature death in mice. Similarly, numerous experiments(59, 61, 64, 67-70) in various animal models involving either inhibiting or knocking out the ENaC channels have resulted in decreased lung fluid absorption. Thus, there appears to be direct evidence that, ENaC constitutes the limiting step for Na^+ absorption in epithelial cells of the lung, and is essential for the adaptation of newborn lung to air breathing. It has also been proposed that different combinations of the various subunits comprising the ENaC channels (α, β, and γ) could produce varying conductance and regulatory properties(71). The three subunits expressed together produce a 100-fold channel activity in comparison with that of α-ENaC alone(66, 72, 73). Single-channel studies for each of the subunits reveal high, moderate, or low selectivity for sodium over potassium (71). Although these channels also show differences in other characteristics, including conductance and amiloride sensitivity, they all appear to play a role in alveolar fluid balance (74-76).

Amiloride is a specific inhibitor of sodium channels and has served as a means of studying sodium transport(77) in the alveolar epithelium. O'Brodovich and co-workers(59) using newborn guinea pigs, they demonstrated that intraluminal instillation of amiloride delays lung fluid clearance. In their experiment, guinea pigs who received saline intratracheally, breathed normally and had arterial O_2 saturations (SaO_2) > 94%. In contrast, guinea pigs that had instillation of amiloride, had chest wall retractions and low oxygen saturations (88 ± 3.6% (SD) SaO_2) ($P < 0.01$). Extravascular lung water (EVLW) per gram of dry lung weight four hours after birth was significantly greater in newborns that received amiloride (8.3 ± 1.1, n = 5) than in those that received saline (5.6 ±

0.9, n = 7, P < 0.01). This demonstrated that intratracheal amiloride before the first breath resulted in respiratory distress, hypoxemia, and an abnormally high EVLW, concluding that epithelial sodium transport contributes to normal lung liquid clearance after birth. Furthermore in animal studies, by either inactivating or blocking the ENaC subunits, numerous investigators have demonstrated abnormality in the alveolar fluid balance (55, 57, 78, 79).

In healthy newborn infants, experimental studies on airway epithelial ENaC expression suggest a distinct sensitivity profile of each subunit for Na^+ and K^+ over a period of 48hrs postnatally (80, 81) . In preterm infants, ENaC expression is dependent on gestational age (80)(Figure 1-4) Hence, low expression of subunits in preterm infants during the first day after birth may contribute to respiratory distress syndrome.

Lack of expression of ENaC leads to decrease in the sodium transport across the lung epithelia through ENaC channels and hence a net decrease in the trans epithelial movement of alveolar fluid (55, 59, 60, 63, 64),this has been a contributory factor in in several disease states, including transient tachypnea of the newborn, sepsis, preterm labour, and Respiratory distress syndrome(RDS) (82).

Gowen et al(82) were the first to demonstrate that human neonates with Transient Tachypnoeic of the Newborn(TTN) had immature lung epithelial sodium transport. More recently Barker et al (83) measured the nasal transepithelial potential difference in 31 premature infants born less than 30 weeks gestation. The nasal transepithelial potential difference (N-PD) is a measure of the net electrogenic transport of Na^+ and Cl^- across the epithelial

layer, this is a correlate to the EnaC activity in the lung epithelium. In their study on premature infants, Barker and colleagues assigned infants to a diagnosis of RDS (22 infants) or non-RDS (9 infants) on the basis of clinical and chest x-ray criteria. They observed that the maximum N-PD increased with gestational age at birth (−1.5 mV/wk.; p <0.05) and birth weight (−1.2 mV/100 gm; p <0.01) and N-PD was lower in infants with RDS (-16.5 +/- 0.6 mV) than in those without RDS (-22.0 +/- 1.3 mV) (p<0.001). Infants without RDS had N-PD values similar to normal full term infants. Hence they concluded that that Na+ absorption across nasal epithelium increases with increasing birth weight and gestation. Impairment of Na+ absorption across the respiratory epithelia of very premature infants may contribute to the absence or poor lung fluid absorption in these infants, thus contributing to the respiratory distress associated with surfactant deficiency.

Helve et al (81) studied the expression of ENaC in term(N=61) and preterm(N=29)neonates and demonstrated that all the ENaC subunit levels are significantly lower in preterm infants(α-ENaC: p < .0001; β-ENaC: p = .0038; γ-ENaC: p = .0065), also expression of ENaC subunits correlated with gestational age (Figure 1-4)(80).

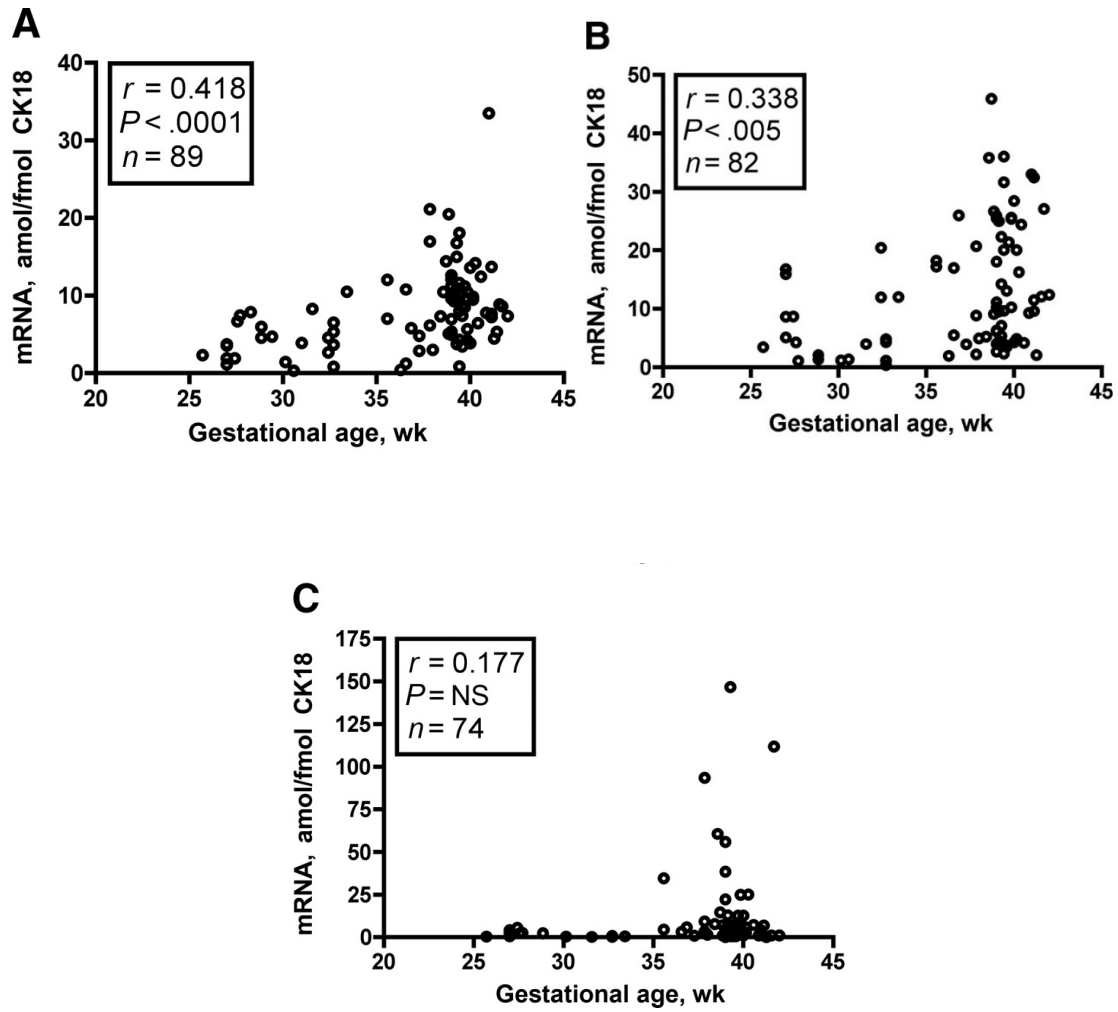

Figure 1-4: Correlation between ENaC subunit expression and gestational age in airway epithelium in newborn infants 1–5 h after birth: **A:** α -ENaC, **B:** β-ENaC, and **C:** γ-ENaC.
[Appendix III for copyright status*].*

1.6.2 Role of hormones in lung fluid clearance

Walters and Olver(84) found that intravenous infusion of epinephrine or isoproterenol led to the absorption of liquid from potential airspaces and this effect was blocked with propranolol (a β-adrenergic blocking agent). That finding suggested that β-adrenergic agonists stimulate sodium uptake by the lung epithelium, driving liquid from the lung lumen into the interstitium(57) for it to be absorbed through the pulmonary circulation or lung lymphatics .

Faxelius and colleagues (85) measured the lung function of 42 infants who were born either vaginally or by caesarean section. They performed lung function tests at 30 minutes and at two hours of age. Umbilical arterial blood was also analysed simultaneously for pH, concentrations of catecholamine and cortisol. Tidal volume and minute ventilation measured at 30 minutes and two hours after birth were lower in infants delivered by caesarean section than in those delivered vaginally. Similarly, dynamic compliance was lower at 30 minutes in the group that were delivered by caesarean section rather than vaginally and this difference was significant at two hours($p<0.01$). The catecholamine and cortisol concentrations at birth were higher in the vaginal group than in the group delivered by caesarean section. Two hours after birth there was a significant correlation ($r= 0.84$) between the catecholamine concentrations of the infants born vaginally and dynamic lung compliance. They postulated that the lower dynamic lung compliance in infants delivered by elective caesarean section was due to the delayed absorption of liquid in the lung secondary to a lack of catecholamine surge.

Thyroid hormones have an important role in lung fluid absorption by increasing the sensitivity to catecholamine released during birth(86-88). Closer to term, the ability of epinephrine and cAMP to switch lung liquid secretion to absorption increases progressively(86) . Barker and co-workers (87) demonstrated that in thyroidectomised fetal sheep triiodothyronine restored the inhibitory effect of epinephrine on lung liquid production. In their experiment, they compared the effect of lung fluid absorption in thyroidectomised and non-thyroidectomised ewes. They later infused epinephrine to investigate the effect of lung fluid absorption in both the groups. The lung fluid reabsorption in the

controls (-17.8 ± 4.8 ml/hr) was significantly higher than the thyroidectomised ewes (3.7±4.0) ($p<0.001$) and some of the ewes were still in the secretory phase. Chan et al(89) also demonstrated that antenatal treatment of preterm fetal sheep with thyroxine improved postnatal pulmonary function. Both cortisol and T3 are required for epinephrine-induced lung liquid absorption and act synergistically via mechanisms that depend on protein synthesis(88, 90).

In further studies with terbutaline (β-adrenergic agonist) and aminophylline (phosphodiesterase inhibitor) Chapman et al demonstrated the effect of intrapulmonary terbutaline and aminophylline on net production of lung luminal liquid over time. In their experiments terbutaline, increased lung fluid resorption from 11 ± 2 to -3 ± -2 mL/h and aminophylline further increased lung fluid reabsorption to -8 ± 2 mL/hr. This effect was reversed by amiloride. Thus, phosphodiesterase inhibition enhances the beta-adrenergic effect of terbutaline on sodium-dependent absorption of liquid from the lung lumen of fetal lambs(91).

1.6.3 Role of trans pulmonary pressures in lung fluid clearance

Large forces applied to the infant's chest and abdomen by the vaginal 'squeeze' during delivery can cause significant reductions in lung fluid volume(56, 57, 92). The intrathoracic pressures produced during delivery range from 88-265 cm H_2O(93, 94). Following the delivery of the head, fluid is noted to be expelled from the nose and mouth. Since the thorax and abdomen offer relatively little resistance compared to the head and the shoulder the "vaginal squeeze" of the chest and abdomen increases the trans-pulmonary pressure leading to the expulsion of the lung fluid(95).

In a study, Berger and colleagues(96) aimed to determine the volume of lung fluid of the fetal lamb just before a normal vaginal delivery at term, to assess the extent to which an excess of liquid in the airspaces might contribute to the respiratory morbidity that accompanies elective caesarean delivery. In their experiment, they instilled an impermeable tracer (1251-labeled human serum albumin) through a cannula in to the trachea two weeks before the expected date of delivery. They then measured the volume of lung liquid just before the vaginal delivery in eight fetal lambs. This volume was compared with that measured in a second group of 10 fetal lambs studied 7 days before the expected date of delivery (term = 147 days). The volume of lung liquid present just before delivery was 6.8± 1.0 ml /kg (n = 8) compared with 28.2 ±1.8 ml/kg (n = 10) in the second group of lambs studied before the onset of labour at 140 days of gestation. They concluded that the bulk (>75%) of the liquid that fills the lungs of the fetal lamb at 140 days of gestation is cleared at some time before normal term birth, suggesting that the adverse respiratory impact of elective caesarean delivery may be largely explained by denying the fetus this important adaptive mechanism. Similar animal experiments suggest that the explanations which relied on “Starling forces” and “vaginal squeeze” account for less than 25% of the fraction of the fluid absorbed (58, 96, 97). A higher occurrence of respiratory morbidity in near-term and term infants delivered by elective caesarean sections has been observed by many investigators(98-104),a higher incidence of transient tachypnea of the newborn was observed in these studies.

The delay in expulsion of lung fluid is postulated to contribute towards the increased respiratory morbidity in infants born by Caesearn section. Unlike animal studies, it is ethically and physically challenging to establish the precise

mechanisms contributing to the high incidence of respiratory morbidity in infants delivered by elective caesarean section.

1.7 Establishing and maintaining functional residual capacity

Avery and Mead(105) based on calculating anatomical dimensions of the alveoli and the surface tension properties of the lung suggested that a pressure of 25-30 cm H_2O may be needed to aerate the alveoli soon after birth. Furthermore, Grunewald et al(106) in his experiment on fresh still born infants of various gestational ages, established that a critical pressure in the order of 20-25 cm H_2O was needed to open the alveoli. The clearance of lung fluid and the commencement of breathing leads to air entry in to the alveolar spaces. This rapid change to gas exchange at the alveolar level commences at the end of the first inspiratory effort, however in infants who do not take their first breath, positive pressure ventilation is needed to inflate their lungs. On the first lung inflation either spontaneously or by mechanical ventilation, and at the end of expiration some gas is retained, this is crucial for establishing a functional residual capacity (FRC) of the lung. An FRC is the volume of gas in the lung at the end of expiration and is in continuity with the airways. Optimal lung mechanics and alveolar surface area for efficient ventilation and gas exchange is crucial for normal FRC formation. The establishment of an FRC at birth represents one of the important aspects of the respiratory adaptation. In the immediate postnatal period, a combination of lung surfactant properties and various mechanical factors such as magnitude of the inspiratory effort, respiratory muscle strength, chest wall and lung compliance, lung fluid clearance are some of the main contributors to the formation FRC.

1.7.1 Infant's first Breath

In the early 1960s, Fawcitt, Lind and Wegelius (107) used a high speed roentgenographic technique to study lung aeration immediately after birth of full term infants. They reported that the upper airway muscles seemed to be involved in the initial inflation of the newborn lung. In their observational study, they reported that before the first lung inflation, the upper part of the rib cage is drawn in and following a successful inspiration the intrathoracic trachea dilates and the air fills the posterior lung bases. All parts of the lung do not aerate immediately after the first breath and following expiration some air remains in the lung which contributes to the formation of the functional residual capacity (FRC). During the same period Karlberg and colleagues(108) reported changes in tidal volume and intra-oesophageal pressure changes during the onset of breathing in full term infants. They obtained volume and pressure loops from the 18 of the 79 infants and concluded that the respiratory adaptive changes occurred rapidly and a residual volume was established with the beginning of the first breath. The total intra-thoracic pressure changes in the first breath varied between 40-100 cm H_2O, this magnitude of pressure decreased in the subsequent breaths following the first breath, suggesting the need for a high airway opening pressure during resuscitation of a new born infant. Milner and colleagues designed a measuring system which contained a low-resistance pneumatograph and dual pressure transducer to estimate the lung volumes and oesophageal pressure during the first breath in 24 term born infants. They reported that the term born infants generated a mean negative intrathoracic pressure of 52.3 cm H_2O during the first inspiration and a positive pressure of 71.3 cm H_2O during expiration. They reported that the mean inspiratory volume

of the first breath was 37.7ml and the FRC was 15.1 ml(94) .Furthermore, during the first phase of expiration a high positive pressure was generated and nearly 40% (~15 mls) of the inhaled air was retained which contributed to the formation of FRC. Some of the key findings reported by Milner's study related to the first breath were, that the peak transpulmonary pressure was greater than 30 cm H_2O reaching up to 100 cm H_2O during inspiration i.e. much greater than the pressures of 5-7 cm H_2O recorded in self ventilating infants(109), in addition the airway opening pressure varied during the first breath and large airway opening pressures were unnecessary as previously thought.

The first breath is probably the largest (i.e. generating the highest negative intra-thoracic pressure) breath during the neonatal period, with inspiratory volumes of above 40 mls in term born infants (4, 110, 111).

1.7.2 The role of the first breath in establishing an FRC

Karlberg et al (111, 112) studied lung volumes and trans-pulmonary pressure changes during the spontaneous first breaths. In a small a group of 11 newborn infants they observed that five infants produced a negative intra thoracic pressure of 20-40 cm H_2O, before the lung expansion occurred. This high negative intra-thoracic pressure is thought to be caused by an increase in volume of the surrounding thoracic cage following lung expansion.

Roentegraphic studies (113-115) on first breath demonstrated that there were changes in the shape of the thoracic cage before or after the first breath and the contraction of the diaphragm seem to be responsible for this negative intra-thoracic pressure. In some of the respiratory loops recorded during their first breath studies, Karlberg demonstrated that for lung inflation of any

magnitude to happen, a negative intrathoracic pressure of 20-40 cm H_2O was created. Thus, they concluded that similar airway “opening pressure” was necessary for lung inflation. This is in support with the findings of Gruenwald et al’s observation of the still born infant lung and also Avery and Mead’s calculations of the influence of surface tension as discussed previously. However, if there was a positive pressure at the mouth which helped in lung inflation, there should have been a small negative intra-thoracic pressure which was not demonstrated in all Karlberg’s respiratory loops. What was clear from their observations was that some infants managed to open the lung with very little negative intra-thoracic pressure (<20 cm H_2O). Similar findings were reported by Milner’s team in their earlier studies(116). One possible explanation for this was that both Milner et al(116) and Karlberg et al (27) had underestimated the true efforts of the baby. It is well established that if a pressure device is placed too high in the oesophagus, the pressure will be under-recorded. Milner’s group therefore carried out a further set of measurements using a dual pressure transducer, only accepting data when the lower pressure transducer was obviously in the stomach and the upper pressure transducer in the oesophagus(93). This inevitably meant that the lower pressure transducer was in the lower 2±3 cm of the oesophagus, that is, optimally placed. They reported that similar inspiratory volumes inspiratory volume of 37.7 mls and an FRC of 15.1 ml was generated with a mean negative intrathoracic pressure of 52.3 cm, a positive pressure during expiration of 71.3 cm H_2O. This confirmed that some of the previous oesophageal pressure measurements had under recorded the intrathoracic pressure changes associated with the first inspiration. Milner and Saunders (4, 117) repeated the

work of Karlberg using an oesophageal balloon and reverse plethysmography to measure the intra-thoracic pressure and lung volume respectively. They demonstrated that the airway opening pressures needed for lung expansion was in the range of 30 cm H_2O.Furthermore, in their series of investigations in to infant's first breath mechanics, they observed that on an average 40mls of air was drawn in during their first breath. The mean FRC at the end of the first breath was 18 ml(5ml/kg)(93).In a further study by the same group in term born infants, they observed a strong correlation between inspiratory volume and FRC($r=0.77$, $p<0.004$). Analysis of the first breath in newborn rabbits(118) showed similar patterns of inspiratory gas volumes and FRC formation associated with the first breath.

Currently, there are no data on the formation of FRC in preterm infants and its association with the first inspiratory effort.

1.7.3 Role of initial lung inflation

The first lung inflation either by spontaneous inspiration or artificial lung inflation during resuscitation is required to overcome the surface tension and the viscosity of the lung fluid. To achieve this, large trans-pulmonary pressures are needed, hence the infant's first spontaneous breath is characterized by a deep inspiration, and usually an equally prolonged expiration. In a study, twenty asphyxiated term infants were resuscitated with positive pressure ventilation with a set pressure of 30 cm H_2O which was delivered through an endotracheal tube immediately after birth. Milner and colleagues(119) demonstrated that only five of the twenty infants had formed an FRC after the first inflation and a mean FRC of 36.9 mls were formed by 30 seconds. Furthermore, there was no

significant difference between the FRC at 30 seconds in babies who had breathed and those who had not. They also reported that on 12 occasions sudden changes in FRC were associated with active inspiratory efforts. These inspiratory efforts were frequently prolonged, suggesting that, spontaneous first breath by the infant compared to non-breathing infants rapidly improves FRC. This may also suggest that an increased muscle tone in the diaphragm and chest wall, may aide in the formation of FRC. Furthermore, on four occasions, they observed a stepwise increase in FRC that were produced by mechanical lung inflation, during resuscitation, this presumably indicates the point at which the physical characteristics of the lungs have changed sufficiently to allow the lungs to remain inflated. In the same study, the first mechanical lung inflation only produced an FRC in 5 of the 20 infants producing a mean FRC of 7.5 mls. This is in contrast to spontaneously breathing babies in whom there was a mean increase in FRC of 17.3 ml following the first breath. In all the infants studied by Milner's group, only one of 41 babies was there no gas retention following the first spontaneous breath(4, 116).

There was progressive sequential increase in lung volume with the first few inflations during resuscitation of asphyxiated infants. Despite the fact that an FRC was not formed, progressive increase in tidal volume in response to the same inflation pressure and progressive fall in the opening pressures was observed. It was also interesting to note that an active inspiratory effort produced a further rise in tidal volume in the absence of a change in FRC. It was usually only in association with the baby's respiratory efforts that the tidal volume increased from an initial mean value of 18.6 to 28.5 ml (4, 93, 116),which was comparable with the mean volume of the first spontaneous

breath. The progressive change in the mechanical properties of the lungs may be caused by release of surfactant from the respiratory epithelium. It is difficult, however, to explain on the basis of surfactant alone why some babies retained gas within their lungs on mechanical lung inflation and why others failed to do so.

Maintaining an FRC after birth has been described in several different animal models [7] and spontaneous breathing plays a significant role. For instance, procedures that reduce spontaneous breathing activity, such as intra-thoracic sectioning of the vagus nerve, was associated with an inability to maintain an FRC [50].

1.7.4 Role of active expiration

The expiratory effort following the first inspiration is often slow and prolonged (108, 116, 120), a pattern clearly documented for the first hours of extra uterine life. Large oesophageal pressure (intra-thoracic pressure) swings have been recorded (4, 94, 108, 116), suggesting active recruitment of the expiratory muscles in generating a positive airway pressure. This promotes clearing of the fluid from the lung and a more even lung expansion. The average amount of air retained in the lung after the first expiration have been estimated to be 11-19 ml in different studies(4, 27, 94, 116, 120), with a large inter-subject variability. This represents 10-20% of the FRC at rest in a 48 hrs old infant.

Spontaneously breathing infants demonstrate some degree of “braking” during the early part of the expiration phase. The 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. Kosch and colleagues aimed to investigate determinants of the end expiratory volume in newborn infants. They studied the airflow, tidal volume and respiratory muscle EMG in eight full term spontaneously breathing infants. They observed that the EMG evidence of respiratory muscle activity was absent during the latter part of expiration in both the supine and upright postures, consistent with passive expiration, also expiratory breaths frequently were associated with marked retardation of expiratory airflow (braking) without any diaphragm muscle activity in the EMG, which led to an increase in the expiratory lung volume. (121, 122). “Braking” during early expiration was more prevalent following the establishment of FRC, therefore contributing to the maintenance of FRC rather than the formation during the first hours after birth. In contrast the infants also used other respiratory manoeuvres were a forced expiratory manoeuvre generated by the abdominal muscles to move air through a closed or constricted glottis(123) was thought to contribute to maintaining to FRC. These respiratory manoeuvres which include grunting are also widely assumed to contribute towards lung fluid absorption(110).

1.7.5 Role of surfactant

Pulmonary surfactant reduces airway collapse and provides stability to the peripheral lung units by reducing the surface tension at the air/liquid interface, thus maintenance of air reservoir at the end of expiration. Surfactant deficiency impedes this process hence there is a failure of creation of an end expiratory lung volume (FRC) after the initial lung inflations. In animal models, it has been demonstrated that the presence of surfactant improves lung aeration and maintaining FRC (124-126). The surface tension acting along the concave

curvature of the air/liquid interface must act to reduce the hydrostatic pressure in addition to reducing lung recoil and its tendency to collapse at end-expiration.

In addition, the surfactants may contribute to the clearance of the lung fluid by reducing lung recoil and by acting as a water repellent(127).

1.7.6 Mode of delivery and FRC formation

The mode of delivery and its effect on the magnitude of FRC has been thought to be due to the increased volume of lung fluid in infants born by caesarean section. Various studies have demonstrated the effect of the mode of delivery on FRC formation in term infants**.** An FRC of approximately 30ml/kg of body weight (128) is usually achieved within the first two hours in vaginally delivered term infants (129), but much later (5-6h hours) in infants delivered by elective lower segment caesarean section (LSCS)(130).

Milner and colleagues (130) measured lung volumes in 26 infants born by vaginal delivery and 10 infants delivered by elective LSCS. The mean thoracic gas volume in vaginally born infants in the first six hours of life was 32.7 ml/kg body weight and this was significantly higher than that of infants delivered by elective LSCS (19.7 ml/kg body weight) ($P<0.001$). They also measured the chest circumference of all infants and there was no significant difference between the groups, suggesting that the total lung volumes were similar. The lower thoracic gas volumes in infants born by caesarean section, suggested a higher amount of lung fluid when compared to infants born by vaginal delivery.

Boon and colleagues(131) studied thoracic gas volumes(TGV) in 25 infants born by vaginal delivery (32.2 ml/kg) and 15 infants born by elective LSCS (21.6

ml/kg). They demonstrated that (TGV) was significantly greater in the first six post-natal hours versus but not at 48 hours (35.4 ml/kg and 30.4 ml/kg respectively). They suggested that by 48 hours the fluid had been drained by the pulmonary lymphatics and the pulmonary circulation, which closely parallels the time course for resolution of transient tachypnea in the newborn infant. The seven infants born by emergency CS had intermediate values, which increased from 28.3 ml/kg at two-six hours to 35.5 ml/kg at 18-30 hours, the latter being similar to vaginally delivered infants. This differential effect of emergency CS when compared to elective caesarean section, may be an effect of catecholamine release during labour, ameliorating the rate of lung fluid reabsorption in emergency CS compared to elective CS babies. Vyas and colleagues (94) also demonstrated a significant difference in the mean initial FRC between infants delivered by elective caesarean section (10.8 ml) or vaginal delivery (18.9 ml) ($P<0.01$). The same group in a further study showed that vaginal squeeze pressures (mean of 145.4 cmH_20) affected the inspiratory volume of the first breath and hence formation of FRC, probably by enhancing the clearance of lung fluid (132). Thus, both mechanical (delivery pressures) and non-mechanical factors (ephinephrine surge) induced by labour are important in the clearance of lung fluid and help with the formation of an FRC.

1.7.7 Functional Residual Capacity in prematurely born infants

Preterm infants have weak respiratory muscles, a highly compliant chest wall and inadequate surfactant. These factors lead to inadequate inspiratory pressure to overcome the high surface tension and the frictional forces to achieve lung aeration. The highly compliant chest wall deforms during diaphragmatic contraction, thereby reducing the inspired tidal volume and is

unable to resist lung recoil, resulting in a lower lung volume at the end of expiration (133-135). Furthermore, the preterm lungs are less responsive to lung fluid reabsorption mechanisms including sodium reabsorption through the ENaC channels, thus are less efficient in clearing lung fluid (83, 136, 137) as discussed previously. The degrees of respiratory effort and surfactant deficiency vary significantly according to the gestational age of the infants with more extremely premature infants having the weakest respiratory effort and severe surfactant deficiency. Thus, extremely premature infants usually require respiratory support to establish and maintain FRC and pulmonary gas exchange at birth (70, 110) (Fig 1-5).

The trans-pulmonary pressure gradients achieved during spontaneous breathing can be replicated by mechanical lung inflation, enabling it also to drive airway liquid clearance in preterm infants. Most very preterm infants now are exposed to maternally administered antenatal corticosteroids, which greatly improve postnatal pulmonary function. In a study assessing the effect of antenatal steroid on FRC formation, McEvoy and colleagues measured FRC in prematurely born infants born between 25-34 weeks' gestation. They demonstrated that infants exposed to a full course of antenatal steroids had a significantly higher FRC (29.5 ml/kg) than 20 age matched, untreated infants (19.3 ml/kg) ($p<0.001$). Static compliance was also higher in the treated versus the untreated group. The authors concluded that the higher FRC may be due to structural changes or may be secondary to the changes in surfactant production or a combination of both (138).

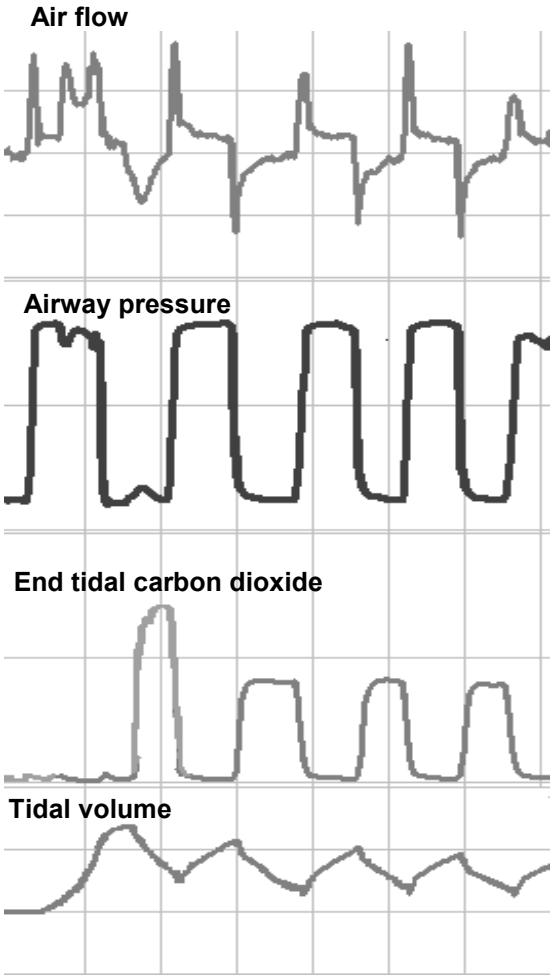

Figure 1-5: Formation of FRC in a prematurely born infant following an inspiratory effort by a preterm infant born at 26 week gestation.
(Trace obtained during the resuscitation of the infant in this research study)

1.8 The role of neonatal pulmonary reflexes

Pulmonary reflexes are active in the newborn period and the lung afferents play an important role in regulation and timing of breathing in the newborn infants.

1.8.1 Hering-Breuer inflation reflex

The pulmonary stretch receptors are stimulated when the inspiratory lung volume(139) is increased, this leads to a shortening of the inspiratory time, or

by prolonging the expiratory time (140). This reflex also is known as the Hering–Breuer inflation reflex(HBIR), and is mediated through the vagus nerve(141).In preterm infants, the Hering-Breur reflex are stronger and the preterm infants depend on this for their respiratory rate, than the term born infants. Olinsky et al.(142) used airway occlusion in 16 preterm and 14 term born infants. Occluding the airway at the end of expiration, resulted in no volume change in the subsequent inspiratory effort hence no lung distension signals through the lung receptors were produced. Preterm infants had a more prolonged inspiratory time following the occlusion (53%) compared to term infants (25%), suggesting that in preterm infants the afferent information were important and stronger for the duration of lung inflation. They demonstrated a strong correlation between the inspiratory period and total respiratory period, thus concluding that the effect of HBIR reflex is to increase the respiratory rate. They suggested that the purpose of such an exaggerated reflex is likely to prevent full emptying of the lung and maintain lung volume at end expiration.

In a more recent study Hassan et al (143)measured the strength of the HBIR in 22 term infants between 1-5 days after birth. They observed that there was a progressive increase in strength of the HBIR with maximal stimulation of the reflex at ~ 4ml/kg above FRC. The strength of the HBIR significantly correlated with respiratory rate, suggesting that HBIR influences respiratory patterns in the newborn. The strength of the reflex was found to be weak in infants of 32 weeks' gestation, increasing in strength at 36–38 weeks and decreasing thereafter(144).

1.8.2 Hering-Beurer deflation reflex

The Hering–Breuer deflation reflex (HBDR) is activated on deflation of the lung and results in inspiratory augmentation. Hannam et al.(145) in their study evaluated the Hering-Breuer deflation reflex in term and preterm infants, they observed that unlike term infants who responded to the deflation reflex by shortening their expiratory time followed by prolonging their inspiratory time, preterm infants responded to the deflation reflex by a rapid reduction in lung volume and a shortened inspiratory effort and a tendency to have a brief apnoea. This may be due to the immaturity of the reflex arc responsible for the transmission of the HBDR in the preterm infants. Stimulation of the Hering Beurer deflation reflex would limit preterm infants making spontaneous respiratory efforts during resuscitation due to the cessation of inspiration, this may prevent the baby from taking their first breath. In contrast, Head observed that newborn mammals responded to lung inflation by making an inspiratory effort, i.e. Head's paradoxical reflex (146, 147) This reflex has been demonstrated in newborn infants and is thought often to be responsible for the first inspiratory lung volume and contributes towards the formation of an FRC(28, 148).

1.8.3 Head's paradoxical reflex

In 1889, Head demonstrated that, when conduction in the cervical vagus nerves of rabbits was partially blocked by cold, inflation of the lungs caused a strong and prolonged inspiratory effort which is usually referred to as Head's paradoxical reflex(146, 149). This contrary to the inhibition of breathing seen when vagal conduction was intact (the Hering-Breuer inflation reflex).

Hoskyns et al (119) in a study of term and preterm infants, aimed to study the adequacy of initial inflations (first three lung inflations) in these infants. They observed a reflex in 41% of the preterm infants and of these 80% demonstrated a Head's paradoxical reflex. They also reported that there was a significant ($p<0.001$) correlation between the presence of reflex and achieving an adequate tidal volume (4.4ml/kg) during the initial lung inflation, however this was not significant in term infants. Boon et al(148) studied the total gas volumes and intra oesophageal pressures during resuscitation of twenty term infants. In their study although 47% of the mechanical lung inflations was associated with a HBIR, eleven percent demonstrated the Head's paradoxical response. These studies suggest that triggering the Head's reflex which increases the inspiratory volume hence a rapid formation of FRC which is crucial for adequate gas exchange during neonatal resuscitation. This indicates that Heads paradoxical reflex may also augment the ventilation (Fig 1-6) of premature infants with low lung compliance.

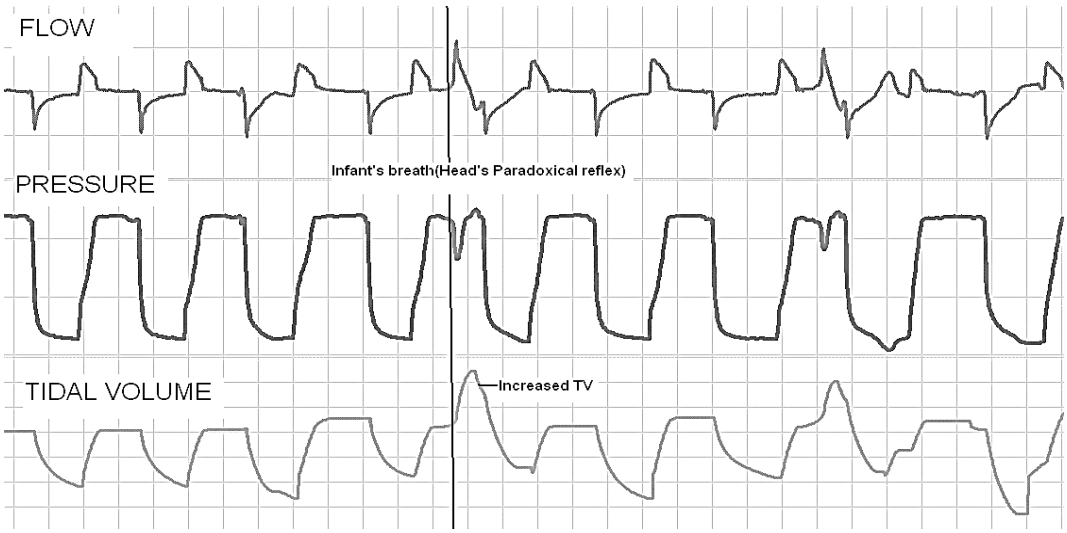

Figure 1-6: Infant's inspiratory effort in response to lung inflation, this is also associated with augmentation of tidal volume. This physiological trace was obtained during the stabilisation of a 24-week infant included in the current research study.

1.9 Pulmonary circulation and gas exchange

1.9.1 Pulmonary circulation

Oxygenation in the fetus is through the placenta and oxygenated blood flows into the fetus through the umbilical veins. The oxygenated blood enters the left atrium from the right atrium through the foramen ovale. This then enters the left ventricle and then to the aorta. The blood received back to the right ventricle is mainly from the superior and inferior vena, which is poorly oxygenated. Less than 20% of the cardiac output enters the pulmonary arteries due to high pulmonary vascular resistance, the larger portion enters the aorta through the ductus arteriosus(150, 151) The oxygen tension in fetal pulmonary arterial blood is ~18 mmHg and the oxygen saturation ~50%(150, 152).Since, however, fetal blood contains high levels of fetal haemoglobin which has a higher affinity to

oxygen than adult haemoglobin, there is sufficient oxygen delivery to the lung to support it growth and metabolic functions(153).

After birth, the lung is the organ for gas exchange. Pulmonary blood flow increases from 21% of the ventricular output in the fetus to the total cardiac output after birth(151). Following the establishment of respiration, the pulmonary arterial pressure gradually decreases while the systemic pressure increases. The mean pulmonary arterial pressure drops to nearly 50% of mean systemic pressure by the end of the first day and drops to the adult level within the first two weeks of life(152, 154). Once the systemic pressure is greater than the pulmonary, the foramen closes. The ductus arteriosus begins to close within the first few hours after birth and by 15 hours of age there is very little blood flow across the ductus arteriosus (155, 156). This dramatic change in the pulmonary circulation of the newborn is primarily attributable to the marked decrease in pulmonary vascular resistance (PVR) postnatally. Numerous events, which include ventilation, oxygenation, increasing shear stress of blood flow, changes in the activities of a number of vasoactive agents such as nitric oxide and prostaglandins(157-159) contribute to the drop in PVR and maintenance of a low PVR postnatally.

In the fetal circulation the PVR is much higher than the systemic circulation resulting in the right to left shunting through the ductus arteriosus and foramen ovale. Following the cessation of the placental flow which happens immediately after the cord is clamped following birth, the PVR falls rapidly to approximately 10 percent of the fetal values hence the pulmonary blood flow increases tenfold(160).

Several mechanisms lead to the fall in PVR. Tietel and colleagues(161) studied the sequential effect of three important components of the birth process: ventilation, oxygenation, and umbilical cord occlusion on the blood flow patterns in the near-term sheep fetus. In their study of 16 term or near term lambs, lung inflation alone increased the pulmonary blood flow by four-fold and a further increase was observed if 100% oxygen was used. They concluded that the majority of the transition from the fetal to neonatal circulation is initiated by ventilation alone and can be explained by a decrease in pulmonary vascular resistance. The further decrease in pulmonary vascular resistance was caused by oxygenation and umbilical cord occlusion. On further evaluating each of these components on its own, they observed there was only a small increase in the ventricular, however a combination of ventilation, oxygenation and cord occlusion led to a significant increase in the ventricular output similar to that seen at birth. Inflation of the lung also stimulates pulmonary stretch receptors which leads to reflex vasodilation of the pulmonary vascular bed(162) through the sympathetic system(vagus nerve). A combination of endogenous mediators like nitric oxide, prostaglandins, bradykinin, adenosine, and histamine(163) contribute towards decreasing and maintenance of pulmonary vascular tone.

1.9.2 Gas exchange in the newborn lung

Studies investigating the pulmonary gas exchange in term and preterm infants have been performed by collection of expired gases over a five-minute period immediately after birth. At the same time oxygen uptake during and immediately after ventilation through an endotracheal tube was also studied. The rates of expired carbon dioxide rose from 6.5ml/kg/min at 15 seconds to 10ml/kg/min by two minutes. The oxygen uptake mimicked the CO_2 elimination

with a rapid rise to 12ml/kg/min at two minutes and stabilising to 8ml/kg/min at five minutes of age. Rates of expired CO_2 in spontaneously breathing infants born vaginally were compared to the infants born by caesarean section. Infants born by caesarean section had a much slower rise (below 6ml/kg/min) in CO_2 for the first 90 minutes after birth, subsequently to 8-9ml/kg/min at four minutes of age. The preterm infants showed a similar pattern to infants born by caesarean section. The results of this study are in agreement with earlier findings that pulmonary adaptation to extrauterine life is completed rapidly in healthy, vaginally delivered infants, whereas those who are born by caesarean section have a slower adaptation.

More recently, improvements in arterial oxygenation in minutes after delivery have been studied by pulse oximetry. Dawson et al(164) reported reference ranges of oxygen saturation levels and heart rate in the first 10 minutes of life. Of the 468 infants who did not need any intervention or supplemental oxygeno121ne hundred and twenty one infants were born between 32-36 weeks of gestation and 39 infants were born <32 weeks of gestation. The median saturation levels in preterm infants at one, five and ten minutes were 62% (range 47–62%), 86% (86–92%) and 94% (91–97%) respectively. The patient in their study achieved a mean heart rate of 96/min (72–122) at one minute of age and all infants had a heart rate >100/min after two minutes of age. The gold standard for measuring oxygen levels is co-oximetry, from an arterial blood gas, however this is challenging at birth. Variations in pulse oximetery methods may affect findings, furthermore in their study some of the SPO_2 during the first few minutes were less than 70%. At this level, the

oximeter may not measure the SpO_2 accurately. Hence, adapting these findings may not always be possible, during the stabilisation of prematurely born infants.

1.10 Resuscitation in term born infants

Approximately 5-10% of term born infants need some form of support to establish breathing at birth (165-168). The decision to commence resuscitation is based on the clinical condition at birth. ILCOR recommends (169) that resuscitation should be commenced if the infant does not breathe and the heart rate is below 100 beats per minute soon after birth.

1.10.1 Stabilisation and suctioning

All newborn babies need to be stabilised by keeping warm and aim to maintain the body temperature between 36.5 - 37.5 ◦C, suctioning of the oral cavity is only necessary in a floppy infant and if there is plenty of fluid or meconium in the oral cavity. It has been advised to not blindly suction the hypo pharynx and all oropharyngeal suction should be performed under direct vision through a laryngoscope(170, 171).

1.10.2 Ventilation

Ventilation is required in approximately 3–5% of all newborn infants and in preterm infants there is even a greater need (172-174). Once ventilation is achieved, heart rate will increase rapidly and normalise. There is a strong association between gas exchange and heart rate; this is demonstrated to be achieved between 1 and 2 min in vaginally born infants and a few minutes further in infants born by caesarean section (175). Currently, positive pressure is delivered though a self-inflating bag or t-piece device. The peak inspiratory

pressure is set at 30 cm H_2O and is decreased or increased based on the assessment of chest rise. An expiratory pressure [continuous positive airway pressure (CPAP)] has been shown to improve ventilation and to help establish an adequate functional residual capacity (176).Although the ILCOR do not recommend prolonged inflation times during the first five lung inflations(177) due to lack of scientific evidence, the UK resuscitation council continue to advocate prolonged inflation times of 2-3 seconds for the first five lung inflation during resuscitation of term born infants(178) as there is no evidence to refute that prolonged lung inflations helps to achieve FRC earlier.

1.10.3 Endotracheal intubation

The indication for endotracheal intubation is failure to ventilate by bag and mask. Intubation was reported to be needed in 1 in 600 infants by Leone et al(173). With improvement of mask design including cushioned rim and adequate sizes for every birth weight, endotracheal intubation is becoming rarer including in in preterm infants. Moreover, recent studies indicate that apparently, the use of non-invasive ventilation in the delivery room may be associated with less oxygen need and days of ventilation (179); however, a reduction in the incidence of chronic lung disease has not been definitely established.

1.10.4 Oxygen during resuscitation of term born infants

Clinical studies have shown that resuscitation with ambient air (21%) compared to 100% oxygen reduces neonatal mortality, time to first breath and 5 min Apgar score(180). Recent international guidelines recommend starting resuscitation of term or near term babies with air instead of supplemental

oxygen (169) . This advice is based on animal studies and 10 clinical studies. The meta-analysis and systematic review that summarised the 10 studies included 2134 enrolled term or near term infants in need of resuscitation. Neonatal mortality was 12.8% in infants resuscitated with 100%, and 8.2% in those with 21% oxygen [relative risk (RR): 0.69; 95% confidence interval (CI): 0.54–0.82]. The number needed to treat with 21% O_2 to save one life was 25. When the six strictly randomised studies were analysed separately, neonatal mortality was 3.9 and 1.2% in 100% and 21% groups respectively. The Relative risk was 0.32 for those babies resuscitated with 21% oxygen (95% CI).

1.10.5 Chest compressions

In newborn babies who have been ventilated adequately for 30 s without a rise in heart rate >60 bpm is an indication indications for chest compressions. This is carried out with 30 breaths and 90 compressions/min, however it is a difficult task to accomplish and there are no clinical studies to refute a 3:1 ratio of cardiac compression to ventilation.

1.11 Prematurity and postnatal adaptation

The preterm infant has several disadvantages regarding extra uterine adaptation of the respiratory system. The chest wall of preterm infants is very complaint and weak respiratory muscles make it difficult for these infants to generate large inspiratory pressure to overcome the high surface tension and frictional forces to achieve effective lung aeration. 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 (83, 137, 181).

Retention of lung liquid in the air spaces reduces lung gas volumes, promotes non uniform aeration and delays the formation of FRC (83, 137, 181). Currently, most preterm infants receive antenatal corticosteroids, which stimulate surfactant production and greatly improve postnatal pulmonary function and mature liquid clearance mechanisms, thereby enhancing lung aeration at birth(70, 182).

With the use of antenatal steroids many very preterm infants breathe and establish an FRC with only nasal continuous positive airway pressure (NCPAP) as support(183). In infants who do not adapt rapidly, mechanical lung inflation may be necessary. Most studies have investigated the first breaths of term infants; it cannot be assumed that the results of these studies can be applied to preterm infants. The lungs of very preterm infants are vulnerable, and inappropriate ventilatory support immediately after birth can cause lung injury, and may be closely associated with the development of bronchopulmonary dysplasia(184, 185).

1.11.1 Resuscitation of prematurely born infants

Many preterm infants will need additional support in the form of oxygen supplementation or mechanical ventilation to allow adequate oxygenation and ventilation even if they are breathing spontaneously. Similar to term born infants, the prematurely infant must replace fetal lung fluid with air, establishing functional residual capacity (FRC) in the lung, and increase pulmonary blood flow, transitioning from placental to pulmonary gas exchange. The lung is also stiff due to the lack of surfactant and may need high airway opening pressure to overcome the airway resistance. The lung tissue is extremely fragile and is

prone to injury and inflammation if inadvertently high airway pressures are used during resuscitation. Mechanical lung inflation requires delivery of an appropriate tidal volume to achieve adequate gas exchange. Clinical assessment including colour, tone, heart rate and chest rise are recommended by ILCOR (169)to evaluate the response to ventilation during neonatal resuscitation. The tidal volume (TV) delivered is rarely measured hence the airway pressure is not adjusted to optimize TV to avoid volutrauma or under ventilation (186-188).

Positive pressure ventilation during resuscitation may cause lung injury through various mechanisms, including high airway pressure (barotrauma),over distention (volutrauma), repeated alveolar collapse and re-expansion (atelectrauma). Antenatal infection and inflammation (biotrauma)(189) also contributes towards lung injury acquired during resuscitation of prematurely born infants. These injuries cause leakage of proteinaceous fluid and blood into the airways, alveoli, and lung interstitium, inhibiting surfactant function, and contributing to lung injury(189). Hence, extreme caution and close monitoring of lung inflation during resuscitation is crucial to prevent long term morbidity.

1.11.2 Lung injury during preterm resuscitation

Inflating the lung immediately after birth exposes the preterm lung to injury and the degree of injury is hypothesised to be proportional to the inflating pressures and tidal volumes(190, 191), hence the consensus to use “gentle” ventilation strategies during resuscitation of prematurely born infants.

Numerous animal experiments have been performed to evaluate the degree of lung injury comparing different lung inflation strategies during resuscitation in

a surfactant deficient preterm lung. Björklund and co-workers(184) compared lung function during resuscitation of premature lambs. The control group received standard mechanical ventilation support and the experimental group received large volume(35-40ml/kg) initial inflation breaths followed by standard ventilation. Both groups received surfactant at 30 min of age. They reported that the lambs inflated with large lung volumes had a lower mean lung compliance (0.99 ml/cm H_2O) compared to 2.87 ml/cm H_2O in controls at four hours of age, they also needed higher inspiratory pressures (37cm H_2O compared to 25 cm H_2O in controls) and had a reduced mean inspiratory capacity (24 ml/kg compared to 37ml/kg) compared to the lambs not exposed to high lung volumes during resuscitation. This suggests that even a few large volume, lung inflations are detrimental to lung mechanics.

In a more recent study(192) evaluating the effect of tidal volume and lung inflammation in preterm lambs, tidal volumes of 8ml/kg and 15ml/kg were found to induce high levels of pro inflammatory cytokines IL-1β, IL-6 , IL-8 and protein carbonyls (a marker for oxidative injury) when compared to the non-ventilated lambs(controls). Similarly, Hilman et al (191)found that preterm lambs ventilated with 50 cm H_2O and a tidal volume of 15ml/kg had increased protein and inflammatory cell counts in the bronchoalveolar lavage fluid (BALF) when compared to lambs who were maintained on placental support with no ventilator support (controls). Wada et al.(193), found that although increasing tidal volumes to 20 ml/kg improved FRC, it resulted in a reduced compliance and increased protein in the alveoli in the lungs of premature lambs compared to those ventilated with tidal volumes of 5-10ml/kg.

Over inflation of a preterm lungs with large tidal volumes increased microvascular protein permeability contributing to lung oedema(194). Many experiments evaluating lung injury, have focussed on the relationship between volume and end expiratory pressures, lung volumes that approach total lung capacity(TLC) stretches the lung and initiates an inflammatory cascade and induces lung injury(195) during resuscitation. Similarly, ventilation of the injured lung from volumes below the normal FRC results in a similar inflammatory cascade and induces lung injury(196), the injuries are amplified in the presence of other pro inflammatory mediators such as oxygen exposure or presence of endotoxins(197).

The level of inspired oxygen to be used during preterm resuscitation has been controversial (198-201), however there is an increasing body of evidence demonstrating the effect of oxygen free radical injury in prematurely born infants (202, 203).This has led to international consensus on the need for blood oxygen level monitoring during preterm resuscitation (169).

1.11.3 Resuscitation techniques in preterm infants

Newborn resuscitation equipment and practices vary within and between countries (172-174, 204).In the UK, the equipment used and techniques practiced are guided by the UK Resuscitation Council. All staff involved in new born care should undertake a standardised Newborn Life support provider course, however whether these standards are achieved in the UK is yet to be established.

1.11.4 Positive pressure ventilation

The aim of resuscitation in a newborn infant is to effectively mimic the infants' respiratory effort aiding the formation of the FRC, exchange and stimulate tidal breathing. Positive pressure ventilation with a peak inspiratory pressure (PIP) of 20-25cm H_2O and a prolonged inflation time of 2 to 3 seconds is recommended during the resuscitation of prematurely born infants (Resuscitation Council UK, 2010).

The use of continuous positive airway pressure (CPAP) with positive end expiratory pressure (PEEP) in resuscitation of preterm infants may prevent collapse on end expiration which helps in maintaining the FRC thus reducing the need for intubation (205-207). Use of PEEP in resuscitation has shown to have many advantages including preserving surfactant(208), improving gas exchange(209) and preventing airway collapse(210, 211). In rabbits, addition of PEEP during resuscitation was found to increase the FRC (pups ventilated with PEEP (19.9ml/kg) compared to pups where no PEEP(2.3 ml/kg)) (212). Naik and colleagues (213) further investigated the effects of PEEP during the resuscitation of preterm lambs. In their study, use of PEEP during resuscitation achieved tidal volumes (9-11ml/kg) with significantly lower PIP compared to the group where no PEEP was used. Following the experiment, the lambs were euthanised and the right lung was inflated and fixed. Morphometric measurements of the proportion (percentage fractional areas) were performed. They observed that the percentage of collapsed alveoli was reduced to 5% with 7 cm H_2O PEEP and 10% with 4cm H_2O PEEP compared to 38.5% with no PEEP. Furthermore, using 4cm H_2O was associated with significantly lower levels of total protein, IL-13, IL-6 and neutrophil counts in the alveolar fluid

compared to that of lungs receiving PEEP of 0 and 7 cm H_2O. Those findings indicate that using a PEEP of 4 cm H_2O can improve lung function and reduce lung inflammation during preterm resuscitation. In preterm neonates receiving ventilation following surfactant therapy, Da Silva et al.(214) measured pulmonary mechanics in 21 preterm infants. They observed that using a PEEP of 5 cm H_2O rather than 2 cm H_2O increased the FRC from 18.4 ml/kg to 26.2 ml/kg. They also observed a non-linear but significant ($p<0.01$) increase in the FRC with increase in PEEP from 2 to 5 cm H_2O. Polgolase *et al*.(215), found that increasing PEEP gradually in ventilated preterm infants, from 4 to 10 cm H_2O, increased the oxygen index and had potentially deleterious effect on the pulmonary blood flow. Similarly, Herman et al.(216) found that increasing PEEP in ventilated preterm infants, from 0 to 5 cm H_2O, increased arterial oxygenation but further increasing PEEP to 10cm H_2O provided no additional improvement. The effect of increasing PEEP also has detrimental effect on systemic and pulmonary blood flows and cardiac function(217). Those results suggest a PEEP of 4-5 cm H_2O may be beneficial but increasing the PEEP beyond 5 cm H_2O may be detrimental to pulmonary blood flow and gas exchange.

The peak pressure needed during resuscitation of preterm infants is variable. Resuscitation guidelines recommend 20-25 cm H_2O initially; however higher levels may be needed. Hoskyns et.al(218) reported that during lung inflation via an endotracheal tube, a PIP of 25-30 cm H_2O rarely achieved tidal volume greater than 4ml/kg. In contrast, Hird et al(219) found that a median of 22.8 cm H_2O was needed at preterm resuscitation and rarely a PIP of > 30 cm H_2O was needed. “Adequate chest rise” has been used in clinical studies to evaluate lung expansion during new born resuscitation, however visual assessment of chest

expansion and tidal volume is subjective. In a recent study, Poulton et.al(220) compared the assessment of chest rise made by observers with measurements of tidal volume during resuscitation of prematurely born infants. The clinicians underestimated the tidal volume by at least 3.5 mls and the agreement between the clinical assessment and tidal volume was poor.

Monitoring respiratory functions during resuscitation may improve gas exchange and reduce lung damage by providing the clinicians accurate and immediate feedback during resuscitation.

1.11.5 Assisted ventilation devices used during preterm resuscitation

Lung inflation devices used during preterm resuscitation vary across countries (172-174, 204). The ILCOR have made attempts to standardise equipment used at preterm resuscitation (221). The devices to be used should be operator controlled, easy to use, and achieve adequate lung inflation to aide gas exchange. Commonly the interfaces used for lung inflation in preterm resuscitation include face masks or endotracheal tubes, the use of laryngeal mask has rarely been studied.

Self-inflating bags had been the most commonly used device for newborn resuscitation, however they have been replaced by the T-piece resuscitator in developed countries. In mechanical models, inflation pressures were achieved more consistently when using T-piece resuscitators than with self-inflating bags or flow-inflating bags(222, 223). It has been reported that ventilation devices that produce the largest tidal volumes are those that achieve high pressures for sustained periods and that most bag and mask ventilation systems fail to reach adequate tidal volumes(224). A T-piece face mask resuscitation device which is

more commonly used is a pressure limiting device, the pressure is delivered by the clinician by occluding the port on the t-piece with their finger. This system is designed to allow maintenance of the desired inflation pressures for longer durations if necessary. Resuscitation studies using manikins have demonstrated that using a t-piece system resulted in less variation in the pressures delivered more frequently than bag operated devices(225). In mechanical models the ability to deliver a sustained inflation and maintaining PEEP was consistent with a T-piece resuscitator than a self-inflating bag (225, 226).

In preterm infants PPV administered via a t-piece rather than a self-inflating bag produced longer inflation times during resuscitation (227).

1.11.6 Lung inflation times during positive pressure ventilation

Maintaining a sustained inflation during the initial lung inflations during newborn resuscitation has been found to improve the formation of FRC. In a study of 10 term infants Vyas et al (228) found that using an inflation time of five seconds increased the inspiratory lung volumes (33.6 ml/kg) compared to one second (18.6 ml/kg) and that this may aide with the formation of FRC by the end of the first inflation. It has been hypothesised that by limiting peak pressure and using sustained inflations will lead to a higher tidal volume and rapid formation of FRC. A study investigating the effects of sustained lung inflation in preterm rabbits found that the first inspiratory volume significantly increased with inflation duration from a median of 0.2 ml/kg for 1 second inflation to 4.5 ml/kg for 5-second inflation, 10.4 ml/kg for 10-s inflation and 23.4 mL/kg for 20-s

sustained inflation. The lung was uniformly aerated, and the FRC fully recruited after a 20-second sustained inflation. (229) .

In a study in human infants, aimed to investigate the effects of prolonged lung inflation on lung injury, Harling and co-workers(230) compared the effects of five second inflation times to one second inflation time during initial resuscitation of prematurely born infants (<31 weeks gestation) by assessing the levels of inflammatory markers in the bronchial lavage fluid. They found no significant differences in cytokine levels at 12 hours and the requirement for ventilation was the same in both groups at four hours of age.

Numerous studies on preterm infants have attempted to study the effect of prolonged lung inflation and respiratory outcomes. Linder and colleagues(231) performed a randomized controlled trial to compare their sustained pressure – controlled inflation strategy to routine intubation and ventilation. They found no differences in the number of infants subsequently requiring intubation or mechanical ventilation. Te Pas and Walther(232) randomized 207 preterm infants to a sustained initial inflation of 10 seconds followed by early nasal CPAP or repeated inflations using a self-inflating bag followed by CPAP. They observed a significant reduction in the incidence of intubation at 72 hours in the sustained inflation group (37% versus 51% p=0.04) and further noted a reduction in the incidence of BPD in the group (22% vs 34%;p=0.015).

Although sustained inflations appear to be a method of opening the lung and achieving an initial FRC there are no data suggesting that it reduces lung injury or BPD. More importantly, monitoring lung inflation volumes may restrict lung injury by preventing volutrauma.

1.11.7 Efficacy of Preterm resuscitation

Currently positive pressure ventilation via a facemask interface is recommended to be used as the initial mode for supporting the pulmonary transition in the prematurely born infants(169). During preterm resuscitation, the pressure delivered to inflate the premature lung is limited to 20-25cm H_2O to prevent lung damage, however this is only achieved if there is no leak in the system. In a study on newborn resuscitation simulation, administering PPV to manikins, Wood et al. demonstrated that on average, 55% of the inspiratory volume given was lost due to face mask leak(233).When a respiratory function monitoring (RFM) was introduced during manikin resuscitation, the display of tidal volume and face mask leak during simulation reduced face mask leak by over 50% (234). Schmölzer and colleagues (235)measured tidal volumes and facemask leak during the resuscitation of preterm infants. They compared the resuscitators' assessment of the leak and tidal volume against the values recorded by the RFM. The median face mask leak was estimated to be 29% (range 16-63%) of the inspired tidal volume and more importantly, the resuscitators underestimated the extent of the leak. Furthermore, the median expiratory tidal volume was 8.3ml/kg and varied widely (5.3-11.3 ml/kg). In addition, assessing chest rise did not provide an accurate impression of the tidal volumes delivered during resuscitation. This suggests that the desired tidal volumes are not being consistently achieved due to facemask leak, hence respiratory function monitoring during resuscitation of preterm infants might improve the efficacy of resuscitation.

1.12 Monitoring resuscitation of prematurely born infants

The assessment of the response to resuscitation in the clinical setting is similar to term born infants, this includes chest rise, clinical signs like tone, colour and respiratory effort. ILCOR recommends the routine use of transcutaneous oxygen saturation monitoring to measure blood oxygen levels and heart rate, however these do not provide information on the respiratory functions during resuscitation. It is widely accepted that these methods may be inadequate to accurately guide the clinician to effectively resuscitate the preterm infant nor the infant's response to the resuscitation [52-54].

A recent and an important development in this field has been the introduction of respiratory function monitors (RFM) as a tool for monitoring respiratory parameters in real-time, during newborn resuscitation. Clinical studies(233, 234, 236) have shown them to be beneficial in identifying face mask leaks and in teaching correct mask hold and positioning techniques during simulation-based mannequin.

The superiority of RFM over traditional techniques has been repeatedly demonstrated (237). They can be extremely useful in providing resuscitators with information about the magnitude of face mask leaks, pressure and tidal volume being delivered which are central to the efficacy of resuscitation. Furthermore, most infants being resuscitated begin to breathe on their own eventually and these spontaneous breaths, as well as their interaction with mechanical inflations, can provide valuable information to the clinician during stabilisation of a prematurely born infant (238, 239).

There is a lack of data describing the acute responses of preterm infants to resuscitation. The use of respiratory function monitoring during preterm resuscitation has the potential to provide vital information and also help to develop robust evidence based guidelines to be followed at preterm resuscitation. This may also inform us about the minimum pressures necessary to provide adequate tidal exchange, and the formation of an air reservoir (functional residual capacity). In combination with a heart rate and oxygen saturation monitor, the RFM has the potential to inform the clinicians of the heart rate and oxygen saturation responses during resuscitation. These data are essential to enable the development of resuscitation strategies aimed at establishing effective tidal ventilation and oxygenation, while minimising the potentially injurious effect of lung over distension in this vulnerable group of infants.

1.12.1 Pulse Oximetry monitoring during preterm resuscitation

Pulse oximetry non-invasively measures blood oxygen saturation (SpO_2) and heart rate (HR) continuously. In most modern medical monitoring equipment, calibration is rarely needed before the commencement of monitoring and the values closely correlates with arterial oxygen saturation(240).Pulse oximetry is based on the changes in the infrared light absorption characteristics of oxygenated and deoxygenated haemoglobin. The sensor consists of two light emitting diodes (LED) which are placed around a hand or foot. The changes in absorption during the arterial pulsatile flow and non-pulsatile component of the signal are analysed. SpO_2 is estimated from the change in light absorption across the pulsatile vascular bed. Since the light absorption peaks occur with each heartbeat, heart rate can also be measured accurately.

Numerous studies (241-245) have reported variable rates(20-100%) of success in accurately measuring SpO_2 by the first minute of birth, the success rose to 63-100% by five minutes of age. In these studies, the most common reason for failing to obtain a measurement was motion artefact, however the presence of vernix, poor perfusion, oedema, high ambient light and acrocyanosis also resulted in artefacts. With advance in pulse oximetry technology, artefact has been less of a problem.

Supplemental oxygen to preterm infants have been a major area of research due to the morbidities of retinopathy of prematurity, lung injury and long term neuro-developmental concerns secondary to oxygen free radical injury. Previously oxygen therapy at preterm resuscitation had been ignored, however increasing body of evidence related to oxygen free radical injury has been established in animal studies(246). Optimising supplemental oxygen therapy in preterm infants and the reduction of oxygen related morbidity has led to establishment of physiological oxygen limit is preterm infants. Dawson and co-workers (164, 247) established a reference range for oxygen saturation during resuscitation of prematurely born infants. The current ILCOR guidelines(169) advocate the use of oxygen blenders and oxygen saturation monitoring to optimise oxygen saturation based on these reference ranges.

1.12.2 Monitoring pulmonary end-tidal carbon dioxide

There is limited evidence on the monitoring of expired carbon dioxide levels during preterm resuscitation. Currently, two non-invasive methods of monitoring carbon dioxide levels are available, (i) transcutaneous ($TcPCO_2$) monitoring and (ii) exhaled carbon dioxide ($EtCO_2$) detection by qualitative or quantitative

methods. A CO_2 detector (qualitative) has been recommended by the current ILCOR to confirm correct Endo tracheal tube(ETT) placement during intubation of a newborn infant(221). A mainstream capnography (quantitative) device is placed in line with the respiratory gas stream and a side stream capnography device utilizes a sampling line that continuously samples gas through a sampling line. Both capnography methods provide a continuous visual display of carbon dioxide values.

The use of a CO_2 detector has been shown to significantly reduce the time to confirm ETT placement (248). Misplacement of ETT can result in increased adverse outcomes due to hypoxia or lung collapse (249, 250). In most studies, the use of $ETCO_2$ in estimating gas exchange, however has demonstrated a poor correlation with blood $PaCO_2$ levels (251-253).

Advances in technology and a more robust main stream capnography could help clinicians analyse the resuscitation responses and facilitate understanding of expired carbon dioxides levels and their relation to tidal volume, FRC and infant's respiratory efforts during preterm resuscitation. The expired CO_2 levels could be a potential surrogate marker for lung aeration and gas exchange. Hence monitoring expired CO_2 would help in better understanding of pulmonary gas exchange immediately after birth.

1.13 Hypothesis

Respiratory function monitoring will determine the efficacy of initial resuscitation of prematurely born infants and the contribution played by the infant's respiratory efforts. In addition, the following were hypothesised to be true:

1. The delivered inflation pressure, duration of inflation and expired tidal volumes will be variable during the first five inflations.
2. Prolonged inflation times will not improve tidal volumes during the first five inflations.
3. Infants' respiratory efforts will immediately increase end tidal CO2 levels and maintain higher levels with subsequent lung inflations.
4. Efficacy of resuscitation would be better through an endotracheal tube compared to face mask due to large leaks in the later.
5. Clinicians would find the Respiratory Function Monitoring useful during preterm resuscitation.
6. Newborn resuscitation practices will be consistent across the UK, regardless of the level of neonatal care provided by the local units.

1.14 Aims

- To study the initial five lung inflations during face mask resuscitation of prematurely born infants and the influence of the infant's inspiratory efforts on tidal volume.

- To assess the length of inflation times used during preterm resuscitation and determine the effect of prolonged inflations on inflation flow times.

- To study the temporal changes in end tidal CO_2 levels during initial lung inflation and the effect of the infant's first inspiratory effort.

- To study the effects of increasing inflation pressures on tidal volume and end tidal CO_2 during resuscitation of prematurely born infants.

- To assess and compare the initial responses to lung inflation delivered via an endotracheal tube and a face mask, and to evaluate the magnitude of expired tidal volumes in relation to the infant’s first inspiratory effort.

- To determine the factors affecting the formation of initial functional residual capacity in preterm infants resuscitated at birth.

- To evaluate the use of respiratory function monitoring at resuscitation of prematurely born infants.

- To survey current new born resuscitation practices in the United Kingdom.

Chapter 2 : Methods

All preterm labour were identified by the clinical and research team at King's College Hospital NHS foundation trust and Guy's and St Thomas' Hospital NHS Foundation Trust over the period of the study. Imminent delivery of a preterm infant was communicated to the clinical team by the labour ward staff. The neonatal clinician team or the research team set up the research equipment in conjunction with the routine resuscitation equipment used during preterm delivery. The research equipment was left on a standby mode, the recordings of the physiological data were commenced immediately following the delivery of the preterm infant by clicking the "on" button. The physiological parameters were displayed and recorded on a laptop computer which can be reviewed at a later date. Parents were approached for an informed consent to use of the recorded data, once the mother is stable and transferred to the postnatal ward.

2.1 Subjects

All preterm infants born before 34 weeks of gestation King's College Hospital NHS foundation trust and Guy's and St Thomas' Hospital NHS Foundation Trust, between 1st March 2010 and 31st April 2012 were eligible for this study. Infants with antenatal diagnosis of congenital respiratory, cardiovascular and abdominal abnormalities were excluded from this study.

2.2 Ethical approval

The study was approved by the Outer London North Research Ethics committee (Ref no: 09/H0724/38); their opinion was that, as this was an observational study, parental consent was needed only for analysis of the data. Informed written consent was obtained once the mother was transferred to the post-natal ward. Research and development departmental approval were

obtained from both hospitals. Recruitment for the study commenced King's College Hospital NHS foundation trust and Guy's and St Thomas' Hospital NHS Foundation Trust on the 1st March 2010.

2.3 Standard Resuscitation protocol

The practice at both units during the study period included compulsory attendance of junior / senior trainee paediatrician at all deliveries of infants born less than 34 weeks of gestation, in anticipation of them needing resuscitation at birth. All paediatricians were trained in standardised newborn resuscitation according to the Resuscitation Council, UK guidelines(2005)(254) and were aware of the principles and guidelines to be followed at preterm resuscitation. Labour ward staff informed the neonatal team of all imminent preterm deliveries.

Prematurely born infants who needed resuscitation at birth were clinically assessed by the clinician and positive pressure ventilation was delivered with a t-piece device (Neopuff Infant resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand), which is a continuous flow, pressure limiting device with a build in manometer and a positive end expiratory pressure (PEEP) valve. The t- piece was attached to a face mask (Marshall, Bath, UK); and the clinician selected a size 0 or 1 sized face mask aiming to achieve adequate face mask seal during the resuscitation. An oxygen saturation probe was placed on the infant's right hand and connected to the monitor. An oxygen blender was incorporated in the ventilation circuit which would help the clinician to titrate oxygen delivery according to the infant's oxygen saturation. Clinicians were requested to avoid hyperoxia and titrate oxygen according to clinical needs as advised by the UK newborn resuscitation guidelines (2005). There was no clear

guidance on the levels of supplemental oxygen to be used at preterm resuscitation.

2.4 Research Protocol

Labour ward staff informed the neonatal team of all imminent deliveries of less than 34 weeks of gestation. The research monitoring equipment was set up by the clinicians/research team as part of a standard check of the resuscitation equipment in preparation of an imminent preterm birth. The laptop was left on a standby mode and switched to a recording mode as soon as the preterm infant was delivered. Standard ILCOR resuscitation recommendations were being followed(254). Thus, infants who were cyanosed with no respiratory effort, but had a heart rate of at least 60/min received face mask ventilation immediately, using 50% oxygen. The recommendation is to maintain lung inflation for 2-3 seconds during the first five lung inflations. Infants failing to respond within 30 seconds, or who had a heart rate of less than 60 beats/minute on initial assessment were intubated and ventilated using peak inflation pressures of 20-25 cm H_2O and a PEEP of 5cm H_2O, with 50% oxygen, maintaining the first inflation for 2 to 3 seconds. If this failed to produce apparent chest wall movement, inflation pressures were increased incrementally by 2-5 cm H_2O until there was effective chest wall movement. If the heart rate failed to increase, external cardiac massage was commenced in combination with positive pressure ventilation. Where clinically indicated, intravenous drug like Ephinephrine and sodium bicarbonate were administered based on the national guidelines(254). The delivered oxygen concentration was titrated to achieve a saturation level between 85-92%. The monitoring equipment displayed (RFM and laptop computer) air flow, airway pressure, end-tidal CO_2, saturation and

pulse rate in real time. This provided the clinician an immediate feedback on the tidal volume, end-tidal CO_2levels, oxygen saturation and heart rate in real time during the resuscitation. The clinicians were able to view the presence of end-tidal CO_2 to confirm air way patency during face mask ventilation and more importantly, correct placement of endo tracheal tube during resuscitation. They were able to assess the adequacy of ventilation support from tidal volume levels and titrate oxygen delivery based on infants oxygen saturations measured by the in-built pulse oximetry.

2.5 Equipment

A NM3 Respiratory profile monitor (Philips Respironics®) was connected to a Laptop (Dell latitude, Bracknell, UK) with customised Spectra software (version 3.0.1.4; Grove medical, London, UK) and mounted on a mobile trolley. The NM3 respiratory profile monitor (RPM) has a combined flow and carbon dioxide sensor, which was placed between the t-piece and the face mask (Figure 2-1). The RPM and the laptop were connected to an isolating transformer and UPS for stable power during the recording of the resuscitation (Figure 2-2). One mobile trolley with the equipment was readily available at each site for immediate use at preterm resuscitation.

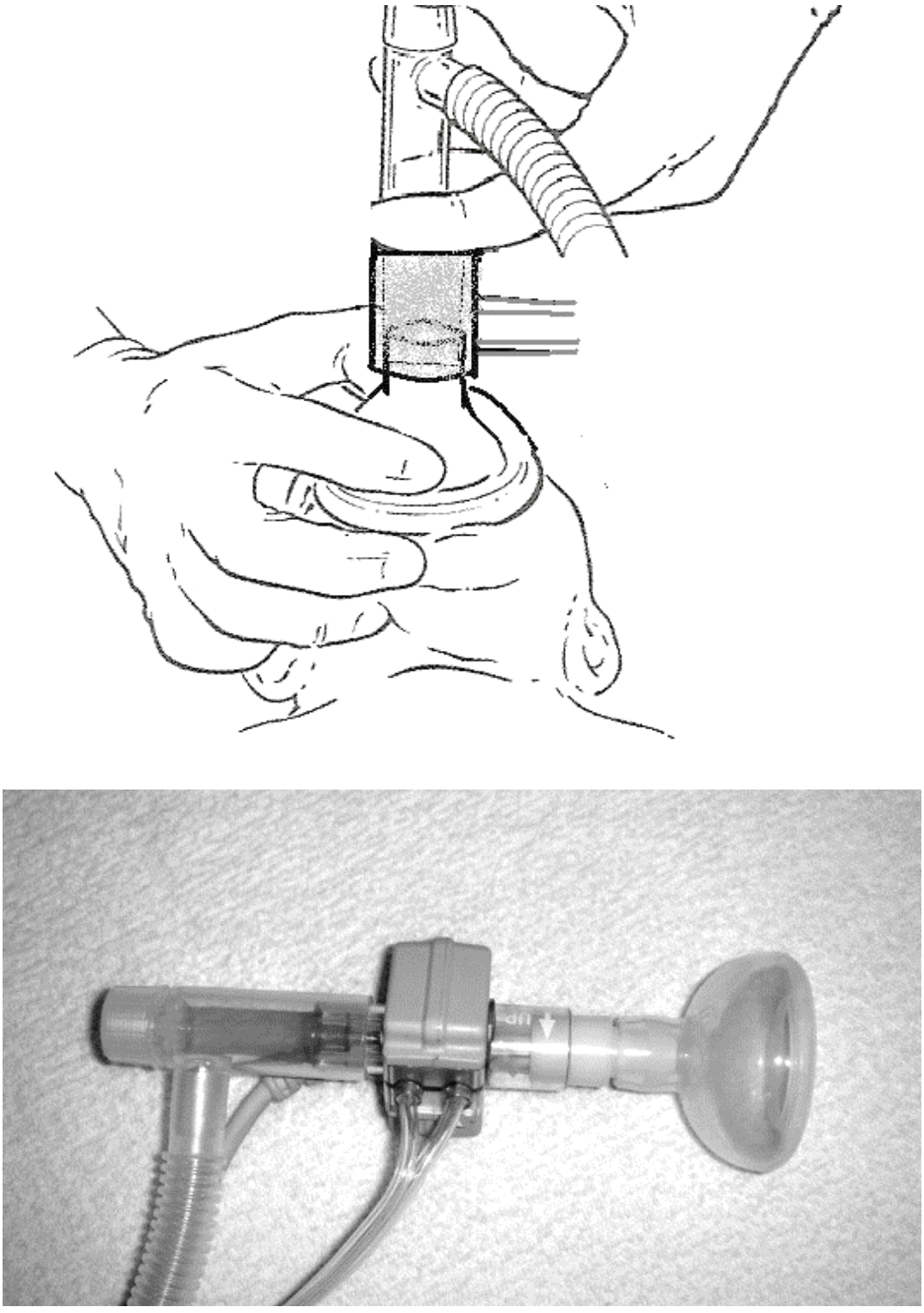

Figure 2-1:Dual flow and CO2 sensor attached between the T-Piece and face mask

[Copyright details in Appendix III]

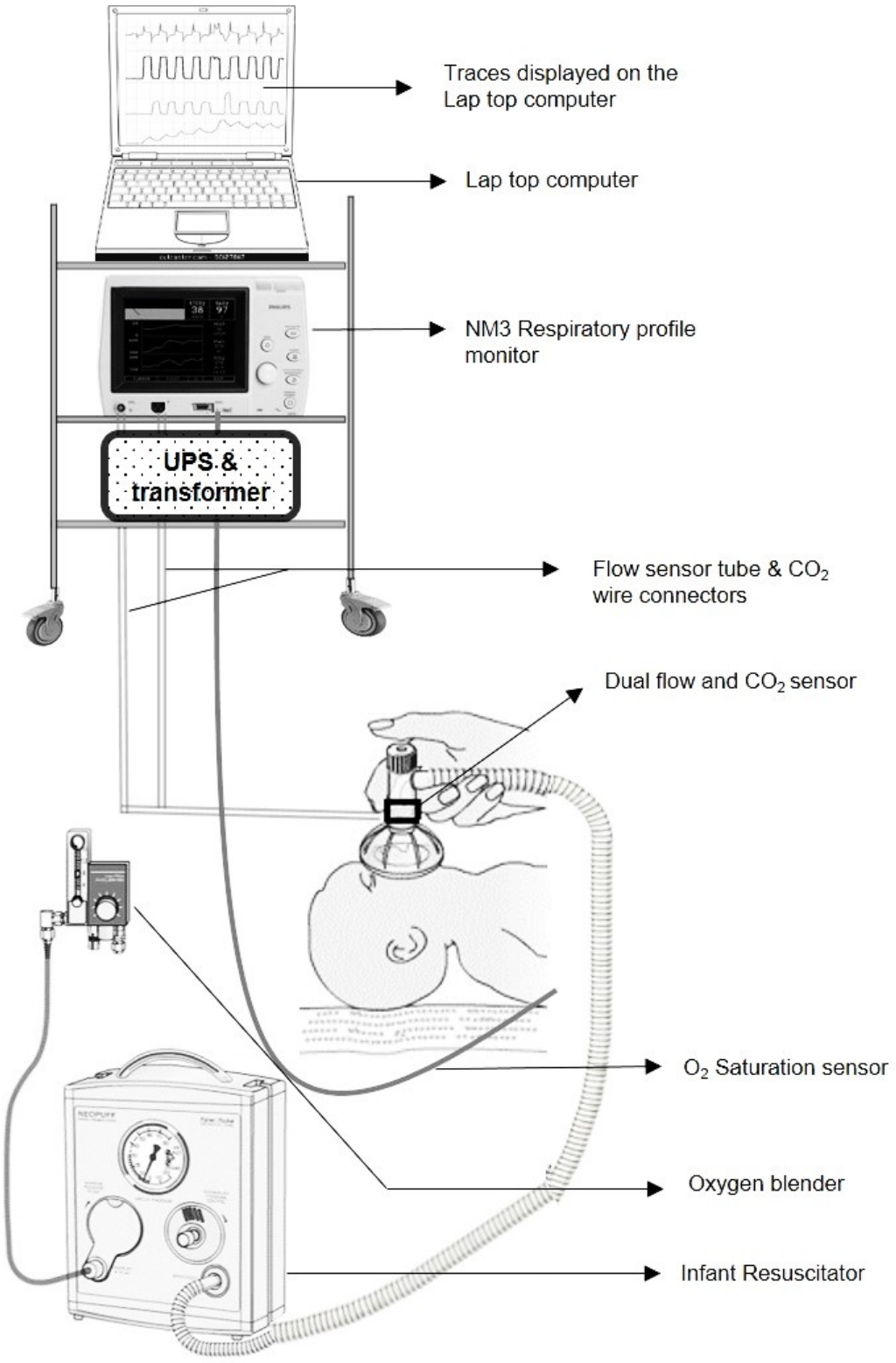

Figure 2-2 : Diagrammatic representation of the equipment used to monitor resuscitation of prematurely born infants

[Copyright details in Appendix III]

2.5.1 NM3 Respiratory Profile monitor

The NM3 monitor is a respiratory profile monitor which displays various respiratory parameters including expired CO_2, oxygen saturation (Figure 2-2).

Equipment	Measuring Parameter	Range	Accuracy (at 760mmHg,room air)
Flow Sensor	Air flow	0.25 to 25 l/min	± 3%
	Tidal Volume	1 - 100 ml	± 3%
	Airway pressure	-120 to +120 (cm H_2O)	± 2%
CO_2 Sensor	End tidal CO_2	0-150 mmHg	0-40 mmHg- ± 2mm Hg
			41-70 mmHg- ± 5%
			71 – 100 mmHg - ± 8%
			101- 150 mmHg - ± 12%
SpO_2 Sensor	Oxygen Saturation	0-100%	± 3%
	Pulse Rate	25- 240 bpm	± 3 bpm

Table 2-1: Range and accuracy of the measured parameters with NM3 monitoring
(Reproduced from NM3 RPM manual)

2.5.2 Research equipment maintenance

Equipment was cleaned prior to use and disinfection/sterilization of all non-disposable equipment carried out using manufacturer and hospital infection control approved techniques after each patient contact. The flow sensor circuit was single use only. Perasafe® (0.2% peracetic acid) was used for non-disposable parts as approved by the company. External housings of the monitor and other equipment were cleaned according to the unit policy. The RPM was bought new and safety checks were undertaken by the company and by the department of Clinical Engineering at the respective hospitals before it was

used. A further service and parameter check was performed by the company (Philips Respironics®), one year after the initial safety check.

2.5.3 Airway Pressure measurement

Airway pressure measurements in the NM3 monitor were made by a fixed orifice differential pressure pneumotachometer. Differential pressure flow sensors incorporated some restriction (point orifice, variable flap, vena constriction, annular obstruction, target or linear flow restrictor) that generates a pressure difference across the sensor. Flexible tubing, attached to either side of the flow obstruction, transmitted the pressure signals to a differential pressure sensor located inside the monitor. Factors that influence the measurement of flow for this type of sensor include the gas molecular weight, temperature and airway pressure (Table 2-2).

2.5.4 Air flow and tidal volume measurement

Airflow was measured using a fixed orifice differential pressure pneumotachograph (Figure 2-1) inserted between the endotracheal tube and the T-piece as described for measurement of airway pressure. The signal from the differential pressure pneumotachograph was amplified in the RPM and was displayed in the monitor. Tidal volume was digitally integrated from the air flow signal in the RPM and was displayed on the RPM monitor.

Compensation Settings					Gas Compensation Effects on Flow		
Insp O2 (%)	**Gas Balance**	**N_2**	**N_2O**	**Helium**	**Temp**	**Humidity**	**Measurement Error**
21	N_2	79	0	0	35° C	50%	---
60	N_2	40	0	0	35° C	50%	-2.50%
40	N_2O	0	60	0	35° C	50%	-14.90%
60	N_2	35	0	0	35° C	50%	-19.60%
30	He	0	0	70	35° C	50%	56.70%
21	N_2	79	0	0	35° C	0%	-0.50%

Table 2-2: Gas composition effect on flow (Reproduced from NM3 RPM manual)

2.5.5 Differential pressure flow sensor

The NM3 Respironics flow sensor is a fixed orifice differential flow sensor and is inserted between the T-piece and the face mask (Figure 2-1) during resuscitation. The pressure drop across the fixed orifice flow sensor is in proportional to the square of the flow (Figure 2-3). Microprocessors in the NM3 RPM were programmed to store the parameters of these flow sensors and to compensate for this non-linear pressure-flow relationship. In addition, recent advances in differential pressure sensor design and technology have made it possible to measure the very low flows reliably. The neonatal flow sensors feature a target geometry composed of a central strut to maintain an acceptable level of flow resistance. In order to reduce mechanical dead space, the neonatal CO2/flow sensors are single piece designs (Figure 2-4).

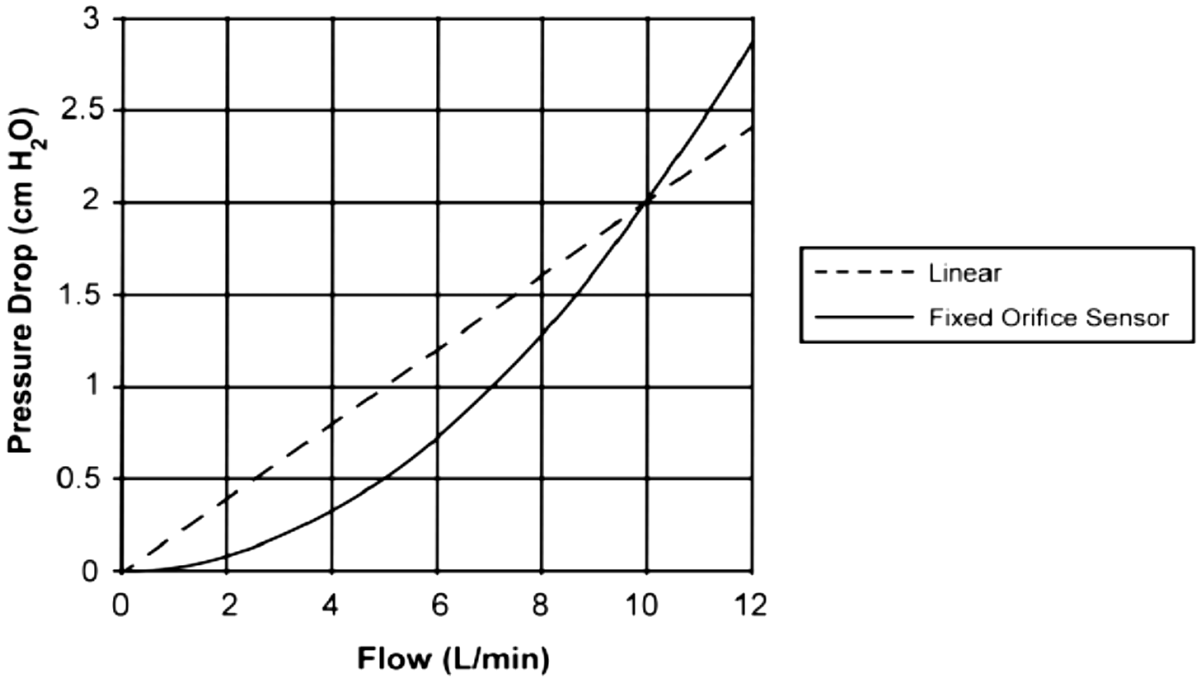

Figure 2-3: Flow versus Pressure Drop for a “Linear” device (i.e. Fleisch pneumotachograph) and “Non-Linear” device (fixed orifice flow sensor)(255) *[Copyright status details in Appendix III]*

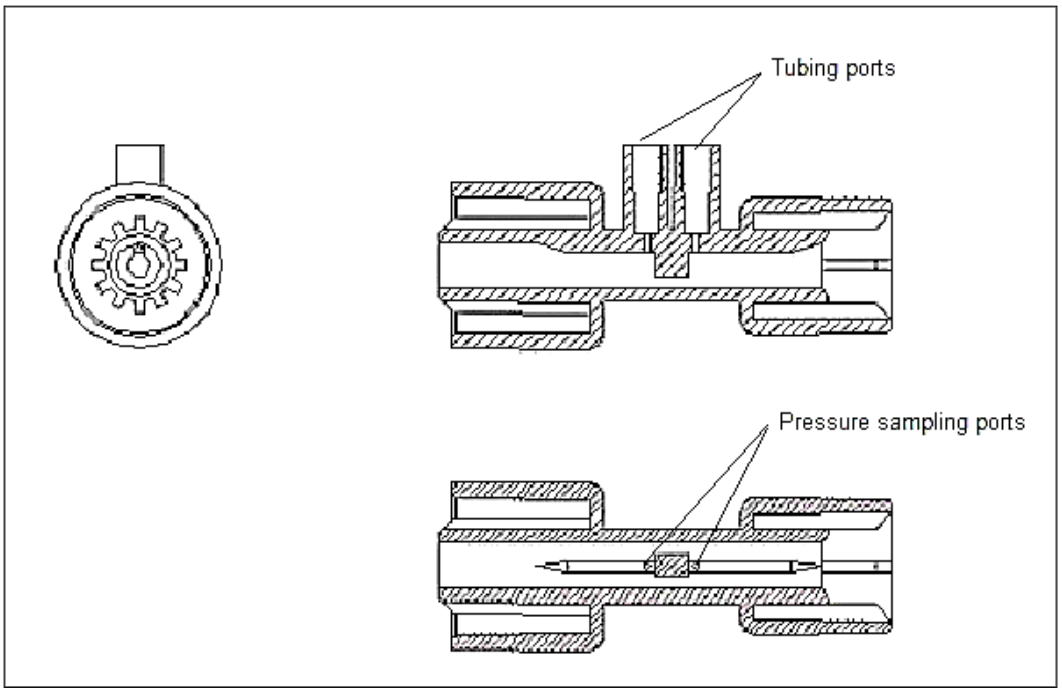

Figure 2-4: Neonatal Flow sensor—side, top and end sections(256*).*

[Copyright status details in Appendix III]

Respired gas flowing through the flow sensor caused a small pressure drop across the two tubes connected to the sensor. The pressure drop was transmitted through the tubing to a differential pressure transducer located inside the monitor, and was correlated to flow according to the factory stored calibration. User calibration was not required due to the ability of the plastic injection mould to repeatedly produce precision flow sensors. The pressure transducer was automatically “zeroed” to correct for changes in ambient temperature and electronics.

As previously mentioned, with a fixed orifice device, the differential pressure varied as the square of the flow. The measured flow was corrected by use of empirically determined coefficients due to variations from the relationship and the assumptions made in developing the flow equations. The relationship between the measured differential pressure to flow (L/min) can be described by the equation,

$$\frac{Pm\ Tstd}{Pstd\ \ Tm}\ \sqrt[K]{\Delta\ P}$$

where P_m P_{std} Tm and T_{std} are the measured and standard pressures (in mmHg) and temperatures (in Kelvin), respectively; K is a correction factor that includes gas composition, and other factors like gas temperature, compressibility, density and molecular mass. ΔP is the differential pressure (in mmHg).

Ideal gas law(257) is applied for correction of calculated flow to standard temperature conditions. Inspiratory and expiratory phases were treated separately with regards to temperature and gas composition due to variable gas temperatures during the respiratory cycle. The NM3 monitor system software

compensations allow accurate flow and volume measurements in the presence of high oxygen concentrations. When compensated, gas density and viscosity effects do not cause significant errors in flow measurement (Table 2-2).

The monitor included an automatic and manual purge feature which provided a flow rate of room air to keep the sensor tubing free from water condensation and patient secretions. The automatic purge cycle used in the neonatal mode was fixed at every three minutes regardless of circuit pressure. Only one side of the sensor tubing was purged during each purge cycle.

Unlike the adult purge mode, the neonatal or paediatric purge mode does not use the full force of the internal pump, but rather pressurized an internal reservoir which was used for the purge. This minimizes the pressure delivered to the circuit to prevent inadvertently high pressures in the ventilator circuit, but does deliver a sufficient pressure to purge the sensor tubing.

Tidal volume is then calculated as the integral of flow: $\boldsymbol{V = \int F\,\Delta t}$ (V = Tidal volume and Δt is change in time).

This integration represents a summation over time; the volume traces seen (Figure 2-5) during the resuscitation are obtained by adding successive sampled values of the flow signal and scaling the sum appropriately. The integral is automatically set to zero every time a recording is started.

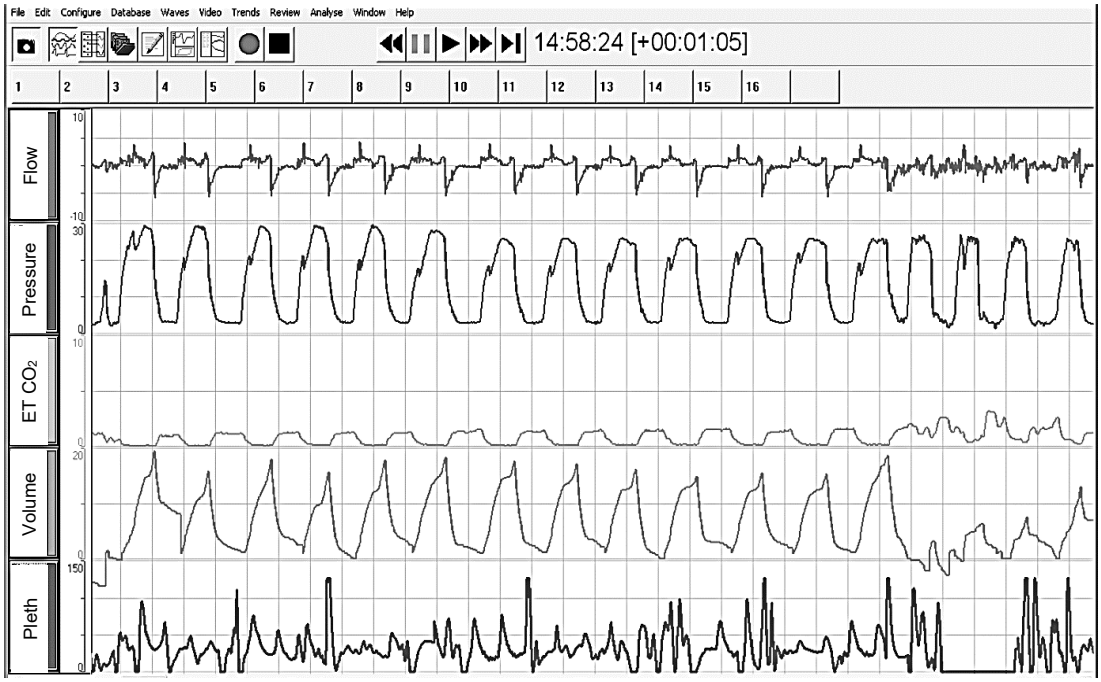

Figure 2-5: Display of air flow, airway pressure, end tidal carbon dioxide, tidal volume and plethysmography traces during resuscitation.

2.5.5.1 Calibration of airway pressure and air flow

Calibration for airway pressure was undertaken every time a new batch (box of 10) of differential flow sensors were used. A two-point calibration check of pressure transducers was performed using a portable digital pressure meter (Comark, Welyn Garden city, UK). The portable pressure meter was calibrated against a water manometer and found to be linear. The linearity of the NM3 differential pressure sensor was tested against the portable digital pressure meter.

The calibration of air flow was performed using a low flow rotameter (0-12 L/min Platon, Roxspur Measurement & Control Ltd, Bramley, Hants, UK). The tidal volume was calibrated at the same time with 2,4,6,8,10,20,25 and 50ml calibration syringe (Model 5510 and 5520, Hans Rudolph Inc).

2.5.5.2 Levels of agreement for airway pressure and air flow estimation

The levels of agreement of airway pressure sensor and linearity was assessed by plotting the digital output acquired by Spectra Software, against applied pressure measured with a digital pressure meter (Comark, Welwyn Garden City, London UK). The airway pressure transducer was tested for both RPM monitors used at King's College Hospital(KCH) and Guy's and St Thomas' Hospital(GSTT) used in the project. This was tested using 5 cmH_2O increments in both instruments, across the range ± 40 cm H_2O.The acquired values were plotted against the measured values. There was a strong positive correlation between the airway pressure measured and the values from the RPM (R^2= 1, P<0.001) and this was the same for KCH and GSTT monitors (R^2 =1; p<0.001). The Bland-Altman plots (Figure 2-6) revealed good agreement between the KCH and GSTT monitor, with all the measurements clustering around the mean. Difference between the two monitor readings for airway pressure flow were within the two standard deviation lines.

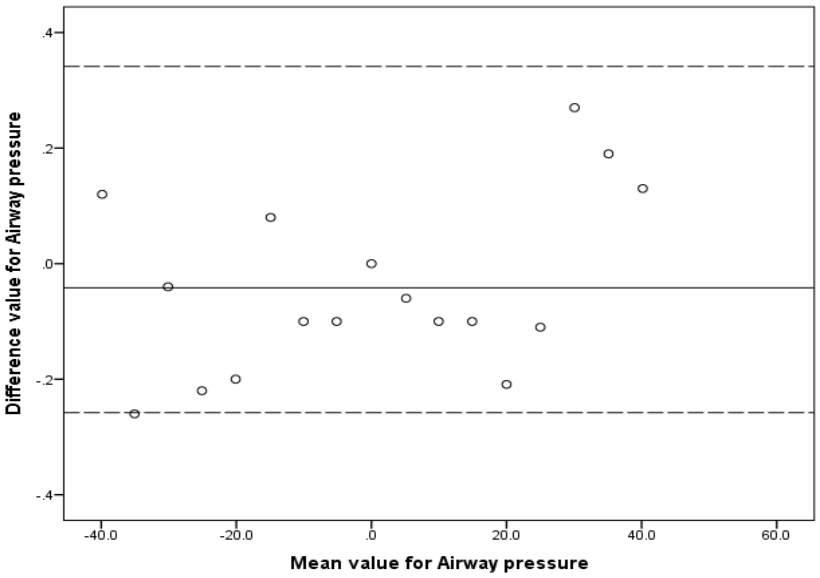

Figure 2-6 : Bland-Altman analysis of difference for airway pressure measured by KCH and GSTT monitors

The levels of agreement of the airway flow sensor was assessed by plotting the digital output acquired by Spectra Software, against air flow measured using a low flow rotameter (0-12 L/min Platon, Roxspur Measurement & Control Ltd, Bramley, Hants, UK). The values of the airway flow were tested for both RPM monitors used during the project demonstrated good levels of agreement. This was tested using one litre/min increments in both instruments, across the range ± 12 litre/min and was found to be linear. Air at 1 to 12 L/min was passed through the pneumotachograph and the results were plotted against the actual flow delivered by the rotameter. The acquired values were plotted against the measured values. There was a strong positive correlation between the airflow measured and the values by the RPM (R^2= 1, P<0.001) and this was the same for KCH and GSTT monitors (R^2 =1; p<0.001).The Bland-Altman analysis revealed good agreement between the KCH and GSTT monitor overall (Figure 2-7), including when tested with 21%, 50% and 100% O_2, with all the measurements clustering around the mean(Figure 2-8). Difference between the two monitor readings for air flow were within the two standard deviation lines.

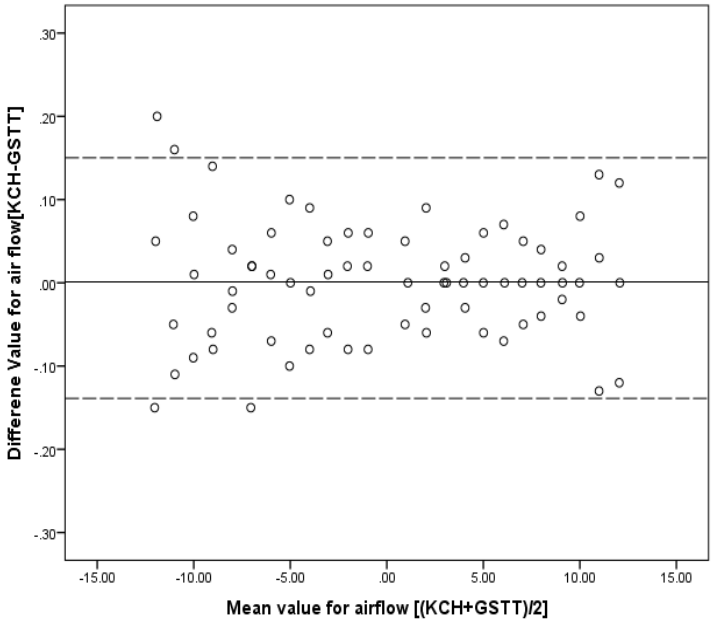

Figure 2-7:Bland-Altman analysis of the difference for measured airflow in KCH and GSTT monitors.

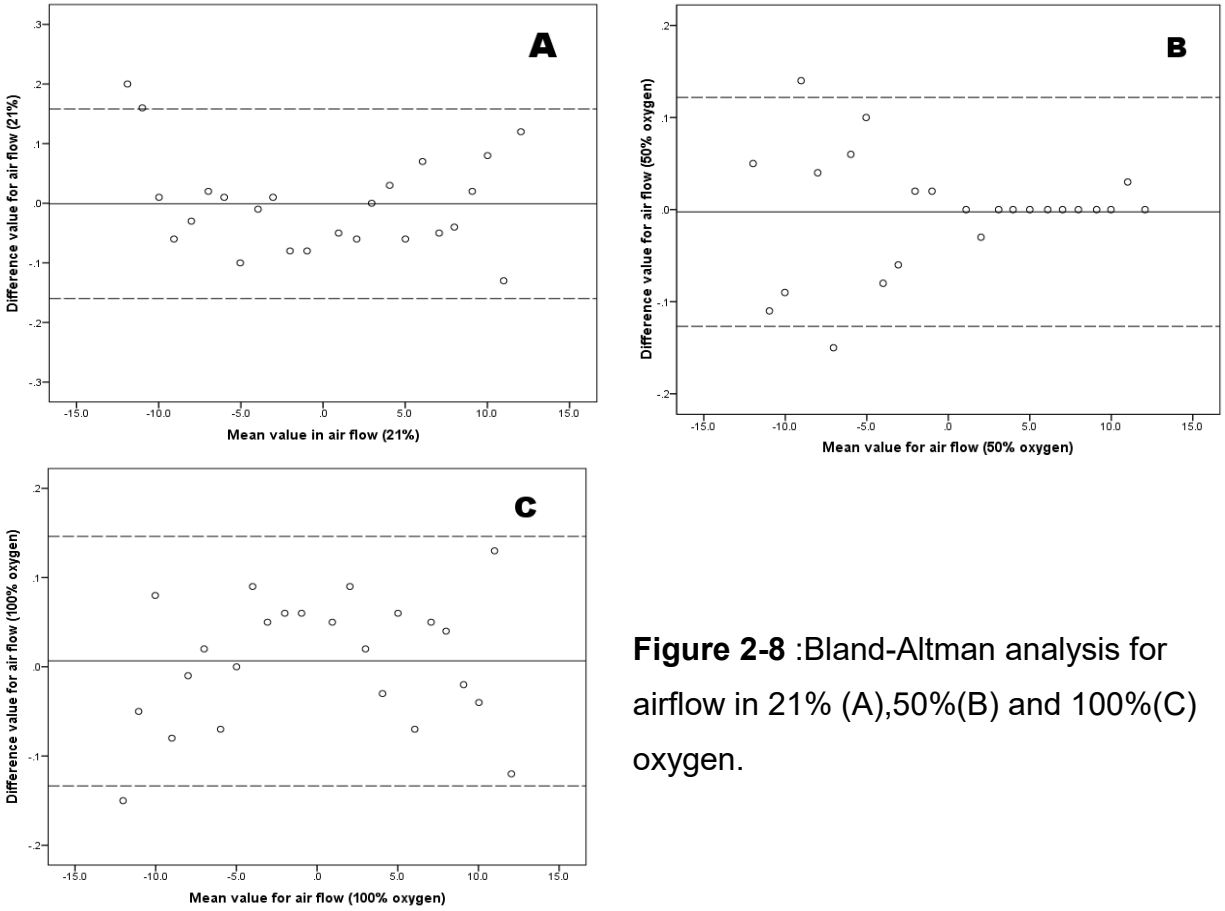

Figure 2-8 :Bland-Altman analysis for airflow in 21% (A),50%(B) and 100%(C) oxygen.

2.5.5.3 Levels of agreement for tidal volume estimation

A set volume of gas volume was delivered to the flow sensor through a calibration syringe at different volumes. The gas volumes acquired through the NM3 RPM was analysed and plotted. The effect of gas composition on the calibration of the pneumotachograph was also investigated. A strong positive correlation between the tidal volume measured by the KCH and GSTT monitors (R^2 =1; p<0.001). The Bland-Altman analysis revealed good agreement between the KCH and GSTT monitor overall (Figure 2-9), including when tested with 21%, 50% and 100% O2, with all the measurements clustering around the mean (**Figure 2-10**). Difference between the two monitor readings for air flow were within the two standard deviation lines.

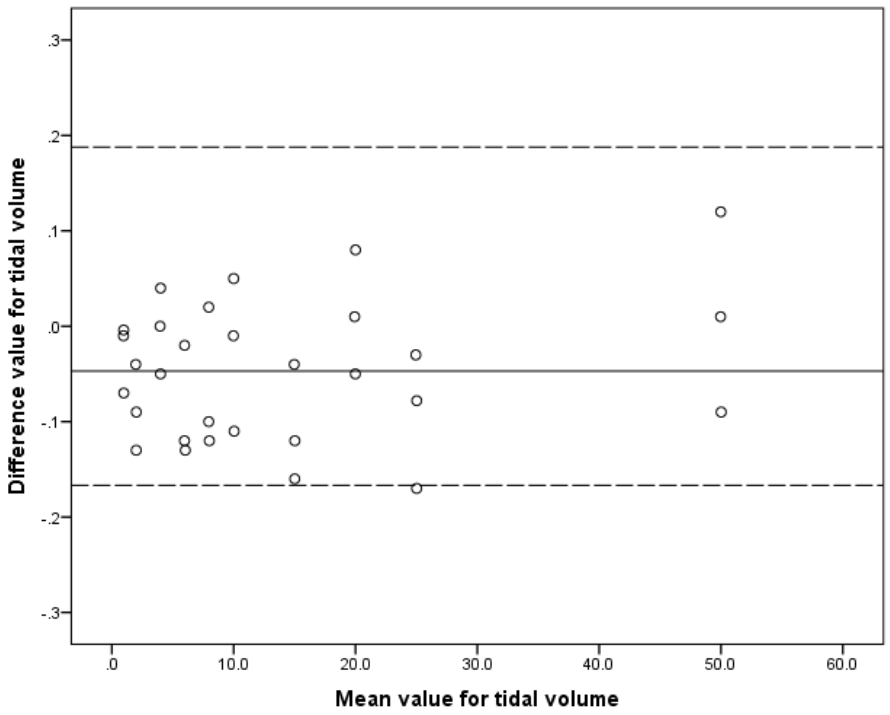

Figure 2-9: Bland-Altman analysis of difference for tidal volume measured by the KCH and GSTT monitors

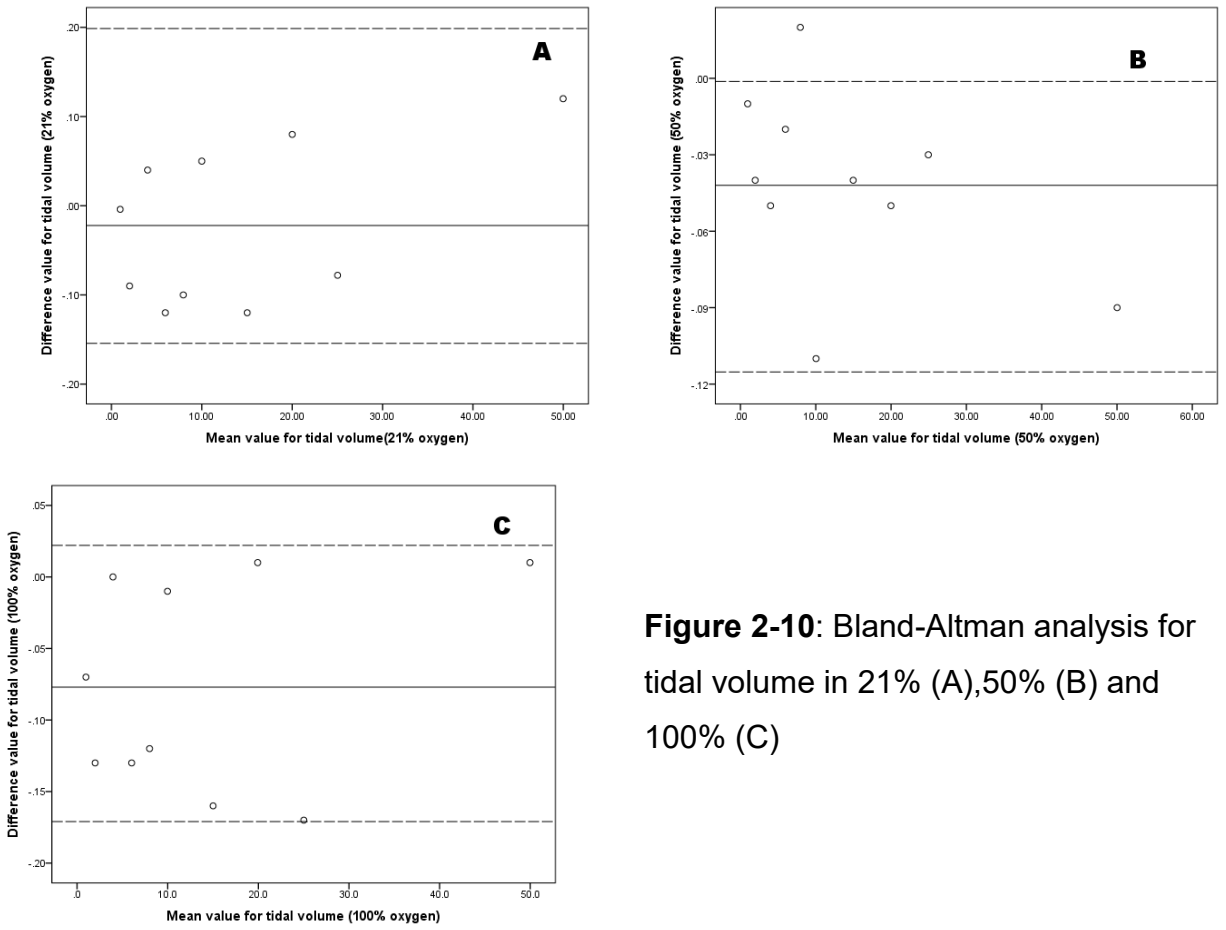

Figure 2-10: Bland-Altman analysis for tidal volume in 21% (A),50% (B) and 100% (C)

2.5.6 Exhaled Carbon dioxide measurment

The NM3 monitor uses the CAPNOSTAT® 5 CO_2 Sensor to measure CO_2 by using the infrared absorption technique. The principle is based on the fact that CO_2 molecules absorb infrared (IR) light energy of specific wavelengths, with the amount of energy absorbed being directly related to the CO_2 concentration. When an IR beam is passed through a gas sample containing CO_2, the electronic signal from the photo detector (which measures the remaining light energy) can be obtained. This signal is then compared to the energy of the IR source and calibrated to accurately reflect CO_2 concentration in the sample. The CAPNOSTAT® 5 CO_2 sensor's response to a known concentration of CO_2 is stored at the factory in the sensor's memory. A reference channel accounts for optical changes in the sensor, allowing the system to remain in calibration

without user intervention. The sensor was able to measure end-tidal CO_2 in the range of 0-150mmHg. The CO_2 sensor slide over the flow sensor and clicked in place once connected (Figure 2-11).

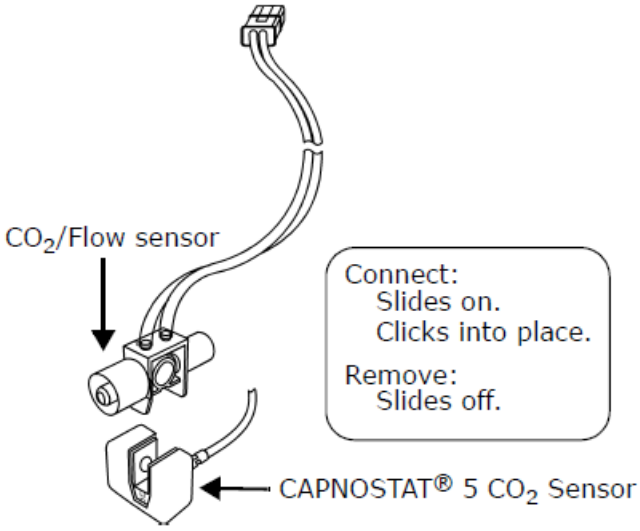

Figure 2-11 : Connecting and removing of Flow and CO_2 sensor
Copyright status details (Appendix III)]

2.5.6.1 Levels of agreement for exhaled carbon dioxide measurement

To evaluate the levels of agreement and linearity of CO_2 estimation, various concentrations of CO_2 gas at 8 litres/ min was connected to one end of the flow sensor. The acquired values were plotted against the measured values. There was a strong positive correlation between the end-tidal CO_2 levels acquired from the RPM and the know concentration of CO_2 (R2= 1, P<0.001) and this was the same for KCH and GSTT monitors (R^2 =1; p<0.001). Bland-Altman analysis revealed good agreement between the KCH and GSTT monitors, with all the measurements clustering around the mean. The acquired measured values were plotted against the known concentration of CO_2 and was observed to be linear for up to 20% CO_2 concentration (Figure 2-12).

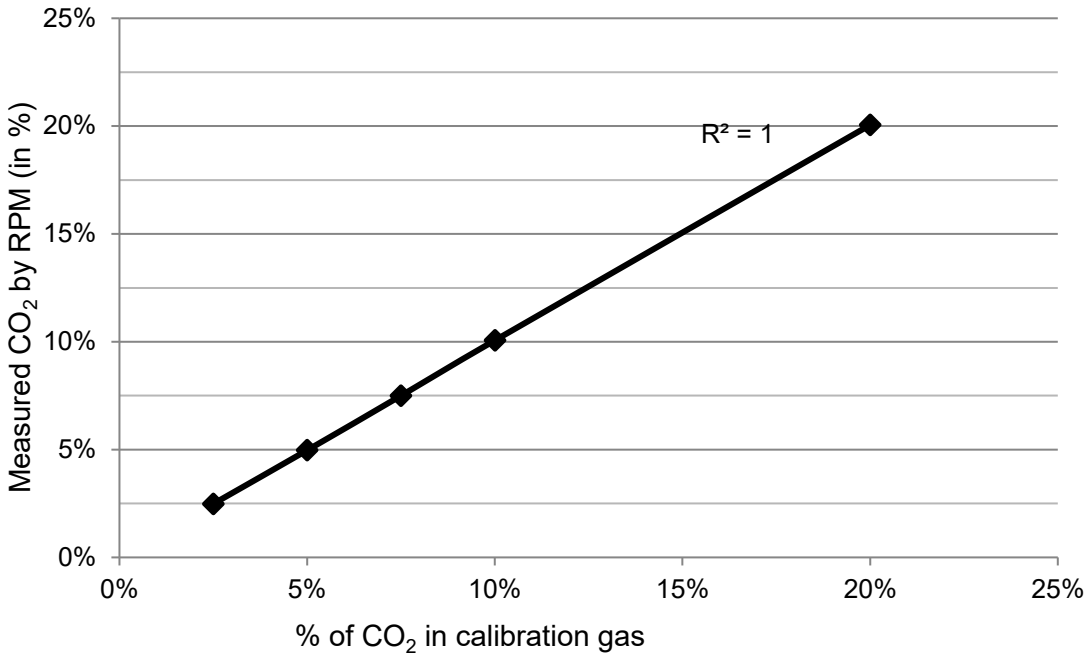

Figure 2-12 : Estimation of CO_2 by the sensor and know concentration of CO_2 gas

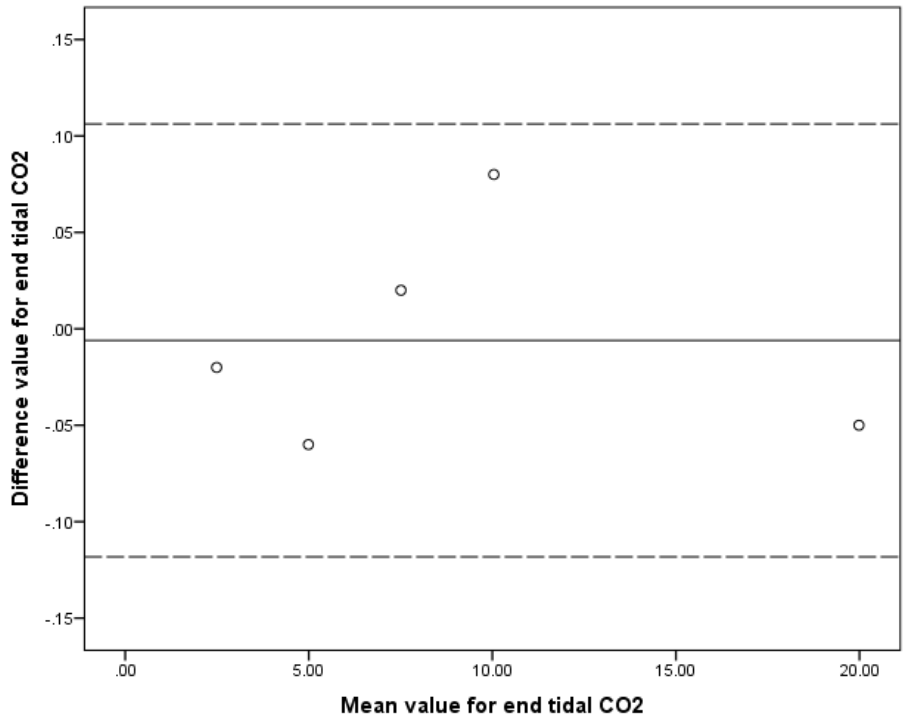

Figure 2-13: Bland-Altman analysis of the difference for measured end tidal CO_2 in KCH and GSTT monitors

2.5.7 Pulse rate and oxygen saturation measurement

Oxygen saturation (SpO_2) was determined using sensors containing infrared light emitting diodes (LEDs). The light from the LEDs are beamed through a pulsating vascular bed such as the infant's finger or toe. The remaining light not absorbed by the tissue reached a photodiode light receptor in the sensor. Oxygen saturated blood absorbs different amounts of light at each wavelength as compared to unsaturated blood. Therefore, the amount of light absorbed by the blood in each pulse can be used to calculate oxygen saturation.

The NM3 monitor was calibrated to measure and display "functional" saturation. This differed from the "fractional" saturation value displayed by most co-oximeters. Functional saturation represented the amount of oxyhaemoglobin as a percentage of the haemoglobin that can be oxygenated. Dysfunctional haemoglobins, [carboxy haemoglobin(COHb) and Meth Haemoglobin(METHb)] are not included in the measurement of functional saturation.

$$\textit{Functional Saturation} = HbO_2^{*}/100-(COHb+METHb)$$

* HbO_2 is oxyhaemoglobin (fractional)

Pulse Rate, derived from the pulse oximetry sensor, was calculated by measuring the time interval between the peaks of the infrared light waveform. The inverse of this measurement was displayed as pulse rate.

2.5.8 Frequency response of the monitoring system

The "time constant" of the measuring system gives a measure of its dynamic response to an input step change and is related to its frequency response. The frequency response of the entire system (transducers – respiratory function monitor (NM3) – computer) was assessed by bursting a pressurised balloon

with a hot wire for airflow and airway pressure (Figure 2-14. The frequency response for end tidal CO_2 was assessed by changes in CO_2 concentration using a solenoid valve used in switching between room air and 5% CO_2. The response to an instantaneous change in signal was recorded on a laptop computer (MacBook, Apple Computer Corp, Cupertino, California, USA) using Chart software (Version 5.0, AD Instruments Pty Ltd, Bella Vista, NSW Australia) with analogue to digital sampling at 40KHz (Powerlab, AD Instruments Pvt Ltd, Bella Vista, NSW Australia).

The Fourier transformation of the response time (T_r) gives the frequency response of the system. The 90-10% response time (T_r) for airflow, airway pressure and end tidal CO_2 were 19 milliseconds, 11 milliseconds and 50 milliseconds respectively. The frequency response of the system was calculated from the equation.

$$f3db = {}^{1}/_{3T_r}$$

f3db = frequency response and Tr = time taken for the pressure change from 10 to 90% of the final resting pressure. The frequency response was 17.5 Hz, 30.3 Hz and 6.6 Hz for airflow, airway pressure and end tidal CO_2 respectively.

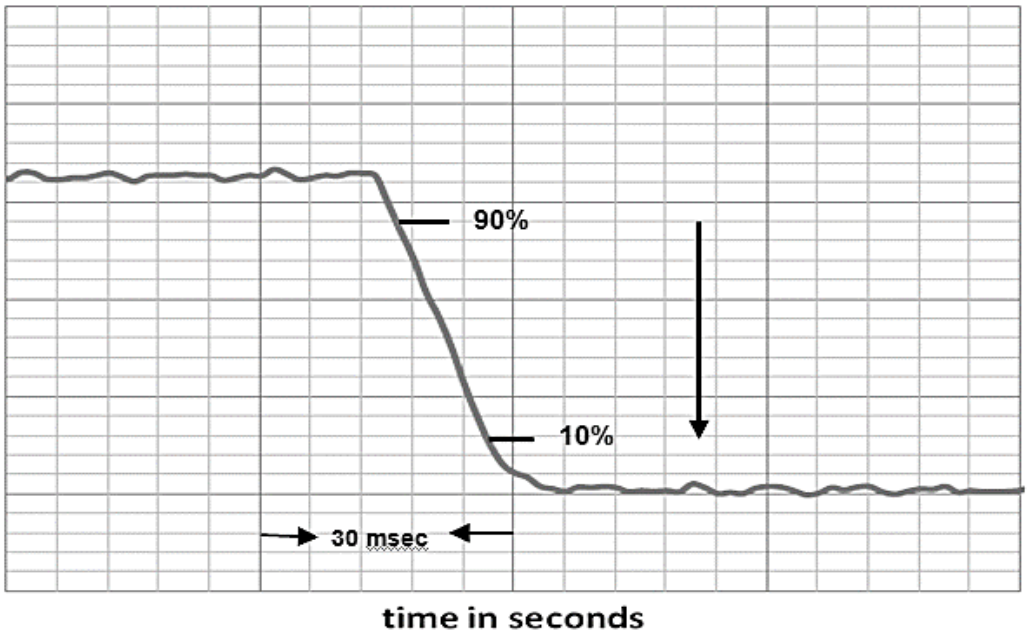

Figure 2-14: The response to a sudden decrease in pressure associated with the bursting of a balloon on the measurement of pressure

2.5.9 Data acquisition and storage

The data from the NM3 monitor was transferred as a digital signal through a RS232 interface. The data was transferred as an ASCII signal to a laptop computer (Dell, UK) which was preloaded with a customised data acquisition software (Spectra, version 3.0.1.4; Grove medical, London, UK). The Spectra software was a type of 'digital chart recorder' and was used to record signals from clinical transducers, patient monitors and life support equipment. In real time the software captured, displayed and performed complex analyses and displayed the results. It also marks events, replay and re-analyse data. Waveforms were recorded in real time, and displayed in graphical form. The display of recorded data was time-based. All datasets were stored on a customised Microsoft Access patient database, which could be reviewed and amended in real time without interruption to the data collection process. The

software was upgraded in December 2009 from the previous version to establish a digital interface with the NM3 monitor. The laptop computer recorded and displayed real time data traces to the clinicians during the resuscitation of preterm infants. The laptop computer was secured to the trolley by a laptop lock. The data stored in the laptop computer was encrypted and transferred on to a secure computer in the research office immediately after data acquisition.

2.5.10 Statistical analysis

Data were analysed for normality using the Kolmogorov-Smirnov, Shapiro-Wilk tests. Student's t-test was used to compare two normally distributed groups and ANOVA with post hoc correction used for more than two groups. Nonparametric data were analysed using the Mann Whitney U test and the Freidman's test for analysis of variance with Dunn's test for multiple comparison. The relationships between variables were examined using regression analysis and Spearman rank correlation, the Chi Squared and Fisher's Exact test were used where appropriate. Data were deemed significant if the p value was less than 0.05. SPSS for windows (version 20 SPSS Inc, Chicago IL, USA) and GraphPad Prism (version 3 for Windows, GraphPad Software, San Diego California USA) were used.

Chapter 3 : The first five inflations during resuscitation of prematurely born infants

The aim of this study was to use a respiratory function monitor in the delivery suite to assess the response of prematurely born infants to initial resuscitation, that is, the first five inflations delivered by face mask and t-piece. A respiratory function monitor was used to record the magnitude of the inflation pressures, inflation durations and expired tidal volumes. An additional aim was to determine any impact of the infant's respiratory efforts during the first five inflations on the expired tidal volume.

We hypothesised that the delivered inflation pressure, duration of inflation and expired tidal volumes will be variable during the first five inflations.

3.1 Patients and methods

The study was conducted at King's College and Guy's and St Thomas' NHS Foundation Trusts between February and July 2010. All infants born before 34 weeks of gestation were eligible for entry into the study unless they had major congenital anomalies. Ethical approval was given by the Outer North London Ethics Committee. The Committee required parental consent only for the analysis of the data; this was obtained once the mother was transferred to the postnatal ward. The monitoring equipment used and the routine resuscitation protocol are described in Chapter 2.

3.1.1 Sample size

The sample size of 30 with five repeated measures was used as it was feasible and the number of observations was sufficient to detect a reasonably small-single sample correlation of 0.55 (two-sided, $\alpha=0.05$, $\beta=0.90$). The correlation between the five repeated inflations was unknown at the outset (but

is reported here to inform future research), and the correlation that could be detected would be smaller than this.

3.1.2 Analysis

The first five inflations given to each infant via the face mask were analysed. The recordings were examined to determine if the infant had made an inspiratory effort during an inflation (Figure 3-1). Inflations with inspiratory efforts were described as ‘active’ and those without inspiratory efforts as ‘passive’. The overall results were analysed, and the active and passive inflations were analysed separately. An arbitrary tidal volume of 4.4ml/kg was used to define an ‘appropriate’ level of tidal volume, as this is twice the anatomical dead space(258). Expiratory volumes were analysed, as it was anticipated that there would be leaks around the face mask and hence the inspiratory volumes might be artificially high. The percentage of ‘face mask’ leak was calculated from the difference in the inspired and expired volumes expressed as a percentage of the inspired volume.

Differences in inflation pressure and expired tidal volume were assessed by one-way analysis of variance(ANOVA). Inflation pressure and expired tidal volume were positively skewed and so were log-transformed (natural log) for analysis. A value of 0.01 was added to all values for the expired tidal volume to deal with zeros. Random effects linear (logistic) models were used to analyse the continuous (binary) serial data and estimate the effects of inflation pressure and face mask leak on expired tidal volume. The results of the models are given as regression coefficients and 95% CI with the percentage of variability between subjects. All statistical analyses were carried out with STATA v 11.

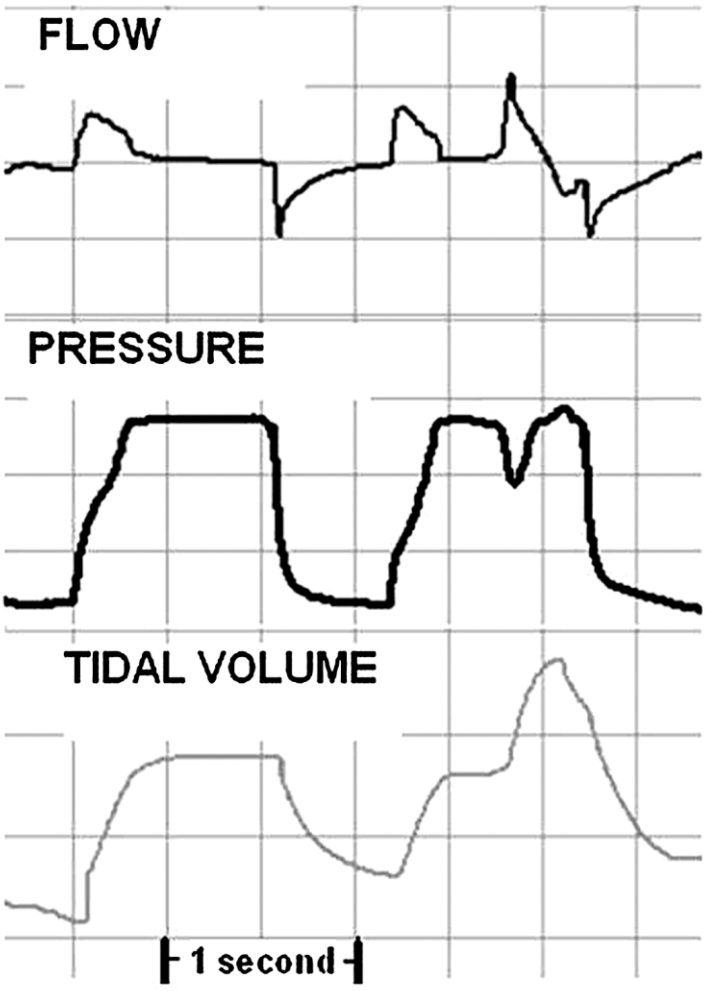

Figure 3-1 Recording of two inflations, a passive inflation (left) and an active inflation (right). Inflations with the infants own inspiratory efforts are described as 'active' and those without inspiratory efforts as 'passive'. During the positive pressure plateau of the active inflation, there is a negative deflection indicating the infant's inspiratory effort, which is associated with inspiratory flow and a greater tidal volume as compared with the volume of the passive inflation.

3.2 Results

Seventy-two infants of less than 34 weeks of gestation were born during the study period. The resuscitation monitoring equipment was available at 54 of the deliveries, but 12 of the infants did not need resuscitation at birth. Six deliveries were multiple births (one triplet pregnancy and five twin pregnancies), as only one respiratory function monitor was available at each hospital only the first infant born of each multiple birth was monitored. Five infants were intubated immediately after birth and so were excluded from this study. Thus, data from 30 infants were included in this study. The 30 infants had a median gestational age of 30 (range 23–34) weeks and the median birthweight of 1445 (range 596–2370) g, 17 (56%) were males and 23 (76%) had been exposed to antenatal

steroids. The majority (73%) were delivered by caesarean section. The median Apgar scores of the 30 infants were 6 (range 2–9) at 1 min and 9 (range 3–10) at 5 min. The results from four inflations could not be analysed due to the poor quality of the volume trace, the results from the other 146 inflations were analysed; 22 (15%) were active and 124 (85%) were passive. On no occasion was there more than one inspiratory effort during an inflation. Overall, the median peak pressure delivered during the first five inflation breaths was 23.7 (range 11.5–38.0) cm H_2O. On only seven inflations were the peak pressures above 30 cm H_2O, and this was during the resuscitation of two babies. The median peak inspiratory pressures for the active and passive breaths were similar, 24.3 (range 19.9–38.0) cm H_2O and 23.5 (range 11.5–37.5) cm H_2O, respectively. Overall, the median inflation pressure (peak pressure minus PEEP) used during the first five inflation breaths was 19.2 (range 11.5–32.4) cm H_2O, with no significant difference between the active and the passive inflations (ratio of geometric means 1.10; 95% CI 0.59 to 2.04; p=0.76)(Figure 3-2). Overall, the median expired volume was 2.5 (0–19.8) ml/kg. Expiratory flow occurred only early in expiration, suggesting that there was no leak around the face mask in expiration. The median expiratory volume of passive inflations was 2.1 (range 0–19.8) ml/kg and of active inflations was 5.6 (range 1.3–12.2) ml/kg (ratio of geometric means 1.85, 95% CI 1.18 to 2.89; p=0.007) (Figure 3-3).

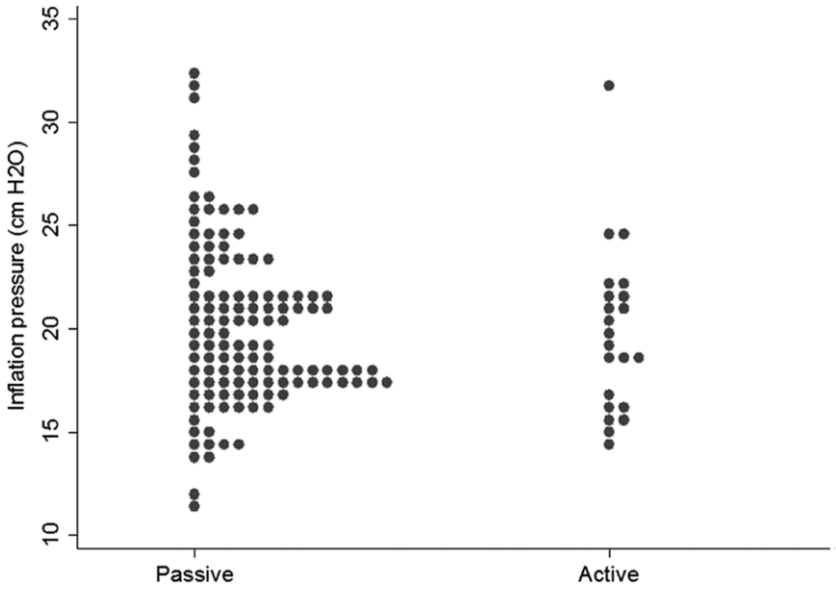

Figure 3-2: Dot plots of inflation pressure (PIP minus positive end expiratory pressure) for passive and active inflations showing values for individual infants. This shows the range of values (vertical axis) and the frequency with which each value occurs is depicted horizontally.

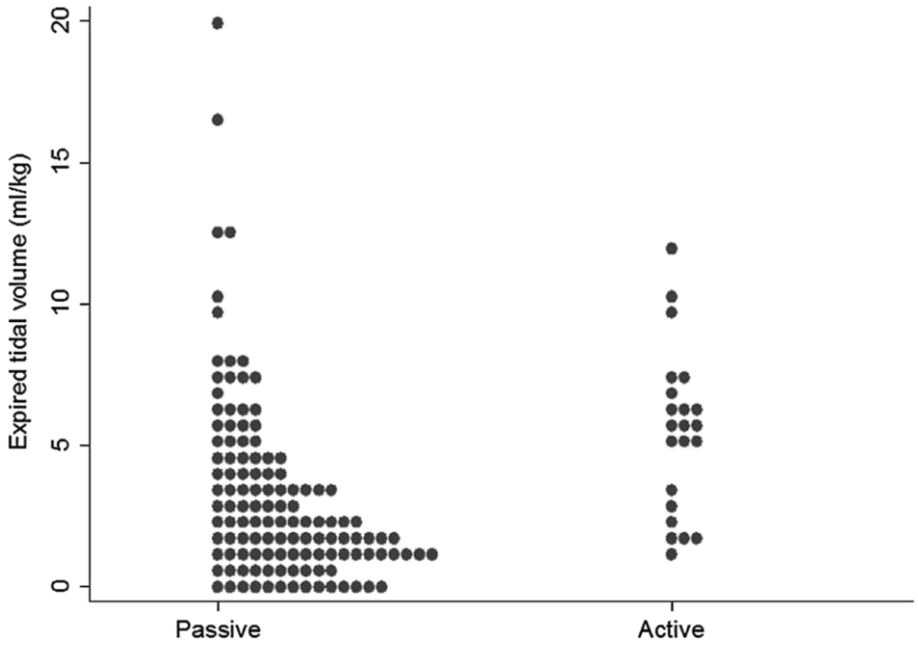

Figure 3-3: Dot plots of expiratory tidal volumes for passive and active inflations showing values for individual infants. This shows the range of values (vertical axis) and the frequency with which each value occurs is depicted horizontally.

The expired volumes were greater than 4.4 ml/kg in 30% of all inflations, in 68% of active inflations and in 22% of passive inflations ($p<0.01$). Overall, the median inflation time was 1.1 (range 0.25–3.7) s; 1.1 (range 0.64–3.7) s for active inflations and 1.0 (range 0.25–3.4) s for passive inflations, (ratio of geometric means 1.12, 95% CI 0.95 to 1.32; $p=0.20$). Overall, the median percentage of the leak around the face mask was 54.5% (range 0–100%), 34.5% (range 0–81.6%) for active inflations and 60.7% (range 5.2–100%) for passive inflations (mean difference in % leak 12.4%, 95% CI 0.9 to 24.0%; $p=0.0354$).

The inflation pressures were positively correlated (R^2 between subjects=0.19; $p=0.04$; regression coefficient (both variables on log scale) 2.21, 95% CI 0.09 to 4.33). The face mask leaks were negatively correlated [R^2 between subjects= 0.051; $p<0.001$, regression coefficient (expiratory tidal volume on log scale) 0.020, 95% CI 0.026 to 0.013] with the expiratory tidal volumes. Since the correlation coefficient of face mask leaks (0.051) is so small, it explains little of the variance between the two factors. There was no significant correlation between the inflation times and the expired tidal volumes (R^2 between subjects=0.05; $p=0.38$; regression coefficient (both variables on log scale) 0.21, 95% CI 0.25 to 0.67). Intra-class correlation coefficients were 0.929 (inflation pressure), 0.507 (expiratory tidal volume) and 0.406 (face mask leak).

3.3 Discussion

This study demonstrated that during the first five inflations delivered by bag and mask resuscitation of prematurely born infants, the expired tidal

volumes, inflation times and inflation pressures were very variable. This was despite all the clinicians having undergone a recognized resuscitation training course(178) and the neonatal unit having a standard resuscitation protocol. Our data highlight that, despite training, the clinicians can perform very differently during the stress of resuscitating prematurely born infants. The overall median expiratory tidal volume (2.5 ml/kg) was similar to the anatomical dead space (2.2 ml/kg)(259) and so unlikely to produce any alveolar ventilation. Upton et al(260) reported similar findings in intubated infants, but we highlight even lower tidal volumes. One reason may be that the current use of PEEP has effectively reduced the inflation pressure by 4 to 5 cm H_2O. Thus, although in our study, the mean peak inflation pressure was 23.6 cm H_2O, the use of PEEP resulted in a reduction in the 'effective' inflation pressure of about 20%. The inflations associated with the infant's respiratory effort (active inflations) had a median expired tidal volume of 5.6 ml/kg, but the median expired tidal volume for passive inflations was only 2.1 ml/kg. Those findings support the suggestion(148, 149, 261) that face mask resuscitation depends on the stimulation of Head's paradoxical reflex, rather than by achieving adequate tidal exchange per se. The higher expired tidal volumes of active compared with passive inflations would suggest that active inflations do not contribute more to the formation of a functional residual capacity.

Infants were eligible for entry into this study if they were born prior to 34 weeks of gestation without congenital anomalies and required face mask resuscitation rather than immediate intubation and ventilation or no resuscitation. Hence, in many respects they were a relatively homogeneous group. There were, however, a wide range of gestational ages and birth

weights, but a much larger study would be required to see if there were differences in the results in subgroup analysis by gestational age or birth weight. The other group of infants who were excluded were the second and third of multiple births, as only one set of equipment was available at each site.

A further study would be required to determine if prematurely born infants of multiple pregnancies respond differently to bag and mask resuscitation. The unit's protocol was to use 4–5 cm H_2O of PEEP which may have influenced variability in the results, but we are unaware of any evidence to support such a hypothesis. It has been reported (262)that 25% of infants suffered airways obstruction during face mask resuscitation. The definition of airways obstruction, however, included a 75% reduction in the expired tidal volume compared with a baseline of the expired tidal volumes of the 10 inflations prior to the obstructed inflation(262).It is possible that such results reflected large leaks, not least as mask leaks of up to 100% have been previously reported(235).Achieving an adequate seal during face mask resuscitation is crucial to its success. In a study (236)assessing the efficacy of resuscitation on manikins, the leaks did not vary significantly between masks, but overall were about 50%. It has been highlighted that training using manikins can result in a reduction of face mask leak(263), but whether this impacts on the performance under clinical conditions remains to be tested.

The use of a respiratory function monitoring during simulated neonatal resuscitation in 25 participants who had received training to improve their face mask technique was also shown to reduce the face mask leak from 27% to 11%.7 In a further study, written instruction and demonstration of the optimal

techniques of positioning and holding the face mask during manikin resuscitation reduced the face mask leak from 57% to 32% with one mask type and 55–33% with another face mask type(264). In our study, the median facemask leak during resuscitation of prematurely born infants was high (54.5%), but similar to that recorded in a previous study (51%)(262)and was significantly inversely correlated with the expiratory tidal volume.

In conclusion, this study demonstrates that although the clinicians were all trained according the NLS, UK guidelines, there were wide variations in inflation pressure, times and expired tidal volumes. A median inflation pressure of 23.6 cm H_2O was used which was in keeping with ILCOR guidelines, a significant correlation was observed between the inflation pressure and expired tidal volume during face mask ventilation ($r^2 = 0.19$, $p=0.04$) suggesting that there may be a need for higher inflation pressures during initial resuscitation in prematurely born infants.

Chapter 4 : Inflation times during the resuscitation of preterm infants and inflation flow times

4.1 Introduction

Studies of the resuscitation of term infants indicated that inflation pressures of 25–30 cm H_2O led to tidal volumes of less than 5 ml/kg and a functional residual capacity (FRC) was rarely formed before the infant made spontaneous breaths in association with lung inflations. Inspection of the tidal volume traces indicated that, although the inspiratory pressure plateau had been maintained for up to 1 s, the tidal volume had not reached equilibrium. When, however, a pressure of 30 cm H_2O was maintained for up to 5 s for the first inflation, the tidal volumes and FRCs generated were similar to those found in spontaneously breathing term infants(228). Those data led to guidelines recommending that the first five inflations given by a face mask resuscitation system should be maintained for 2 to 3 s. Although the International Liaison Committee recommendations of 2006 and 2010 advised that the risk and benefits of that practice have not been evaluated, prolonged inflations continue to be recommended. Data on the effects of the use of a prolonged inflation time during the resuscitation of prematurely born infants are limited. One small randomised trial found no effect on short or long-term outcomes when the first inflation was prolonged for either 2 or 5 s delivered via an endotracheal tube (230).

In a subsequent study, an inflation pressure of 20 cm H_2O maintained for 20 s was associated with a significant reduction in the need for subsequent intubation and use of surfactant and a lower incidence of bronchopulmonary dysplasia(232). In that study, in addition to the prolonged inflation, PEEP was used, and hence, the effect seen could also have been explained by the combination of the prolonged inflation and PEEP or indeed PEEP alone.

Currently, the recommendation in the UK for prematurely born infants is to follow the practice for term infants and use an inflation of 2–3 s for each of the first five inflations of face mask resuscitation(265). In an observational study of the resuscitation of prematurely born infants in the labour suite(266), we reported that, despite apparently adequate training on manikins, inflations were rarely maintained for more than one second. No significant correlation was found between the inflation times and the expired tidal volume, which led us to speculate that prolonging inflation times may not further improve ventilation during the resuscitation of prematurely born infants. To test that hypothesis, a further observational study was undertaken to determine whether there was a relationship between the inflation times and inflation flow times during resuscitation in the labour suite. If prolonged inflation times were to improve ventilation, then it would be expected that inflation flow would continue throughout inflation.

4.2 Materials and methods

The study was conducted at King's College Hospital and Guy's and St Thomas' NHS Foundation Trusts. Infants born before 34 weeks of gestation were eligible for entry into the study. Ethical approval was provided by the Outer North London Ethics Committee. The Committee required parental consent only for analysis of the data; this was obtained once the mother was transferred to the postnatal ward. The same equipment and resuscitation protocol were used as described in Chapter 2(Figure 2-2).

4.3 Analysis

The first five inflations delivered via the face mask were identified. Inflations associated with an infant's inspiratory effort were excluded from the analysis. The inflation pressure (peak pressure—PEEP), inflation time, inflation flow time and expired tidal volume were analysed. The inflation flow time was measured from the start of the positive deflection in the flow trace until the flow trace returned to zero or, in the presence of face mask leak, until the flow trace had dropped back to a plateau. Inflations during which there was a large leak (expiratory tidal volume <25% of the inspiratory tidal volume) were excluded from the analysis. The leaks were divided into constant and variable. A constant leak was defined as one in which the flow rate was constant during inflation, and a variable leak was defined as one in which the inspiratory flow varied during inflation. All inflation measurements were positively skewed and so presented as median with ranges for ease of interpretation. For analysis, it was necessary to log transform the data as the analysis requires normally distributed data. Random effects linear models were used to explore associations to take into account the repeated observations within subjects. Analyses were done using Stata v11.

4.4 Results

Forty infants were included in the study. They had a median gestational age of 30 (range 26–32) weeks and birth weight of 1,225 (range 878–1,525) g; 23 infants were male, 36 had been exposed to antenatal steroids, and 22 were delivered vaginally. The infants had a median Apgar score of 6 (range 4–8) at 1 min and 9 (range 7–9) at 5 min. Two hundred inflations were assessed, 35 were

excluded from the analysis as the infant's respiratory efforts coincided with the inflations, and none were excluded because of a large leak. In six infants, there was no leak; in 24, there was a constant leak; and in ten, there was a variable leak. The median inflation flow times for the three groups were 0.12, 0.11 and 0.13 s, respectively, indicating that the inflation flow times were not being underestimated in the presence of variable leak. Overall, the median inflation pressure was 17.6 (range 12.2 27.4) cm H_2O, inflation time (Ti) 0.89 (range 0.33–2.92) s, expiratory tidal volumes (VTE) 1.01 (range 0.02-11.41) ml/kg and inflation flow time 0.11 (range 0.04–0.54) s. In the infants in whom there was no leak, the median inflation pressure was 17.7 (range 14.4– 25.3) cm H_2O, inflation time 0.78 (range 0.46–1.62) s, expiratory tidal volumes (VTE) 1.1 (range 0.2–7.0) ml/kg and inflation flow time 0.11 (range 0.04–0.35) s, which did not differ significantly from the overall results.

There were no significant relationships between Ti and either the inflation flow time (p=0.83) or VTE (p=0.80) or between the inflation flow time and VTE (p=0.10). There was a significant but weak relationship between the inflation pressure and inflation flow time (R^2 =0.02, p=0.024) (Figure 4-1).

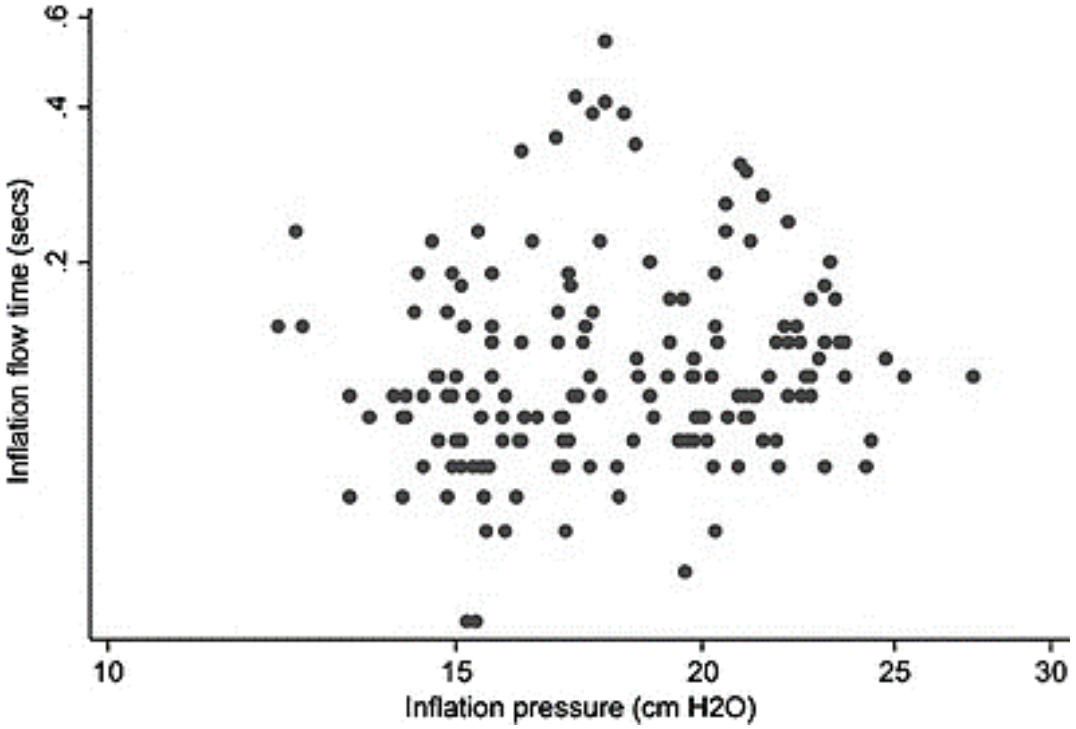

Figure 4-1: Scatter plot of the results of inflation flow time related to inflation pressure of all subjects. Data are plotted on a log scale to reflect the analysis performed. Overall R^2=0.02 and p=0.02 (derived from the random effects model).

4.5 Discussion

No significant correlations between the inflation time and the inflation flow time or the expired tidal volume were demonstrated. Indeed, the median inflation flow time was only 0.11 s, with a median inflation time of 0.89 s. Those results suggest that further prolongation of inflation time would not increase the inflation flow time. A wide variation in the inflation times was recorded, this has been previously reported and the inflation time shown to vary with operator experience and distraction(267) . In this study, all of the inflation times were below the recommended two seconds.

It has recently been suggested that 25% of infants suffer airway obstruction during face mask resuscitation (262). Airway obstruction, however, was defined as a 75% reduction in the expired tidal volume compared with a baseline of the expired tidal volumes of the ten inflations prior to the obstructed inflation(262). It is possible that those results reflect large leaks as mask leaks of up to 100% have been reported(235). In this study, we initially analysed the results only from inflations in which there was no leak, but then analysed inflations in which there were leaks, and our results remained unchanged. In this study, we used a t-piece device and a face mask to resuscitate the prematurely born infants; such a device has been shown in a comparative study to provide the most consistent peak inflating pressure(268).

In a study in which an anaesthetic rebreathing bag without a blow-off valve was used to resuscitate term born infants, the bag was squeezed sufficiently to produce visible chest wall movement. Inflation pressures of 50 cm H_2O maintained for 0.5 s resulted in inspiratory tidal volumes of 10–12 ml/kg and the formation of an FRC by the end of the first inflation(260). Those data suggest that high inflation pressures may be needed to generate adequate tidal exchange.

In this study, a significant, albeit weak, correlations between inflation pressure and inflation flow time was found. Those results suggest that the use of higher inflation pressures might have resulted in longer inflation flow times. In addition, unless sufficient inflation pressures are used to generate adequate tidal volumes, increasing the frequency of inflations would not improve gas exchange.

In conclusion, we have reported that clinicians maintained mean lung inflation times of 0.89 seconds which is much lower than the 2-3 seconds as recommended by the UK resuscitation council. The medial inflation flow times was only 0.11 s, with a median inflation time of 0.89 s. Furthermore, there were no significant relationships between inflation time and either the inflation flow time ($p=0.83$) or expired tidal volume ($p=0.80$) or between the inflation flow time and expired tidal volume ($p=0.10$). There was a significant but weak relationship between the inflation pressure and inflation flow time ($R^2 =0.02$, $p=0.024$) This suggests that prolonged inflation times would not lead to better tidal volume exchange during face mask resuscitation of prematurely born infants.

Chapter 5 : End tidal carbon dioxide levels during the resuscitation of prematurely born infants

5.1 Introduction

Immediately after birth, carbon dioxide elimination only occurs if there is effective ventilation of the lungs and associated vasodilation of the pulmonary vascular bed. In the absence of pulmonary vasodilation only 10% of the cardiac output is available to perfuse the lungs, greatly restricting the delivery of carbon dioxide (CO_2) to the lungs. Thus, assessment of expired CO_2 levels could be used to indicate that pulmonary vasodilation had occurred during resuscitation. Palme-Kilander et al. reported, in infants breathing spontaneously(269) and those who required intubation in the labour suite(175), that expired CO_2 was rarely detected until the infants had made a spontaneous breath, suggesting that the infant's inspiration influenced pulmonary vascular bed vasodilation. In those studies (269), however, expired gas was collected in 15 second aliquots and hence the temporal relationship between the first spontaneous breath and any change in the $ETCO_2$ levels could not be investigated. In this study, the temporal changes in $ETCO_2$ levels and the infant's respiratory efforts during face mask resuscitation in the labour suite were studied. The aim was to determine if the infant's first respiratory effort was associated with a rise in the $ETCO_2$ levels, suggesting that pulmonary vasodilation had occurred. A second aim was to determine whether the $ETCO_2$ levels remained elevated with subsequent inflations not associated with inspiratory efforts, as such data would suggest that the increase in the pulmonary blood flow was maintained.

We hypothesised that infants' respiratory efforts will immediately increase $ETCO_2$ levels and maintain higher levels with subsequent inflations.

5.2 Methods

The study was conducted at King's College and Guy's and St Thomas' NHS Foundation Trusts between March 2010 and December 2010. Infants born before 34 weeks of gestation were eligible for entry into the study. Infants who made an inspiratory effort immediately after birth and before the start of resuscitation were excluded. Ethical approval was provided by the Outer North London Ethics Committee. The Committee required parental consent only for analysis and reporting of the data, this was obtained once the mothers were transferred to the postnatal ward. The monitoring equipment and resuscitation protocol were as described in Chapter 2.

5.2.1 Analysis

The first five inflations given to each infant via the face mask were identified. As leak was expected, expiratory rather than inspiratory tidal volumes were measured. The inflations were subdivided into those in which the inflation was passive, that is not associated with the infant's respiratory efforts and those in which the infant made an inspiratory effort during the inflation (active inflation) as previously described (Figure 5-1).If the infant had not made a spontaneous respiratory effort during the first five inflations, subsequent inflations were examined and the first active inflation was identified. The tidal volumes and $ETCO_2$ levels of the two passive inflations before and after the first active inflation were compared with each other and with the first active inflation. The percentage leak associated with the two passive inflations prior to the active inflation was calculated by relating the expiratory volume to the inflation volume,

$$\left(\frac{TV_i - TV_e}{TV_i}\right) \times 100$$

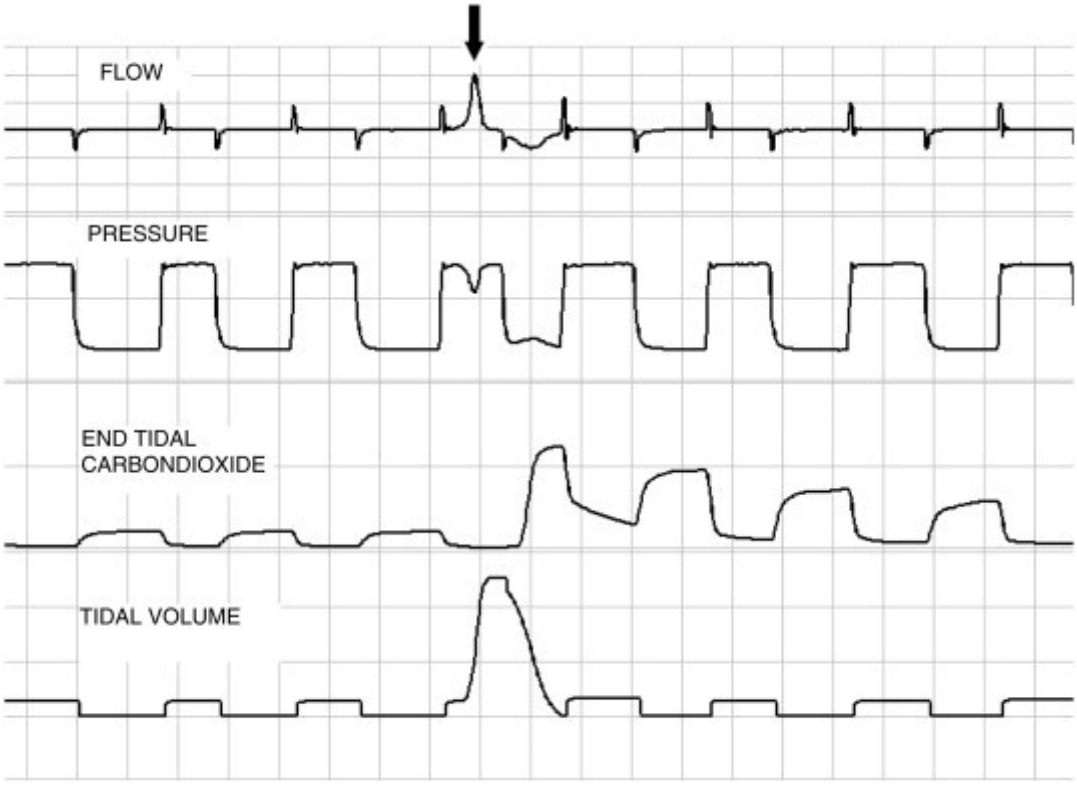

Figure 5-1: Trace showing the air flow, pressure, $ETCO_2$ and tidal volume levels during resuscitation of prematurely born infants. The infant's inspiratory effort is indicated by ↓ and is associated with a positive deflection in the airflow trace, negative deflection of the pressure trace and an increase in the $ETCO_2$ levels and tidal volume.

Further analysis was undertaken excluding inflations with expiratory tidal volumes of less than 2.2 ml/kg, which is the anatomical dead space, as ventilation of less than the anatomical dead space was unlikely to achieve any clearance of CO_2, even in the presence of normal pulmonary blood flow. The ratio of the $ETCO_2$ levels to the expiratory tidal volume expressed per kg body weight was then calculated for each infant for the first active inflation and the two passive inflations before and after the first active inflation.

The data were tested for normality using Shapiro–Wilk test and found not to be normally distributed. Differences, therefore, were assessed for statistical

significance using the Mann–Whitney U-test or Fisher's exact test as appropriate. Statistical analysis was performed using SPSS version 17 (SPSS Inc, Chicago, Illinois). A p value of < 0.05 was accepted as significant.

5.3 Results

Sixty-eight prematurely born infants had respiratory function monitoring during the study period. Data from 28 infants were excluded as the infants had made at least one visible respiratory effort prior to the delivery of the first inflation.

Forty infants with a median gestational age of 30 weeks (range 23–34) and birth weight of 1226g (range 545–2826) were included in the study. Nineteen of the 40 infants (47%) were males, 33 (83%) had been exposed to antenatal steroids and 19 (47%) were delivered by caesarean section. Their median Apgar scores were 6 at 1 min and 8 at 5 min. The mean time from the infant's delivery to the onset of resuscitation was 34 seconds (standard deviation (SD) ± 5.4). The median number of inflations to the first spontaneous inspiratory effort was 4 (range 0–77).

5.3.1 First inspiratory breath (FB)

Two infants made an inspiratory effort with the first inflation and five infants made an inspiratory effort with the second inflation, data for one inflation after the first spontaneous breath was not analysable. Thus, 71 passive inflations preceding the first active inflation (pre-FB), 40 active inflations (FB) and 79 after the first active inflation (post-FB) were analysed. $ETCO_2$ levels tended to increase with increasing expiratory tidal volumes (Figure 5-2).The median leak associated with the pre-FB inflations was 31% (1–71). The median expiratory

volumes of the active inflations (FB) and the subsequent two passive inflations (post-FB) were significantly higher than the two preceding passive inflations (pre-FB) ($p < 0.0001$, 0.001 respectively) (Table 5-1;Figure 5-3). The median FB and the post-FB $ETCO_2$ levels were both significantly higher than the $ETCO_2$ levels pre-FB ($p < 0.0001$, $p < 0.0001$ respectively), but not significantly different from each other ($p = 0.38$) (Table 5-1;Figure 5-4). There were no significant differences between the median inflation pressures of the active inflation and either the pre-FB inflations ($p = 0.79$) or the post-FB inflations ($p = 0.84$). The inflation pressures [peak pressure–positive end expiratory pressure (PEEP)] of the pre-FB inflations and post-FB inflations were similar ($p = 0.90$) (Table 5-1).

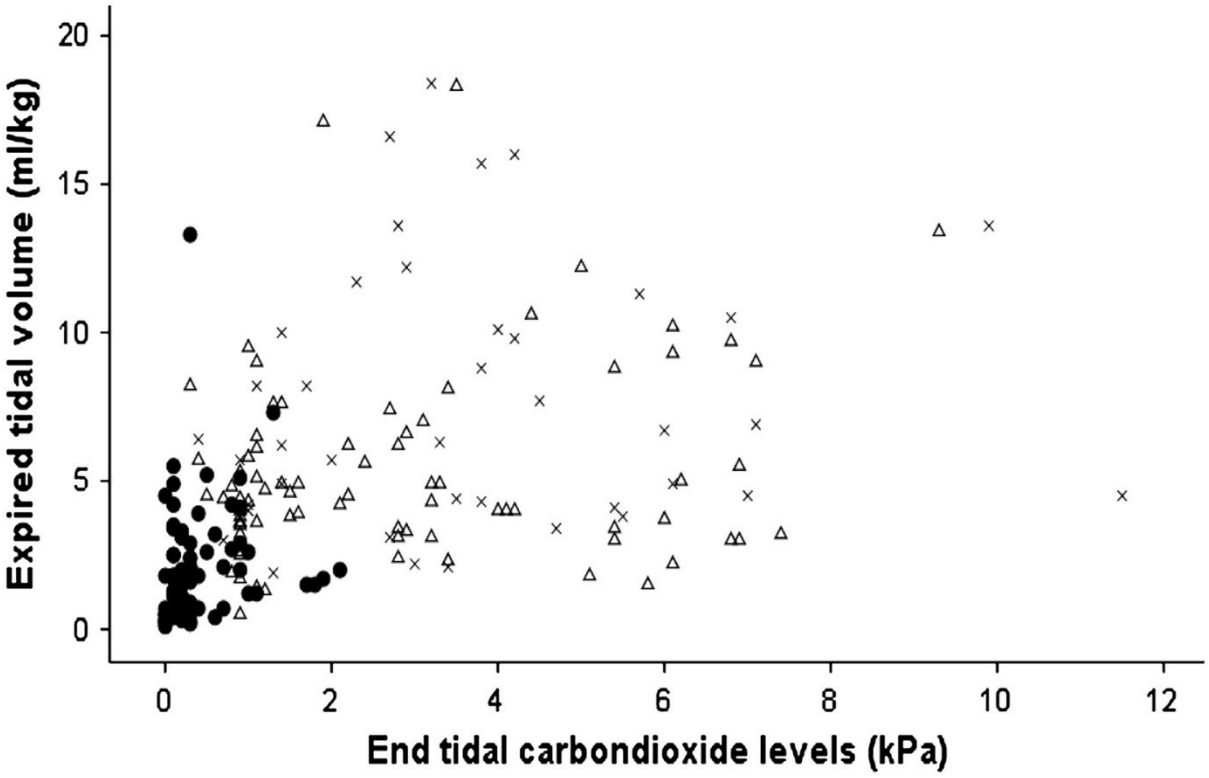

Figure 5-2: Scatter plot of expiratory tidal volumes and $ETCO_2$ levels. • pre-FB; × FB; Δ post-FB.

	Pre-FB	FB	Post-FB
Expired tidal volume (ml/kg)	1.8 (0.7–7.3)	6.3 (1.9–18.4)	4.5 (0.5–18.3)
$ETCO_2$ (kPa)	0.3 (0.1–2.1)	3.4 (0.4–11.5)	2.2 (0.3–9.3)
Inflation pressures (cm H_2O) **(Peak–PEEP)**	20.0 (13.8–26.7)	19.6 (13.7–25.9)	20.2 (13.4–25.9)

Table 5-1: Expired tidal volume, $ETCO_2$ levels and inflation pressures for the two passive inflations before the active inflation (pre-FB), the first active inflation (FB) and the two inflations after the first active inflation (post-FB).

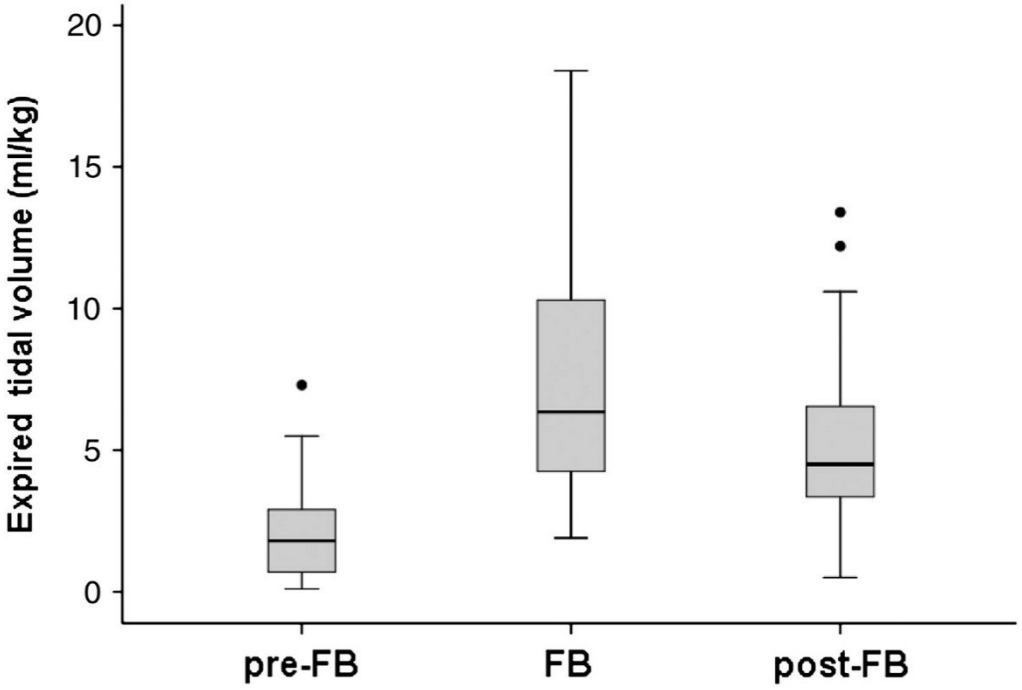

Figure 5-3:Box and whisker plot for tidal volume for the two inflations before the first active inflation (pre-FB), the first active inflation (FB) and the two inflations after the first active inflation (post-FB). The median and interquartile ranges are displayed.

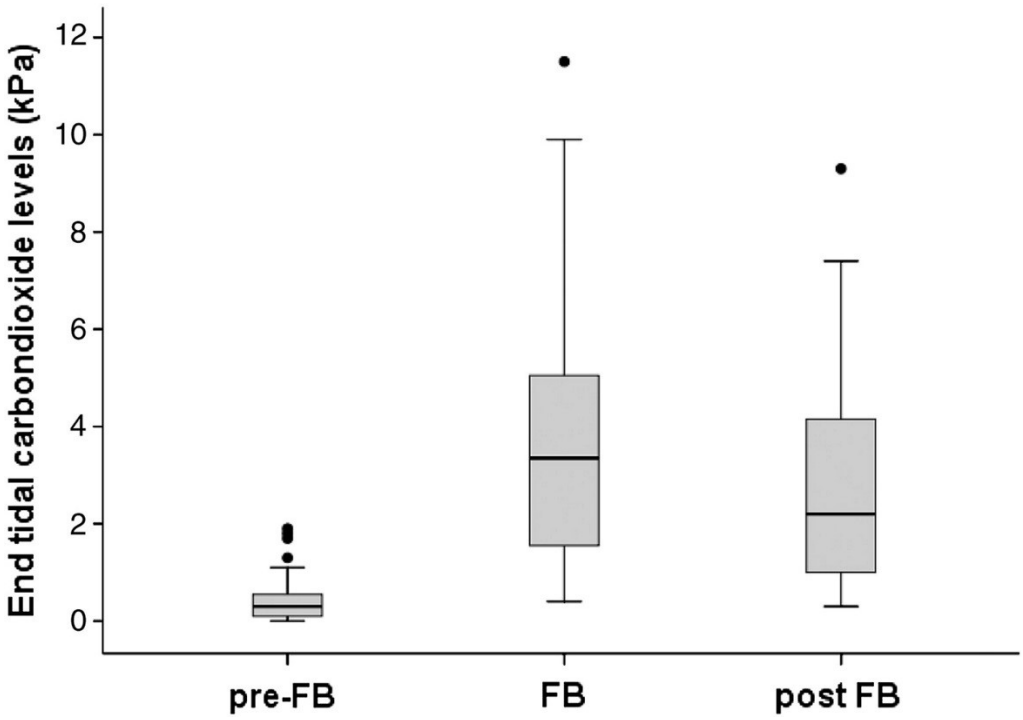

Figure 5-4:Box and whisker plot for $ETCO_2$ levels for the two inflations before the first active inflation (pre-FB), the first active inflation (FB) and the two inflations after the first active inflation (post-FB). The median and interquartile ranges are displayed.

When inflations associated with an expiratory volume of less than 2.2 ml/kg were excluded, there remained 25 passive inflations prior to the first active inflation (pre-FB), 38 active inflations (FB) and 72 passive inflations after the first active inflation (post-FB) for analysis. The median ratio of $ETCO_2$ levels to expiratory tidal volume for the passive inflations (pre-FB) was lower than that for the first active inflation (FB) ($p < 0.0001$). The ratio for subsequent passive inflations (post-FB) was similar to that for the active inflations (FB) ($p = 0.97$) (Table 5-2).

	Pre-FB	FB	Post-FB
Expired tidal volume (ml/kg)	3.4 (2.4–13.3)	6.5 (2.2–18.4)	4.7 (2.2–18.3)
$ETCO_2$ (kPa)	0.3 (0–1.3)	3.4 (0.4–11.5)	2.3 (0.3–9.3)
$ETCO_2$/TVe (kPa/ml/kg)	0.09 (0–0.38)	0.41 (0.06–2.56)	0.41 (0.04–2.77)

Table 5-2: Expired tidal volume, $ETCO_2$ levels and ratio of $ETCO_2$ levels to expired tidal volume for the two passive inflations before the active inflation (pre-FB), the first active inflation (FB) and the two inflations after the first active inflation (post-FB) (excluding inflations with tidal volumes less than 2.2 ml/kg).

5.4 Discussion

These results suggest that pulmonary vasodilation was occurring with the infant's first inspiratory effort during face mask resuscitation, as inflations preceding the infant's respiratory efforts resulted in minimal $ETCO_2$levels, whereas, the median $ETCO_2$ level associated with an active inflation was 3.4 kPa. Our findings are consistent with previous results(269) and (175). Palme-Kilander found that CO_2 could only be identified in the 15 second aliquot of expired gas in which spontaneous inspirations had occurred(269) and (175). In addition, we found that the two passive inflations following the active inflation had a median tidal volume of 4.5 ml/kg and an $ETCO_2$ level of 2.2 kPa despite no increase in inflation pressures. Those findings suggest that pulmonary vasodilation was maintained following the first active inflation. The higher expiratory tidal volumes of the passive inflations after compared to before the

first active inflation, despite no increase in the inflating pressures, suggest that there was also an improvement in lung mechanics after the first active inflation.

The increase in $ETCO_2$ levels with the active inflation, however, could also have been due to the increase in tidal volume. My findings suggest that both were involved as the $ETCO_2$ levels and expiratory tidal volumes were significantly higher with the first active inflation than before it (Table 5-1) and there was a significant correlation between the $ETCO_2$ levels and the expiratory tidal volumes (Table 5-2). When, however, considering inflations with expiratory tidal volumes greater than 2.2 ml/kg, the ratio of the $ETCO_2$ level to the expiratory tidal volumes was similar for the post-FB and FB inflations despite a lower tidal volume for the post-FB inflations indicating that $ETCO_2$ levels were not only influenced by tidal volume (Table 5-2*)*.

A limitation of the study is that particularly in very prematurely born infants it is not always possible to identify inspiratory efforts and so some of the infants may have made an inspiratory effort before the onset of face mask resuscitation. We, however, consider this as unlikely, as the $ETCO_2$ levels were always less than 2.1 kPa, with a median of 0.3 kPa before the first active inflation, i.e. the infant's inspiration occurring with an inflation. A further limitation of our study was that as the expiratory tidal volumes were often less than 2.2 ml/kg, the dead space of the face mask (1–2 ml) could have had a dilutional effect, so that the true $ETCO_2$ levels might have been up to 100% higher. This, however, would only have increased the median $ETCO_2$ levels to 0.6 kPa prior to the first spontaneous breath. Face mask leak could also have resulted in a reduction in the $ETCO_2$ levels. This proved not to be a problem, as examination

of the flow traces indicated that although leaks occurred during inflation, flow during the expiratory phase was consistently zero after tidal expiration despite a PEEP level of 4 to 5 cm H_2O. Nevertheless, it would be interesting to undertake a further study which focused on intubated infants, in whom leaks would be lower, to determine if our findings can be replicated.

Low CO_2 levels assessed by qualitative colorimetric measurements have been used to indicate airway obstruction during resuscitation (270)and (271). Airway obstruction, defined as at least a 75% reduction in the delivered expired tidal volume, has been reported to be common during face mask resuscitation of prematurely born infants(262). In this study, none of the infants had evidence of airway obstruction as previously defined(262) prior to the infant's first breath. Hence, we do not feel that airway obstruction explained the significantly lower $ETCO_2$ levels prior to the first active inflation. Some prematurely born infants are effectively resuscitated in the labour suite, that is, they achieve an adequate heart rate, without making a spontaneous breath. Under such circumstances, it is likely that the inflating pressures were of sufficient magnitude to result in adequate alveolar ventilation. We have previously found a positive correlation between the magnitude of inflation pressures and the expired tidal volumes(272).

Unless lung function is normal, $ETCO_2$ levels will be lower than arterial CO_2 levels, but the discrepancy is not so great as to explain the very low $ETCO_2$ levels we report before the first active inflation. The $ETCO_2$ levels associated with the first active inflation and the subsequent two passive inflations were still low compared to arterial CO_2 levels (5–7 kPa) reported

immediately after birth(273-276), despite tidal volumes similar to those reported in newborn infants after adaptation at birth. Those results then suggest that the pulmonary circulation in these prematurely born infants being resuscitated may have remained partially constricted. That hypothesis is consistent with the findings of Dawes et al.(277)and Cook et al.(278) who reported that inflation of the lungs of newborn lambs with 100% nitrogen led to a partial vasodilation of the pulmonary vasculature, but that further vasodilation depended on an increase in the arterial oxygen content. Our study design did not allow documentation of the time to the stabilisation of the $ETCO_2$ levels, so we are unable to comment as to whether or when further pulmonary vasodilation occurred.A clinical implication of our results is that the absence of detectable $ETCO_2$ levels may not necessarily indicate that an endotracheal tube has been misplaced, although this study needs to be repeated with intubated prematurely born infants. Our results could explain why on certain occasions $ETCO_2$measurements have failed to identify successful endotracheal intubation (279).

In conclusion, initial face mask resuscitation did not result in adequate alveolar ventilation or adequate gaseous exchange as determined by CO_2 clearance, unless the inflations were associated with an inspiratory effort by the infant. Our results suggest that the infant's inspiratory efforts led to an increase in $ETCO_2$ levels, partly as a result of the increase in tidal volume, but also as a result of pulmonary vasodilation. A key observation of our study, is that improved carbon dioxide elimination, likely due to pulmonary vasodilation, occurred at the onset of the infant's respiration.

Chapter 6 : Prematurely born infants' response to resuscitation via an endotracheal tube or a face mask

6.1 Introduction

The United Kingdom advisory document on resuscitation of new born infants (280) recommends that the initial five inflations during resuscitation should be provided via a face mask proceeding to intubation if the infant fails to respond with an increase in heart rate and oxygen saturation and the onset of regular respirations. Unfortunately, the use of a face mask during resuscitation is associated with leaks, which can be as large as 90% (262, 266). There is evidence that resuscitation via a facemask is not producing significant gaseous exchange, as in Chapter 5,(281) the expired carbon dioxide level rarely exceeded 0.5kPa during the first five inflations (281). Furthermore as in Chapter 3 (272) the median tidal volume delivered via a face mask, in the absence of inspiratory efforts by the infant, was in the region of 2.1ml/kg, which is less than the anatomical dead space. The expired tidal volume, however, was much larger if the infant made an inspiratory effort during the inflation(272). That results from Chapter 3 (272) supports the hypothesis that successful face mask resuscitation is dependent on stimulating the infants to make inspiratory efforts via the Head's paradoxical reflex (218). An alternative approach to the ILCOR recommendations is to proceed immediately to intubation, but there is a paucity of information on the efficacy of resuscitation of prematurely born infants via an endotracheal tube. Hoskyns and colleagues(218) reported that a tidal volume of greater than two anatomical dead spaces (i.e. 4.4ml) was only generated in five of 21 intubated, prematurely born infants during the first three inflations when an inflation pressure of 30 cm.H_2O was used(218). That inflation pressure is higher than the initial peak pressures of 20-25 cm.H_2O as currently recommended. That recommendation is the result of anxieties about the adverse effects of

volutrauma documented in animal models during resuscitation (184, 195). We hypothesised that, using currently recommended pressures, the first five inflations via an endotracheal tube would not produce expired tidal volumes greater than 4.4 ml/kg unless the infant made an inspiratory effort. In addition, we hypothesised that due to leak around the face mask(262, 266), the expired tidal volumes and end tidal carbon dioxide levels during resuscitation would be significantly lower for inflations delivered by a face mask rather than an endo tracheal tube.

Our aim, therefore, was to assess prematurely born infants' responses to resuscitation via an endotracheal tube or via a face mask. In particular, we wished to determine if the first five inflations via an endotracheal tube produced expired tidal volumes greater than 4.4 ml/kg. An additional aim was to determine if the outcome of the first active inflation, the infant's inspiratory effort coinciding with an inflation, was similar by resuscitation via an endotracheal tube or a face mask.

6.2 Methods

Prematurely born infants without congenital anomalies, requiring resuscitation at birth at King's College Hospital NHS Foundation Trust or Guy's and St Thomas' NHS Foundation Trust, London, UK were eligible for entry into the study. The study was carried out between March 2010 and February 2012. Consecutive infants born at less than 29 weeks of gestation requiring resuscitation at birth using either oral intubation with a Cole's endotracheal tube (size 2 or 2.5) or a face mask (Marshall size 0) and who had respiratory monitoring were entered into the study. The decision to proceed to immediate

intubation at birth was made by the clinical staff caring for the infants, on the basis that the infant had a heart rate of less than 60/min and no respiratory effort as determined by clinical observation.

The clinicians involved in the resuscitation of infants had all been trained in newborn life support and had received the Resuscitation Council, UK NLS provider certificates. Everyone had completed at least 12 month training on a tertiary level neonatal unit. They had also been trained to operate the respiratory function monitor. During resuscitation, the respiratory function monitor was set to display tidal volume, flow and inflation and positive end expiratory pressures. Ethical approval was granted by the Outer North London Research Ethics Committee who required parental written consent only for analysis of the data, which was obtained when the mother was on the postnatal ward. The resuscitation protocol and equipment used was as previously described.

6.2.1 Analysis

The inflation pressure [the peak inflation pressure minus the positive end expiratory pressure (PEEP)], inflation time, expiratory tidal volume, and leak and peak expiratory CO_2 levels for each inflation were recorded. The first active inflation (the infant's inspiratory effort coinciding with an inflation) was identified as we have previously described(266). When the infant makes an inspiratory effort during inflation there is a downward deflection in the airway pressure trace(266). Data from the first active inflation and the two inflations immediately before and after the active inflations were analysed. The time from the onset of resuscitation to the onset of the first active inflation and, when available, the

time from birth to the first active inflation were recorded. Some of the results from infants resuscitated by the face mask have been previously reported(266, 281), none of the data collected during resuscitation via an endotracheal tube have been previously reported.

6.2.2 Statistical analysis

Differences were assessed for statistical significance using either a paired Wilcoxon test or the Mann–Whitney U-test. Analysis was undertaken using IBM SPSS Statistics for Windows, version 20.

6.3 Results

Data were analysed from thirty-five infants (20 of whom required immediate intubation at birth) with a median gestation of 25 weeks. There were no significant differences in birth weight, gender, and use of antenatal steroids mode of delivery or Apgar scores at 1 and 5 min between the two groups (Table 6-1). Two of the infants receiving face mask resuscitation, but none of those intubated were observed to make a spontaneous breath before the onset of positive pressure ventilation. Two infants in the intubation group were extubated within 5 min of birth. The median time to intubation was 52 (range 39–78) s. Thirteen infants were intubated at the first attempt, four at the second attempt and three at the third attempt.

	ETT	Face mask	P
n	20	15	
Gestation age (weeks)	25 (23–27)	25 (23–28)	0.98
Birth weight (g)	670 (530–1035)	678 (545–1346)	0.56
Male	9 (45%)	5 (33%)	0.72
Antenatal steroids	17 (85%)	12 (80%)	0.98
Vaginal delivery	17 (85%)	12 (80%)	0.98
Apgar at 1 min	5 (2–8)	6 (2–9)	0.96
Apgar at 5 min	8 (4–10)	8 (5–10)	0.87

Table 6-1:Demographics by type of resuscitation. Data are presented as median (range) or n (%).

Before the first active inflation, only 27% of the infants receiving resuscitation via an endotracheal tube had expiratory tidal volumes greater than 4.4 ml/kg. Both groups had significantly higher expiratory tidal volumes with the first active inflation compared to before it [7.7 versus 2.8 ml/kg in the intubated infants ($p < 0.001$) and 5.2 versus 1.6 ml/kg in the face mask infants ($p < 0.001$)]. The end tidal CO_2 levels were significantly higher with the first active inflation than with the inflations before it and were 4.8 kPa and 0.36 kPa respectively in the intubated infants ($p < 0.001$) and for the infants resuscitated by a face mask 3.2 kPa and 0.2 kPa respectively ($p < 0.001$). All the infants responded to resuscitation and were transferred to the neonatal unit. None of the infants had a pneumothorax in the labour suite or within the first 24 h after birth developed stridor or a pneumothorax. There were no significant differences in the neonatal

outcomes of the two groups, which are only reported to give an indication of the severity of the infants' conditions (Table 6-2).

	ETT group	**Face mask**
n	20	15
Death	3 [15%] (respiratory = 2; sepsis = 1)	2 [13.3%] (respiratory = 2)
BPD (oxygen at corrected 36 weeks)	6 (35%)	5 (38.5%)
IVH (grades 3 and 4)	3 (17.6%)	2 (15.3%)

Table 6-2: Neonatal outcomes.

(BPD= Bronchopulmonary dysplasia; IVH = Intraventricular Haemorrhage)

The median inflation pressures and inflation times before during and after the first active inflation were similar with no significant differences between the two groups (Table 6-3). For the inflations before the first active inflation and the first active inflation, the expiratory tidal volumes ($p < 0.01$, $p < 0.01$ respectively) and the $ETCO_2$ levels ($p = 0.016$, $p = 0.026$ respectively) were higher in infants resuscitated via an endotracheal tube compared to those resuscitated via a face mask. The median leak level was significantly higher during resuscitation via a face mask compared to via an endotracheal tube ($p < 0.001$). The time to the first active inflation from the onset of resuscitation was shorter with resuscitation via an endotracheal tube rather than via a face mask ($p = 0.023$). The time from birth to the first active inflation which was available in 15 of the face mask group and 12 of the intubated infants was similar (means of 64 and 61 s respectively; $p = 0.42$).

	Face mask	ETT	P
n	**20**	**15**	
Inflation pressure (cm H_2O)			
Pre	16.9 (14.5–21.6)	17.2 (13.6–23.6)	0.14
Active inflation	16.9 (14.5–21.6)	17.2 (13.5–27.7)	0.47
Post	17.1 (14.5–21.6)	17.7 (14.9–22.4)	0.13
Inflation time (seconds)			
Pre	0.5 (0.3–1.3)	0.6 (0.3–2.1)	0.16
Active inflation	0.65 (0.5–1.1)	0.5 (0.3–2.1)	0.09
Post	0.62 (0.3–0.9)	0.4 (0.3–2.1)	0.1
Expiratory tidal volume (ml/kg)			
Pre	1.6 (0.2–13.3)	2.8 (0.2–9.9)	< 0.01
Active inflation	5.2 (3–13.6)	7.7 (4.2–15)	< 0.01
Post	4.3 (1.5–18.3)	6.0 (1.9–15)	0.18
ETCO2 levels (kPa)			
Pre	0.2 (0–0.9)	0.36 (0–1.8)	0.016
Active inflation	3.2 (0.4–6.9)	4.8 (0.53–11.5)	0.026
Post	2.8 (0.45–5.6)	3.4 (0.4–9.3)	0.49
Time from onset of resuscitation to the first active inflation (seconds)	24 (2–112)	12 (2–62)	0.023
Leak during the two inflations pre-FB, FB and post-FB (%)	44 (21–88)	14 (2–22)	< 0.001

Table 6-3: Comparison of inflation pressures, inflation time, expiratory tidal volume and ETCO2 levels by type of resuscitation. Data are presented as median (range).

6.4 Discussion

In this study assessing prematurely born infants' response to initial resuscitation via an endotracheal tube, expired tidal volumes frequently did not exceed the anatomical dead space of 2.2 ml/kg before the first active inflation, as we have previously demonstrated in infants resuscitated via a face mask(266). The $ETCO_2$ levels prior to the first active inflation in infants resuscitated by either method were close to zero indicating that effective ventilation was not occurring(281). The first active inflation was almost always associated with significantly higher expiratory tidal volumes and $ETCO_2$ levels in infants resuscitated either by an endotracheal tube or a face mask. It is possible that the increased dead space due to the respiratory monitor might have affected the $ETCO_2$ levels, but as the dead space was only 0.8 ml, the effect was likely to be small and was present throughout the study period so influencing the $ETCO_2$ levels before, during and after the first active inflation. In one study(270), airway obstruction was reported as common during face mask resuscitation, but this was evidenced by low CO_2 levels as detected by a colorimetric method. A low CO_2 level, however, could also indicate lack of pulmonary vasodilation. Our results suggest that neither face mask nor endotracheal resuscitation produces adequate ventilation before the first active inflation and that pulmonary vasodilation, a prerequisite for adequate CO_2 exchange, may be partly dependent on an active inflation. Recently, both Schilleman et al.(282) and Kaufman et al.(283) also found that expiratory tidal volumes during resuscitation were greater when associated with the infant's inspiratory efforts, confirming our previous results in infants resuscitated via a

face mask(266). Their studies, however, differed from the data we now report in that neither study (282) and (283) included intubated infants.

We focused on the first active inflation and the two breaths before and after it, as we have previously demonstrated the expired tidal volumes are significantly greater during an active rather than a passive inflation(266). In both groups, expired tidal volumes and $ETCO_2$ levels before the first active inflation were low. A possible explanation was the peak inflation pressure used, 20 to 25 cm H_2O. The advantages of using PEEP levels of 4–5 cm H_2O have been highlighted (169), but adding PEEP reduces the inflation pressure to as low as 15 cm H_2O. It has been claimed that PEEP pressures of 4 to 5 cm H_2O cannot be achieved using flows of 5 l/min (284). This was not our experience, we measured both the peak inflation and PEEP pressures in all infants and the required PEEP levels were always generated. The finding that the first active inflation was significantly earlier from the onset of resuscitation in the intubated infants, but there were no significant differences from the time of delivery to the first active inflation may reflect the additional time needed to pass an endotracheal tube. The initial inspired oxygen concentration was 21% in both groups, so differences in the inspired oxygen concentration did not account for the “delay” in the first active inflation in the face mask group.

Only two infants were observed to make respiratory efforts before resuscitation. This is in contrast to the observations of O'Donnell and colleagues(285) who, using video cameras and microphones, found evidence of respiratory efforts in 80% of prematurely born infants. This suggests that breathing efforts may have been missed by the clinical staff in our study. The

$ETCO_2$ levels in this study, however, were very low before the onset of the first active inspiration, 0.2 kPa in the face mask group and 0.36 kPa in those intubated at birth, indicating that any respiratory efforts missed by the clinical staff had not produced any effective respiratory exchange. The low $ETCO_2$ levels might be interpreted as incorrect placement of the endotracheal tube. Repetto and colleagues (286), however, found that $ETCO_2$ levels were unreliable in identifying misplaced endotracheal tubes. Similarly, Schmolzer and colleagues(287) evaluated air flow though the endotracheal tube and compared this to the colour change in the CO_2 detector. They reported that in approximately one third of the cases, CO_2 detectors did not correctly identify the tube placement. hence, we would not advise reintubation if any $ETCO_2$ was detected, this information can be misleading before the lungs are open for gas exchange.

Recently Hooper et al(288). demonstrated that monitoring changes in expired CO_2 provided important information to guide PPV immediately after birth. In the absence of mask leak or airway obstruction, an inability to detect expired CO_2 indicates that gas has not reached distal alveoli to allow gas exchange. They observed that increasing expired CO_2 levels in subsequent inflations indicated increasing aeration of distal gas-exchange regions. However, an increase in expired CO_2 was not directly associated with the functional residual capacity nor the tidal volume.

A possible explanation for the higher expiratory tidal volumes and $ETCO_2$ levels during resuscitation via an endotracheal tube is the significantly higher leak during face mask resuscitation. It is also important to recognise that

all infants in the study were intubated with a Cole's tube, hence may have lesser leak around the tube. These results may not be similar if a straight endo tracheal tube was used due to a higher leak in the later. As the infants in the two groups were of similar gestational ages and had similar Apgar scores at 1 and 5 min, we have no evidence that the intubated infants were "sicker". We would suggest that the higher $ETCO_2$ levels in the intubated infants reflect their higher expired tidal volumes. A recent randomised trial (289) of non-invasive respiratory support via either a face mask or a nasal tube in the delivery room was terminated early on the grounds of futility. Those results(289), therefore, do not suggest if we had used a different method of delivering non-invasive respiratory support compared to intubation it would have influenced our results.

Our study has strengths and some limitations. We studied consecutive infants who fulfilled the eligibility criteria and respiratory monitoring was available. We were able to monitor both expiratory tidal volumes and $ETCO_2$ levels in both intubated infants and those resuscitated by a face mask. Despite all those involved in the resuscitations having been appropriately trained and a protocol being available, the latter was not always followed. In particular, the inflation times during the first inflations rarely were the recommended 2 to 3 s. Since there was no randomisation of the infants to the intubation or face mask group, there could be selection bias on which infants were intubated immediately after birth, which could confound the results.

In conclusion, the first five inflations via an endotracheal tube rarely produced expiratory tidal volumes greater than 4.4 ml/kg. Resuscitation via an endotracheal tube or via a face mask was most effective, as indicated by higher

expiratory tidal volumes and $ETCO_2$ levels, when the infant's inspiratory effort was provoked. How prematurely born infants' inspiratory efforts are most effectively provoked during resuscitation requires further investigation. In particular, studies should be undertaken to try and reduce leak, which is a particular problem during face mask resuscitation. In addition, studies need to be undertaken to assess the response to longer inflation times (2 to 3 s) and to compare higher peak inflation pressures (25 cm H_2O) to 20 cm H_2O. Assessments should also include expiratory tidal volumes, $ETCO_2$ levels and the time to first active inflation.

Chapter 7 : Evaluation of respiratory function monitoring at the resuscitation of prematurely born infants

7.1 Introduction

Respiratory function monitoring has been used to assess how neonatal staff performs in “resuscitating” manikins(234, 263, 264, 290) and during the resuscitation of prematurely born infants(220, 235, 291) .The aim of this study was to determine whether trainees found respiratory function monitoring useful when resuscitating prematurely born infants in the labour suite, what decisions they made on the basis of the RFM and whether those decisions were evidence based.

We hypothesised that the trainees would find RPM useful during preterm resuscitation. The availability of real time information would assist them in decision making during preterm resuscitation.

7.2 Methods

Trainees who had undertaken respiratory function monitoring were asked to anonymously complete an electronic web-based survey in 2012 indicating their trainee level (Appendix I), how often they used the monitoring and if they found the monitoring helpful. Trainees less than four years from qualification were classified as “Junior” and the rest were classified as “Senior” trainees. They were also asked if they adjusted the peak inflation pressure based on the tidal volume and if so what tidal volume they considered appropriate from a range of 4 to 8 ml/kg. Further questions included whether they would reintubate if the expired carbon dioxide (CO_2) monitoring showed a little or no expired CO_2 or if, the chest was not moving but there was expired CO_2, would they reintubate or increase the inflation pressures. Another question was, if the oxygen saturation

was less than 85 % at 1 min, would they increase the inflation pressure or increase the inspired oxygen concentration to 30–50, 50, 50–75, or 75–100 %.

7.3 Results

Fifty-one of the 57 trainees (90%) completed the survey; approximately half were junior trainees that are less than 4 years from qualification. Forty-one percent had used the monitoring between one and five times; 49 % between five and ten times; 8 % between 10 and 15 times; and 1 % more than 15 times. Thirteen found it extremely easy, 35 easy, and three hard to set up.

Eighty-three percent said they found the delivery of tidal volume helpful and 58 % said they adjusted the peak inflation pressure based on the tidal volume recorded by the monitor. A range of tidal volumes was considered adequate by the trainees: 5 ml/kg (52 %), 4 ml/kg (33 %), 6 ml/kg (13 %), and 7 ml/kg (2 %).

If the end tidal carbon dioxide monitoring showed a little or no expired CO_2, 30 trainees said they would reintubate. Thirty two said that they would not reintubate but would increase the inflation pressures if the chest was not moving, but there was expired CO_2; a third of junior trainees said they would reintubate.

If the oxygen saturation monitoring showed the SaO_2 was less than 85 % at 1 min, no senior trainee said they would increase the inspired oxygen concentration, but 50 % of junior trainees said they would increase the inspired oxygen to between 30 and 50 % ($n = 10$); to 50 % ($n = 13$), to between 50 and 75 % ($n = 5$), and to between 75 and 100 % ($n = 4$).

7.4 Discussion

To my knowledge this is the first study evaluating RFM in clinical use. It has demonstrated that the usefulness of respiratory function monitoring during neonatal resuscitation, however this is dependent on the trainee's level and their response to tidal volume titration and use of oxygen is often not evidence based. This could also due to the lack of robust evidence for tidal volume and oxygen levels during preterm resuscitation. Although animal studies have demonstrated that high rather than low levels are associated with poorer outcomes (185), but have not investigated volume targeted levels within the tidal volume range.

In a study evaluating tidal volume levels in spontaneously breathing preterm infants, a wide range between 4-8 mls/kg are being reported(123). This is may be a reason for the wide levels of tidal volumes considered by the clinicians in our study, however majority considered 5mls/kg to be appropriate. This is despite the studies of prematurely and term born infants during ventilation on the neonatal unit demonstrating that volume targeted levels (VT) 6 ml/kg rather than lower volume targeted levels were associated with both lower amounts of desaturation (292)and levels of inflammatory markers (292).In addition, the work of breathing, as determined by measurement of the pressure time product, was only less at 6 ml/kg than as baseline (that is no volume targeting) both during weaning and acute respiratory distress in prematurely born infants(293, 294).These variations in tidal volumes reported in preterm studies leads to uncertainty amongst clinicians on the levels of tidal volume targeting during resuscitation of prematurely born infants.

The majority of trainees reported that they would reintubate if the end tidal carbon dioxide monitoring showed a little or no expired CO_2. This is done despite understanding that expired CO_2 levels may not be detectable in poor or no cardiac output states. One study(270) evaluating the use of expired CO_2 levels during preterm resuscitation, suggested that many infants during positive pressure ventilation in the labour suite have airway obstruction as detected by the absences of expired CO_2, however this cannot differentiate circulatory failure. It has subsequently been accepted that such device measuring expired CO_2 cannot differentiate between airway obstruction and circulatory failure(295). In Chapter 5, I have demonstrated that the presence of expired carbon dioxide may reflect pulmonary vasodilation occurring with the onset of the infant's respiratory efforts (281).

Subsequently, in rabbits, Hooper and colleagues, with phase contrast X-ray imaging, demonstrated that that expired CO_2 levels closely correlated to lung volumes at end inflation and were first detected when approximately 7 % of the distal lung volumes were aerated(288) . In the same study, they reported that an increase in expired CO2 was not directly associated with the functional residual capacity or the tidal volume during resuscitation of preterm rabbits. In a further study by Schmolzer et.al on preterm infants, they reported that expired CO_2 levels during the preterm resuscitation could reflect the degree of lung aeration based on the tidal volume levels associated with expired CO_2. In addition, expired CO_2 levels in prematurely born infants also correlated with tidal volumes (296). Those data suggest that better lung aeration with higher lung inflation pressure may be necessary, rather than reintubate in some circumstances like very low lung compliance secondary to severe surfactant

deficiency. Senior rather than junior trainees increased the inflating pressure if expired CO_2 was detected, but there was no chest movement, which given the above evidence is appropriate.

Pulse oximetry, if placed immediately after birth, can give a signal within 90 s(297). Recent studies have reported a wide range of pre-ductal SpO_2 levels in newborns that do not need resuscitation. They reported that there was a steady increase in oxygen levels during the first 10 min(164). At 1 min, the median oxygen saturation is 66 % (10th and 90th centiles; 33 and 85 %), at 5 min is 89 % (72 and 97 %), and at 10 min is 96 % (87 and 99 %)(297). Babies born prematurely or by caesarian section have lower SpO_2 levels which increase more slowly. An algorithm has been developed which is adapted by ILCOR and is currently advocated for the use in oxygen titration during preterm resuscitation. Nevertheless, the junior trainees stated that they would increase the inspired oxygen concentration to a variety of levels if at 1 min the SpO_2 was less than 85 %.

This study has a number of strengths and some limitations. All of the trainees surveyed had been trained according to UK guidelines and in the use of the respiratory function monitoring. The survey was completed anonymously so there was no pressure on individual trainees, to give particular responses. The trainees' responses, particularly those of the junior trainees reflected a lack of evidence-based guidelines, but also that they were unaware of certain aspects of the literature. The study was carried out in two tertiary centres, but the trainees had worked at various neonatal units as part of their structured training programme.

In conclusion, this study has demonstrated that respiratory function monitoring during neonatal resuscitation is dependent on the trainee's level and that their response is often not evidence based. The majority of clinician's reported that the display of tidal volume was very useful and more than half of them informed that they would titrate the expired tidal volume to 5-6ml/kg by modifying the peak pressure.

Chapter 8 : Survey of UK newborn resuscitation practices

8.1 Background

Surveys of newborn resuscitation practices (172-174, 204) have revealed differences between and in countries, but the equipment and techniques used in the UK are guided by the UK Resuscitation Council, and staff involved must undertake a newborn life support course(178).The course teaches the knowledge and skills required to undertake a structured approach in the management of a newborn infant during the first 10-20 minutes in a competent manner. The staff are taught to understand the processes underlying apnoea, bradycardia and poor condition at birth. They are expected to be competent in practical airway management and ventilatory support. We hypothesised, therefore, that in the UK there would be consistency of practice regardless of the level of neonatal care, and our aim was to test this hypothesis.

8.2 Methods:

A questionnaire (Appendix II) was sent to the lead paediatrician of 212 hospitals with newborn units. The survey was undertaken between July 2011 and October 2011.The 2010 ILCOR recommendations(178) were in place during the survey period. Differences in resuscitation practices according to the level of neonatal care were assessed for statistical significance using the χ^2 test.

8.3 Results

There was an 85% response. The majority of hospitals who responded were neonatal intensive care units (NICUs) (93%) and local neonatal units (LNUs) (98%), but only 40% of those with special care units (SCUs) replied. In most

hospitals (90%), resuscitation was performed in the delivery room, but a side room was used in 6% and in 4% for infants born by caesarean section.

A pressure-controlled T-piece device with positive end expiratory pressure (PEEP) was the commonest mode (86%) of providing positive pressure ventilation (Table 8-1). There was, however, variation in the PIP used with different levels of neonatal care, for term ($p<0.001$) and prematurely born infants ($p<0.001$). There was also a difference in the level of PEEP used with different levels of neonatal care for term ($p<0.001$) and prematurely born infants ($p<0.001$). Oxygen blenders were more commonly used in hospitals with NICUs ($p<0.001$). A greater proportion of hospitals with NICUs initially used an FiO_2 of 0.21 for infants born at term ($p<0.001$) and prematurely born infants ($p=0.001$).

	SCU (N=41)	LNU (N=81)	NICU (N=58)
Positive pressure ventilation			
Equipment			
T-piece with PEEP	37 (90.2%)	66 (81.5%)	52 (89.7%)
SIB with PEEP valve	2 (4.9%)	6 (7.4%)	3 (5.2%)
SIB without PEEP valve	2 (4.9%)	9 (11.1%)	3 (5.2%)
Maximum PIP (cm H_2O) used for term born infants			
25–30	27 (65.9%)	71 (87.7%)	50 (86.2%)
20–24	12 (29.3%)	9 (11.1%)	5 (8.6%)
15–19	1 (2.4%)	1 (1.2%)	1 (1.7%)
No data	1 (2.4%)	0 (0%)	2 (3.4%)
Maximum PIP (cm H_2O) used for prematurely born infants			
25–30	5 (12.2%)	5 (6.2%)	3 (5.2%)
20–24	30 (73.2%)	69 (85.2%)	51 (87.9%)
15–19	4 (9.8%)	1 (1.2%)	2 (3.4%)
No data	2 (4.9%)	6 (7.4%)	2 (3.4%)
Set PEEP (cm H_2O) for term born infants			
No PEEP	8 (19.5%)	13 (16%)	3 (5.2%)
2–3	2 (4.9%)	3 (3.7%)	1 (1.7%)
4–5	27 (65.9%)	63 (77.8%)	48 (82.8%)

	SCU (N=41)	LNU (N=81)	NICU (N=58)
6–8	1 (2.4%)	0 (0%)	4 (6.9%)
No data	3 (7.3%)	2 (2.5%)	2 (3.4%)
Set PEEP (cm H_2O) for preterm infants			
No PEEP	8 (19.5%)	10 (12.3%)	1 (1.7%)
2–3	2 (4.9%)	4 (4.9%)	1 (1.7%)
4–5	26 (63.4%)	63 (77.8%)	50 (86.2%)
6–8	2 (4.9%)	0 (0%)	4 (6.9%)
No data	3 (7.3%)	4 (4.9%)	2 (3.4%)
Oxygen blender used	23 (56.1%)	55 (67.9%)	51 (87.9%)
Initial set FiO_2 for resuscitation of term infant			
0.21	13 (31.7%)	32 (39.5%)	49 (84.5%)
0.3–0.5	6 (14.6%)	13 (16%)	4 (6.9%)
1	2 (4.9%)	6 (7.4%)	0 (0%)
No data	20 (48.8%)	30 (37%)	5 (8.6%)
Initial set FiO_2 for resuscitation of preterm infant			
0.21	10 (24.4%)	18 (22.2%)	25 (43.1%)
0.3–0.5	10 (24.4%)	31 (38.3%)	27 (46.6%)
1	1 (2.4%)	3 (3.7%)	1 (1.7%)
No data	20 (48.8%)	29 (35.8%)	5 (8.6%)
Oxygen saturation monitoring (term infant)	14 (34.1%)	33 (40.7%)	24 (41.4%)
Oxygen saturation monitoring (preterm infant)	17 (41.5%)	53 (65.4%)	41 (70.7%)
Temperature monitoring	13 (31.7%)	17 (21%)	7 (12.1%)
CO2 detectors	4 (9.8%)	16 (19.8%)	14 (24.1%)
Polythene bag for preterm<28-week gestation	38 (92.7%)	77 (95.1%)	56 (96.6%)
Adrenaline in less than 24 week gestation	5 (12.2%)	3 (3.7%)	6 (10.3%)
Adrenaline in 25–28 week gestation	25 (61%)	58 (71.6%)	43 (74.1%)
Sodium bicarbonate (in all infants)	17 (41.5%)	46 (56.8%)	27 (46.6%)

Table 8-1: Resuscitation practices based on the level care provided by the hospital

SCU: special care units; LNU: local neonatal unit; NICU: neonatal intensive care unit; PEEP: positive end expiratory pressure; PIP: peak inflating pressure; SIB: self-inflating bag

Use of oxygen saturation monitoring varied significantly between hospitals with different levels of neonatal care for term ($p=0.005$) and prematurely ($p=0.002$) born infants. Temperature and expired carbon dioxide (CO_2) monitoring were used in a minority of hospitals, with significant variation between the level of neonatal care provided ($p<0.01$). In the majority of hospitals (95%), prematurely born infants were placed in a plastic bag.
In a greater proportion of hospitals (70% vs 7.8%), epinephrine was given for resuscitation of infants born between 25 and 28 weeks of gestation compared with those born at <25 weeks ($p<0.001$). In all hospitals, a senior trainee, a junior trainee and a neonatal nurse attended deliveries of prematurely born infants. Consultants routinely attended deliveries of infants in 87% of hospitals for infants born at less than 24 weeks of gestation, almost all consultants in SCBU (97%) and LNU (93%) attended and only 80% of NICU consultants attended the delivery. In 25-28 weeks gestation birth, consultant attended the delivery in 68% of the units, of which 78%, 71% and 51% were from SCBU, LNU and NICU respectively. In 29 to 36 weeks gestation birth only 17% of deliveries were attended by a consultant. A transport incubator was used in 44% of hospitals, a resuscitaire with T-piece or self-inflating bag by 44% and 12% used either.

In conclusion, with the exception of monitoring equipment and the use of resuscitation drugs, this survey highlights that the recommendations of the UK Resuscitation Council are followed in the majority of hospitals, but the aspects of practice differed according to the level of neonatal care provided.

Chapter 9 : Discussion

The studies undertaken for this thesis used a novel way of monitoring, to understand physiological responses during the resuscitation of prematurely born infants. Clinicians attending preterm delivery are guided by the ILCOR recommendations, but these are not always based on evidence from clinical studies. At birth, the lungs of preterm infants are vulnerable, yet little distinction has been made between ventialtory approaches in term and prematurely born infants. The general aims of this thesis was to gather data that could lead to a better understating of the physiological responses following premature births and improve respiratory support for these vulnerable group of infants. This could be a knowledge base for developing large randomised control trials.

Ventilation strategies in preterm infants has been least studied and the guidance has been extrapolated from studies on term born infants or mammals. It is now well established that large lung inflations can induce trauma to the preterm lung. Ventilation strategies include, limitations of peak inspiratory pressure to 20-25 cm H_2O and using prolonged inflation times to establish an FRC.

In our study (**Chapter 3**), although the recommended peak inspiratory pressures were used, clinicians never achieve the recommended lung inflation times. These lung inflations rarely achieved adequate tidal volumes(>4.4ml/kg) until the infant commenced breathing. We did observe a significant correlation between the inflation pressure and expired tidal volume during face mask ventilation (r^2 = 0.19, p=0.04), suggesting that there may be a need for higher inflation pressures during initial resuscitation of prematurely born infants. It is also important to further explore the role of pulmonary reflexes during preterm

resuscitation. Currently, expired tidal volumes are measurable and has been used as an indirect marker for adequate lung inflation immediately, however this does not inform the formation of FRC.Neverthless, with current technological, this may be possible in the near future. Meanwhile, clinical studies using various lung inflation pressure could inform the effectiveness of such interventions on the formation of FRC in preterm infants.

Clinicians hardly maintained a sustained lung inflation during all our studies. This intervention has been demonstrated to influence FRC formation in animal studies, however this is yet to be established in preterm infants. In our study (**Chapter 4**), there were no significant relationships between inflation time and either the inflation flow time ($p=0.83$) or expired tidal volume ($p=0.80$) or between the inflation flow time and expired tidal volume ($p=0.10$). While analysing the physiological traces, we observed that the flow drops to zero as soon as the peak pressure is reached. This suggests that prolonged inflation times would not lead to better tidal volume exchange during face mask resuscitation of prematurely born infants. Currently, large multicentred randomised controlled trials are recruiting patients and we await the outcomes of these trials.

Gas exchange during any resuscitation is reflected by the levels of expired CO_2, so far this has been used only to estimate correct endo tracheal tube position during preterm resuscitation. The expired CO_2 levels are influenced by the lung inflation and pulmonary artery perfusion, with less understanding of the later. We evaluated (**Chapter 5**) the expired CO_2 levels and observed that end-tidal CO_2 levels were significantly higher ($p<0.001$) when inflations were

associated with the infants' respiratory effort. This was also associated with significantly higher levels of expired tidal volume. This likely indicates that pulmonary blood flow increases with the onset of spontaneous respiratory efforts. Measuring the volume of expired CO_2 (volumetric CO_2) may be a surrogate marker of lung aeriation which needs to be evaluated in future studies.

Face mask leak has a negative effect on the efficacy of resuscitation and high face mask leaks up to 75% was observed in some of the infants studied for this thesis. We compared the efficacy of resuscitation though a face mask and endotracheal tube (**Chapter 6**). Tidal volume and expired CO_2 were significantly higher in the ET group. However expiratory tidal volumes rarely were greater than 4.4 ml/kg unless associated with infants own inspiratory efforts. Similarly, the expired CO_2 levels were higher following the infants own inspiratory effort. This suggests that mechanisms that stimulates infants' own effort will improve the efficacy of preterm resuscitation, hence further research in this field is necessary.

Respiratory function monitoring has influenced newborn resuscitation training and more recently has been used in monitoring preterm resuscitation. In our survey (**Chapter 7**) aimed to determine the usefulness at preterm resuscitation, the clinicians reported it to be useful and more than half of them informed that they would titrate the expired tidal volume to 5-6ml/kg by modifying the peak pressure. It is important to further study the short and long term outcomes of infants whose respiratory functions were monitored during resuscitation.

9.1 Strengths and weakness of the studies

The study participants were all less than 34 weeks of gestation and 87% of the infants were exposed to antenatal steroids, hence they were relatively a homogenous group, infants were studied sequentially. There was only one monitor available at each site hence in multiple pregnancies only the first born infant received monitoring. Hence, a limitation is that these data do not represent the 'whole' population of preterm infants.

The clinicians were trained to use and record data on the RFM, but did, as shown by the results, did not always follow guidelines. Nevertheless, this gave the opportunity to analyse different levels of inflation time and pressure. Since it was a prospective study the real time feedback from the RFM may have influenced some of the results.

9.2 Subsequent studies to the initiation of this thesis

Currently, the adequacy of inflation pressures during resuscitation is based on the observation of chest rise during lung inflation. In a observational study, Poulton et al(220) compared chest rise observed from two different angles (head view versus side view) and different level of experience (junior staff versus senior staff). Overall the accuracy of clinical assessment of chest wall movement was poor and did not appear to be influenced by either the observers' position or the level of experience. Hence, clinical assessment on its own can lead to delivery of inadvertently high or low tidal volume during preterm resuscitation.

Some studies (289, 298) have used a PIP of 30 cm H_2O during resuscitation but did not report tidal volume levels during the initial lung inflations. In the study

described in Chapter 4 it was highlighted that clinicians rarely used inflation times beyond the recommended two seconds. Importantly, there was no significant correlation between the inflation times and tidal volume (p=0.83).

In a recent study, Lista and colleagues (299) compared a group of premature infants treated with sustained inflations (15 seconds) to a historical cohort treated with CPAP at 5 cm H_2O. They reported the “sustained-inflations group” was less likely to require mechanical ventilation or to develop Broncho pulmonary dysplasia(BPD). The study, however, was not prospective or randomized, which limits its usefulness. More recently, the same group, , randomized 291 preterm infants (25–28 weeks’ of gestation) to either a sustained inflation of 25 cm H_2O for 15 seconds, followed by CPAP or CPAP alone in the delivery room, both delivered via a mask and a T-piece resuscitator. The primary endpoint was need for mechanical ventilation in the first 72 hours after birth. Secondary endpoints included the need for and duration of respiratory support and survival without BPD. They reported that fewer infants were ventilated in the first 72 in the sustained inflation group than in the control group (53 versus 65%; p = 0.04). In contrast to their earlier retrospective study, there was no significant difference in survival or the rate of BPD. Pneumothorax was seen in 6% in the sustained inflation group and 1% of the controls (p = 0.06).

Monitoring exhaled CO_2 during newborn resuscitation has been advocated for correct ETT positioning (170). Recently, Schmolzer et al(298) aimed to measure changes in exhaled carbon dioxide and tidal volume to assess lung aeration in preterm infants requiring respiratory support immediately after birth.

They reported the expired CO_2 levels in 31/51 preterm infants who were spontaneous breathing since birth and placed on nCPAP had significantly higher levels of CO_2 levels (ranging between 18–30 vs. 13–18 mmHg, $p<0.05$, respectively) compared to the infants who did not breathe at birth received PPV initially, this difference was not observed at 10 min of age. This may suggest that spontaneously breathing infants have better gas exchange which is similar to the findings from our study. More recently there has been increased interest in understanding the relationship between lung aeration, and pulmonary blood flow during resuscitation or preterm infants. Hooper and colleagues (288)aimed to determine the relationship between lung aeration and expired CO_2 levels, they measured expired CO_2 levels and lung volumes in ventilated newborn lamb and rabbits during phase contrast (PC) X-ray imaging. In both animal models, expired CO_2 levels significantly ($p<0.0001$) related to tidal volumes and CO_2 clearance/breath increased exponentially when tidal volumes were greater than 6 mL/kg.

A recent randomized trial by Schmölzer et al. demonstrated that an RFM additional to clinical assessment was associated with significant reduction in leak during mask PPV in preterm infants(235). A recent systematic review (300)aimed to establish the role of respiratory function monitoring in reducing mortality and morbidity, concluded that there were no studies which qualified for the review.

9.3 Clinical implications of the results of this thesis:

1. The presence of an RFM provides real time data during resuscitation, this should improve the efficacy of preterm resuscitation.
2. Tidal volume in spontaneously breathing infants are 4-5ml/kg; there is increasing evidence of volume trauma with higher tidal volumes during preterm resuscitation. It is then essential to monitor tidal volume during resuscitation, which can minimise lung injury and contribute towards improved outcomes in extremely preterm infants Long term studies will be necessary to inform the benefits of this monitoring.
3. An integrated system to measure respiratory parameters and oxygen saturations and heart rate could help clinicians to rapidly assess and titrate respiratory support during resuscitation and stabilisation.
4. Since the use of RFM at preterm resuscitation is being recognised as important, further training and protocols to interpret and intervene resuscitation responses may be necessary before routine use.

9.4 Future Research:

Respiratory function monitoring is rapidly emerging as a research tool during newborn resuscitation; over the last two years there has been more than 40 published studies where RFM has been used in clinical research.

1. It is important to determine whether such monitoring does impact on the effectiveness of resuscitation. Multi-centred randomised control trial will inform the effectiveness of such monitoring and more importantly, may help to delineate the contribution of interventions during preterm resuscitations to long term outcomes.

2. If brief use of higher inflation pressure but volume controlled resuscitation strategies may rapidly establish gas exchange and reduce lung injury during preterm resuscitation.
3. Studies to explore the role of volumetric estimation of expired CO_2 and its relation to the degree of lung aeration may be useful in clinical practice.

9.5 Conclusions

Initial lung inflation through a face mask or endotracheal tube produced very low tidal volume and expired CO_2, unless it was associated with infant's own respiratory effort. Current preterm resuscitation techniques are variable due to lack of robust evidence.

Monitoring respiratory function during preterm resuscitation is feasible and has the potential to improve clinical care by providing real time feedback during resuscitation of prematurely born infants.

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APPENDIX I : **RFM Evaluation questionnaire**

Respiratory function monitoring at resuscitation of prematurely born infants - A user survey

1. Have you used respiratory function monitoring at the resuscitation of prematurely born infants?
   Yes: □ No: □
   If yes, please answer the questions below

2. Are you a
   □ SHO
   □ ANNP
   □ SPR
   □ CONSULTANT

3. How many times have you used the equipment?
   .....

4. How easy was it to set up and use the equipment?
   □ Extremely Easy
   □ Easy
   □ Hard
   □ Extremely hard

5. Was display of delivered tidal volume helpful during resuscitation?
   Yes: □ No: □
   Please comment if it was useful.

.....

6. Did you adjust the peak inflation pressure based on the tidal volume?
   Yes: □ No: □

   If so what tidal volume do you consider adequate
   □ 4 ml/kg □ 5 ml/kg
   □ 6 ml/kg □ 7 ml/kg
   □ 8 ml/kg

7. Did the flow and volume trace help you to assess if you had an adequate face mask seal?
   Yes: □ No: □

8. Did you reintubate if the end tidal carbon dioxide monitoring showed little or no expired CO_2?

   If so how often?
   .....

9. If the chest wasn't moving, but there was expired CO2, would you:

□ Not reintubate but increase the pressures
□ Reintubate

10. Oxygen saturation monitoring at resuscitation of prematurely born infants: If the O2 saturation was <85% at one minute did you.....

□ Do nothing
□ Increase the FiO2 – if so to what level?
□ Increase the inflation pressure

11. If you increased the FiO2, to what level did you increase it?

□ 30-50%
□ 50%
□ 50-75%
□ 75%-100%

12. Do you think respiratory function monitoring should be used routinely at resuscitation of prematurely born babies?

Yes □ No □

Please add any other comments

.....

.....

.....

APPENDIX II : **Questionnaire: Survey of UK newborn resuscitation**

Name: .....

Hospital: .....

1. **What level of intensive care do you provide (BAPM Standards,2010)**

   □ Level 1 (SCBU) □ Level 2 (Local Neonatal Unit) □ Level 3 (NICU)

2. **Is resuscitation conducted in:**

   □ Delivery room □ Separate room adjacent to the delivery room

3. **How do you provide positive pressure ventilation in the delivery room?**

   □ T-piece resuscitation (e.g.: Neopuff®)

   □ Self- inflating bag with PEEP valves (e.g.: Ambu® PEEP valve)

   □ Self- inflating bag without PEEP valves

   □ Other (please specify): .....

4. **What are the initial pressures set for resuscitation?**

   Term infant: PIP..... cm H_2O PEEP ..... cm H_2O

   Preterm Infant: PIP.....cm H_2O PEEP .....cm H_2O

5. **Do you use oxygen blenders at resuscitation?**

   □ Yes □ No

6. **If you use oxygen blenders, what is the initial FiO_2 set to be used during resuscitation?**

   Term infants: .....

   Pre-term infants: .....

7. **Do you use a pulse oximeter during newborn resuscitation?**

   Term infant: □ Yes □ No

   Preterm Infant: □ Yes □ No

8. **Which other monitoring do you use during resuscitation?**

a) Temperature □ Yes □ No

b) Separate heart rate monitoring □ Yes □ No

9. **Do you routinely apply plastic wrap/bag for all infants born less than 28 week gestation?**

□ Yes □ No

10. **Do you routinely use CO_2 detectors in the delivery room to confirm intubation?**

□ Yes – Colorimetric method (e.g.: Pedicap®)

□ Yes – Capnography (e.g.: End tidal CO_2)

□ No

11. **Do you transport infants needing respiratory support from the delivery room to the newborn unit using a:**

□ Transport incubator

□ Resuscitatire with auto-breath

□ Resuscitaire with T-Piece ventilation (e.g. neopuff®)

□ Resuscitaire with self-inflating bag

□ Others (please specify): .....

12. **Do you give sodium bicarbonate during resuscitation?**

□ Yes □ No

13. **Do you give adrenaline to an infant of:**

Less than 24 weeks □ Yes □ No

25-27 weeks □ Yes □ No

14. Which of the following staff routinely attend the newborn resuscitation team for prematurely born infants?

Less than 24 weeks	**25-28 weeks**	**Greater than 29 weeks**
□ Consultant	□ Consultant	□ Consultant
□ Registrar/Specialty trainee 3-8	□Registrar/Specialty trainee 3-8	□ Registrar/Specialty trainee 3-8
□ SHO/Specialty trainee 1-2/FY1-2	□ SHO/Specialty trainee 1-2/FY1-2	□ SHO/Specialty trainee 1-2/FY1-2
□ Neonatal Nurse practitioner	□ Neonatal Nurse practitioner	□ Neonatal Nurse practitioner
□ Neonatal nurse	□ Neonatal nurse	□ Neonatal nurse

COMMENTS:

.....

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APPENDIX III : **Permissions**

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