Studies and Observations on Different Kinds of Oxygen Monitoring, Oxygen Therapy, and Associated Morbidities in Preterm Infants

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Glossary

(A-a) DO_2^{50}	Alveolar to arterial oxygen tension difference at an inspired oxygen concentration of 50%
AC	Assist control
ALTE	Acute life threatening event
AVIOx	Achieved versus intended pulse oximeter saturation study
ANOVA	Analysis of variance
BMP	Bone morphogenetic protein
BOOST	Benefits of oxygen study
BPD	Bronchopulmonary dysplasia/Chronic lung disease
CF	Cystic fibrosis
CGA	Corrected gestational age
CI	Confidence interval
COIN	Continuous positive airway pressure or intubation at birth
COHb	Carboxyhaemoglobin
COT	Canadian oxygen trial
DeltaMSaO_2	Variability of mean arterial oxygen saturation
DPG	Diphosphoglycerate
ELBW	Extremely low birth weight
FiO_2	Fraction of inspired oxygen
IFCC	International federation for clinical chemistry and laboratory medicine
IFDAS	Infant flow driver and surfactant multi-centre randomized trial
kPa	Kilopascal
MDI	Mental developmental index
Met Hb	Methylhemoglobin

MPO	Myeloperoxidase
$MSaO_2$	Mean arterial oxygen saturation
NEC	Necrotising enterocolitis
NeOProM	Neonatal Oxygenation Prospective Meta-analysis
NICHD	National Institute of Child Health and Human Development
P50	Partial pressure of oxygen required to saturate blood at 50% level
PAO_2	Partial pressure alveolar oxygen
PaO_2	Arterial blood partial pressure oxygen
$PaCO_2$	Partial pressure arterial carbon dioxide
PDGF	Platelet derived growth factor
PDI	Psychomotor developmental index
PIO_2	Partial pressure inspired oxygen
PVL	Periventricular leukomalacia
RLF	Retrolental firbroplasia
ROP	Retinopathy of prematurity
RRR	Relative risk reduction
RT-PCR	Reverse transcriptase-polymerase chain reaction
SaO_2	Arterial oxygen saturation
SD	Standard deviation
SIDS	Sudden infant death syndrome
SO_2	Oxygen saturation
SpO_2	Pulse oximetry saturation
SPSS	Statistics package for the social sciences
STOP-ROP	Supplemental therapeutic oxygen for pre-threshold retinopathy of prematurity trial

SUPPORT	Surfactant positive airway pressure and pulse oximetery trial
$TcPCO_2$	Transcutaneous carbon dioxide tension
$TcPO_2$	Transcutaneous oxygen tension
TGF	Transforming growth factor
V_A/Q	Ventilation/perfusion ratio
VEGF	Vascular endothelial growth factor
VG	Volume guarantee
VLBW	Very low birth weight
V_{max} Frc	Maximum expiratory flow at functional residual capacity
Z score	Multiples of standard deviation from mean for any given variable

Declaration

I declare that this thesis has been composed by myself. The results described herein are a product of work carried out at the Simpson Centre for Reproductive Health, as part of a research partnership. I have been the principal researcher. This work has not been submitted for any other degree or professional qualification. Data from present studies can be accessed by contacting the clinical supervisor of this thesis Dr Ben Stenson, at the neonatal unit Simpson Centre for Reproductive Health, Edinburgh, who has access to the stored data files.

Signed ..... Date.....7/10/10.....

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I would like to thank a number of groups of people without whom the research could not have been carried out. Firstly, thanks are due to the medical, nursing and auxiliary staff of the neonatal unit at Simpson's. Secondly, I would like to thank the parents, who consented for their children to enter the two studies. This was generally at a very anxious time in their child's life and it was very altruistic. Finally, I would like to thank the contributor's other research fellows and supporting authors, especially for the fourth study.

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I would like to dedicate this thesis to my family and hope that the time I have spent on writing it up has not jeopardised the strong bond between us all.

Abstract

Introduction

Oxygen is ubiquitous, can be life saving, and is one of the most commonly used therapies in neonatal intensive care for the past 60 years. Despite this there is no consensus among neonatologists as to what is the most appropriate way to monitor oxygen, what target level to aim for, and how to change inspired oxygen levels. There may be two or more distinct time periods that can be defined, in the early life of extreme preterm infants who go onto suffer from bronchopulmonary dysplasia (BPD) for which the best oxygen target levels need to be clearly identified.

Infants with BPD have difficult early years, often failing to thrive, requiring frequent readmission to hospital for respiratory exacerbations, and having significant chance of other morbidities of prematurity. Yet current definitions of BPD based on the use of oxygen therapy alone give wide variations in the incidence of disease that reflect little more than clinician variation and have little relevance to the severity of any underlying pathology.

Objectives

To compare methods of oxygen monitoring, look at how infants oxygen dissociation curves affected oxygen tensions achieved, and see how our reaction to monitors affect oxygen stability. Finally, to measure V/Q and shunt non-invasively in infants with BPD at 36 weeks corrected gestational age and examine whether this would be a useful physiological definition of BPD. Four studies were carried out.

Study 1

Aimed to determine whether care based on transcutaneous oxygen tension ($TcPO_2$) or saturation (SpO_2) monitoring is associated with less time spent with high oxygen tension and less variability of oxygenation.

Care based on SpO_2 monitoring was associated with more time spent with high oxygen tension, more time with low oxygen tension, more variability in oxygen tension and more variability in oxygen saturation than care based on $TcPO_2$ monitoring.

Within the target ranges studied SpO_2 monitoring was associated with significantly more variable oxygenation than $TcPO_2$ monitoring.

Study 2

Aimed to describe the range of oxygen tensions likely to be achieved in the first three weeks of life in a population of high risk preterm infants at currently targeted oxygen saturation levels, and to determine whether infants who develop adverse outcome have different haemoglobin oxygen dissociation characteristics than infants who remain well.

Saturations within the range 85-95% (as currently being investigated in the NeOProM collaberation) largely exclude hyperoxia in preterm infants <29 weeks gestation but permit PaO_2 values lower than those recommended in traditional guidelines. There was no significant association between BPD, ROP, death or combined outcome and initial percentage of fetal haemoglobin or haemoglobin oxygen affinity (P50) in the first week of life.

Study 3

Aimed to see which nurse oxygen adjustment practices influence oxygen stability and degree of adherence to oxygen saturation targets in preterm ventilated infants by separating out the variation in oxygen stability attributable to the condition and behaviour of the baby from that attributable to the nurse oxygen adjustment practices. Variations in oxygen adjustment practices were also related to nursing seniority.

After controlling for the intrinsic instability of the infant we found that larger and more frequent changes in FiO_2 may contribute to instability of oxygenation. More senior nurses achieved less hyperoxic time and, made smaller oxygen changes. Stability of oxygenation in ventilated preterm infants is influenced by the oxygen adjustment practices of the staff who care for the baby. These are potentially modifiable practices.

Study 4

Aimed to quantify the severity of gas exchange impairment in preterm infants with BPD in a graded fashion and to partition this between the contribution made by reduced ventilation/perfusion ratio (V_A/Q) and that due to right to left shunt, using non-invasive measurements of PIO_2 and SpO_2.

The predominant gas exchange impairment in BPD is a reduced V_A/Q described by the right shift of the SpO_2 vs PIO_2 relationship. This provides a simpler method for defining BPD that grades disease severity.

Summary

In summary this series of studies found that the method by which oxygenation is monitored and the ways that staff adjust oxygen levels have an important influence on the oxygen levels achieved. The overall oxygen affinity of the neonatal blood did not appear to be an important determinant of the risk of adverse outcome. Individual infants vary widely in their stability in terms of oxygenation. The optimal oxygen levels for developing preterm infants remain uncertain and this is the subject of a major prospective international research collaboration (NeOPRoM). Interpretation of the results of the clinical trials of different saturation targets that are currently recruiting will be difficult unless good data on compliance with protocol are gathered. A simple non-invasive measure of gas exchange impairment that might better grade disease severity of BPD has been defined. These studies will help to focus future research, and should assist clinicians in achieving improved compliance to oxygen targets.

1. Chapter 1. Background

1.1. History of oxygen use and its monitoring in neonates

"A remarkable life-giving gas" produced by heating mercuric oxide was first described in the scientific literature by Joseph Priestley, an English clergyman and amateur chemist in 1774[1]. He demonstrated that, when compared with the ordinary atmosphere, mice lived longer in a jar of this "eminently breathable air". However, Priestley warned,

> *"though pure dephlogisticated air[oxygen] might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body; for, as a candle burns out much faster in dephologisticated than in common air, so we might, as may be said, live out too fast and the animal powers be too soon exhausted in this pure kind of air. A moralist, at least, may say, that the air which nature has provided for us is as good as we deserve."*

But the temptation to treat patients with the novel gaseous substance was irresistible[2]. See Figure 1 for a picture of Priestley.

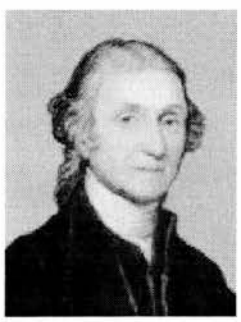


Figure 1: Joseph Priestley

Oxygen was discovered by a Swedish chemist, Carl Wilhelm Scheele[3], in 1772. Joseph Priestley, independently, discovered it 1774 and published his findings the same year, three years before Scheele published. Antonie Lavoisier[2], a French chemist, was the first to recognize it as an element, ending the theory of "phlogiston" and coined its name "oxygen" in 1777- which comes from a Greek word that means "acid-former".

Oxygen was first used in newborn infants by Francois Chaussier in 1780, to treat those who failed to establish normal breathing[4]. By the end of the 19th and early 20th century "preterm infants" special care units were starting to be established. It was in the "preterm infants" special care unit at the Michael Reese Hospital, Chicago, established in 1914, where Julius Hays Hess designed a special bed which delivered both heat and oxygen to the preterm infant[5]. Later in 1928 Flagg, described a detailed procedure for intubation and intermittent positive pressure insufflation using a mixture of oxygen and carbon dioxide for resuscitation of asphyxiated newborns[4].

Oxygen therapy was more widely introduced into neonatal practice in the 1930's and 40's, following observations that it could be used as a treatment for periodic breathing[6], and that skin colour was an unreliable indicator of an infant's blood oxygen level[7 8]. This was hastened by the arrival of newly designed incubators in the late 1940s that made it possible to give infants high concentrations of oxygen for prolonged periods. During this time period oxygen was used liberally until it was linked to the development of retinopathy of prematurity (ROP)[9-13]. This was recognised when there was a sudden appearance of ROP in Britain following the introduction of the NHS in 1948, which had allowed the funding of liberal concentrations of oxygen to be given to preterm infants. After this the amounts of oxygen used were reduced dramatically. Preliminary studies published in 1954 showed that turning down the FiO_2 to less than 40% was associated with a marked reduction in the incidence of ROP[11]. This led clinicians in the 1950-60's to turn

down oxygen levels throughout the neonate's life, including during the first 24 hours of life.

However, the preliminary studies that had prompted the reduction in FiO_2 had recruited infants after 24 hours of life and, as Cross showed, there was a significant rise in first day neonatal deaths during this period when oxygen was restricted to less than 40% [14]. Figure 2 shows a plot of deaths per 1000 live births in the United States of America from 1937-1968. First day deaths are labelled as day 0. It has been estimated that this severe restriction of supplemental oxygen, resulted in 16 children dying or surviving with severe disability for each child whose sight was saved[15]. In the next 20 years over 150,000 premature babies died of hypoxic respiratory failure[14-16].

Figure 2: Crosse 1973: Cost of preventing retrolental fibroplasia? Lancet 2:954-956

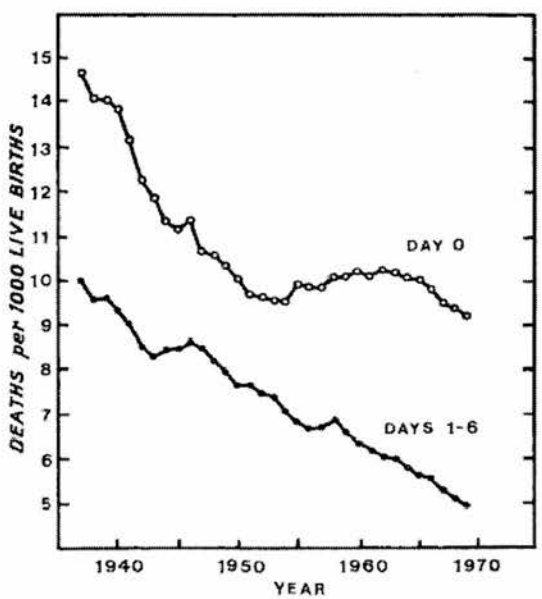


Fig. 3—Deaths per 1000 live births for the years 1937–68: United States.

When transcutaneous PO_2 probes became available in the 1970's it was thought that the problem of how much oxygen to give neonates would soon be solved. But this unfortunately was not the case, possibly because ROP is not only linked to the absolute oxygen levels achieved, but also to oxygen variability and possibly CO_2 levels[17-20]. New trials of oxygen therapy guided by monitoring techniques were not performed.

During the 1980's, with the introduction of antenatal steroids, surfactants and modern ventilation strategies, more premature infants were surviving and the incidences of problems such as BPD, ROP, neurological problems and NEC were increasing[21-24]. Saturation monitors were introduced in the 1980's, and perhaps because of their relative convenience, these started to be used in favour of transcutaneous monitoring. More recently, there have been trends towards accepting lower oxygen levels, and weaning infants from ventilators to CPAP more quickly[25]. With further increases in the survival rates of the most premature infants, the morbidities of prematurity have increased further[26-29].

Oxygen has been one of the most commonly used therapies in neonatal intensive care for the past 60 years. Despite its essential role, excess amounts of oxygen in the blood (hyperoxia) are causally linked to a variety of neonatal conditions including BPD, NEC, ROP and adverse neurological outcome[9-13 18 30-37]. Although there must be an optimum range of oxygenation to balance the competing risks of mortality, ROP blindness, BPD, and brain damage, there is no consensus among neonatologists as to what is the most appropriate way to monitor oxygen, what target levels to aim for, or how to change inspired oxygen levels[8]. Figures 3-4 summarise data describing oxygen saturation monitoring policies in the United Kingdom and US[38 39].

Figure 3: National survey of oxygen monitoring policies

Oxygen saturation monitoring policies in the UK. Results from a telephone survey of 100 units with 3 or more intensive care cots caring for babies of less than 28 weeks' gestation in 2001. High (A) and low (B) oximeter alarm settings[39].

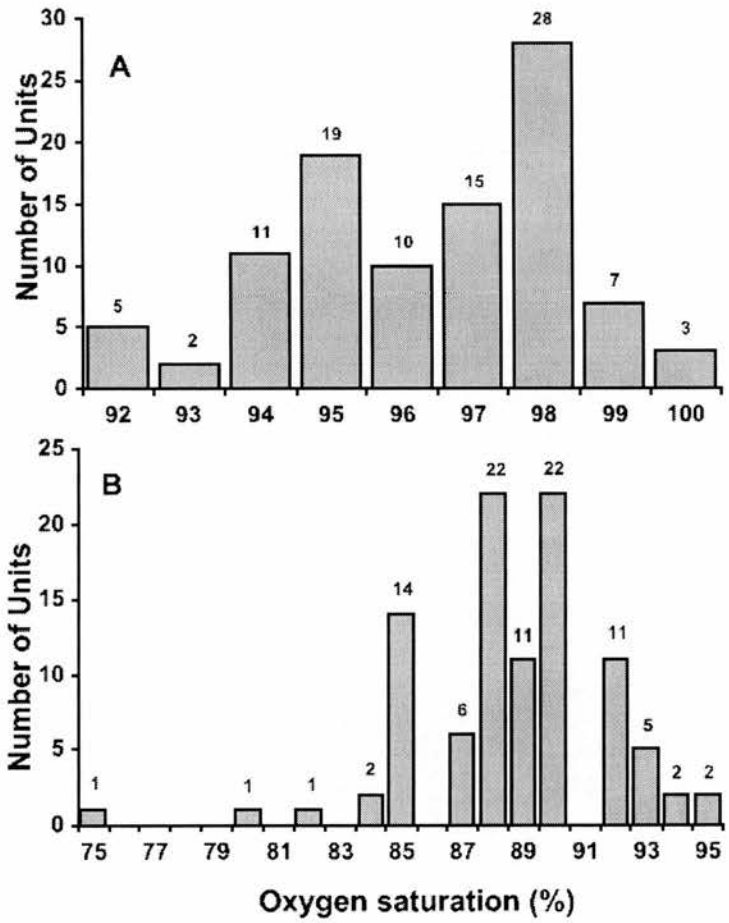


Figure 4: Frequency distribution of SpO_2 thresholds for administration of supplemental oxygen

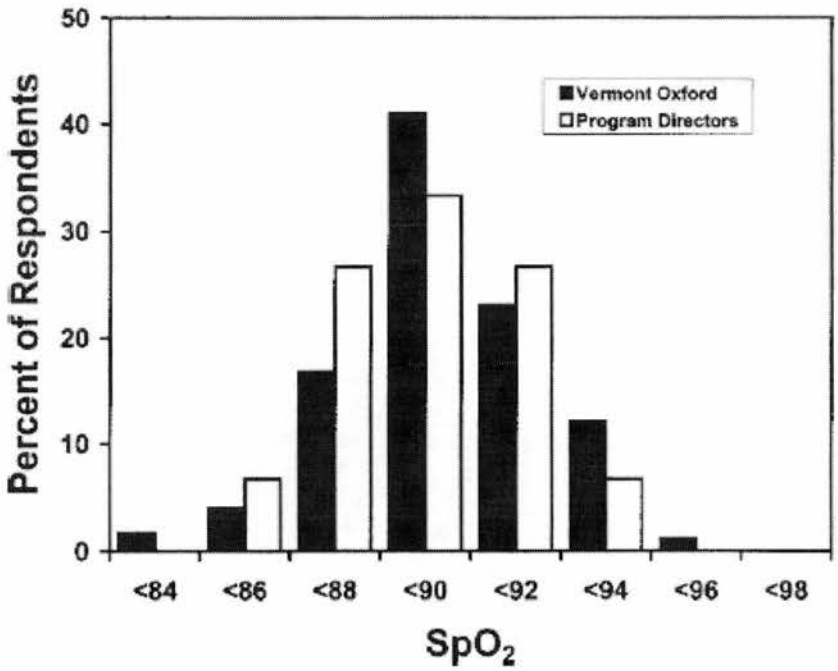


Figure. Frequency distribution of SpO_2 thresholds for the administration of supplemental oxygen at 36 weeks' PMA by members of the Vermont Oxford Network and by neonatal-perinatal medicine fellowship program directors. SpO_2, Pulse oximetry saturation.

1.2. Normal physiology and physiological effects of supplemental oxygen

Oxygen saturation and oxygen tensions are far lower during fetal life than after birth. Nicolinin[40] et al evaluated fetal acid-base status on 66 blood samples taken for rapid karyotyping from 58 growth-retarded fetuses. Before blood sampling, Doppler blood flow studies of the umbilical artery showed end-diastolic frequencies to be absent in 32 fetuses (Group 1) and present in 26 (Group 2). There were no perinatal deaths in Group 2 whereas mortality in Group 1 was 65.4%. They found the average PO_2 in Group 2 to be 3.26 kPa, equivalent to an arterial saturation of 66%. This was

significantly higher than the PO_2 in group 1 which was 2.20 kPa, equivalent to a saturation of 35%. Although this is not evidence that saturations of 66% are normal in human fetuses, it is evidence that saturations of this level are not low enough to affect mortality. Simona Nava et al, and Soothill et al described oxygen tension in over 350 fetuses from 16-39 weeks gestation who underwent fetal blood sampling for a range of different indications[41 42]. The fetuses were either not affected by the condition under investigation or it was one which would not affect blood gas and acid-base status. They found that the 95% confidence interval for normal fetal umbilical venous oxygen tension was about 20 – 60 mm Hg (2.7-8 kPa), decreasing with increasing gestational age. This is equivalent to a range of oxygen saturation of about 60 – 90%. It is important to note, with all three of these studies, that this is the umbilical venous saturation, not systemic blood saturation. During labour, saturations fall intermittently even lower to 30-40%[43] without adversely affecting the vast majority of infants.

Preterm newborns have red blood cells that largely contain fetal haemoglobin, and, consequently, they have a higher oxygen affinity. A study by Emond et al showed that the mean P50 (the partial pressure of oxygen [PaO_2] required for 50% saturation of haemoglobin) was 18.3 +/- 0.9 mm Hg (2.5+/- 0.3kPa) and the P90 was 40.8 +/- 3.6 mm Hg (5.4 +/- 0.5 kPa). This shows that when treating very low birth-weight newborns with oxygen, a PaO_2 of 41 mm Hg (5.5 kPa) is enough to saturate 90% of haemoglobin at physiological pH[44].

Normal oxygen saturation in healthy term and preterm infants during the first 24 hours of life has been studied extensively and found to be a median of 98% with a range from 80% to 100%[45]. During the first weeks of life, healthy preterm and term infants have arterial oxygen saturations between 93% and 100% with mean/median values from 97% to 99%[46 47]. The preterm infants in these studies ranged from 30 to 36 weeks of gestation[45-47]. Beresford et al[48] demonstrated that healthy one week old

and 6 month old preterm infants have mean saturation values of around 97% in air and Parkins et al[49] showed similar values in healthy term infants at 3 months of age.

Sjostedt and Rooth suggested over 50 years ago that premature infants could be nursed in <21% oxygen. They found that growth and development were normal in infants nursed in as low as 15-16% oxygen[50]. More recently Parkins et al showed that many infants at the age of 2 months to 6 months of age could be nursed without marked desaturation in 15-16% oxygen. However 1 in 8 developed severe and prolonged hypoxaemia[49].

Pure oxygen has been compared with room air as the initial gas used to resuscitate newborn infants[51]. These trials show that use of 100% oxygen during resuscitation is not advantageous. The high FiO_2 appears to depress spontaneous respiration. Time to first cry and Apgar scores are lower. Mortality rate may even be higher with high FiO_2 and long term neurodevelopmental outcome is not improved[52], although follow up data are limited.

On the other side of the coin however, alveolar hypoxia has a well described association with pulmonary artery hypertension resulting from hypoxic pulmonary vasoconstriction[53]. Low oxygen levels increase pulmonary resistance and increase airway resistance[54 55]. Administration of supplemental oxygen could conceivably help to reduce the impact of morbidities associated with being born prematurely[54 56].

Fugelseth et al compared the consequences of hypoxaemia and resuscitation with room air versus 100% oxygen on cardiac troponin 1, cardiac output and pulmonary artery pressure (PAP) in newborn pigs[57]. They noted that hypoxaemia affected the myocardium and PAP. But found that reoxygenation with 100% oxygen showed no benefits compared with room air in normalising myocardial function and PAP.

Halliday et al studied 10 infants with severe bronchopulmonary dysplasia, showing increased pulmonary vascular resistance in infants when PaO_2 was allowed to fall from an average 62 mmHg (8.3 kPa) to 54 mmHg (7.2 kPa), by reducing the infants inspired oxygen concentration. He concluded that to avoid pulmonary hypertension it is best to keep PaO_2 above 55mmHg (7.3 kPa). Infants in this study were not followed up longitudinally[54]. Alpert et al described case studies of two young hypoxemic patients whom they had studied by radionuclide angiography, finding improved right ventricular performance when they were given supplemental oxygen. Both patients were substantially older than the population of infants of interest to this thesis, and were suffering from a different clinical entity from preterm infants with BPD[56].

Adamson et al observed 60% venous admixture in four infants with BPD while breathing room air, but only 20% admixture when breathing 100% oxygen[58]. Abman et al measured pulmonary artery pressures of six infants with bronchopulmonary dysplasia using cardiac catheterisation[59]. They found significant decreases in pulmonary artery pressure, from mean 48 mmHg prior to oxygen supplementation while breathing air, to mean 25 mmHg when given 80% oxygen. They also studied three infants as they received supplemental oxygen by nasal cannula, at flow rates between 2-3 L/min, which they suggested were similar to levels used for outpatient therapy. They suggested that most of the benefit occurred at much lower oxygen concentrations, which could be administered by nasal cannula at home. However these flow rates would undoubtedly produce oxygen levels that are not much lower than the 80 % they originally used[60 61].

Narong Simakajornboon et al described a group of preterm infants who were born at a mean gestation of 30 weeks and studied in a sleep laboratory at a mean of 38 weeks corrected gestational age[62]. Supplemental oxygen was associated with an increase in total sleep time and percentage time in quiet sleep, with reciprocal changes in active sleep. In addition there was an improvement in respiratory stability as evidenced by

a decrease in apnoea, periodic breathing and bradycardia without adverse affects on alveolar ventilation. However, the cardiorespiratory events described were minor, and of unlikely clinical significance. To be entered into the study, infants had to have been cardiovascularly stable for at least a week prior to the study. Having been free from cardiorespiratory monitor alarms in the nursery for at least 1 week before the study, the infants are a subset of extremely well preterm infants.

Harris et al found improvements in sleep patterns following implementation of increased supplemental oxygen in seven infants with chronic lung disease who were judged to have stable oxygen saturation by their physicians[63]. Two of these infants were already in supplemental oxygen, one had chronic lung disease secondary to meconium aspiration syndrome, and six were failing to thrive.

Sekar described more central apnoea and desaturation in sleeping infants with BPD than in preterm controls. Oxygen saturation, central apnoea, and periodic breathing all improved with supplemental oxygen therapy, which may have improved central respiratory stability[64]. Fitzgerald found targeting saturation to at least 93% optimised sleep architecture in a group of infants with BPD[65].

To summarise, infants with BPD have difficult early years, often failing to thrive, requiring frequent readmission to hospital for respiratory exacerbations, and having significant risks of other morbidities of prematurity [66-69]. There is no clear evidence so far for what level of oxygen is best to balance all the risks at any particular time period in their lives[8].

1.3. Oxygen radical disease

Oxygen is essential for most carbon based life. However when it is delivered in excess to infants with immature oxygen defences it causes oxygen radical disease. This occurs when oxygen causes damage through the formation of reactive intermediates and peroxidation of membrane lipids.

Frank et al showed that premature neonatal rabbits are highly susceptible to oxidative stress, and fail to adequately up regulate antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroidase[70]. Further he showed that under-nutrition led to reduced tolerance of newborn rat pups to hypoxia[71]. Under nutrition and hyperoxia were additive in reducing lung DNA content, and growth. Delemos and Davis showed that hyperoxia is an important trigger of the lung damage associated with BPD in animals who they ventilated to produce a premature neonatal lung model similar to BPD[72 73]. Wilborn et al found that morphological changes in the lung associated with BPD are mitigated by agents that reduce oxidative injury (superoxide dismutase and catalase)[74].

Coalson demonstrated that 7 d of mechanical ventilation of preterm baboons of 140 d gestation with 100% oxygen severely reduced the numbers of alveoli. The same interference with septation occurred after surfactant treatment and ventilation without exposure to large amounts of supplemental oxygen if the baboons were more preterm at 125 d gestation[75-77]. The large decrease in surface area was associated with a decreased and dysmorphic pulmonary microvasculature. These anatomic changes were associated with persistent increases in white blood cells and cytokine levels in airway samples.

Warmer et al exposed neonatal mice to 85% oxygen or air for 28 days[78]. Neonatal hyperoxia resulted in decreased alveolar septation, increased terminal air space size,

and increased lung fibrosis. Hyperoxia caused an increased number of inflammatory cells in lung tissue and in lung lavage fluid. Analysis of lung tissue RNA by RT-PCR showed that hyperoxia increased expression of the proinflammatory cytokines interleukin-1α and macrophage inflammatory protein-1α. Prolonged neonatal hyperoxia caused functional changes, decreasing lung volume and pulmonary compliance.

Stephane Dauger et al[79] exposed a group of mouse pups to 65% O_2 (hyperoxic mice) and compared them to a control group of mice brought up in a normoxic environment (normoxic mice) during their first postnatal month, and examined their lung histology and pulmonary mechanics. They found the hyperoxic mice had fewer and larger alveoli than normoxic mice secondary to impaired alveolarisation. However ventilatory function and body growth were preserved. They concluded that hyperoxic exposure during lung septation in mice may cause irreversible lung injury and breathing pattern abnormalities in adulthood at O_2 concentrations lower than previously thought.

Bland et al[80] investigated the effects of mechanical ventilation with air or 40% O_2 on pulmonary expression of genes that regulate formation of alveoli and blood vessels in lungs of newborn mice. Alveolarization and angiogenesis occur mainly after birth at term gestation in mice. They found that mechanical ventilation of 2-4 day old mice for 8 hrs with 40% O_2 reduced lung mRNA expression of VEGF-A and one of its receptors, VEGF-R2 in addition to PDGF-A and tenascin-C, all of which are genes known to affect formation of alveoli and blood vessels in the developing lung. Mechanical ventilation alone purely reduced lung mRNA expression of PDGF-A and tenascin-C. Mechanical ventilation of 4-6 day old mice with 40% oxygen for 24 hrs caused similar changes in mRNA expression but also yielded lung structural changes indicative of diminished septation compared with lungs of unventilated control pups that spontaneously breathed 40% O_2 for a similar time. They found that these molecular and structural changes occurred without apparent lung inflammation as

assessed by histology and measurements of proinflammatory cytokines, myeloperoxidase (MPO) activitiy, or lung water content.

Alejandre-Alcazar et al[81] investigated the effects of hyperoxia (85% oxygen) on transforming growth factor (TGF)-β and bone morphogenetic protein (BMP) signalling in neonatal mice. They compared mice exposed to 21% or 85% oxygen for the first 28 days of life. They found growth and respiratory compliance were significantly impaired in mice exposed to 85% O_2, and these mice also showed a pronounced arrest of alveolarization, accompanied by dysregulated expression and localization of receptors. TGF-β signalling was potentiated, whereas BMP signalling was impaired in the lungs of pups exposed to 85% O_2. TGF-β has potent antiproliferative properties on epithelial cells and some types of smooth muscle cells. Exposure to 85% O_2 led primary alveolar type II cells to be more susceptible to TGF-β-induced apotosis. As proliferation and differentiation of alveolar type II cells are key steps in the alveolarization process, this was felt to be partly responsible for the arrest of alveolar development in these mice. Exposure of primary lung fibroblasts to 85% O_2 modulates the expression of extracellular matrix and extracellular matrix-remodelling components induced by TGF-β by significantly enhancing the TGF-β-stimulated production of the α1 subunit of type I collagen ($I\alpha_1$), tissue inhibitor of metalloproteinase-1, tropoelastin, and tenascin-C. Further as BMPs have been accredited with key roles in early lung development, particularly lung branching, their data demonstrated that hyperoxia significantly affects TGF-β/BMP signaling in the lung, including processes central to septation and, hence, alveolarization.

Vento et al showed that resuscitation with 100% oxygen increases the oxidative stress for at least one month, and increases both time till first cry and ventilation time to achieve sustained respiratory pattern, compared with room air resuscitation[82 83]. Temesvari and colleagues found that 100% oxygen resuscitation of newborn piglets with pneumothorax-induced asphyxia had no advantage compared to room air. On

the contrary, early neurological outcome was significantly impaired in the oxygen resuscitated compared with room air resuscitated animals[84].

Naumburg et al found an association between brief exposure of pure oxygen at birth and childhood lymphatic leukaemia, in a population based case-control study[85].

Kondo et al measured reactive oxygen species produced during resuscitation after asphyxia in newborn piglets[86]. In animals resuscitated with 100% oxygen, the mean maximal chemiluminescence (a marker of reactive oxygen species) was significantly higher compared with animals resuscitated with air. In the latter group there was hardly any increase in oxygen free radical production during resuscitation. Animals given 100% oxygen only, without previous asphyxia, also experienced an increase in free radical production, but not as much as in animals exposed to asphyxia and reoxygenation. This suggests that hypoxia, when preceeding reoxygenation, leads to augmentation of free radical production, and that room air resuscitation limits the production of free radicals.

A multivariate analysis by Van Marter et al found that inspired oxygen concentrations were higher in infants who developed BPD compared with those who did not. Being given 100% oxygen in the first day of life almost doubled an infant's risk of BPD. However, arterial oxygen tension and oxygen saturation were equivalent for those who developed and those who did not develop BPD[87]. The lung epithelium is exposed directly to the inspired oxygen tension in kPa whereas the other organs are only exposed to the oxygen tension in the blood. On the other hand, in studies by Buss et al and Winterbourn et al, no significant differences in levels of oxidant markers were found between infants who did or did not develop BPD or ROP[88 89].

Irrespective of absolute oxygen saturation, oxygen variability has been conclusively linked to ROP but not so far to BPD, NEC or neurological complications. There is some speculation that the vascular damage related to hypoxia or hyperoxia may be more a consequence of sudden decreases and increases in oxygen level, which are associated with episodic oxidant damage, rather than hypoxia or hyperoxia per se[17-19]. Oxidative stress has been linked to the development of BPD, ROP, NEC and PVL[34 90 91].

McColm et al found that rats raised in a relatively hypoxic but variable oxygen environment (mean 17% oxygen) develop less severe retinal vascular abnormalities than those raised in variable oxygen around higher oxygen means (21 and 24 % oxygen)[18]. White et al[92] found that low-level oxygen supplementation (PIO_2=17.9-24.7%) during early lung development in rats did not affect alveolar development.

These studies suggest that early care given to newborn infants, may put some infants at greater risk of developing BPD by increasing their oxidative stress in the first few days to weeks of life. Efforts to set an oxygen level may be too simplistic because oxygen variability may also play a strong role in outcome.

In a model system of pulmonary hypertension caused by chronic hypoxia in calves, Stenmark identified vascular adventitial fibroblasts that proliferate and migrate into the media of resistance vessels in the presence of hypoxia[77 93]. These hypoxia-sensitive cells express matrix metalloproteinase-2, and inhibitors of this metalloproteinase block migration of the cells into the vessels. These fibroblasts of adventitial origin may be sentinel cells that can transdifferentiate and contribute to pulmonary hypertension.

Niijima et al measured the changes in cerebral blood flow velocity in response to a transient threefold increase in oxygen tension in a group of 17 premature infants using duplex Doppler[94]. Measurements of blood gas tensions as well as blood pressure and cerebral blood flow velocity were made over a period of 20 minutes on three occasions for each infant; during normal oxygenation, hyperoxia, and normal oxygenation. The authors found that there was a fall in cerebral blood flow velocity in 15 of the 17 premature infants with hyperoxia. There was no significant change in either $PaCO_2$ or blood pressure during the period of hyperoxia. Suggesting that hyperoxia reduces cerebral blood flow velocity independently of the effects of hypocapnia or hypotension.

1.4. How much oxygen? - the evidence so far

The first sign that oxygen could be damaging as well as life saving came when retinopathy of prematurity was observed in preterm infants – a pathology that had not been encountered in adults. High inspired oxygen concentrations were clearly linked to the development of retinopathy of prematurity in the 1950's. Retinopathy of prematurity (formally Retrolental Fibroplasia) was first described in 1942. Crosse was the first to notice the link between this new disease and oxygen[10], following the formation of the NHS which led to funding for the widespread use of liberal oxygen levels in premature infants. Campbell, Evans and Patz soon followed up this theory with more evidence. By 1954, ROP had blinded about 10,000 infants[8-10 33 95]. In 1954-56, 3 RCTs enrolling 341 infants, showed that breathing unrestricted concentrations of inspired oxygen, after 48 hours of life was associated with increased risk of ROP, without any benefit in mortality[11]. During the era following these studies, arterial oxygen levels were not measured, so the concentration of inspired oxygen could not be targeted to meet each baby's needs. To prevent ROP, all premature infants were restricted to breathing less than 40% inspired oxygen from birth. Unfortunately a design/interpretation flaw with these studies was that they did not enrol infants until after day one of life. Retrospective studies show that this

restriction of oxygen from birth actually led to a sharp increase in the number of fatalities from hyaline membrane disease. In the next 20 years over 150,000 premature babies died of hypoxic respiratory failure[14-16]. It is important to reognise that these problems with increased mortality were observed in an era when invasive ventilation tehniques were not widely available. For every infant whose sight was saved, it is estimated that 16 died[8 14-16] and many others developed spastic diplegia[96]. The epidemic of blindness stopped – but at heavy cost. This might have been avoided had a larger RCT determined if oxygen restriction from birth increased or decreased death and disability. It seems remarkable, in retrospect, that no further randomised controlled trials were conducted until the 1990s.

Two recent studies have looked at whether increasing oxygen several weeks after birth may reduce long term morbidity such as ROP and developmental problems[97 98]. The American STOP-ROP (supplemental therapeutic oxygen for prethreshold retinopathy of prematurity) trial, recruited 649 infants with confirmed prethreshold ROP in at least one eye, with mean gestation 25.4 weeks and mean postmenstrual age of 35 weeks. The infants were randomised to a conventional oxygen arm with pulse oximetry targeted at 89% to 94% saturation or a supplemental arm with pulse oximetry targeted at 96% to 99% saturation, for at least 2 weeks, and until both eyes were at study end points. The study showed that supplemental oxygen slightly reduced the number of babies with prethreshold retinopathy who went on to develop disease severe enough to require retinal surgery. However a post hoc subgroup analysis showed that benefit was only seen in infants without evidence of plus disease (dilated and tortuous vessels in at least 2 quadrants of the posterior pole) at recruitment (32% vs 46%). Surprisingly supplemental oxygen significantly increased adverse pulmonary events (defined as 1 or more episodes of pneumonia or BPD exacerbation) after recruitment (13.2 vs 8.5%), and at 50 weeks postmenstrual age also increased oxygen dependency (46.8 vs 37.0 %), numbers still in hospital (12.7 vs 6.8%), and the need for diuretics (35.8 vs 24.4%). Growth, developmental

milestones or eventual retinal outcome as assessed 3 months after the expected date of delivery did not differ between the 2 arms.

The benefits of oxygen saturation targeting (BOOST) trial was an Australian randomised, double blind, multicentre study which recruited 358 infants between 1996 and 2000. Collaborating units had different policies with regard to optimum oxygenation in the period immediately after birth (as in the STOP-ROP trial), but monitoring was done by a specified Nellcor N-3000 pulse oximeter after recruitment for as long as supplemental oxygen was deemed necessary. These infants were recruited if they were born at less than 30 weeks gestation and still in oxygen at a post menstrual age of 32 weeks. Trial oximeters were specifically modified to keep saturation in the range of 91 to 94% or 95 to 98%, depending on allocation at entry, while displaying a figure in the range 93 to 96%. The results showed that growth (weight, length, or head circumference at corrected age of 12 months) and developmental outcome was not different between the study groups. Infants in the higher oxygen arm experienced a longer duration of oxygen treatment, had a higher rate of diagnosis of chronic lung disease, and had a higher frequency of home-based oxygen therapy. There was a non-significant trend to increased deaths due to pulmonary causes in the high saturation group. All this was associated with an increased burden on health services.

It is important to recognise that both of these studies started their intervention several weeks after birth when most oxygen damage may have already occurred, ie missing out at least the first two weeks of life. It is just this time when arguably the most damage might be occurring from oxygen. No trial since the 1950's has studied the early postnatal period. However trials are now taking place in the UK, Canada, US, Australia and New Zealand, randomising infants to higher or lower saturation ranges and these are planning a prospective meta-analysis of their data in order to maximise their power to identify small differences between groups in long term

neurodevelopmental outcome. This collaboration is known as NeOProM see appendix B.

An observational study by Win Tin linked oxygen limits to outcome[31]. This study involved 295 infants who survived to infancy after delivery before 28 weeks gestation in the north of England from 1990 to 1994. This observational study showed that infants who were given enough supplemented oxygen to maintain an oxygen saturation of 88% to 98%, as measured by pulse oximetry, for at least the first 8 weeks of life, developed ROP severe enough to be treated with cryotherapy 4 times as often as babies only given enough oxygen to maintain an oxygen saturation of 70 to 90% (27.2% vs 6.2%). Surviving infants with higher oxygen target levels were also ventilated longer (31.4 vs 13.9 days), more likely to be in oxygen at postmenstrual age of 36 weeks (46% vs 18%), and more likely to have a weight below the 3rd percentile at discharge (45% vs 17%). There were obvious short-comings in the study, mainly because the different oxygen limits were at different units and there may have been other inter-unit variability which was responsible for the differences other than their oxygen policies[99].

Bradley et al presented a follow-up of Tin's cohort of infants comparing the cognitive, adaptive and behavioural performance in the two groups of children, who were exposed to two different oxygen saturation monitoring policies in the first eight weeks[100]. They undertook standardized assessments (Wechsler Scales, Vineland Scales and Behaviour Checklist) on surviving children born before 28 weeks gestation, between 1990 and 1994 in the north of England, and cared for under either "low" saturation policy (target 80-90%) or "high" saturation policy (target 94-98%) at 10 years, covering intellectual function, academic attainment, adaptive function and behaviour. Of 123 survivors 100 (81%) were assessed, which is higher than other studies in this area. The two groups were comparable in terms of gestational age, birth weight and gender. Unsurprisingly for this high risk cohort, performance was about one standard deviation below the population mean, however, there were no

significant differences seen in the two groups (see Table 1, which compares neurodevelopmental outcome at 10 years between infants cared for either under low or high saturation policies). They concluded that "Low" oxygen saturation targeting is not associated with any disadvantages, in terms of cognitive, adaptive or behavioural presentation in children at 10 years of age.

Table 1: Neurodevelopmental outcome of high/low oxygen saturation targeting

Table 1		
	Low saturation(80-90%),n=59	High saturation(94-98%),n=64
Full scale I.Q. Mean(SD)	82.7(24.9)	76.3(23.6)
Verbal comprehension	87.2(25)	80.4(23)
Reading	88.5(17.6)	83.2(21.6)
Spelling	86.4(16.8)	84.1(21.1)
Math reasoning	86.7(20.3)	83(20.4)
Numerical operation	85.8(17.4)	79.4(19.8)
Vineland scale <2nd C(%)	36.3	37.5
Vineland motor scale< 6yrs equiv	27.3	26.7
Behaviour problems >95th C	15.9	14.3

Anderson et al surveyed 318 US NICU's and received a response from 142, reporting less Grade III/IV ROP (2.4% vs. 5.5, P<0.001) and less ROP surgery (1.3% vs. 3.3%, 61% RRR, P<0.037) in US NICUs with functional SpO_2 upper limit less than or equal to 92% vs >92%[101].

Sun et al reported evidence from seven NICU's from the Vermont Oxford Network with differing policies on target SpO_2 levels[102]. A total of 1544 ELBW infants born in these units were included in the analysis. Grade III/IV ROP (10% vs. 29%, P<0.0001), ROP surgery (4% vs. 12%, P=0.0002) and BPD (27% vs. 53%, P<0.0001) were less common in infants born in NICUs with SpO_2 upper alarm limits less than or equal to 95% as opposed to above this.

Deulofeut and Sola compared rates and severity of short- and long-term morbidities in very low birth weight infants treated before and after the implementation of a change in clinical practice designed to avoid hyperoxia[103]. They looked at all infants with birth weight below 1250 g who were admitted to two Emory University NICU's from January 2000 to December 2004. A change in practice was instituted in January 2003 with the objective of avoiding hyperoxia in preterm infants with target O_2 saturation (SpO_2) at 93 to 85% (Period II). Before the change in practice, SpO_2 high alarms were set at 100% and low alarms at 92% (Period I). Survival was similar between both periods. The rates for any retinopathy of prematurity, supplemental oxygen at 36 weeks post-conceptional age and the use of steroids for chronic lung disease were significantly lower in the infants born in Period II. There was no difference in the rates of necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia. At 18 months corrected age (CA), the infants treated during Period II had a higher Mental Developmental Index (MDI) scores (80.2 vs 89.2; P 0.02) and similar Psychomotor Developmental Index (PDI) scores (83.9 vs 89.4; P 0.08) than those treated during Period I. The alarms limits used in Period I were remarkably permissive of oxygen over-use given the existing evidence linking high oxygen levels to ROP. They were unable to show a reduction in stage 3-4 ROP but this may have been due to low numbers, limiting their statistical power, as they did show a trend. However despite the limitations of the before-after methodology, this is further evidence that avoiding high oxygen tensions may lead to a reduction in BPD.

The studies by Tin, Chow (see below), Anderson, and Sun suggest that a lower SpO_2 may reduce retinal surgery by 61-100%; chronic lung disease by 49-61%; and poor growth by 62%. It is not yet possible to say with any confidence whether such care increases or decreases the number of non-disabled survivors.

In a study of the effect of oxygen therapy on weight gain of 22 infants in home oxygen Groothuis et al, found that when home oxygen therapy was discontinued by parents against medical advice in 7 infants, this led to their infants experiencing significant deceleration in weight gain, and when the oxygen therapy resumed their weight gain improved, but never regained their original weight centile [104].

Perhaps the most significant evidence concerning which infants require supplemental oxygen at home once discharged, comes from Moyer-Mileur et al[105]. They describe a cohort of infants in supplemental oxygen who were being followed up for broncopulmonary dysplasia. Successive sleep studies split the infants into two groups. Group 1 consisted of infants whose saturation decreased to between 88% and 91% for more than 1 hour of sleep. Group 2 consisted of infants whose sustained minimum saturation was 92% or greater for the study. Supplemental oxygen was then stopped, infants were reviewed again in clinic in 4-6 weeks later. After this the mean z score for weight gain decreased from – 0.62 to -5.11 ($p< 0.001$) in infants in Group 1. Mean z scores for weight gain did not change for Group 2 infants after supplemental oxygen was stopped. Secondly average daily weight gain was not different between the two groups at the time supplemental oxygen was stopped but decreased dramatically after supplemental oxygen was stopped in Group 1 infants. So there was a significant difference in average daily weight gain between the two groups after supplemental oxygen was stopped. However their title "Eliminating sleep-associated hypoxemia improves growth in infants with bronchopulmonary dysplasia" was arguably not demonstrated by their study. It did not have a treatment group (where supplemental oxygen was stopped) or comparable control groups

(where treatment was not stopped), and, despite the title, they did not make this conclusion in their discussion.

A further interesting point made nicely by this paper was that there was no correlation between overnight sleep study results and a twenty minute day time oxygen saturation study, also performed as part of the protocol. Clearly it is important to assess these infants at their nadir, which is during deep sleep.

In summary, there may be two or more distinct time periods that can be defined, in the lives of extreme preterm infants who go onto suffer from bronchopulmonary dysplasia for which the best oxygen target levels need to be clearly defined. There is precious little evidence for what oxygen level to aim for from birth in extreme preterm infants prior to the development or otherwise of bronchopulmonary dysplasia and other morbidities of prematurity. It may well be that following the early weeks of life the level of oxygen required to balance the numerous risk factors for morbidity swings to a higher level. By the time of discharge this oxygen target may again change for a further time in the infants who still have the worst lung function, to allow better growth, and reduce the incidence of sudden infant death.

1.5. Equipment for monitoring oxygen and its problems

It is still not clear how to optimise oxygen administration. Indwelling arterial catheters have been widely used to monitor arterial oxygen tension, but no controlled trials have ever shown that their use reduces the risk of permanent retinal damage[30] [106] or the morbidities related to oxygen toxicity. In the 1970's, transcutaneous electrodes were introduced in an attempt to solve the problem of supplemental oxygen causing ROP. Unfortunately, it failed although analysis of data did suggest that retinopathy was more common when the transcutaneous reading reached or exceeded 80mmHg (10.7 kPa) in the first week of life[32].

Transcutaneous oxygen tension ($TcPO_2$) is a measure of the partial pressure of oxygen dissolved in the blood, and is obtained by measuring the amount of oxygen that diffuses through a baby's skin. Transcutaneous monitors have several limitations in that they are sometimes very inaccurate. They require calibrating which can be difficult and time-consuming, and leads to periods of time when no oxygen level is displayed. They need repositioning as they can cause skin burns if left on too long. This makes them unsuitable in the extreme preterm infants, with friable skin. Although originally data relating oxygen damage to morbidities used transcutaneous monitors to control oxygen, most recent studies have used saturation monitors.

Oxygen saturation (SpO_2) monitoring measures the percentage of the available oxygen binding sites on haemoglobin molecules in the blood that are saturated with oxygen. This measurement is accurate in the 80-100% saturation range at a range of heart rate, blood pressure, packed cell volume, $PaCO_2$ and pH values in infants and also seem to be more accurate than $TcPO_2$[107]. This is also true in very low birth weight infants. These devices are non-invasive, easy to use, and do not require calibration or cause heating of the skin. However, their accuracy diminishes toward lower ranges of oxygen saturation (<80%). They have a relatively high rate of false alarms[108-110], often caused by poor signal resulting from motion artefact. They are also light sensitive, and different monitors use different techniques fractional/functional. But, perhaps most importantly, because of the shape of the oxygen dissociation curve small changes in oxygen saturation above 95% can mask large increases in oxygen tension (reduced sensitivity to hyperoxia)[30 111-113]. Although they utilise the same technology, saturation monitors produced by different manufacturers have slightly different algorithms, for converting the light signal into a saturation value, meaning that there is variation between monitor readings between different manufacturs[109-111 113]. Current safety specifications required of SpO_2 monitors are quite lax, requiring SpO_2 readings to only be within +/- 3% of the actual saturation for 68% (1 SD) of the time (Clause 50.101.2.2 of ISO 9919).

With both monitoring methods, upper and lower alarm limits are set and the nursing staff adjust the infant's inspired oxygen concentration as required. Changes in infant behaviour or well-being cause the oxygenation to fluctuate, as do changes in the inspired oxygen concentration in response to alarms.

At present there have been no studies that have directly compared these two forms of oxygen monitoring. The gold standard, arterial blood gas measurement, has the drawback of occurring only every 3-4 hours, and there is an obvious need to monitor in-between. Most of the time the infant's oxygen level is therefore dependent on the method of monitoring.

1.6. Physiology of desaturation events

To understand how to best keep infants within target range we must first start to understand the physiology of desaturation events.

1.6.1. Apnoea

Upton et al[114] studied airway patency during apnoeas in 24 preterm infants (median birth weight 1120 g and gestation 29 weeks) on 83 occasions by measuring upper airway airflow. Airway patency was detected by the transmission of cardiac impulse up the airway and airway closure by its absence. A total of 309 apnoeas of at least five seconds' duration were recorded. One hundred and eighty (58.0%) were central, 109 (35.5%) mixed, and 20 (6.5%) obstructive. Airway closure was noted in 47% of apparently central apnoeas. Airway closure occurred as apnoea lengthened; the airway remained patent in 38% of apnoeas of 5-9 seconds, 17% of those 10-14 seconds, and 11% of those 15-19 seconds' duration. Airway closure occurred in every apnoea of greater than or equal to 20 seconds. In 72% of mixed apnoeas, airway

closure was recorded during the central element and this usually preceded obstructive breaths. In 20% of mixed apnoeas and 15.5% of the total group, the airways closed, having previously been patent. This occurred after a mean of 3.5 seconds (range 1-17). Mixed apnoea produced a significantly greater drop in arterial oxygen saturation than central apnoea, but only because of the greater duration of mixed apnoea. These authors concluded that airway closure occurs in both central and mixed apnoea and appears to be important in the pathophysiology of mixed apnoea. Central and mixed apnoea are part of a continuum of airway closure and not separate entities. This suggests that simply turning up the oxygen dial in response to these events will not quickly bring these infants out of their hypoxemic state.

Idiong et al[115] analyzed 198 episodes of mixed apnoea of various lengths (≥3 seconds) observed in 33 preterm infants (birth weight, 1.4 ± 0.1 kg [mean ± SEM]; study weight, 1.7 ± 0.1 kg; gestational age, 29 ± 1 weeks; postnatal age, 33 ± 4 days). The great majority of these episodes (88%) had a central, followed by an obstructive, component. Infants were studied by using a nosepiece and a flow-through system. Respiratory efforts (abdominal and chest movements) were recorded. Of the apneas, 20 were <5 seconds; 78, 5 to <10 seconds; 45, 10 to <15 seconds; 27, 15 to <20 seconds; and 28, ≥20 seconds. Of the 198 mixed apnoeas, 151 (76%) occurred in the absence of any respiratory effort; 43 (22%) showed a simultaneous cessation of the cardiac oscillation and respiratory effort; and 4 (2%) showed diaphragmatic activity appearing after cessation of the cardiac oscillation (airway occlusion). This suggests that apnoea is associated with later airway closure in the vast majority of cases.

1.6.2. Ventilatory "splinting"

Bolivari et al noted that most hypoxemic episodes in preterm infants undergoing mechanical ventilation were triggered by active expiratory effort that produces a large decrease in lung volume, so called "splinting"[116]. It is not clear whether the rapid development of hypoxaemia is caused, as they suggest, by a reduction in lung

volume leading to closure of small airways and the development of intrapulmonary shunts, or whether it is explained by the shape of these infants' inspired oxygen vs saturation curves, whereby a small decrease in the alveolar oxygen pressure caused by the reduction of tidal volumes during the periods of active expiratory effort led to a steep fall in oxygen saturations achieved.

Hummler et al[117] also found in a population of unstable (at least two episodes of desaturation per hour) ventilated preterm infants, that close to 90% of all episodes of desaturation were preceded by an increase in esophageal pressure, indicating a rise in pleural pressure, which suggests the occurrence of a forced expiratory effort. These episodes were also observed by Esquer et al[118] in preterm infants following extubation from prolonged ventilation. Esquer et al found that most hypoxemia episodes in preterm infants presenting with recurrent episodes of hypoxemia after mechanical ventilation were associated with abdominal muscle contraction and loss in lung volume. This contraction of abdominal muscles increases intra-abdominal pressure and leads to forced exhalation, hypoventilation and hypoxemia.

1.6.3. The peripheral arterial chemoreflex in preterm infants

The peripheral arterial chemoreceptor reflex, in response to hypoxia, includes both ventilatory (hyperventilation), and cardiovascular "diving reflex" (bradycardia and peripheral vasoconstriction) changes[119]. In more mature animals and humans the bradycardic response mediated by peripheral arterial chemoreceptors is usually counterbalanced by tachycardia elicited by pulmonary stretch receptors activated by hyperventilation of lung[120 121]. Therefore the response to a short hypoxic exposure results in hyperventilation, tachycardia and peripheral vasoconstriction. In preterm infants, inhibitory influences predominate and such exposure results in apnoea, and unmasking of the bradycardic response of the chemoreflex.

The contribution of peripheral arterial chemoreceptors to baseline ventilation is greater in premature infants versus term infants, contributing to the greater frequency of periodic breathing and apnoea seen in preterm infants[119 122 123]. This contribution of peripheral arterial chemoreceptors to baseline ventilation increases with postnatal maturation[124-126].

Both hypoxia and hyperoxia in the preterm infant may lead to a response from peripheral chemoreceptors. A biphasic ventilatory response to decreased inspired oxygen is well described in preterm infants. During the first minute of hypoxia, preterm infants typically show a rapid increase in minute ventilation, followed by a decline in ventilation to baseline or below usually evident by 3 minutes[126]. The early excitatory phase of the hypoxic ventilatory response is caused by peripheral chemoreceptor stimulation, and decline is thought to be secondary to hypoxemia-induced central depression of respiration overriding the initial peripheral chemoreceptor stimulation. This hypoxic ventilatory depression is secondary to descending inhibition from the upper brainstem, midbrain, or higher structures.

However Alvaro et al[127] found that preterm infants born at 29 (+/- 0.4) weeks, studied at 17 (+/- 3) postnatal days responded to hypoxia (15% O_2) by a sustained decrease in ventilation ie their initial hyperventilatory response was completely blunted. It is unclear if this was because of their extreme prematurity.

Nock et al[126] found evidence that older preterm infants mean (SD) gestation 30 (2) with greater number of apnoeic episodes at mean (SD) postnatal age 38 (17) days have an enhanced peripheral chemoreceptor activity to hypoxic exposure resulting in increased ventilatory activity, which did not attenuate after 3 mins. This may explain their apnoeas, through a centrally mediated drop in respiratory drive, following lower $PaCO_2$.

Preterm infants also show increased chemoreceptor response to hyperoxia. After standardising baseline oxygen saturations to 83 +/- 1%, by giving 16 +/-0.6% inspired oxygen, in response to a single breath of 100% O_2, premature infants reduced their minute ventilation by 40% in contrast to 14% in term infants[128]. Apnoea was more frequent in preterm infants than term infants. The decrease in minute ventilation attributable to peripheral chemoreceptor activity was secondary to a reduction in breathing frequency in the more immature infants versus tidal volume in more mature infants. Cross et al[129] also found greater reduction in minute ventilation in preterm versus term infants in response to 100% O_2.

Mild hypoxaemia increases baseline chemoreceptor activity in preterm infants. Haider et al found that the baseline O_2 concentration in preterm infants was a significant predictor of the percentage reduction in ventilation in response to hyperoxic challenges[130]. The lower the baseline O_2 concentration prior to the hyperoxic challenge the greater the reduction in ventilation and the longer the apnoeic event. Thus apnoea is a frequent response in preterm infants to exposure to 100% oxygen. This is particularly significant in our preterm infants with lung disease who tend to run with lower oxygen saturations because of the nature of their disease. This in turn may increase their baseline chemoreceptor activity and increase their risk of periodic breathing and apnoea. Furthermore, Lofaso et al[131] using flow through barometric plethysmography found that repeated hyperoxia exposure (exposure to 100% oxygen) to Swiss mouse pups led to increased respiratory depression measured by decreased respiratory rate and increased total apnoea duration, an effect that became stronger with repeated exposure. Whereas exposure to 30 % O_2 significantly inhibited ventilation, but this effect did not become stronger with repeated exposure.

1.7. Oxygen targeting, adherence to targets and response to monitoring

1.7.1. Importance of oxygen targeting

Altered regulation of vascular endothelial growth factor (VEGF) from repeated episodes of hyperoxia and hypoxia, has been suggested as one of the factors in the pathogenesis of ROP[132]. This is backed up by the link, noted by Cunningham, between transcutaneous oxygen variability and ROP[19]. In his study, infants who required treatment for ROP, had significantly more variable transcutaneous oxygen readings. So far oxygen variability has not been linked to other morbidities such as BPD or neurological complications. Excess amounts of oxygen in the blood (hyperoxia) are causally linked to a variety of neonatal conditions including BPD, NEC, ROP and adverse neurological outcome[9-13 18 30-37], therefore adherence to oxygen targets is important as well. There has been little research into human response to monitoring.

1.7.2. Adherence to target

Investigators have given preliminary reports of data on compliance with target ranges and have shown substantial variation between individuals and between centres. Sun et al[133] studied the ability of 35 NICU nurses caring for 10 ELBW infants to keep infants within a target range of 80-92%. 51% of nurses were able to limit hyperoxia exposure (defined as $SpO_2 > 95\%$) to <1% of their 12 working hours, but 9% failed to prevent hyperoxia 20% of the time. The length of time exposed to hypoxemia varied from 1.7% to 17.4% of 12 working hours. Overall 62% of total recorded time was within the prescribed range (SpO_2 80-92%), 9% in hyperoxemic range (defined as $SpO_2 > 95$), and 7% in hypoxemic range (defined as $SpO_2 < 80\%$).

In the AVIOx study[134], compliance with saturation policy was monitored in 84 infants born at less than 28 weeks of gestation in 14 centres. Oxygen saturation policy limits ranged between 83% and 92% for lower limits and 92% and 98% for upper limits. Compliance was measured during a 72 hour period in each of the first 4 weeks of life in infants who were in oxygen. Data were compared with the pulse oximeter saturation target range prescribed by local institutional policy. For infants who received respiratory support, median pulse oximeter saturation level achieved was 95%. Center-specific median levels were within the intended range at 12 centers. The proportion of time spent within the intended saturation range varied substantially from 16-64% between centres. Most non-compliance was above the intended target range, with 20% to 73% of time spent above intended range.

Rasmussen et al[135] studied 20 haemodynamicaly stable preterm infants receiving positive pressure support. The target saturation range was 88-92%, alarms were set at 84% and 96%. The "motivated carers" in this study maintained the infants in this range 29% of the time. 20% of time was spent below a saturation of 88%, 10% of time below 84%, 49% of time was spent with saturations above 93% and 9% of time was spent above 96% saturated. In the STOP-ROP study[97] 8% of median saturations in the lower target range group fell in the higher target range. This suggests that there was a substantial issue with compliance.

Clucas et al prospectively collected data on the alarm limits set in infants with gestational age <32 weeks or birth weight <1500 g in 144 infants, finding lower alarm limits were set correctly 91.1% of the time but upper alarm limit was set correctly only 23.3%[136]. Infants with an upper alarm limit set correctly on a particular day had a significantly lower birth weight, gestational age, postmenstrual age, and postnatal age than infants who had the upper alarm limit set too high. Use of assisted ventilation, higher inspired oxygen concentrations, and more frequent changes in inspired oxygen concentration, were all associated with improved odds of having an appropriately set upper alarm limit. The study suggested that compliance

with unit policy for upper pulse oximeter alarm limit for infants receiving oxygen was poor, as limits were commonly set incorrectly, although compliance was better for infants at higher risk of adverse outcomes. Clucas et al reported that a memo was sent to all staff citing the new standard for oximetry limits in the neonatal unit, however it was not clear from the paper how this was reinforced. Several factors may have contributed to this lack of compliance in their new protocol such as how the memo was dispersed, whether staff read the memo, whether the guideline was accessible at the bed side, resistance from staff worried about possible deleterious affects of the new guideline, lack of staff education, a problem with the clarity of the guideline. Unfortunately, none of this was addressed in the paper and so it is not clear that this is not just teething problems with the new guideline and whether compliance would rise to levels previously shown.

Nghiem et al[137] attempted to compare pulse oximeter saturation limits targeted by nurses for extremely preterm infants during routine care with nurse opinions regarding appropriate pulse oximeter saturation limits and with policy specified pulse oximeter saturation limits to identify factors that influence pulse oximeter saturation limits targeted by nurses. They conducted a web based survey of neonatal staff nurses in US level III NICUs. Among those eligible, 2805 (45%) nurses in 59 (60%) NICUs responded. Forty (68%) of 59 NICUs had a policy that specified a pulse oximeter saturation target range for extremely preterm infants. Among 1957 nurses at NICUs with policies, 540 (28%) accurately identified the upper and lower limits of their NICU's policy and also targeted these values in practice. NICU-specific SDs for individual nurse target limits were less at NICUs with versus without a policy for both upper and lower limits. They concluded that the presence of policy-specified pulse oximeter saturation limits, nurse group opinion, and individual nurse opinion were independently associated with individual nurse pulse oximeter saturation target limits during routine care of extremely preterm infants. The presence of a policy reduced the influence of individual nurse opinion on targeted pulse oximeter saturation limits and reduced variation among nurse target limits within NICUs.

In Nghiem's study, nursing staff were surveyed concerning saturation levels targeted, and this was compared to a gold standard, which was nurse managers' opinions of the actual unit policy on saturation target range for infants of less than 28 weeks gestation. It did not include any data on the oxygen saturation levels achieved by the nursing staff, or the actual oxygen saturation targets used during each period (there may be a difference between unit policy targets, nursing staffs memory of targets, and the actual target set on an infant's saturation monitor at any one time). Although 63 % of nursing staff may not have been aware what the unit saturation policy was for saturation monitoring, this does not mean that they were not still targeting the correct levels. Monitors may equally have been set the shift before, or defaulted to set oxygen limits. This effect was not analysed or discussed. The only conclusion that can be drawn from this paper is that a small proportion of nursing staff in the study could correctly identify their units oxygen saturation limits, and a smaller proportion actually targeted these limits. Other conclusions made by the researchers are not clearly supported by their analysis.

1.7.3. Interventions to achieve better compliance

1.7.3.1. Unit policy adjustment

Laptook et al[138] compared the distribution of SpO_2 levels achieved following a change in the pulse oximeter goal range and high alarm limit, for oxygen saturation (SpO_2) in premature infants in oxygen. This prospective, observational analysis compared infants in Group 1 (February 2002 to April 2002, n=23), where pulse oximeter alarms were set at 80% (low) and 96% (high), and the goal range was 90–95%, with infants in Group 2 (May 2002 to August 2003, n=49), where the high alarm was lowered to 94%, and the goal range was 88 to 94%. The SpO_2 values for 24 h were downloaded from Nellcor pulse oximeters during the two periods and the percent time within, above and below the goal range were derived and compared. Groups were similar except for use of postnatal steroids (Group 2 > Group 1). The

percent time within (57.7±9.8 vs 59.4±12.4%), above (15.4±10.6 vs 14±9.4%) and below (26.9±9.7 vs 26.6±10.2%) the goal range was similar for Groups 1 and 2, respectively. However, the percent time with SpO_2 <80% increased significantly for Group 2 (4.0±2.7 vs 1.9±1.4%). Although conclusions should be guarded because of the study design, they suggest that lower oxygen saturation goals might increase time spent in the hypoxic range. However one could also argue that this is evidence that tighter alarm limits increase hypoxia time

A paper by Chow et al describes how a continuous quality improvement process including an educational program and implementation of a new oxygen management policy in a level 3 neonatal unit, was associated with a dramatic decrease in retinopathy of prematurity[37]. The oxygen management policy was designed to reduce the repeated episodes of hypoxia-hyperoxia in very low birth weight infants. The improvement process involved new policies on monitoring, avoidance of repeated increases and decreases of FiO_2, minimisation of "titration" of FiO_2, modification of previously used alarm limits and a staff education program. The paper did not define the policies that were in place prior to the intervention, perhaps because these were not under very close control. Nor did it present information regarding compliance with individual aspects of the new initiative. This makes it difficult to determine which aspects of their intervention may have been the most important. If their infants were exposed to considerable hyperoxia prior to the intervention, then reducing this alone could have explained most of the change in levels of ROP.

Another study, by VanderVeen et al, found that lowering oxygen saturation alarm limits for infants at risk for retinopathy of prematurity (ROP) was associated with a reduction in its incidence and/or severity[35]. Levels of ROP in two cohorts of infants before and after a change in oximeter alarm policy were compared. Oxygen alarm limit range was reduced from 87-94% to 85-93% for all infants with a birth weight 1250 g or less and/or gestational age 28 weeks or less, and maintained until 32 weeks postmenstrual age, or until oxygen saturations were consistently greater than 93% in

room air. ROP data were prospectively collected, and they compared the rate and severity of ROP in the year after the oximeter alarm policy change, to the rates in the immediately preceding 3 years. In the year after the oximeter alarm limit policy change, 4 of 72 infants developed prethreshold ROP, compared with 44 of 251 infants in the previous 3-year epoch (17.5% vs 5.6%, p= 0.01). Similarly, only 6 of 144 eyes developed prethreshold ROP in the year after the policy change, compared with 84 of 502 in the previous 3 years (16.7% vs 4.2%, p= 0.001). They concluded that a simple change in oximeter alarm parameters in the first weeks of life for infants with a birth weight 1250 g or less may decrease the incidence of prethreshold ROP.

In a similar study by Wright et al[139], the incidence of threshold ROP in infants whose birthweight was between 500 and 1500 grams fell from 7.3 to 1.3% ($p < 0.05$), following the introduction of reduced oxygen protocol and training to minimize fluctuations in SpO_2 and to adjust FiO_2 in small increments. This was an observational study, prior to and following, implementation of the reduced oxygen protocol and training. The study took place in three neonatal intensive care units in the US with varying saturation target ranges prior to implementation of the new policy. All limits were changed in a downward direction to then target saturations of 83-93 %, and were visited by one of the study's authors. Infant mortality rates did not change significantly following the implementation of the reduced oxygen protocol.

1.7.3.2. Effect of ventilation mode on compliance with target range

Adubakar et al[140] found that assist control with volume guarantee (AC + VG) mode was associated with less variability of SpO_2 than synchronised intermittent mandatory ventilation with volume guarantee (SIMV + VG), however the mean saturation achieved during this mode of ventilation was significantly higher: 95 % vs 91%, which means that they must have achieved much higher levels of modifiable

hyperoxia during this method of ventilation (their target range was 88-92%). This was not commented on in their discussion.

Hummler et al[117] set out to test the hypothesis that ventilated very low birth weight infants with frequent hypoxemic episodes would have at least 20% less time with hypoxemia (defined as SpO_2< 80%) when volume-controlled synchronized intermittent mandatory ventilation (SIMV) was used rather than pressure-controlled SIMV. A randomized cross-over study design was used, in 15 mechanically ventilated very low birth weight infants with frequent hypoxemic episodes. The infants were exposed in random order to volume-controlled and pressure-controlled SIMV for 4 h each. The target tidal volume during volume-controlled SIMV was matched to the tidal volume measured during pressure-controlled SIMV. FiO_2 was adjusted using uniform criteria to maintain SpO_2 within the target range (SpO_2 80–92%). The primary outcome measure was the time with an SpO_2< 80%. Although tidal volume was maintained better during desaturations with volume-controlled SIMV, there was neither a significant difference in time with an SpO_2< 80% (expressed as proportion of total experimental time; median, interquartile range)—volume-control 10.6% (9.2–13.7%) vs. pressure control 10.8% (8.3–13.3%)—nor in FiO_2 exposure. However, during volume-controlled SIMV, the infants spent less time with an SpO_2 above the target range (20% vs 25.9, p=0.04) and had fewer associated bradycardias (2 vs 3, p=0.03).

This was a small study, with only 15 patients, and may have lacked sufficient power to detect a small difference in the primary outcome, but it does suggest that, if there is a difference, it is small. Hummler et al's finding of reduced time spent in the hyperoxic range is very significant, and may represent a method that might be used to achieve better compliance to oxygen target levels. The explanation of why less hyperoxia was achieved probably represents difference in nursing staff reaction to desaturation events. Staff were less likely to increase inspired oxygen levels during desaturation events (non significant trend) or made smaller oxygen adjustments (not

measured in the study). As a result, volume-controlled infants tended to have less deep desaturation events (not significant), better preserved tidal volumes during desaturation events and fewer associated bradycardias. The authors also found evidence that close to 90% of all episodes of desaturation were preceded by an increase in esophageal pressure, indicating a rise in pleural pressure, which suggests the occurrence of a forced expiratory effort.

1.7.3.3. Computer oxygen targeting

Bhutani describes 3 protocols for adjusting inspired oxygen, in a group of infants with bronchopulmonary dysplasia, mean gestation 26 weeks at an average of 41 days[141]. The infants' oxygenation was monitored using pulse oximetry with target saturation of 95%, range from 92 to 96%. The three methods were: 1) standard neonatal intensive care protocol with oxygen delivery evaluated at 20 minute intervals: 2) bedside manual control with FiO_2 manipulation every 2 to 5 minutes; and 3) adaptive control with on-line adjustment of FiO_2, according to specifically designed adaptive program. Saturation values within a steady 94 to 96% range were achieved for 54% of the time with standard protocol, compared to 69% ($P<0.01$) with bedside manual control and 81% ($P<0.01$) with adaptive control. Although the authors reported that "fluctuations in SpO_2 values and overshoots were less apparent with adaptive control of oxygen delivery", they presented no data to demonstrate this. Further they did not present data that suggested how the variation in inspired oxygen or end oxygen saturation variation was affected by these different protocols.

Claure et al found a significant increase in the duration of normoxemia (75% of time within range) when using closed-loop FiO_2 control to maintain SpO_2 within a target range compared with continuous manual FiO_2 adjustments by a nurse (66% of time within range) in a group of ventilated infants who presented with frequent episodes of hypoxemia[142]. However they failed to show significant reductions in the number of hypoxemic or hyperoxemic episodes/hour, or the duration of these events.

Urschitz et al developed a system for automatic oxygen control and hypothesized that this system is more effective than routine manual oxygen control in maintaining target arterial oxygen saturation levels[143]. They performed a randomized controlled crossover clinical trial in 12 preterm infants receiving nasal continuous positive airway pressure and supplemental oxygen. Periods with automatic and routine manual oxygen control were compared with periods of optimal control by a fully dedicated person. The median (range) percentage of time with arterial oxygen saturation levels within target range (87–96%) was 81.7% (39.0–99.8) for routine manual oxygen control, 91.0% (41.4–99.3) for optimal control, and 90.5% (59.0–99.4) for automatic control (ANOVA: $p = 0.01$). Pairwise *post hoc* comparisons revealed a statistically significant difference between automatic and routine manual oxygen control (Dunnett's test: $p = 0.02$). The frequency of manual oxygen adjustments was lowest in automatic control (Friedman's test: $p=0.001$). They concluded automatic oxygen control may optimize oxygen administration to preterm infants receiving nasal continuous positive airway pressure and reduce nursing time spent controlling oxygen levels. Closed loop or adaptive controlled inspired oxygen concentration may be the way forward, reducing some of the burden of alarms placed on nursing staff and allowing them more time to carry out more of their ever extending role when looking after the extreme preterm neonate.

These studies suggest that close control of inspired oxygen be it manually or by computer control, leads to less variability in oxygen saturation in the infant. This raises various questions: (1) How does staff seniority affect overall oxygen control? (2) How does staff knowledge and education affect oxygen control ? (3) How does one's attitude to oxygen control affect the oxygen variability? - do you regularly turn the FiO_2 dial or do you let the infant wander? (4) Do tight targets lead to more stable oxygen? (5) How does tight control of oxygen affect overshoots and end oxygen variability? (6) How does the amplitude of the change in inspired oxygen to a given

desaturation affect variability and overshoot? (7) How does the method of monitoring affect the end oxygen variability?

1.8. Oxygen dissociation characteristics of extreme preterm infants

Oxygen saturation measurements are widely used in neonatal units to monitor levels of oxygen in extreme preterm infants and to decide whether they require supplemental oxygen or not. The gold standard measure of oxygen levels in the blood, namely oxygen partial pressure of an arterial blood sample (PaO_2), can only be measured every few hours. This means that, most of the time, infants' blood oxygen levels are controlled by responding to alarm limits set on oxygen saturation measurements i.e. aiming to keep infants' saturation between set limits.

Most recent research trying to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants, has used oxygen saturation monitoring. Older research related transcutaneous PO_2 achieved to morbidity and mortality[19] [32]. Unrestricted use of oxygen has been unequivocally linked to retinopathy of prematurity, and has been linked to other morbidities such as BPD, NEC[91], and neurological problems[34]. Yet there is a worry that using inappropriately low oxygen levels might also increase these morbidities.

Over the last few years there has been a trend to reduce the oxygen saturation limits accepted, following concerns that we might be giving too much oxygen. Furthermore, there has been a multi-centre randomised controlled trial designed to determine what are the best oxygen saturation limits to run infants at, to minimise these morbidities. In the backdrop to these studies, it is important to know how oxygen saturation relates to PaO_2 in extremely low birth weight infants. This has

been well studied in the 90-100 % saturation range, but has not been clearly defined below this[30 112].

Limited published data indicate that there is a wide range of PaO_2 values for a given saturation in preterm infants[112 144]. The data available do not describe the full range of saturation values encountered in contemporary practice, or the more immature infants now cared for. This population of infants is at particularly high risk of adverse outcomes associated with oxygen radical disease, and it might be that the difference in PaO_2 achieved with different saturation limits is what actually relates to morbidity and mortality. An infant's oxygen dissociation curve may play an important role in how their Hb gives up oxygen and therefore end organ damage.

Shyang-Yun Shiao et al[145] examined 660 arterial blood gas samples in the first five days of life, in a population of 78 neonates between 25-38 weeks, comparing functional pulse oximetery saturation at time of sampling against arterial oxygen tension. They produced a sigmoid best fit curve comparing the two variables over the range 30-100 mm Hg (90-99 % saturation). This suggested that in order to maintain arterial oxygen tension of 50 to 75 mm Hg using pulse oximetery, the saturation range required to achieve this would be 95-97 %. However, their conclusion that the safety limits for pulse oximeters are higher and narrower in neonates (95-97%) than adults, is disturbing given the lack of evidence in the study for the stated normal oxygen tension range[146-148], the wealth of evidence for significant increase in morbidity if high saturations (typically above 95%) are maintained[31 34 35 37 101-103], and the lack of evidence that lower oxygen saturation limits cause increased morbidity[31 100]. The authors' reference for this PaO_2 range actually quotes 45-65 mmHg for preterm infants which they have mainly studied, and one assumes their conclusion is mainly aimed at this population[147]. Clearly we still do not have a definitive study to suggest what oxygen levels to aim for in preterm infants to minimise morbidity, though there is a substantial body of observational evidence that

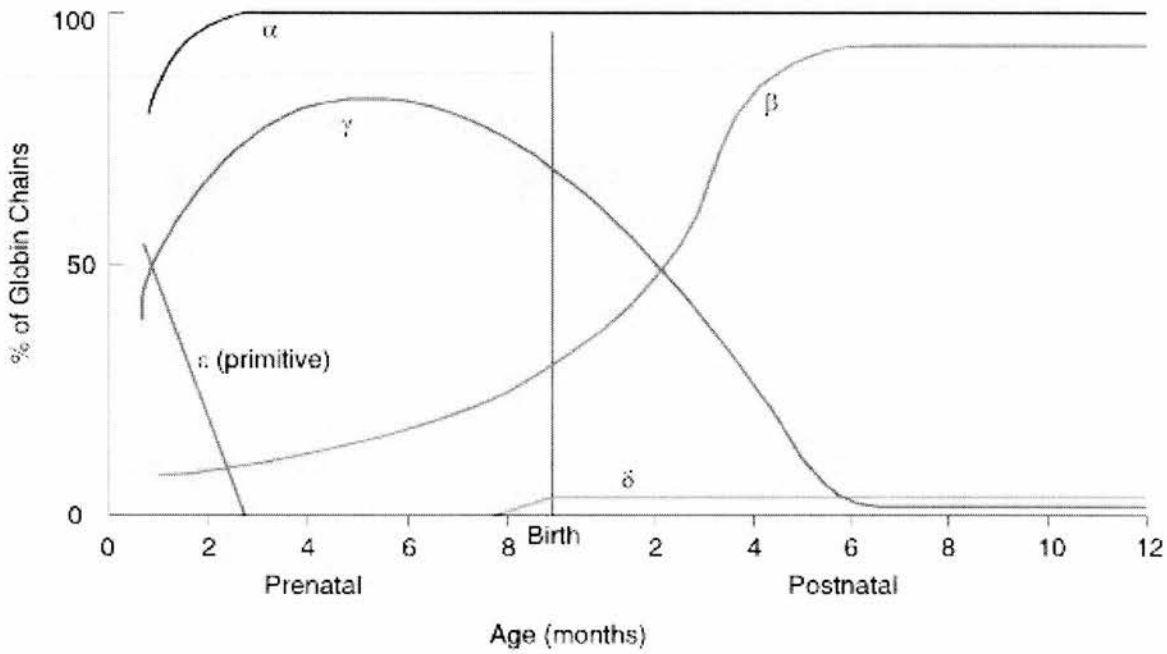
aiming for saturations above 95% in extreme preterm infants is associated with increased rates of ROP.

There were also further, significant, methodological problems in the paper. Firstly, the authors' choice of such a wide gestational range does not help applicability to any particular population of infants. They possibly should have excluded more mature infants or discussed them separately. They have not given acid base status and temperature of the infants, which will affect the shape of the dissociation curve through the Bohr affect. They have not mentioned the saturation or PaO_2 range or variation that this data is obtained over. If all their data points were above 95% this might affect the shape of their lower dissociation curve, and points much below this should not be predicted from this data. They have not given the mean and SD number of blood gas samples obtained from their infants. They have plotted sigmoid curves for the dissociation curve but have not quoted confidence intervals for this, or given a measure of variation of PaO_2 for each saturation. Their use of SPSS sigmoid curve plotting is questionable as although this approximates their points to a sigmoid shape, the shape created may not be the same shape as a dissociation curve. They have given their curve fitted PaO_2 values for pulse oximetry saturation but have not given confidence limits for their data. 19 % of the infants they included had heart defects "causing signs and symptoms of central shunting". This again might affect the pulse oximetery oxygen saturations obtained and therefore the shape of their dissociation curve. They have not discussed the placement of their arterial line and saturation probes.

Because the range of PaO_2's for a given saturation may be so wide, targeting saturation limits may be over-simplistic. This information would be vital when designing large multi centre studies.

It is well know that the oxygen dissociation curve varies with gestation, fraction of fetal/adult haemoglobin, pH and 2,3 diphosphoglycerate (DPG)[149]. DPG is not affected by gestation however[149 150]. See Figures 5-7[149 151 152].

Figure 5: Relative amounts of globin chains present during fetal development[151]



Relative amounts of the several globin chains (ε, α, γ, β, and δ) present during fetal development and the first year of life.

Figure 6: Fetal haemoglobin vs adult haemoglobin oxygen dissociation curve[152]

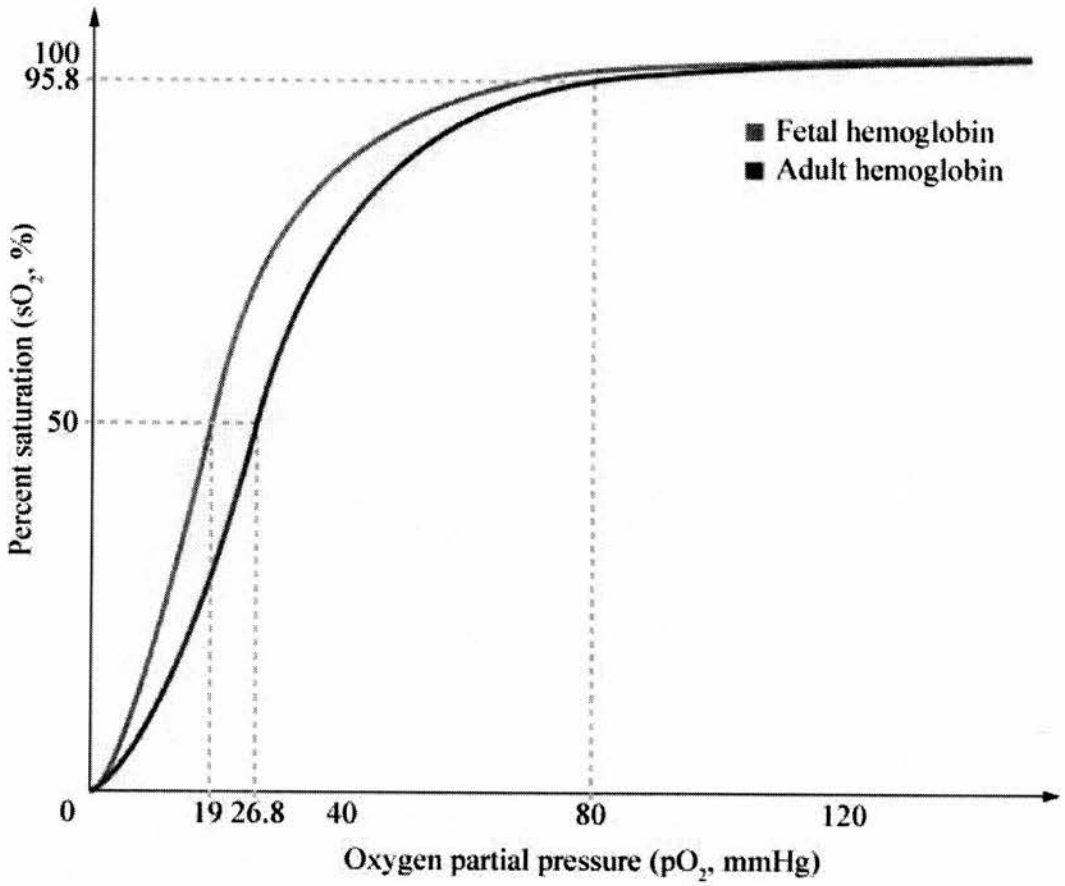
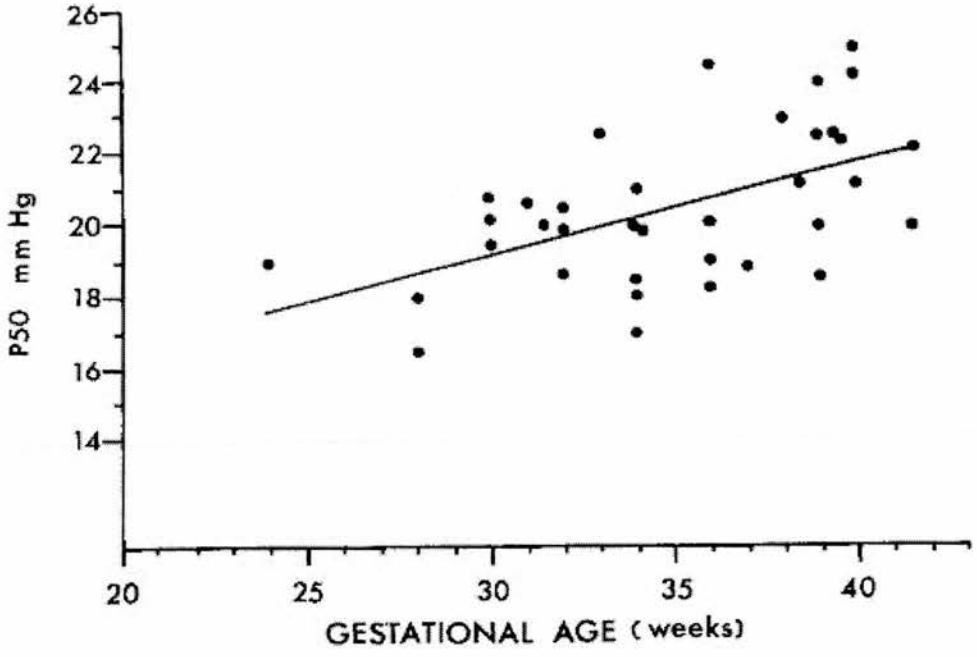


Figure 7: Blood P50 in relation to gestational age[149]



Blood P50 in relation to gestational age. Solid line is calculated linear regression line; $r = .62$; $P < .001$.

The oxyhaemoglobin dissociation curve relates oxygen saturation (SO_2) and partial pressure of oxygen in the blood (PO_2), and is determined by haemoglobin's affinity for oxygen, that is, how readily haemoglobin acquires and releases oxygen molecules from its surrounding tissue.

From the equilibrium equation ($Hb_n + n\ O_2 <=> (HbO_2)_n$), Hill[153] described the following equation:

$$\theta = \frac{[L]^n}{K_d + [L]^n} = \frac{[L]^n}{(K_A)^n + [L]^n}$$

Equation 1:Equilibrium equation

Where:

θ - fraction of ligand binding sites filled (in our case saturarion)

$[L]$ - ligand concentration (PO2)

K_d - dissociation constant derived from the law of mass action (equilibrium constant for dissociation)

K_A - ligand concentration producing half occupation (ligand concentration occupying half of the binding sites) (P50)

n - Hill coefficient, describing cooperativity (and many more, depending on the system, in the case of which the Hill equation is used) (2.7 for Hb)

meaning:

$$\text{Saturation} = K^* PO_2^n/(1 + KPO_2^n)$$

Equation 2: Oxyhemoglobin dissociation curve equation

With a value for n of around 2.73, K=1/P50

Which can be rearranged as:

$$PaO_2 = n\text{Log}(SpO_2/100\text{-}SpO_2)/P50$$

Equation 3: Oxygen tension from saturation and P50

It was determined that haemoglobin consisted of 4 subunits. Adair[154] postulated 4 equilibrium reactions with constants generating an equation of the form:

$$\text{Saturation} = (a_1p+2a_2p2+3a_3p3+4a_4p4)/[4*(a_1p+a_2p2+a_3p3+a_4p4)]$$

Equation 4: Adair equation

Where a_1-a_4 are the "Adair parameters" and p is the oxygen tension.

Hill's equation was modified by Severinghaus[155], to fit the standard human blood O_2 dissociation curve to within +/- 0.55% from saturation 0-100%

Fractional saturation (S) :

$$S = (((PO_2^3+150\ PO_2)^{-1} \times 23{,}400) + 1)^{-1}$$

Equation 5: Fractional saturation (by Severinghaus)

Measurement of the P50 in whole blood, defined as the oxygen tension corresponding to 50% oxygen saturation, gives a quantitative measure of haemoglobin affinity. Originally Aberman suggested that P50 could be accurately calculated from single measurements of oxygen tension (PaO_2) and the corresponding oxygen saturation (SO_2)[156]. Wimberly subsequently improved on this mathematical model of the oxyhemoglobin dissociation curve, which was tested[157] [158], and subsequently approved by the IFCC.

$$P50=\exp[\ln PaO_2-0.37*\ln(sat/1-sat)]$$

Equation 6: Single point P50 calculation

This equation was further explored by Burnett who suggested further recommendations to minimse error in P50[159].

The affects of respiratory or metabolic acid-base disturbance and temperature on the oxygen dissociation curve were described by various authors (Roughton, Severinghaus, Kelman)[155] [160] [161]. It is also possible to calculate a virtual oxygen

pressure to correct blood samples that are taken under non standard conditions eg temp, $PaCO_2$ and pH which will affect the shape of the oxygen saturation dissociation curve. This corrects oxygen pressure to standard conditions namely Temp 37 degrees, pH 7.40 and $PaCO_2$ 5.33 kPa (40 mmHg):

$[PO_2 \text{ virtual}] = [PO_2 \text{ actual}]*10^{(0.024(37-T)+0.40(pH-7.40)+0.06(\log10(40)-\log10(PaCO_2))}$.

Equation 7: Virtual arterial oxygen tension correcting to standard conditions

T – Temperature

1.9. Defining bronchopulmonary dysplasia and its underlying pathology: Clinical and physiological definitions of bronchopulmonary dysplasia

Despite great improvements in the survival of infants born prematurely there continues to be a large number of infants who develop bronchopulmonary dysplasia (BPD). This causes them to remain in hospital longer, prolongs their requirement for supplemental oxygen and is associated with long-term morbidity and an increased risk of mortality. Reducing BPD remains a major focus of clinical and research activity. However, an objective definition of BPD is first required to allow reliable interpretation of clinical trial outcomes and to serve as a baseline in prognostic studies. Yet an ideal definition has been elusive. Present definitions such as "the requirement for supplemental oxygen at 28 days of life or 36 weeks CGA" have major flaws.

The first flaw is that the criteria for requirement for supplemental oxygen differs between clinicians and between neonatal units, with the accepted oxygen saturation targets varying substantially between different neonatal units throughout the world[38] [39] [162]. A definition based on the use of oxygen therapy alone gives wide variations in

the incidence of disease that may reflect little more than clinician variation and have little relevance to the severity of any underlying pathology[163].

The second flaw is that these simple definitions are not always a strong predictor of long term pulmonary disease. There is conflicting research as to the long term outcome in preterm infants with BPD - some commentators find prolonged pulmonary pathology[164-168], while others report no significant difference in long term problems between preterm infants who did and did not suffer from clinically defined BPD[169-174]. A frequently quoted paper by Shennan et al described abnormal pulmonary outcomes in preterm infants who had required oxygen at 28 days and 36 weeks CGA and suggested that the requirement for oxygen at 36 weeks was a better predictor of long term pulmonary problems[175]. Unfortunately, in this paper, if an infant required oxygen at term, they were defined as having a poor pulmonary outcome, hardly a convincing long term measure. Even with this definition of poor pulmonary outcome, the positive predictive value for long term pulmonary morbidity was only 63% for infants requiring additional oxygen at 36 weeks CGA, with a likelihood ratio of 6 for a positive test and 0.41 for a negative test. 37 % of infants in this study who needed supplemental oxygen at 36 weeks CGA no longer needed it by term.

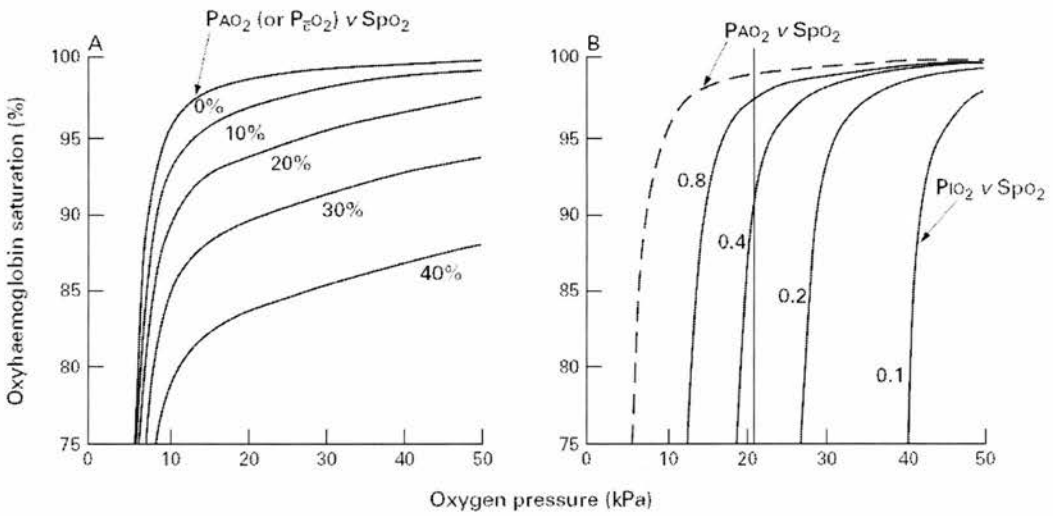
The first flaw in these clinical definitions was addressed by Walsh et al who describe a simple test, by arbitrarily defining a lower oxygen saturation that should be maintained by infants in air, they define a cohort of infants with physiological BPD[163 176]. Infants are defined to have physiological BPD if they require oxygen supplementation to maintain their oxygen saturation above 90%. Using this definition they found approximately 30% of infants diagnosed with BPD by conventional (clinical) criteria could safely and successfully pass an oxygen saturation test where supplemental oxygen was tapered to room air.

This defines a cohort of infants with more severe pulmonary disease than the standard clinical definition of BPD does. This set of infants should be similar even when comparing units, provided that the protocol for the test is adhered to. Walsh et al compared clinically defined BPD with this new physiological definition, and found it led to an average 10% change in the rate of BPD definition at the centres in this study range of 0-44%. This would easily conceal any change in BPD rates in any intervention study. This physiological definition will eliminate bias between clinicians and centres and is undoubtedly an advance. However, healthy preterm and term infants have saturations around 97% in air[48 49], and saturations lower than this must reflect a degree of gas exchange impairment, even if supplemental oxygen is not always deemed necessary. Present approaches to defining BPD classify these infants as disease-free. Walsh et al's approach also defines infants as having BPD or not and is not a graded physiological approach.

It is possible, by non-invasive measurements of PIO_2 and SpO_2, to quantify the severity of gas exchange impairment in a graded fashion and to partition this between the contribution made by reduced ventilation/perfusion ratio (V_A/Q) and that due to right to left shunt[177-182]. Reduced V_A/Q and increased shunt have different effects on the relationship between inspired oxygen pressure (PIO_2) and arterial oxygen saturation (SpO_2). A reduced V_A/Q causes a fall in alveolar and arterial oxygen tension (PaO_2) and a rise in alveolar and arterial carbon dioxide tension ($PaCO_2$). Increasing PIO_2 restores the alveolar PO_2 and SpO_2 to normal, overcoming the effect of the reduced V_A/Q. Increased shunt does not raise $PaCO_2$ but reduces arterial oxygen saturation because the shunted blood is not exposed to alveolar oxygen. Increasing PIO_2 can compensate for only a small amount of shunt because the non-shunted blood is already almost fully saturated and does not carry much more oxygen, other than small amounts in solution when PIO_2 is increased. These independent effects on gas exchange can be represented in the form of plots of oxygen saturation (SpO_2) against inspired oxygen pressure (PIO_2)[177 179-183], as shown in Figure 8.

Figure 8: Plots of oxyhaemoglobin saturation % (SpO_2) vs inspired oxygen pressure in kPa (PIO_2)[181].

(A) Increasing shunt from 0 to 40% lowers the position of the upper part of the curve. (B) Reducing V_A/Q from 0.8 to 0.1 shifts the curve to the right. The right shift of each PIO_2 vs SpO_2 curve from the position of the dissociation curve (dashed line) is the $PIO_2 - PAO_2$ difference in kPa, which includes $PaCO_2/R$. The 0.8 curve represents the normal adult curve which intercepts a PIO_2 of 21 kPa (vertical line) at 97% SpO_2.



At sea level (one atmosphere) the inspired oxygen pressure (PIO_2) in kPa is the same as the inspired oxygen percentage. The curve relating alveolar (mixed capillary) PO_2 to oxygen saturation in the ideal lung represents the shape of the oxy-haemoglobin dissociation curve. Increasing shunt displaces the top part of the curve downwards (Figure 8A) as the maximum SpO_2 obtainable falls. In contrast, reducing V_A/Q shifts the whole curve to the right (Figure 8B). The degree of right shift, using the oxygen dissociation curve as a reference, is determined by the reduction in V_A/Q and rise in alveolar PCO_2. The normal curve is shifted to the right of the haemoglobin-oxygen

dissociation curve by 6kPa, which is largely PCO_2/R (where R is the respiratory gas exchange ratio). Additional right shift compared to normal represents the increase in PIO_2 that will be required to restore the mixed capillary PO_2 to normal levels and thereby permit normal arterial saturation. If multiple pairs of PIO_2 and SpO_2 values are obtained from the same patient then a single pair of shunt and shift values can be derived. This can be done graphically[177-180], by moving a set of shunt curves like those in Figure 8A laterally over the plot of PIO_2 vs SpO_2 data points, until one of the shunt curves superimposes the data points. The degree of shift can then be read off the axis of the graph and the shunt determined by which shunt curve most closely fits the data. Alternatively, the shift and shunt can be calculated using a computer algorithm that derives confidence intervals for the shunt and shift values and coefficients of determination (R^2) for the fit of the data to the shunt and shift model[179-181].

This non-invasive method of partitioning gas exchange impairment has been applied in sick infants[181], and in healthy and sick adults[177 179 180 182] and the results showed a good fit between the model and the clinical data in all age groups and disease states studied. Kjaergaard et al[182] obtained almost identical results non-invasively using saturation measurements to those obtained from simultaneous more invasive measurements.

Iles et al investigated longitudinal changes of interstitial and airways disease in resolving chronic lung disease of prematurity. Thirty-three infants were studied between 35 and 40 weeks of postconceptional age, and then at three monthly intervals throughout their first year[66]. The authors measured mean arterial oxygen saturation ($MSaO_2$) and its variability (deltaMSaO2). $PaCO_2$ and PaO_2 were determined while the infants breathed steady state 50% oxygen via a hood. From these, the alveolar arterial difference was calculated. Airway disease was assessed by the measurement of partial forced expiratory flow volume curves to give V_{max} Frc. They found An $MSaO_2$ of less than 90% in room air at 1 year of age was predicted

between 35 and 40 weeks postconceptional age by an (A-a) DO_2[50] of greater than 29 kpa, with a sensitivity of 0.85 and a specificity of 0.88, and a $PaCO_2$ greater than 7 kpa predicted a specificity of 0.78 and a sensitivity of 0.88. Predictions were strengthened by combining the above criteria and these then gave a sensitivity and specificity of 1. They concluded that measures of gas exchange impairment derived from arterial blood gases sampled around term predict the prognosis of BPD.

Iles et al had previously shown that infants with a low saturation are at increased risk of acute life threatening events. Examining infants with resolving BPD, they found that a mean SaO_2 (actually measured SpO_2) of less than 90% on discharge predicted both hospital admission within three months (sensitivity 1, specificity 0.76), and SIDS/ALTE (sensitivity 1, specificity 0.75)[69]. Moreover, variability of mean individual oxygen saturation greater than 6% also predicted SIDS/ALTE (sensitivity 0.88, specificity 1). The authors concluded that infants with resolving chronic lung disease of prematurity who are at risk of increased morbidity and mortality can be assessed by accurate measurement of mean arterial saturation.

The recent NICHD network consensus definition of BPD[77] categorises infants as no BPD, mild, moderate or severe BPD according to the amount of oxygen supplementation and ventilatory support required up to 36 weeks gestation. These categories predict later respiratory morbidity[184], but they are not physiologically based and later respiratory problems are also seen in a substantial number of infants not identified to have BPD by this definition. Infants with BPD have reduced numbers of alveoli, enlarged airspaces, interstitial fibrosis and variable degrees of small airway narrowing[185]. Defining the degree of physiological impairment associated with this pathology is likely to be more informative than quantifying the preceding exposure to therapies. Like the Walsh test[163], the NICHD network definition[77] is likely to permit infants with saturations lower than those observed in healthy infants to be categorised as no BPD.

2. Chapter 2. Studies[1]

2.1 Study 1: Does the monitoring method influence stability of oxygenation in preterm infants? A randomised crossover study of saturation versus transcutaneous monitoring

2.1.1. Abstract

Introduction

Hyperoxia and variable oxygenation are associated with morbidity in preterm infants. The optimal range of oxygen tensions is not known. The study aimed to determine whether care based on transcutaneous oxygen tension ($TcPO_2$) or saturation (SpO_2) monitoring is associated with less time spent with high oxygen tension and less variability of oxygenation.

Methods

SpO_2 and $TcPO_2$ were measured simultaneously during two 3-hour study periods allocated in random order. During one period supplemental oxygen was adjusted according to $TcPO_2$ (target range 6.0-9.0kPa) and during the other according to SpO_2 (target range 86-94%). During each period readings from the second monitor were not displayed. Both $TcPO_2$ and SpO_2 were downloaded every second. For each period the mean level and the variability (standard deviation) of SpO_2 and $TcPO_2$ and the percentage of time spent above and below target range were calculated and compared.

Results

Nineteen infants, 13 ventilated and 6 on CPAP, were studied at mean corrected gestational age of 27.2 weeks and mean postnatal age of 6.8 days. Their mean FiO_2 at the start of the study was 0.34. Care based on SpO_2 monitoring was associated

[1] All four studies are published. The papers are reproduced in Appendix A

with more time spent with high oxygen tension (median increase 2.62%, p=0.01), more time with low oxygen tension (median increase 17.41%, p=0.01), more variability in oxygen tension (median increase 0.28 kPa, p=0.02) and more variability in oxygen saturation (median increase 0.82%, p=0.01) than care based on $TcPO_2$ monitoring.

Conclusion

Within the target ranges studied SpO_2 monitoring was associated with significantly more variable oxygenation than $TcPO_2$ monitoring.

2.1.2. Background

Hyperoxia and variability of oxygenation have been linked with increased risk of morbidity in preterm infants[18 19 32 34 37]. Oxygen saturation (SpO_2) and transcutaneous oxygen tension ($TcPO_2$) monitors are used widely to monitor oxygen levels in preterm infants. Oxygen therapy is usually adjusted with the aim of keeping the infant's oxygenation within a target range. Specific target ranges vary from unit to unit because there remains uncertainty over the optimal levels[38 186]. Randomised trials are in progress examining different target ranges. Although both types of monitoring device are used, oxygen saturation and oxygen tension are not linearly related to one another. Neither monitoring method is clearly superior in terms of minimising adverse outcome but comparative studies have not been done.

Saturation monitors are non-invasive, easy to use and do not require calibration or cause heating of the skin. They have a relatively high rate of false alarms[108-110], often caused by poor signal resulting from motion. Because of the shape of the haemoglobin-oxygen dissociation curve small changes in oxygen saturation above 95% can mask large increases in oxygen tension so that saturation monitoring may not be reliable in preventing hyperoxia [30 109-113]. Transcutaneous oxygen tension ($TcPO_2$) is a measure of the partial pressure of oxygen dissolved in the blood, and is

obtained by measuring the amount of oxygen that diffuses through a baby's skin. Transcutaneous monitors require calibration and this can lead to periods of time when no oxygen level is being measured. They are sometimes inaccurate [107 110 187 188]. They need to be re-sited regularly to avoid skin damage from heating and can cause skin burns if left on too long. These issues make them more cumbersome and deter some from using them, particularly in more immature infants. The relative convenience of using saturation monitors may be one reason why saturation monitoring has become the predominant method of monitoring oxygenation in the US and in the UK and why more recent studies have focussed on saturation monitoring[19 32 97 98].

With both methods, upper and lower alarm limits are set and the nursing staff adjust the infant's inspired oxygen concentration as required. Changes in infant behaviour or well-being cause the oxygenation to fluctuate, as do changes in the inspired oxygen concentration in response to alarms. Device design and software reflect these levels at different speeds depending on averaging time and this may have its own effect on the oxygen stability of infants. There is evidence from studies in human infants and experimental models that, apart from high or low oxygen levels, excess variability in blood oxygenation may be harmful in itself[18 19]. This contributes to the pathogenesis of retinopathy of prematurity. If one method of monitoring were associated with more frequent adjustments to the inspired oxygen concentration than the other, this may be reflected in a difference in oxygen variability or time spent with high or low oxygen tension. This may represent a source of avoidable harm to the infant.

Study 1 aimed to determine whether infants are exposed to more cumulative hyperoxia or hypoxia or to more variable oxygen tension when oxygen therapy is controlled on the basis of transcutanous PO_2 monitoring or oxygen saturation monitoring.

2.1.3. Methods

The study was carried out in the neonatal unit of the Simpson Centre for Reproductive Health, Edinburgh between February 2004 and January 2005. Preterm infants who were more than 24 hours old, had an arterial line in-situ and were receiving supplemental oxygen were eligible for inclusion in the study if they were considered unlikely to require a major handling procedure such as intubation during the next 6 hours. Infants with known duct dependent congenital heart disease were excluded. Written informed parental consent was obtained in all cases and the study was approved by the Lothian Research Ethics Committee.

Each infant was monitored simultaneously with a SpO_2 monitor, and a $TcPO_2$ monitor. Data from both monitors was downloaded continuously in real time to a cot-side PC for later analysis. The sites of attachment of these monitors were left up to the nursing staff and not standardised between infants as we wished to study the real life implementation of these technologies and this is often limited by the presence of lines and dressings. Functional oxygen saturation was measured using a Siemens Infinity SC 7000 multiparameter patient monitor (Siemens Medical Systems, Inc, Danvers MA). This monitor utilises Siemens' Oxisure^{TM} pulse oximetry technology and Nellcor Oximax saturation probes. The same mutiparameter monitor measured transcutaneous PO_2 using a Radiometer sensor (Radiometer, Copenhagen, Denmark). Although both methods of monitoring were attached to the patient throughout, at any given time information was only displayed to the clinical staff from one monitor at a time, this was achieved by securely taping over the other monitor's display. During two consecutive 3-hour periods allocated in random order by the opening of a sealed opaque envelope, nursing staff adjusted the oxygen therapy for the first 3 hours on the basis of one of the monitors and for the subsequent 3 hours on the basis of the other. The transcutaneous oxygen sensor was maintained at a temperature of 43.5°C. The sensor was sited shortly before the start

of the first monitoring period and monitoring commenced once the transcutaneous PO_2 reading had stabilized. The sensor was re-sited for the second monitoring period. During the $TcPO_2$ monitoring period the nursing staff adjusted the FiO_2 to maintain the infant's $TcPO_2$ within the range 6.0-9.0 kPa. At the start of the study, a blood gas sample was obtained from the arterial line of each infant to ensure that there was close agreement between $TcPO_2$ and PaO_2. Where there was a difference of 1 kPa or more between the 2 values the $TcPO_2$ alarm limits that were set by the nurse were adjusted by the difference between PaO_2 and $TcPO_2$ to the nearest kPa. The downloaded $TcPO_2$ data in these infants was adjusted by the same amount prior to data analysis so that the final data reflected as closely as possible the likely PaO_2 of the infants. During the SpO_2 monitoring period the nursing staff adjusted the FiO_2 to maintain the infant's SpO_2 within the range 86-94%. For each of the two periods alarms were only enabled for the monitor under investigation. The infants were cared for by the nursing staff throughout as normal, with no intervention from study personnel.

Downloaded data for $TcPO_2$, SpO_2, saturation derived heart rate and ECG derived heart rate were analysed using SPSS version 12.0 (SPSS Inc, Chicago, Illinois). Saturation readings where the heart rate measured by the saturation monitor differed from the simultaneous ECG heart rate by more than 10 beats per minute were excluded as artefact from both monitoring periods in order to minimize any motion artefact. For each infant and for each period of monitoring, the mean $TcPO_2$, percentage of time spent with $TcPO_2$ >9.0 kPa, percentage of time with $TcPO_2$ < 6.0 kPa, variability (standard deviation) of $TcPO_2$, mean SpO_2, percentage of time with SpO_2 >94%, percentage of time with SpO_2 < 86% and variability (standard deviation) of SpO_2 were calculated. Transcutaneous PO_2 probes required re-siting during two studies, which led to a period where saturation readings were unblinded until transcutaneous PO_2 readings were available again. These periods were included in the analysis on an intention to treat basis. Because the variables showed non

normally distributed data, the two methods of monitoring were compared using non parametric two related samples test (Wilcoxon test).

2.1.4. Results

Nineteen infants were enrolled in the study. Eleven were conventionally ventilated, 2 received high frequency oscillatory ventilation, 6 were on nasal CPAP. The characteristics of the infants are given in Table 2. No infants were paralysed at time of study. During the six hour study period all infants were clinically stable. None required major handling prodeedure such as intubation.

Table 2: Infant characteristics at the time of enrolment in the study. Data are mean (SD)

	Mean (SD)
Weight (g)	1003 (416)
Corrected gestational age (weeks)	27.2 (2.5)
Age (days)	6.8 (9.5)
Fractional inspired oxygen concentration	0.34 (0.12)

The SpO_2 probe site was post-ductal in 15 infants and pre-ductal in 4 infants. The $TcPO_2$ probe site was post-ductal in 15 infants and pre-ductal in 4 infants. In 9 infants the first monitoring period was SpO_2, and in 10 infants the first period was $TcPO_2$. Saturation data was excluded as artefact for a total of 695 (0.3%) seconds and 608 (0.3%) seconds from the $TcPO_2$ and SpO_2 monitoring periods respectively. $TcPO_2$ data were not available from one 3 hour monitoring period in an infant during the time when the clinical care was based on SpO_2 readings because the $TcPO_2$ monitor was not attached. $TcPO_2$ data was obtainable for 94% of the time when $TcPO_2$ was the monitor displayed to the clinical staff. The transcutaneous PO_2 data of 4 infants was adjusted by the difference between $TcPO_2$ and PaO_2 obtained on the

arterial blood gas taken at the start of the study. In one case the adjustment was 1kPa and in 3 cases the adjustment was 2 kPa.

The outcome data are summarised in Table 3. Figures 9 and 10 show the cumulative data from all the infants for the percentage of time spent at different SpO_2 and $TcPO_2$ according to which method of monitoring was being displayed to the clinical staff.

Figure 9: Percent time spent at each oxygen saturation according to the method of monitoring in clinical use. Combined data from all study infants.

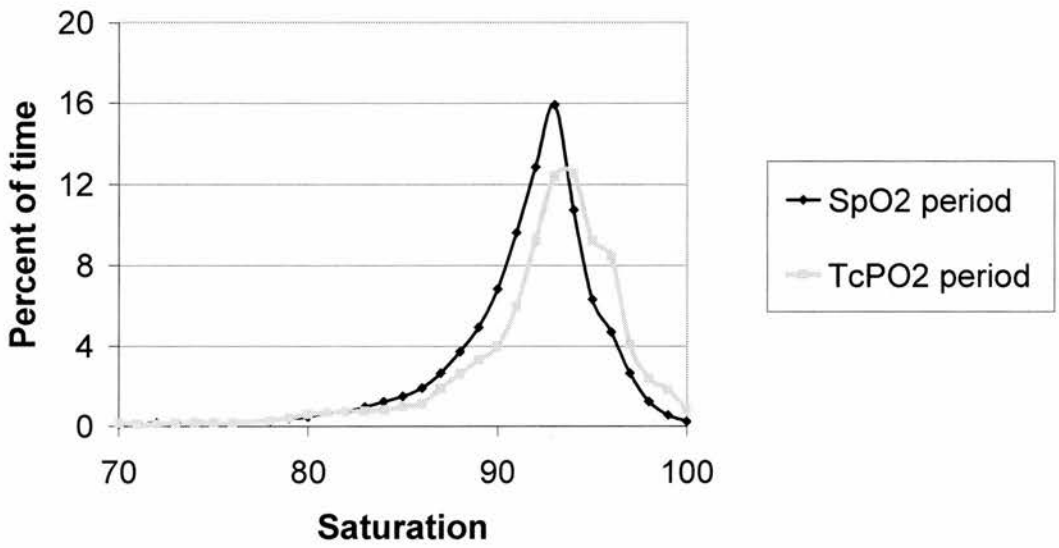
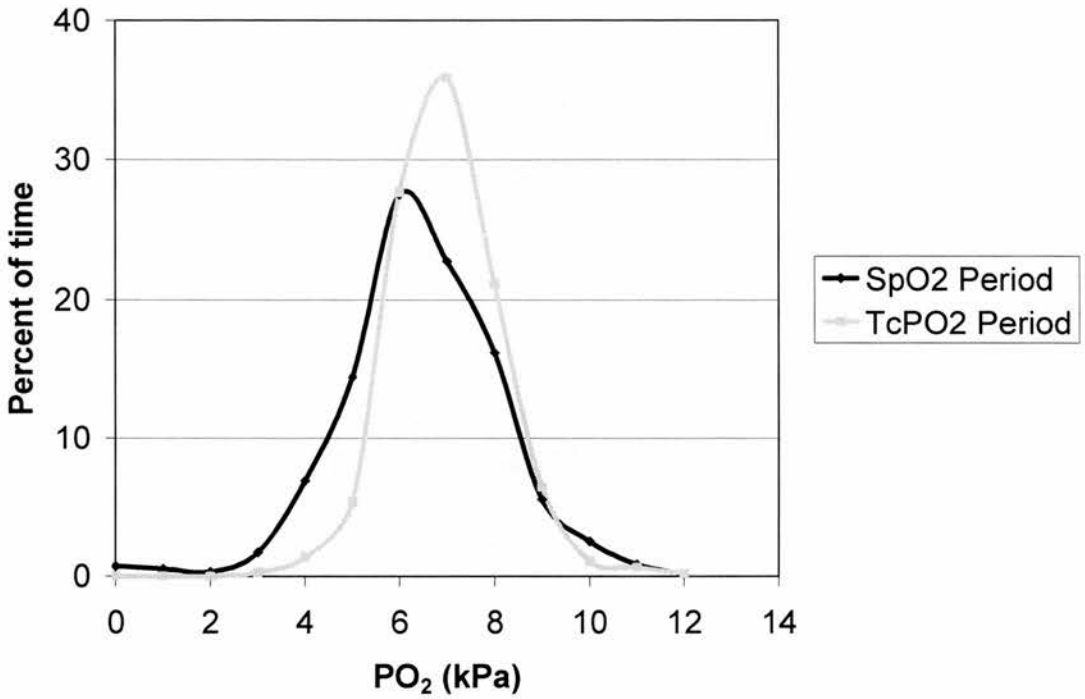


Table 3: Summary data (median - interquartile range) for stability of oxygenation.

	Monitor on display to clinical staff		Median difference within patients	
	$TcPO_2$	SpO_2	(SpO_2 period minus $TcPO_2$ period)	Significance
Mean $TcPO_2$ (kPa)	6.91 (6.34, 7.48)	6.41 (5.54, 7.20)	-0.33 (-1.1, -0.03)	P=0.09
% time with $TcPO_2 > 9.0$ kPa	0.14 (0.48, 3.33)	1.57 (0.31, 9.53)	2.62 (0.12, 13.24)	P=0.01
% time with $TcPO_2 < 6.0$ kPa	11.3 (3.94, 15.4)	31.3 (10.4, 60.12)	17.41 (3.15, 40.20)	P=0.01
Variability (SD) of $TcPO_2$ (kPa)	0.79 (0.41, 1.00)	1.07 (0.58, 1.27)	0.28 (0.01, 0.64)	P=0.02
Mean SpO_2 (%)	92.8 (90.6, 94.5)	91.7 (90.3, 92.1)	-1.16 (-3.24, 0.71)	P=0.06
% time with $SpO_2 > 94\%$	16.1 (7.07, 55.47)	12.1 (4.15, 29.14)	-1.71 (-34.78, 0.22)	P=0.06
% time with $SpO_2 < 86\%$	0.43 (0, 7.91)	4.50 (1.34, 12.35)	1.53 (-0.75, 5.61)	P=0.23
Variability (SD) of SpO_2 (%)	2.75 (1.44, 4.04)	3.33 (1.98, 4.61)	0.82 (-0.02, 1.89)	P=0.01

Figure 10: Percent time spent at each oxygen tension according to the method of monitoring in clinical use. Combined data from all study infants



2.1.5. Discussion

These results show in a randomised study that within the target ranges specified here, controlling oxygen therapy on the basis of transcutaneous PO_2 monitoring is more effective in limiting high and low transcutaneous oxygen tensions and variability in transcutaneous oxygen tension or saturation than controlling oxygen therapy on the basis of saturation monitoring. There was no statistically significant difference in the amount of time spent with low oxygen saturations between the two monitoring methods. When the oxygen treatment was adjusted on the basis of $TcPO_2$ the infants spent more time with high SpO_2 than when control was based on SpO_2 but this was not statistically significant and a high S_PO_2 is unlikely to be harmful if it is not associated with increased oxygen tension. Healthy infants can have saturations of 97% or more breathing air.

These results have important implications for clinical practice. In recent years there has been a trend for transcutaneous monitoring to be rejected in favour of saturation monitoring, perhaps because of the relative simplicity of saturation monitoring. The survival of preterm infants has increased over time but similar improvements in morbidity have not been observed[26 189-193]. There have been no randomised controlled trials comparing the outcomes of infants according to what method of monitoring is used. Epidemiological studies and case series have suggested that high oxygen tensions or oxygen saturations and increased variability of oxygenation may be harmful[19 31] and that limiting these exposures may be associated with improved outcomes[18 37]. The differences in oxygen tension variability observed in this study were large enough to be relevant to the risk of developing ROP[18 19]. Using only saturation monitoring as the basis for administering oxygen may not be the most effective clinical strategy. There are practical difficulties associated with using transcutaneous monitoring that make saturation monitoring more straightforward but these difficulties can generally be overcome in all but the most fragile infants. However it cannot be assumed that these study results, obtained in a research setting, would be replicated fully in everyday clinical use. Randomised trials of different saturation target ranges are under way. It will be important for the interpretation of these trials to gather detailed information about the oxygenation patterns that are actually achieved in the different groups. Further work is required to identify the most effective strategies for minimising the risks of oxygen toxicity.

There are a number of reasons that the oxygenation of infants may be more stable when they are nursed on the basis of $TcPO_2$ rather than SpO_2. Depending on the set averaging time, saturation monitors respond to change more rapidly than transcutaneous monitors. Brief desaturations that trigger the saturation monitor alarms may prompt carers to adjust the inspired oxygen level, whereas the relatively damped signal obtained with $TcPO_2$ may not show these fluctuations or bring about these adjustments. Movement artefact can lead to loss of signal from saturation monitors and this can trigger low saturation alarms and cause an inappropriate

adjustment of the oxygen flow with consequent hyperoxia until the oxygen is re-adjusted. These issues may be reduced by intensive staff education[37]. Saturation monitors incorporating technology that reduces motion artefact, such as Masimo SET may also reduce this problem[194]. To minimise any bias attributable to motion artifact saturation data was excluded from both monitoring periods where there was a difference in heart rate of more than 10 beats per minute between the ECG and oximeter derived heart rates.

The SpO_2 probe and the transcutaneous probe were post-ductal in 15 of 19 infants. As this was a clinical study, the site of the monitors was left up to the clinical staff. Because few babies have significant right to left shunts beyond the first few hours after birth, to the author's knowledge most units do not vary their target ranges according to whether their monitors and lines are pre- or post-ductal. This is unlikely to have had an important effect on the results.

With the limits that were specified for this study, infants spent a significantly longer time during the period when control was on the basis of SpO_2 with a $TcPO_2$ <6 kPa, than during the period when their oxygen was controlled on the basis of $TcPO_2$. The mean $TcPO_2$ and mean saturation of the infants was also slightly higher during the period when their oxygen was controlled on the basis of $TcPO_2$ than during the period when control was on the basis of SpO_2, although these differences were not statistically significant. Other studies have shown that episodes of apnoea occur less frequently in infants with higher mean PO_2 and sleep architecture and pulmonary hypertension may also be affected[53 54 56 59 62-65].

Because saturation and PO_2 are not linearly related it would be expected that target ranges for these two variables will result in different care being delivered. Even though the ranges overlap one another, most infants with $TcPO_2$ approaching 9.0 kPa will have a saturation greater than 94% and most infants with saturation of 86% will

have $TcPO_2$ less than 6.0. There is broad consensus that high oxygen tensions are harmful and should be avoided. Our data suggest that using saturation monitoring with an upper saturation alarm limit of 94% is slightly less effective in this respect than using a $TcPO_2$ limit of 9.0kPa. However, oxygen tensions greater than 11.0kPa were seldom observed in either group. There is far less agreement over how low oxygen tension or saturation should be allowed to go before this becomes a matter for concern. Infants in this study spent considerably more time with lower oxygen tension when they were controlled on the basis of SpO_2 but no more time with low saturation. This may not be important provided that haemoglobin level and cardiac output are adequate. Fetal haemoglobin permits satisfactory blood oxygen content and tissue oxygen delivery at much lower saturation than 86% and oxygen tensions far lower are observed in the healthy fetus. Preliminary data describing 10 year follow of infants cared for with lower saturations do not demonstrate increased adverse outcome[31 100]. Deulofeut et al[103] observed a reduction in bronchopulmonary dysplasia and retinopathy of prematurity and better mental development index scores at 18 months in infants with birth weight $\leq$ 1250g when they adopted lower saturation targets. Long term outcome data from current randomised controlled trials of different saturation target ranges will be capable of showing even modest differences between trial groups in neurodevelopmental outcome.

It was not possible to download simultaneously detailed information about the inspired oxygen concentration that the infants were exposed to as some intensive care equipment does not have the necessary data ports. This should not be overlooked by manufacturers when developing new equipment.

The target ranges employed in this study simply reflected practice in our unit and are not necessarily the ideal. They are within in the range of accepted oxygen targets that have been described. Although some may feel that a lower saturation alarm limit of 86% is quite low, it is clear that other neonatal units use much lower levels[31 37 38 101]. All of the infants in the study were monitored with a single type of oxygen saturation

monitor. Monitors produced by different manufacturers vary from one another in the saturation readings obtained[110].

In conclusion, this randomised crossover study shows that the method of monitoring used to control oxygen therapy in preterm newborn infants has a significant effect on the oxygenation patterns that result. This could have an important effect on the risk of adverse clinical outcome and is worthy of further study.

2.2. Study 2: Oxygen dissociation characteristics of preterm infants

2.2.1. Abstract

Aim

Aim to describe the range of arterial oxygen tensions (PaO_2) likely to be achieved in the first three weeks of life in a population of high risk preterm infants at currently targeted oxygen saturation levels, and to determine whether infants who develop adverse outcome have different haemoglobin oxygen dissociation characteristics than infants who remain well.

Method

In a retrospective cohort of 98 consecutive infants born at <29 weeks gestation, who had arterial lines inserted and at least one arterial blood gas taken while their oxygen saturation was being monitored were studied. The PaO_2 from each arterial blood gas result during the three weeks of life (n=3040) was matched to the SpO_2 at time of sampling. This was determined from the computerised monitoring charts. The mean (95% C.I.) PaO_2 was calculated for each saturation.

Paired t-tests were used to examine whether infant mean P50 in the first week of life, or percentage of fetal Hb in first blood gas were associated with each of four adverse outcomes; BPD, retinopathy of prematurity requiring treatment, death or a combined adverse outcome (death or BPD or ROP).

Results

The 95% confidence intervals of PaO_2 for the SpO_2 range 85-95% were 3.8-8.9 kPa. The mean (95% C.I.) PaO_2 at a saturation of 85% was 5.3 (3.8-6.8) kPa and at a saturation of 95% was 7.2 (5.5-8.9) kPa. We found no significant association between infant birth characteristics, BPD, or ROP and initial percentage of fetal haemoglobin or haemoglobin oxygen affinity (P50). Infants who went on to die had

significantly lower percentage of fetal heamoglobin at first arterial blood gas sampling than infants who survived (76 vs 82 % P=0.006), however when corrected for gestation this affect was no longer statistically significant (p=0.06). There was no association between mortality and mean P50 in the first week of life.

Conclusion

Saturations within the range 85-95% largely exclude hyperoxia in preterm infants <29 weeks gestation but permit PaO_2 values lower than those recommended in traditional guidelines. Haemoglobin oxygen affinity in the first week of life is not an important determinant of adverse clinical outcome.

2.2.2. Background

Pulse oximetry saturation measurements are widely used in neonatal units to monitor levels of oxygen in extreme preterm infants and to decide whether they require supplemental oxygen or not. The gold standard measure of oxygen levels in the blood, oxygen partial pressure of an arterial blood sample (PaO_2), can only be measured every few hours. This means that most of the time infant's blood oxygen levels are controlled by responding to alarm limits set on oxygen saturation measurements, aiming to keep infants saturation between set limits.

Transcutaneous oxygen tension ($TcPO_2$) monitoring was the first form of oxygen monitoring widely used in preterm infants introduced in the 1970's. $TcPO_2$ is a measure of the partial pressure of oxygen dissolved in the blood, and is obtained by measuring the amount of oxygen that diffuses through a baby's skin. Several studies have shown a good correlation between $TcPO_2$ and arterial values[195-197]. Therefore investigators originally investigated the association between levels of $TcPO_2$, $TcPO_2$ variability and adverse outcome. Flynn et al found that retinopathy was more common when the transcutaneous reading reached or exceeded 80mmHg (10.7 kPa) in the first week of life[32]. Cunningham et al found infants who required treatment for

ROP were significantly more likely to have more variable transcutaneous oxygen readings but failed to show an upper limit that might be associated with harm[19]. The study by Flynn et al led to published guidance on PaO_2 monitoring, suggesting that levels of oxygen above 75-80 mmHg should be avoided [198-203]. Later Collins et al found levels of cumulative hyperoxia defined as time spent with and oxygen tension above 60mmHg were associated with disabling cerebral palsy[34].

Other than attempting to achieve values similar to adults and children, evidence for the lower limit of oxygen tensions is equally sparse. Alveolar hypoxia is a well described cause of pulmonary artery hypertension resulting from hypoxic pulmonary vasoconstriction[53]. Halliday et al found infants with severe bronchpulmonary dysplasia, showed increased pulmonary vascular resistance when PaO_2 was allowed to fall from mean 62 to 54 mmHg, and concluded that to avoid pulmonary hypertension it is best to avoid PaO_2 below 55 mmHg (7.2 kPa). Clearly this was in a population of more mature ex-premature infants and this may not be the case in newborn preterm infants. Simona Nava et al[42], and Soothill et al[41] found that the 95% confidence interval for normal fetal umbilical venous oxygen tension was about 20 – 60 mm Hg, decreasing with increasing gestational age. This is equivalent to a range of oxygen saturation of about 60 – 90%.

The relative convenience of using saturation monitors has led saturation monitoring to become the predominant method of monitoring oxygenation in the US and in the UK and this is probably why more recent studies have focussed on saturation monitoring[97 98]. However there is still interest in monitoring $TcPO_2$ and actual values that might be achieved over the range of saturations currently targeted[196 204]. Currently targeted $TcPO_2$ levels were noted in a recent study of German speaking units from Germany, Switzerland and Austria. The median upper and lower limit $TcPO_2$ values were 70 and 44 mmHg (9.3 and 5.9 kPa) respectively. Median upper and lower saturation limits were 95 and 86 respectively.

Unrestricted use of oxygen has been unequivocally linked to retinopathy of prematurity, and has been linked to other morbidities such as BPD[77 78], NEC[91], and neurological problems[34 94 205]. Yet there is a concern that using inappropriately low oxygen levels might also increase these morbidities[14-16 206 207].

There have not yet been definitive studies that determine which oxygen saturation levels are appropriate at any particular gestation or post-natal age[8]. Consequently, the recommended oxygen saturation limits vary considerably between different neonatal units[38 208]. Some units use saturation ranges as wide as 70-90%, and others as narrow as 92-96%[31]. Over the last few years there has been a trend to reduce the oxygen saturation limits accepted, following concerns that we might be giving too much oxygen.

Currently there are a number of prospective randomised controlled trials of oxygen saturation target ranges under way to determine what the best oxygen saturation limits to run infants at, to minimise these morbidities. These are being analysed together in the Neonatal Oxygenation Prospective Meta-analysis (NeOProM)[204]. The outcomes of preterm infants who are kept in two different oxygen saturation ranges are being compared (Either a lower oxygen saturation range 85-89% or a higher range 91-95%).

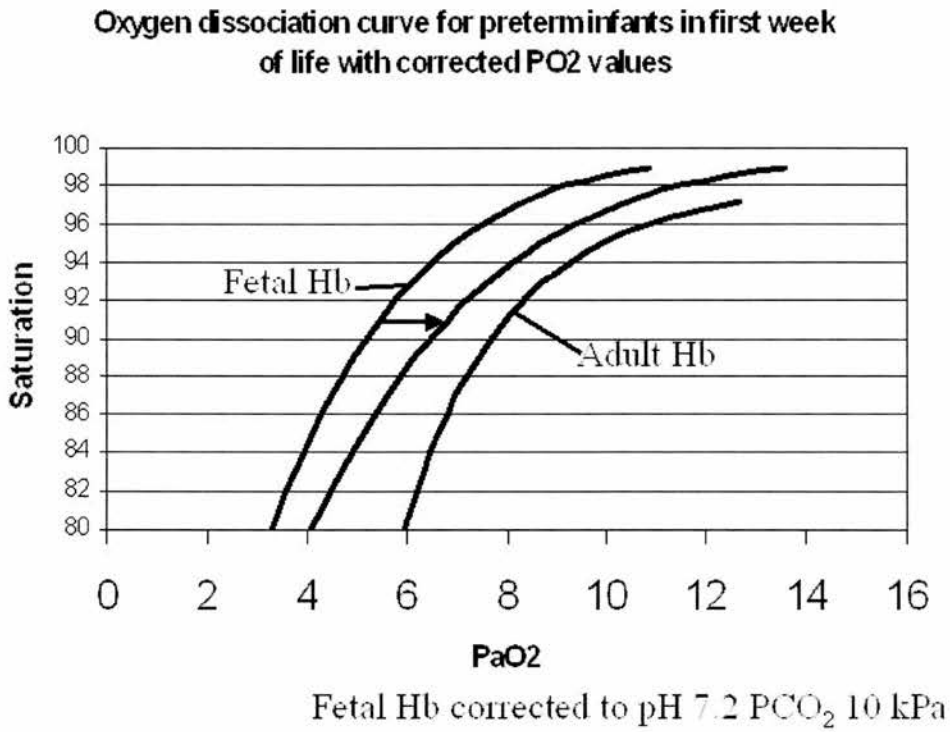
Although pulse oximetry is now the commonest method of monitoring oxygen levels in preterm infants, the limited published data indicates that there is a wide range of PaO_2 values for any given saturation[112]. There are a number of reasons why pulse oximetry does not always provide a close measure of oxygen tension and may not be an ideal parameter to monitor to avoid oxygen related morbidity. Temperature, pH and $PaCO_2$ affect the shape of the haemoglobin oxygen dissociation curve and therefore the PaO_2 for a given saturation. Decreasing pH and increasing $PaCO_2$ shift

the curve to the right, towards that of an adult curve, meaning the PaO_2 for a given saturation would be higher. Recent studies (COIN, SUPPORT, IFDAS)[209-211] have accepted pH down to 7.2 and $PaCO_2$ as high as 8.7 kPa, before extubation is considered a failure. Because clinicians increasingly accept more variation in infants' pH and $PaCO_2$ levels before initiating or increasing ventilatory support[210 212-214] this has the effect of moving infants' dissociation curves to the right towards that of an adult curve (see Figure 11). With each transfusion the preterm infant's haemoglobin-oxygen affinity is shifted closer to that of an adult. Therefore, if it is important to maintain oxygen tension in a particular range, aiming for set oxygen saturation targets may be over simplistic.

Figure 11 shows how fetal haemoglobin is affected by changes in pH and $PaCO_2$. Fetal and adult curves are produced using the Hill equation (equation 3 above) assuming standard conditions pH 7.4, $PaCO_2$ 5.3 kPa. The fetal haemoglobin – oxygen dissociation curve shifts to the right (arrow) if corrected for pH 7.2 and $PaCO_2$ 10 kPa.

There is relatively little data describing the oxygen dissociation characteristics of today's extreme preterm infants over the full range of saturations at which they are currently cared for[44 112]. Brockway and Hay described the mean arterial oxygen tension with 95% confidence intervals in a population of 22 preterm infants with mean gestation 33 weeks, over a range of oxygen saturations from 90-98%[112]. A study by Emond et al showed that the mean P90 in a population of preterm infants mean gestation 26.4 weeks was 40.8 +/- 3.6 mm Hg (5.4 +/- 0.5 kPa), but did not produce mean and confidence limits for PaO_2 over the range of saturations currently targeted[44]. This led Emond to suggest that PaO_2 values of 45 to 60 mm Hg should be adequate to oxygenate VLBW preterm infants[44]. Despite this, guidelines have continued to suggest levels above this[198-202].

Figure 11: Fetal and adult haemoglobin dissociation curves



The aims of Study 2 were to describe the range of oxygen tensions likely to be achieved in the first three weeks of life in a population of high risk preterm infants at currently targeted oxygen saturation levels (including saturations targeted in the NeOProM collaboration), and to determine whether infants who develop adverse outcome have different haemoglobin oxygen dissociation characteristics than infants who remain well.

2.2.3. Method

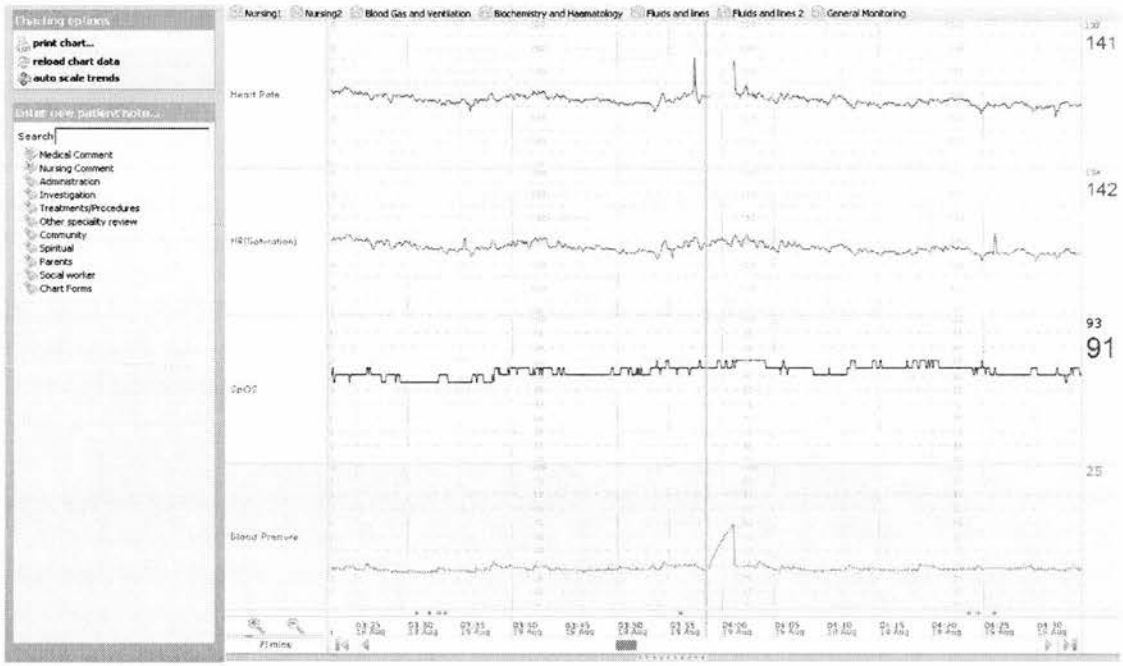
A retrospective cohort of 98 consecutive premature infants, born at <29 weeks gestation, who had arterial lines inserted and at least one arterial blood gas taken while their oxygen saturation was being monitored were studied. Infants requiring

arterial line invasive BP monitoring are always monitored in our intensive care nursery.

All arterial blood gas results were downloaded from the blood gas machines: Radiometer ALB700 series analysers (Radiometer medical ApS, Copenhagen, Denmark), while the infants were monitored with indwelling arterial catheters. Functional pulse oximetry oxygen saturation, measured using a Siemens Infinity SC 7000 multiparameter patient monitor (Siemens Medical Systems, Inc, Danvers MA), was downloaded continuously during the intensive care stay. This monitor utilises Siemens' Oxisure^{TM} pulse oximetry technology and Nellcor Oximax saturation probes. Arterial line and SpO_2 probe sites were determined by the clinical team. The PaO_2 from each blood gas result was matched to the pulse oximetry saturation of the infant at the time of sampling. This was determined from the computerised monitoring charts. At the time of blood sampling, operating the three way tap occludes the arterial line briefly. This leads to an artefactual peak in the blood pressure reading as the infusion pump continues to infuse heparinised saline against the occluded arterial line. This peak is readily identifiable on a plot of continuously downloaded blood pressure data (Figure 12). It has been previously shown that isolated blood gas samples are stable for up to 1 hour, so any time taken for the blood gas samples to be analysed is unlikely to be a factor[215 216].

For the purpose of our analysis, pulse oximetry saturation data from the time of arterial line occlusion was used, assuming this was the same as time of sampling. Following occlusion, arterial pulse wave derived HR disappears from our continuous monitoring charts and there is a steep rise in invasive mean BP recorded (Figure 12). Sampling involves closing off the arterial line tap site, and then slowly taking out a 1.5-2.5ml (dead space) sample of heparinised saline then blood to ensure that arterial blood is sampled, and then taking the blood sample, for analysis.

Figure 12: Monitoring chart showing arterial blood gas sampling



Because the time taken from line occlusion to arterial blood sampling varies between individuals, and the process of sampling may affect infants stability and therefore saturations achieved pulse oximetry saturation was also documented 15 and 30 secs after line occlusion in 1083 samples, to check if there was any significant bias or change in the saturations achieved over this time.

Pulse oximetry monitors rely on pulsatile absorbance patterns made by arterial blood. During patient motion, venous blood also moves, causing pulse oximetry monitors to under-read or simply not pick up a signal at all. They also fail to pick up a reliable heart rate from the arterial pulse waveform. To exclude blood gas samples taken during saturation artefact, only blood samples where pulse oximeter saturation derived HR was within ten beats per minute of invasive blood pressure wave derived

HR at time of sampling were included in the analysis. Paired pulse oximetry saturation and PaO_2 values were documented for each available blood gas result from each infant in the cohort during the first three weeks of life. Values were later broken up into weeks 1 and 1-3 for the analysis. Data on infant's fraction of fetal haemoglobin, COHb and MetHb was also documented.

It has previously been described how temperature, $PaCO_2$ and pH affect the shape of the oxygen dissociation curve and how to create a virtual PaO_2 point from any given PaO_2 value taking into account temperature, $PaCO_2$ and pH values[161 217-220]. We therefore corrected samples to standard conditions using the following equation[161]:

$$[PO_2 \text{ virtual}] = [PO_2 \text{ actual}]*10^{(0.024(37-T)+0.40(pH-7.40)+0.06(\log10(40)-\log10(PCO_2))}.$$

Equation 7: Virtual arterial oxygen tension correcting to standard conditions

T – Temperature

This creates a virtual PaO_2 corrected for known affecting factors. PaO_2 values were automatically corrected for temperature by the blood gas machines, meaning the following equation was used.

$$[PO_2 \text{ virtual}] = [PO_2 \text{ actual}]*10^{(0.40(pH-7.40)+0.06(\log10(40)-\log10(PCO_2))}.$$

Equation 8: Virtual arterial oxygen tension correcting for pH and PaCO2 to standard conditions

The number of blood gas results available for each infant varied depending on how long they had arterial lines in situ and how sick they were.

Both corrected and non-corrected PaO_2 data was examined. Graphs using non corrected PaO_2 data describe likely PaO_2 levels actually achieved in the range of oxygen saturations and acid base conditions currently targeted in contemporary practice. Graphs using corrected data describe the range of oxygen tensions likely to be achieved in ideal conditions in a population of high risk preterm infants over the range of currently targeted oxygen saturation levels.

Curves of mean PaO_2 for a given saturation in the 80-100% range were plotted. To stop any individual infant's data from biasing the results, for each infant the mean PaO_2 (corrected and non-corrected) in the first week of life or in the first three weeks of life, at each saturation point in the saturation 80-100% range was calculated. All infant mean PaO_2s at each saturation point were then combined to calculate a population mean PaO_2, and 2 standard deviations around the mean were also calculated, for each time period.

Infants who developed adverse outcomes including broncopulmonary dysplasia (requirement for supplemental oxygen at 36 weeks corrected gestational age), retinopathy of prematurity requiring treatment, death or a combined adverse outcome (death or BPD or ROP) were compared with infants who remained free of these complications to see whether their dissociation patterns were different. To achieve this, firstly four graphs (one for each adverse outcome) were plotted. On each graph oxygen dissociation curves for the two groups of infants were plotted, one group that went on to suffer from the outcome in question, and the second group of infants that were not affected.

Measurement of the P50 in whole blood, defined as the partial pressure of oxygen required for a 50% saturation of haemoglobin, gives a quantitative measure of haemoglobin-oxygen affinity. Originally Aberman suggested that P50 could be accurately calculated from single measurements of oxygen tension and the

corresponding oxygen saturation[156]. Wimberly subsequently improved on this mathematical model of the oxyhaemoglobin dissociation curve, which was tested[157] [158], and subsequently approved by the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine).

P50=exp[lnPaO2-0.37*ln(sat/1-sat)][158]

Equation 6: Single point P50 calculation

This is Wimberly's equation[158].

This equation was used to calculate P50 from each blood gas result from each infant in the first 3 weeks of life. Average P50 was then calculated for each infant over week 1, 2 and 3 (where available). Only infants who were having arterial blood samples taken could be included and this number fell over successive weeks as infant's arterial access was removed.

Paired t-tests were used to test whether infant mean non corrected P50 in the first week of life, or percentage of fetal Hb in first blood gas were associated with each of the four adverse outcomes BPD (requirement for supplemental oxygen at 36 weeks corrected gestational age), retinopathy of prematurity requiring treatment, death or a combined adverse outcome (death or BPD or ROP).

Multi logistic regression models controlling for gestation, birth weight, and birth weight Z score, were used to examine whether there were any hidden effects in univariate analysis. The Enter Method of Multiple Linear Regression, SPSS version 12.0 (SPSS Inc, Chicago, Illinois), was used by the researcher, see appendix D for full workings. As this was a study of routinely collected clinical data performed by the team caring for the babies, the local ethics advisory committee did not require formal review.

2.2.4. Results

The study took place at the Simpson Centre for Reproductive Health, Edinburgh. 98 consecutive infants who were born from October 2002 to October 2004 at less than 29 weeks gestation were included in the analysis. A total of 3040 blood gas samples from these infants were included in the analysis. 2095 were taken in the first week of life of our infants and of these 2067 were with saturations equal or above 80% and 28 when the saturation was less than 80%. 686 were taken in the second week of life of our infants and of these 667 were with saturations equal or above 80% and 19 when the saturation was less than 80%. 259 were taken in the third week of life of our infants and of these 245 were with saturations equal or above 80% and 14 when the saturation was less than 80%. The mean (SD) number of samples from each infant for weeks 1, 2, 3, 1-3 were 21.4 (15.4), 7 (13.7), 2.64 (7.6), 31.0 (30.7) respectively.

The infants' characteristics are described in Table 4. Thirteen (13.3%) infants died before discharge. Of the survivors, 49 (58%) went on to suffer from bronchopulmonary dysplasia, and 16 (18.8 %) went on to require ROP treatment with laser (threshold defined according to the international classification of ROP[221] [222]).

Table 4: Infant characteristics - mean and SD, or number and percent

	Mean/Number	SD/Percent
Gestation (weeks)	26.7	1.56
Birth Weight (g)	869	214
Birth weight Z score	-0.65	0.99
Crib 2 score	10.8	2.7
Male	51/98	52
Full course antenatal steroid (2 doses 24 hours apart, more than 24 hours prior to delivery)	52/98	53
Partial course antenatal steroid	34/98	35

Figure 13: Plot of all data points PaO_2 vs SpO_2 in the first week of life

Shaded areas show 95 % confidence intervals for PaO_2 likely to be achieved at the higher (91-95%) and lower (85-89%) oxygen saturation ranges currently investigated in NeOProM and the range of PaO_2 values recommended in published clinical guidelines (6.7-10.7 kPa)[198-200 202 203]. The 95 % confidence intervals for the higher and lower limit ranges are 4.6-8.9 kPa and 3.8-7.15 kPa respectively. The full NeOProM study PO_2 range 95 % confidence intervals will therefore be 3.8-8.9 kPa. If corrected for ideal conditions using equations to correct for pH, $PaCO_2$ and temperature[161 217-220] the confidence intervals become 3.6-8.7 kPa.

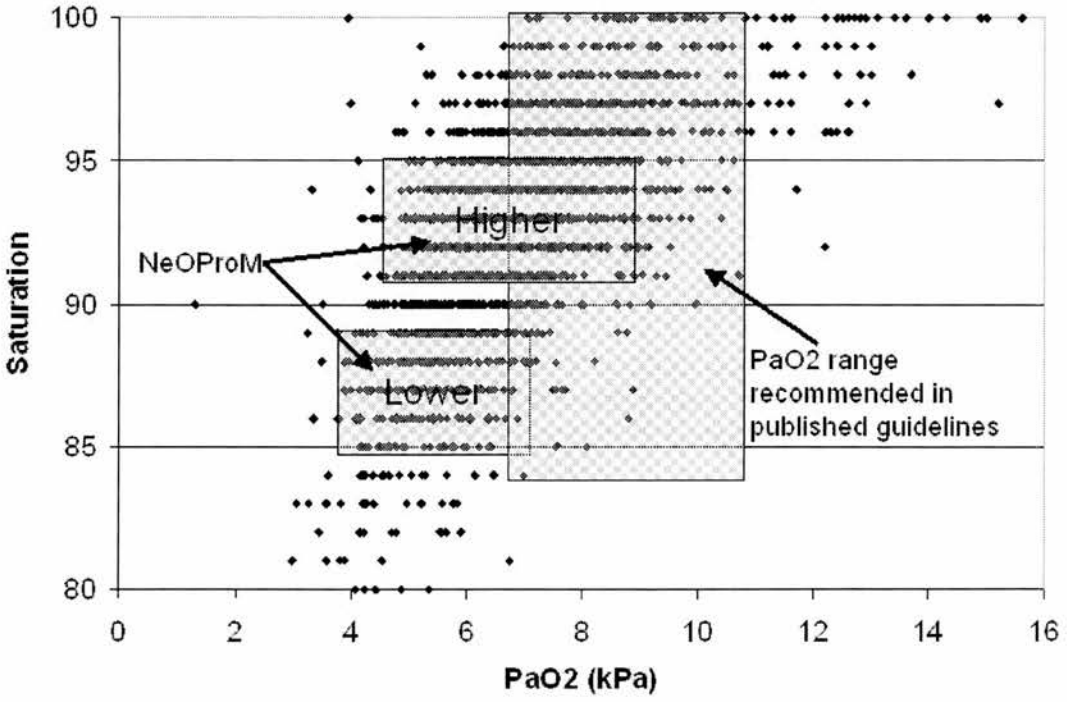


Figure 14: Plot of mean and two standard deviation curves for PaO_2 (non-corrected) for a given saturation data from week one only, data from 98 infants, 2067 separate data points.

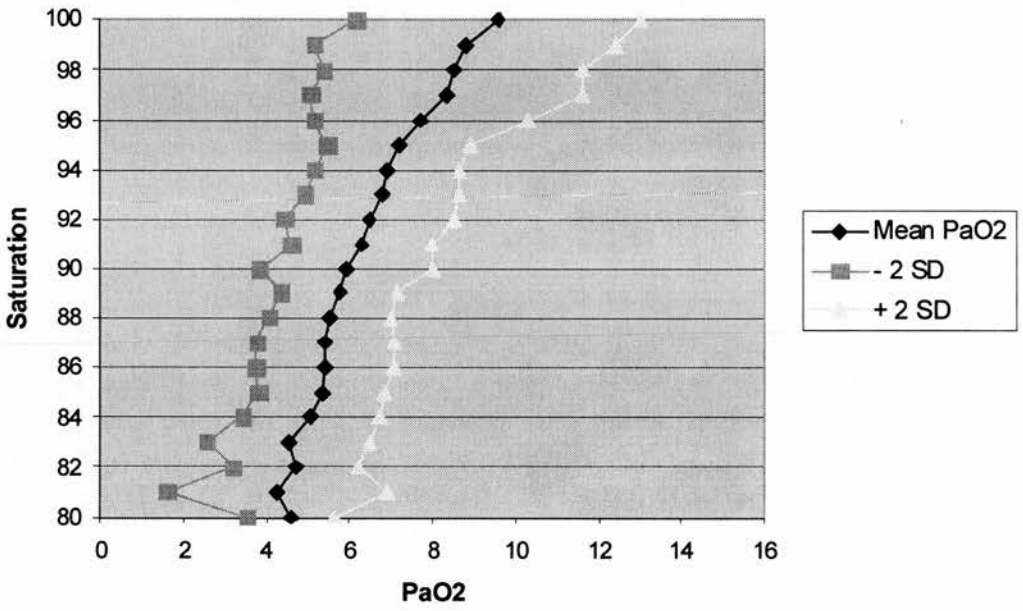


Figure 15: Plot of mean and 2 standard deviation curves for PaO_2 (corrected) for a given saturation data from week one only, data from 98 infants, 2067 separate data points.

A sigmoid curve estimation plot of mean PaO_2 vs saturation data fitted a sigmoid curve with the equation: Sat=e^(4.7487+(-1.3675/PaO_2)), with Rsq of 0.996, suggesting it closely fits a predicted sigmoid shape.

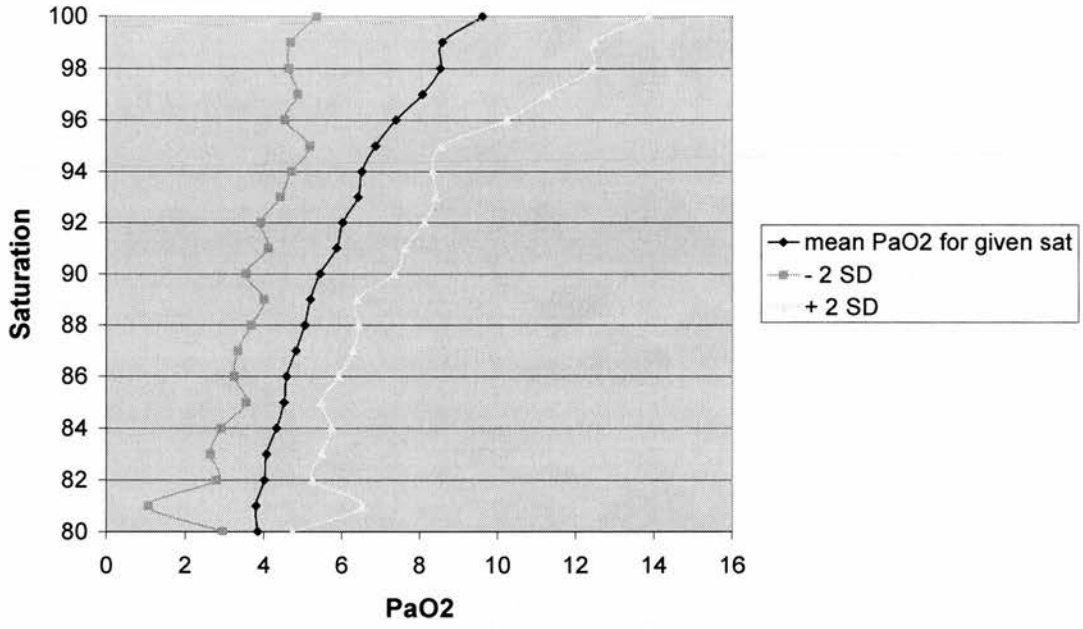
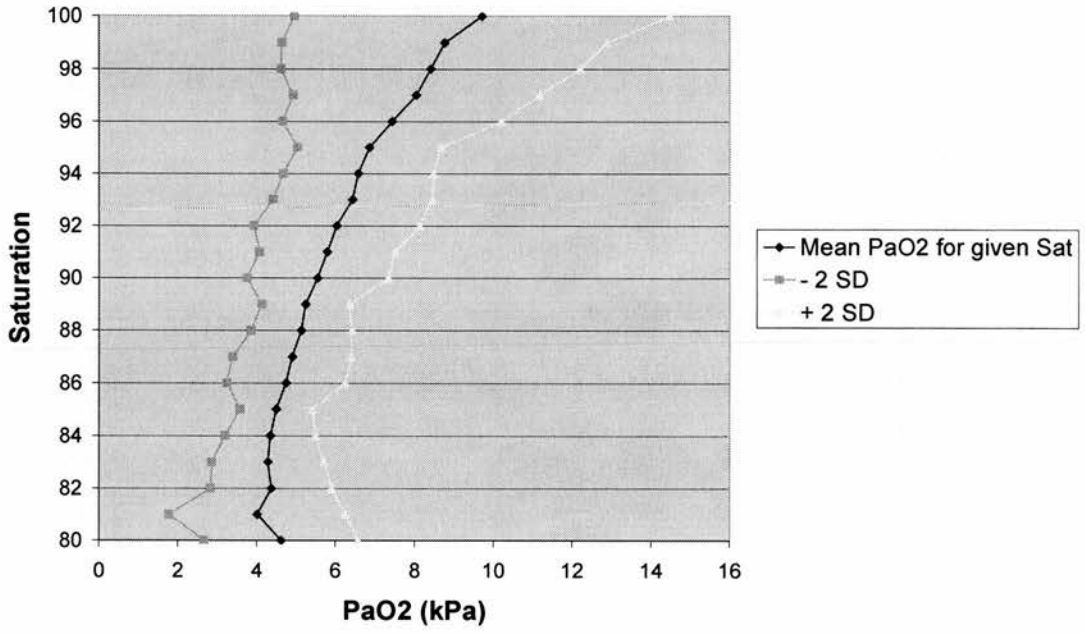


Figure 16: Plot of mean and 2 standard deviation curves for PaO_2 (corrected) for a given saturation data from weeks 1-3 included, data from 98 infants, 2979 data sets.



In all the above curves the confidence intervals widened considerably at saturations above 95, as would be expected because the dissociation curve becomes flatter.

Figure 17: Mean week 1 dissociation curves for PaO_2 (non-corrected) for a given saturation according to whether the infants went on to suffer from BPD or not, data from surviving 85 infants, 49 who went on to suffer from BPD (1128 data sets), 36 who did not suffer BPD (575 data sets) total 1703 data sets.

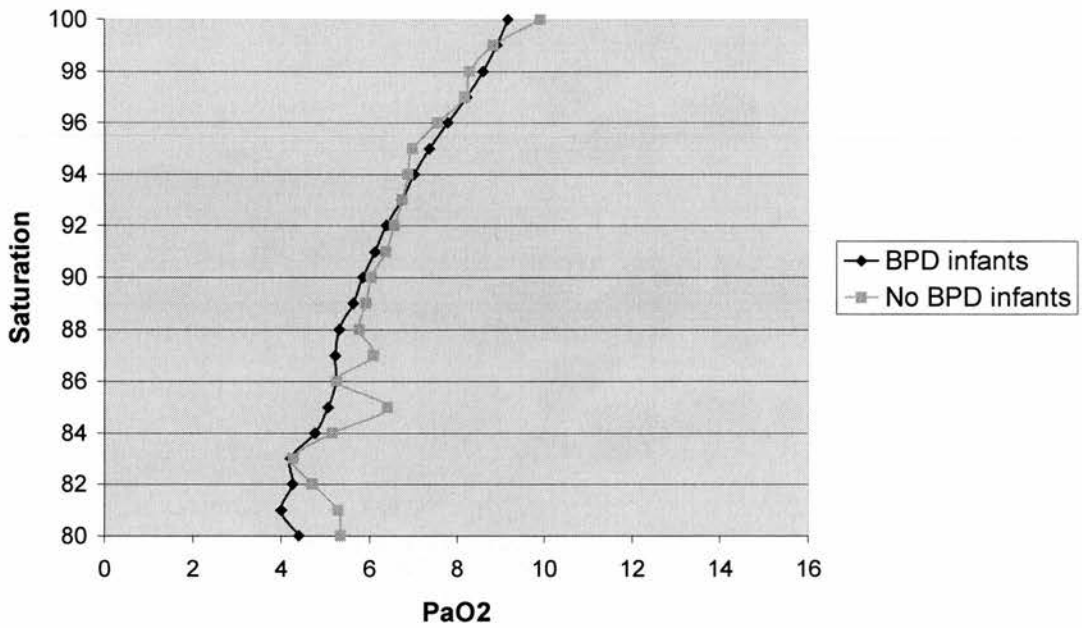


Figure 18: Mean week 1 dissociation curves for PaO_2 (non-corrected) for a given saturation according to whether the infants went on to require treatment for ROP or not, data from 85 surviving infants, 16 who went onto suffer from ROP (526 data sets), 69 who did not suffer from ROP (1177), total 1703 data sets.

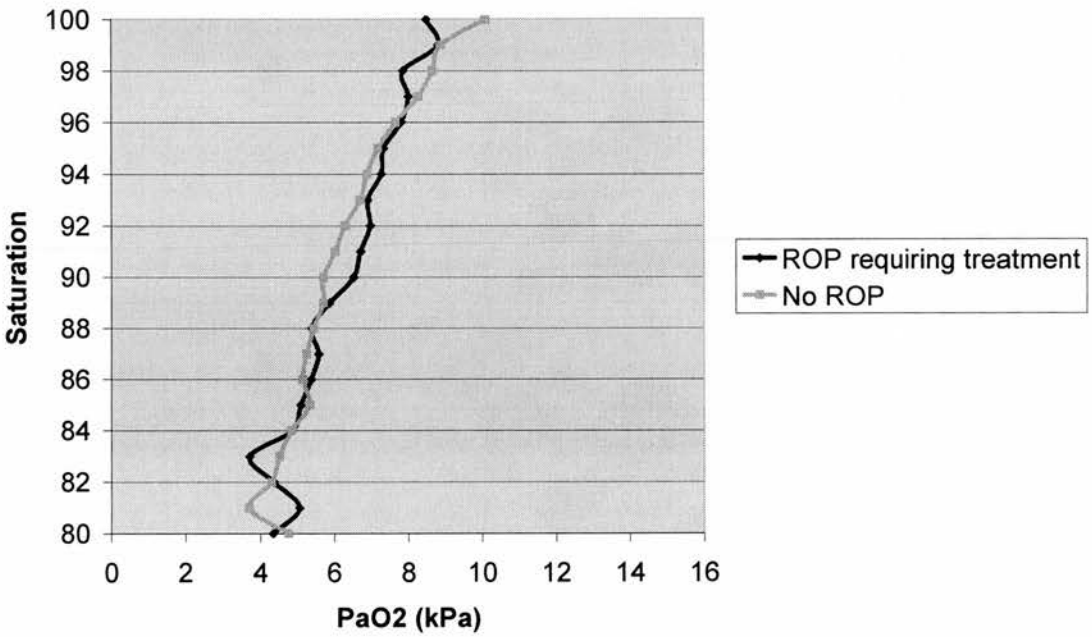


Figure 19: Mean week 1 dissociation curves for PaO_2 (non-corrected) for a given saturation according to whether the infants survived or died, total 98 infants, 13 infants died (364 data sets), 85 infants survived (1703 data sets), total 2067 data sets.

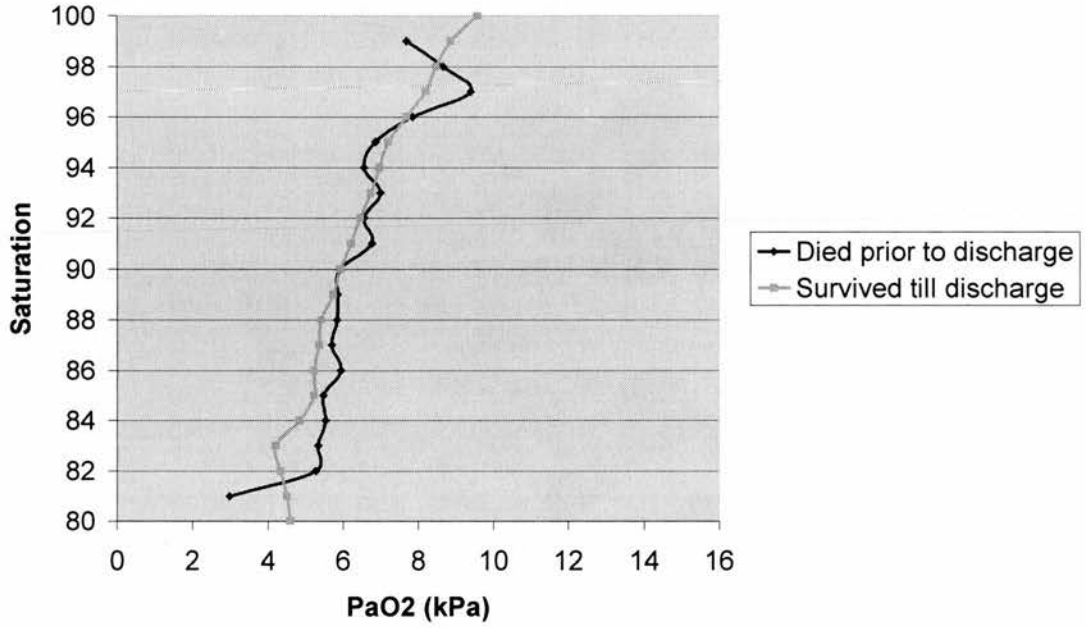
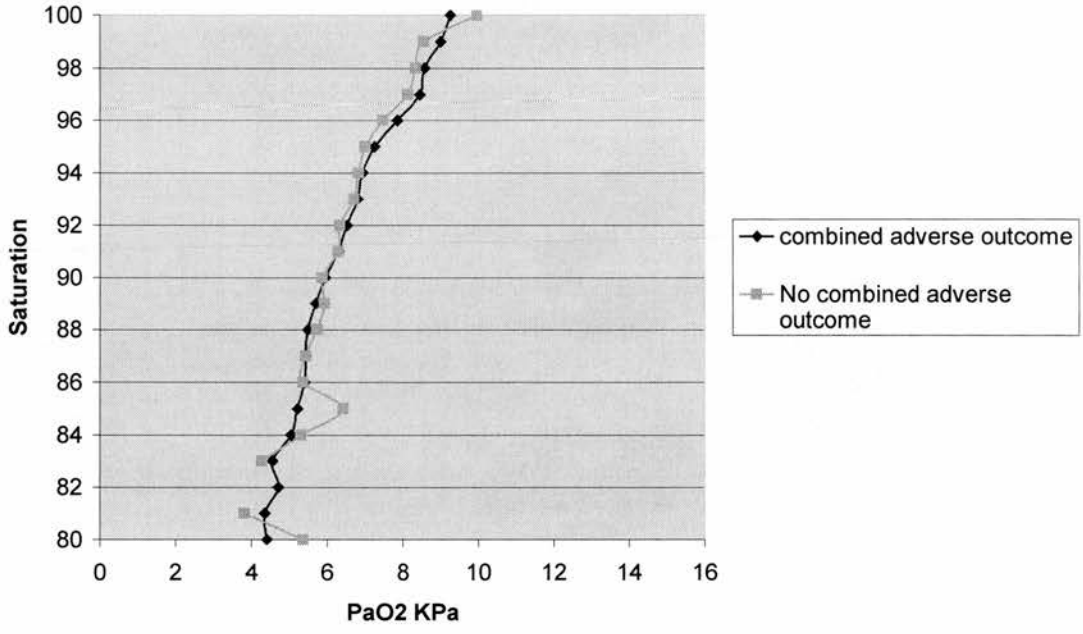


Figure 20: Mean week 1 dissociation curves for PaO_2 (non-corrected) for a given saturation according to whether the infants suffered from any adverse outcome or not, total 98 infants, 66 who went on to suffer from any adverse outcome (1607 data sets) and 32 who did not (460 data sets), total 2067 data sets.



The mean (SD) P50 for weeks 1, 2 and 3 were 2.35 (0.26), 2.35 (0.21), 2.53 (0.19) kPa, (17.6 (1.93), 17.6 (1.54), 19.0 (1.43) mm Hg) respectively (calculated using corrected PaO_2 using equation 6). Data was available for 97, 33 and 15 infants respectively. The average percentage of fetal Hb in first arterial blood sample taken for each infant was 81.7 % (n=97 infants, mean age 0.23 days). Mean values for COHb % was 1.6 and mean MetHb % was 0.8 for all samples over the first three weeks.

Pulse oximetry saturation was documented at time of arterial line occlusion, and again 15 and 30 seconds later for 1083 blood gas samples from 39 infants. Analysing

only data points where the mean saturation between the two time points was 80 or above left 1047 and 1046 samples respectively. The mean (SD) difference between saturation at time of arterial line occlusion and 15 and 30 seconds was -0.028 (1.27) and -0.017 (1.69). A bland altman plot of these results is shown in figure 21.

Figure 21 Bland Altman plot of this data. The mean saturation difference between saturation at time of line occlusion and 30 seconds plotted against their mean saturation.

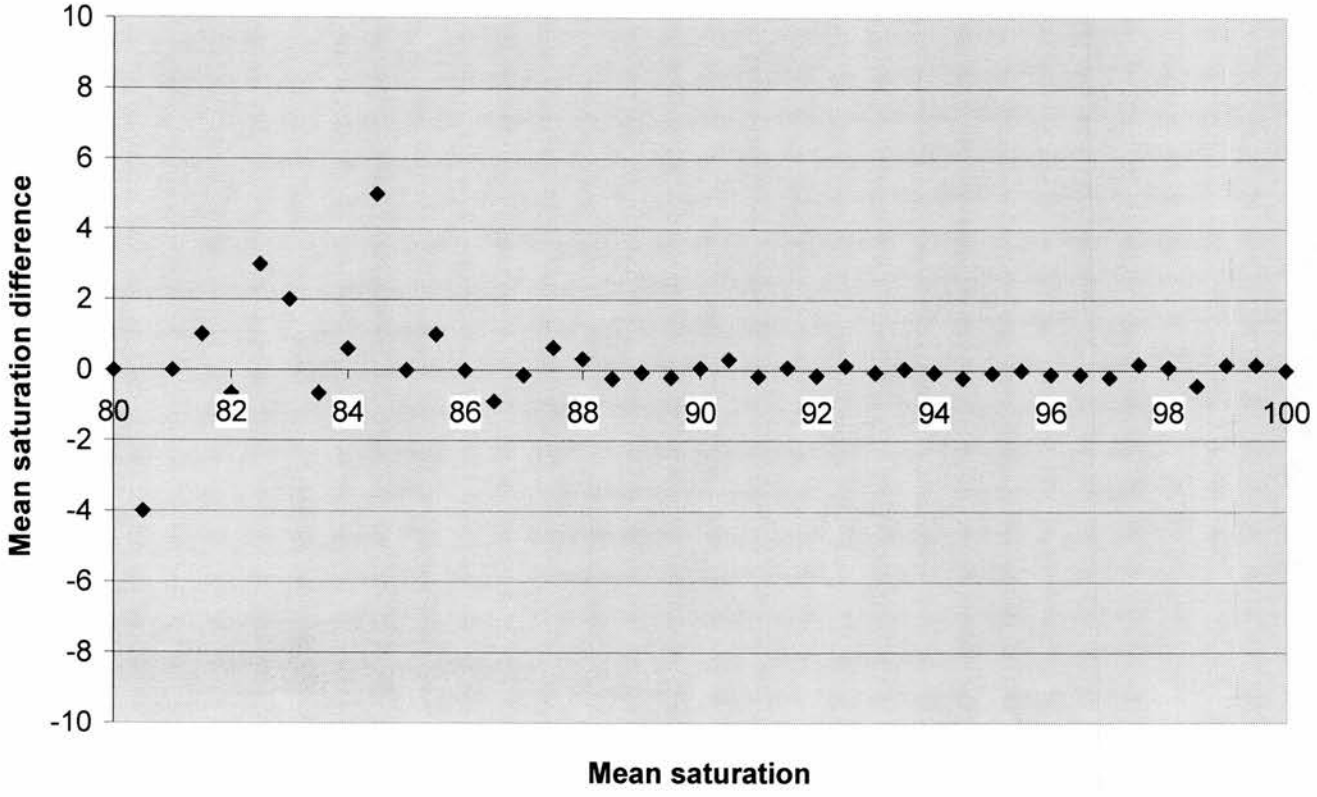


Table 5: Results of paired t-tests comparing infants who went on to suffer from BPD with infants who did not (85 surviving infants)

	BPD n=49	No BPD n=36	Univariate Significance
Gestation	26.6	27.1	0.15
Birth weight z score	-0.8	-0.4	0.09
Birth weight	835	944	0.02
Fetal haemoglobin percent	82.7	82.1	0.67
Mean P50 in the first week of life (mmHg)	18.6	18.1	0.23

Neither percentage fetal haemoglobin in first blood sample or mean P50 in the first week of life were significantly different between the two groups. Adding fetal Haemoglobin or P50 together or separately to multi logistic regression models (controlling for gestation, birth weight z score and birth weight) failed to bring out any hidden effects.

Table 6: Results of paired t-tests comparing infants who went on to suffer from ROP with infants who did not (85 surviving infants)

	ROP n=16	No ROP n=69	Univariate Significance
Gestation	25.2	27.2	<0.001
Birth weight z score	-0.3	-0.73	0.12
Birth weight	768	908	0.12
Fetal haemoglobin percent	80.3	82.9	0.16
Mean P50 in the first week of life (mmHg)	19.2	18.2	0.56

Neither percentage fetal haemoglobin in first blood sample or mean P50 in the first week of life were significantly different between the two groups. Adding fetal Haemoglobin or P50 together or separately to multi logistic regression models (controlling for gestation, birth weight z score and birth weight) failed to bring out any hidden effects.

Table 7: Results of paired t-tests comparing infants who went on to die with infants who survived (data from 97 infants as no normal birth weight data available for a 22 week gestation infant therefore excluded)

	Died n=13	Survived n=85	Univariate Significance
Gestation	25.8	26.8	0.02
Birth weight z score	-0.64	-0.65	0.99
Birth weight	790	881	0.15
Fetal haemoglobin percent	76.3	82.4	0.006
Mean P50 in the first week of life (mmHg)	19.0	18.4	0.33

Infants who went onto die had significantly lower percentages of fetal haemoglobin in their first blood sample on univariate analysis, however when controlled for the other variables in a multi logistic regression analysis, this was no longer statistically significant (p=0.06). Mean P50 in the first week of life was similar between the two groups. Adding fetal Haemoglobin or P50 together or separately to multi logistic regression models (controlling for gestation, birth weight z score and birth weight) failed to bring out any hidden effects.

Table 8: Results of paired t-tests, comparing infants who went on to suffer from any combined outcome (BPD, and/or ROP and/or death) with infants who remained well (data from 97 infants as no normal birth weight data available for a 22 week gestation infant therefore excluded)

	Combined outcome present n=66	Combined outcome not present n=32	Univariate Significance
Gestation	26.4	27.3	0.006
Birth weight z score	-0.69	-0.55	0.51
Birth weight	829	951	0.008
Fetal Haemoglobin percent	81.1	82.9	0.25
Mean P50 in the first week of life (mmHg)	18.7	17.9	0.09

Neither percentage fetal haemoglobin in first blood sample or mean P50 in the first week of life were significantly different between the two groups. Adding fetal Haemoglobin or P50 together or separately to multi logistic regression models (controlling for gestation, birth weight z score and birth weight) failed to bring out any hidden effects.

2.2.5. Discussion

This study describes the range of oxygen tensions likely to be achieved in the first three weeks of life in a population of high risk preterm infants at currently targeted oxygen saturation levels. In the first week of life the SpO_2 range 85-95% results in a range of PaO_2s that is much lower than published guidance on PaO_2 monitoring[198-202]. We have found no evidence that infants who develop adverse outcome have different oxygen dissociation characteristics than infants who remain well.

Graphs of the standard oxygen saturation dissociation curve for extreme preterm infants using actual temperature corrected infant data have been plotted. Further curves that have been corrected for ideal acid base conditions have also been plotted, from a large cohort of infants who had a large number on blood gas samples (2076 samples when infants were saturated over 80% in the first week of life). This has allowed calculation of a mean PaO_2 vs saturation curve that closely fits a predicted sigmoid shape, Rsq 0.996.

In the first week of life the SpO_2 range 85-95% investigated in current controlled trials of oxygen saturation target ranges (NeOProM) is likely to achieve mean PaO_2 levels between 4.5-6.9 kPa (33.8-51.6 mmHg). Although some may feel this oxygen saturation target is quite low, it is clear that many neonatal units use much lower levels[31 37 38 101]. This would indeed achieve oxygen tensions below Emonds' suggested reduction in limits (45-60 mm Hg), from those suggested by the American Academy of Paediatrics and the American College of Obstetricians and Gynecologists (50-80 mmHg)[44 198 203] and many other oxygen tension guidelines[199 200 202]. From available research it is not possible to say with confidence what oxygen saturation or tension range will be associated with optimal outcomes. However as current studies are investigating what oxygen saturation levels give the best outcome, it would seem sensible that the associated PaO_2 range will also be preferential.

The present study found no association between infants' oxygen saturation dissociation curves and outcomes such as ROP, BPD, mortality or combined outcome. This is despite the effects that differing pH and $PaCO_2$ may have on some infant's oxygen dissociation characteristics. Further, the plots of dissociation curves for infants with and without adverse outcome were strikingly similar, with no suggestion of difference that may simply have been too small to identify with the available sample size.

There was no association between fetal haemoglobin percentage at birth or mean P50 in the first week of life and BPD, ROP, combined outcomes in our univariate or MLR models. This was whether fetal Hb fraction and mean P50 were included together or separately in these models. The percentage initial fetal haemoglobin present in infants who went on to die was lower on univariate analysis but when controlled for the other variables in a multi logistic regression analysis, this was no longer statistically significant. Whether this is an effect of primitive haemoglobin still being present in the circulation, transfusions prior to first arterial sample, or sampling error is open to question. There was no association between mean P50 in the first week of life and death. Non-corrected P50 values were used in this analysis because we did not want to correct for the effects that pH and $PaCO_2$ have on the preterm infants oxygen dissociation curve. It is the effect that these acid base disturbances have on infants' oxygen affinity that we hypothesised could put some infants at risk of adverse outcome.

Most infants' haemoglobin was mainly fetal haemoglobin (mean 81.7% on first blood sampling). This is reflected in the fact that the infants' mean P50 was 17.6 mmHg in the first week. This is very similar to the quoted value for fetal haemoglobin rising to a mean of 19 mmHg over the third week of life, which is closer but still lower than the adult value of 26.6 mmHg.

Unlike previous studies, this study used retrospective data that the clinicians looking after the infants would have responded to in clinical practice. Both non-corrected PaO_2 data and PaO_2 corrected for ideal acid base conditions have been plotted[112 223]. Previous papers used standard conditions but did not fully correct for the effects that alterations in temperature, pH and $PaCO_2$ had[112]. When corrected for this effect, PaO_2 at any given saturation in ideal conditions is lower. Previous papers assumed that these factors make little difference in the limited range of pH and $PaCO_2$ ranges that they analysed blood gas data from.

Permissive ventilation strategies used in contemporary practice result in infants with more hypercapnia and lower pH[209-214]. Physiology predicts that this would result in a reduction in haemoglobin oxygen affinity (Bohr effect). Lower oxygen affinity in turn requires a higher oxygen tension to achieve any given saturation and increases the amount of oxygen given up in end organs. This may potentially lead to increased tissue hyperoxia. Despite this, the current study has not found an association between infants' intrinsic oxygen affinity and outcome. This may in part be because modern oxygen saturation targets already achieve lower oxygen tensions than has been the case historically, as the current study has also shown.

Current neonatal oxygen saturation targets are based on limited evidence. Previous authors have noted that babies grow perfectly well in utero with venous umbilical blood supplying them that is only 70-80% saturated[40-42]. During labour, infant saturations fall even lower to 30-40%[43] without affecting the vast majority of infants. Preterm newborns have red blood cells that have a high oxygen affinity. A study by Emond et al showed that the mean P50 was 18.3 +/- 0.9 mm Hg (2.5+/- 0.3kPa) which is comparable to current study data (their mean gestation was 26.4 weeks and the current study was 26.7 weeks). A single point method of calculating P50 was used, which may be slightly less accurate, but the mean (SD) corrected P50 in the current study was 17.6 mm Hg (1.93), which is very close to Emond's previous result in a similar population of infants.

Because this was a retrospective examination of blood gas data and SpO_2 data routinely downloaded from study infants, it was not possible to control where the SpO_2 probes were situated, or where the arterial blood was sampled. Data on whether these were pre or post ductal was not available, however this varies in clinical practice. Most babies do not have significant right to left shunts and it is not common for neonatal units to have different saturation target ranges according to the site of the saturation probe or arterial line other than when caring for an infant with PPHN. There is also no reason to believe that saturation is monitored in different places according to whether infants go on to suffer from adverse outcome or not.

Although blood gas data was matched to functional pulse oximetry at time of arterial sampling, timing of sampling varied and sometimes took several minutes. Sampling duration was not measured. Sampling in itself may change oxygenation as infants may be disturbed by staff opening the incubator and obtaining the sample. Functional pulse oximeter values from the time of arterial line occlusion were used in this analysis, as it was felt important to see what these values were prior to disturbance from sampling procedure itself. Nursing/medical staff in general do wait for infants to have been stable prior to taking blood gas samples. One could argue that the procedure might affect saturation and therefore saturations over the first 30 seconds of the sampling procedure were analysed, although there was an unsurprising spread of oxygen saturation differences (1.69%) around the mean this was not significant considering the unstable nature of the infants and this was not in any particular direction over sampling time, therefore representing natural variation rather than bias from sampling procedure. Therefore no significant difference in saturations achieved at line occlusion and thirty seconds later were seen.

This data will predict, for clinicians using pulse oximetry saturation monitors, the likely range of oxygen tensions that they are exposing their infants to in the first three weeks of life in a population of high risk preterm infants over the range of currently targeted oxygen saturation levels. The data is further evidence that although

saturation monitoring may not always be reliable in preventing hyperoxia[30 109-112], infants who have a saturation below 95% are extremely unlikely to be in a hyperoxic oxygen tension range, the 95th centile for saturation of 95 % is 8.9 kPa (67 mmHg) even in the acid base conditions used in contemporary clinical practice. The current oxygen saturation target limits typically used[199 200 202 224] are likely to achieve lower PaO_2 levels than currently published guidance on PaO_2 monitoring[198-203]. This data demonstrates that the two target ranges used in the studies that make up NeOProM have PaO_2 ranges that overlap substantially so unmasking by knowledge of simultaneous values of oxygen tension is unlikely. If PO_2 is the main determinant of oxygen toxicity then such small differences in oxygen tension between groups may be unlikely to result in a significant difference in clinical outcome.

There are variations between saturation monitors, particularly between monitors that monitor functional or fractional saturation. Most monitors, including Siemens Oxismart™ and Masimo (used in the NeoProM collaboration) now measure functional saturation. Differences between functional oximeters within the studied range are small (usually less than 1%)[111 225-229]. Emond et al[44] used co-oximetry to measure the P90 of blood from a population of preterm infants with mean gestation 26.4 weeks and obtained a mean P90 of 40.8 +/- 3.6 mm Hg (5.4 +/- 0.5 kPa), which is similar to the mean PaO_2 of 5.9 kPa at a saturation of 90% from our data.

This study uses Nellcor Siemens' Oxismart™ pulse oximetry technology where as current NeOProM studies use Masimo monitors. However there have been a number of previous studies in similar populations of infants showing that although manufacturers would argue that there may be differences in precision, missed hypoxemias, drop outs, and false alarms between modern saturation monitors and masimo monitors, there is very little bias either between monitors or between monitors and formal oximetry measurements (usually less than 1%)[111 225-229].

In summary this study describes the range of oxygen tensions likely to be achieved in the first week of life in a population of high risk preterm infants at currently targeted oxygen saturation values[38] [208]. In the first week of life the SpO_2 range 85-95% (investigated in NeOProM) results in a range of PaO_2s that is much lower than the range recommended in published clinical guidelines based on oxygen tensions and indicates that a shift towards lower oxygen tensions has taken place with current care practices based on saturation targeting. If lower saturation targets are accepted as safe by further research then lower PaO_2 targets will also be safe. Current controlled trials of oxygen saturation target ranges are targeting oxygenation levels that are likely to achieve mean PaO_2 levels between 5.3-7.2 kPa (40-54 mmHg) or 3.8-8.9 kPa (28.5-66.7 mmHg) for 95 % of the time. The study found no evidence that infants who develop adverse outcome have different oxygen dissociation characteristics than infants who remain well. This data would be interesting to people involved in researching oxygen use in preterm infants in the first few weeks of life[204].

2.3. Study 3: How inspired oxygen adjustment practices affect oxygen level and variability in ventilated preterm infants.

2.3.1. Abstract

Aim

The aim of this study was to explore whether nurses' oxygen adjustment practices influence oxygen stability and degree of adherence to oxygen saturation targets in preterm ventilated infants by separating out the variation in oxygen stability attributable to the condition and behaviour of the baby from that attributable to the care-giver practices. Variations in oxygen adjustment practices were also related to nursing seniority.

Method

The oxygen adjustment practices of 24 trained neonatal nurses were studied while caring for 13 ventilator dependent infants during 133 12-hour shifts. The average time per shift that each individual infant spent with saturation (SpO_2) >94% whilst receiving supplemental oxygen, the variability (standard deviation) of SpO_2 and the time spent with SpO_2 <86% were calculated. After determining average values for each infant the oxygen adjustment practices of the nurses who for ≥ 50% of their shifts the infant in their care was more unstable by these measures than the average of all the recorded shifts for that infant, were compared with the practices of the remaining nurses. Oxygen adjustment practices compared were number of increases in FiO_2 per shift, mean size of increase in FiO_2, mean FiO_2 variability, mean FiO_2 administered and mean SpO_2 maintained. The oxygen adjustment practices from a cohort of 34 nurses who looked after one of the 13 infants for 3 or more shifts (number shifts 164) were examined to test whether they were associated with different levels of nursing experience.

Results

FiO_2 was increased a mean (SD) 24 (11) times per 12 hour shift overall. The mean (SD) size of the individual increases was 9.3 (3.2) %. Nurses whose babies spent more time hyperoxic than average (24 vs 14%) made larger increases in FiO_2, (9.9% vs 7.6%, p=0.02) but not more frequent increases. Nurses whose babies showed greater than average variability in SpO_2 increased the FiO_2 more frequently (28 vs 21 times per shift, p=0.03) but not in larger steps. Nurses whose babies spent most time with SpO_2<86% (16 vs 10%) also made more frequent (29 vs 20 times per shift, p=0.003) but not larger increases in FiO_2. More senior nurses achieved less hyperoxic time and made smaller oxygen changes. Their infants tended to be sicker, requiring higher oxygen levels to achieve lower mean oxygen saturations. Senior nursing staff allowed their infants to spend more time with lower oxygen saturations.

Conclusion

After controlling for the intrinsic instability of the infant we found that larger and more frequent changes in FiO_2 may contribute to instability of oxygenation. More senior nurses achieved less hyperoxic time and made smaller oxygen changes. Stability of oxygenation in ventilated preterm infants is influenced by the oxygen adjustment practices of the staff who care for the baby. These are potentially modifiable behaviours.

2.3.2. Background

In ventilated preterm infants, inspired oxygen levels are usually adjusted with the aim of maintaining stable oxygenation, with oxygen saturation or tension kept within some defined acceptable range of values. There is very little evidence from prospective trials to define specific values and consequently oxygen saturation control policies vary substantially between neonatal units in the UK[38]. However, oxygenation patterns have been linked to the risk of BPD, ROP, NEC and adverse neurological outcomes in preterm infants[19 34 35 37 91]. It has also been shown that the

oxygen saturation targets aimed for affect the absolute oxygen saturation levels achieved[97 98 133-135].

Several investigators have reported data on the proportion of time infants in their centres are kept within target oxygen saturation range (compliance) and have shown substantial variation between infants, care givers and between centres[133-135]. It is difficult to know how much of this variation reflects the clinical behaviour of the infants themselves and how much is determined by the oxygen adjustment practices of the caregivers and studies have not attempted to separate these issues.

Chow et al described how a continuous quality improvement process including an educational program and implementation of a new oxygen management policy in a level 3 neonatal unit, was associated with a dramatic decrease in retinopathy of prematurity[37]. The new oxygen management policy was designed to reduce the repeated episodes of hypoxia-hyperoxia in very low birth weight infants. The improvement process involved new policies on monitoring, avoidance of repeated increases and decreases of FiO_2, minimisation of "titration" of FiO_2, modification of previously used alarm limits and a staff education program. The paper did not define the policies that were in place prior to the intervention, perhaps because these were not under very close control. Nor did it present information regarding compliance with individual aspects as the new initiative. This makes it difficult to determine which aspects of their intervention may have been the most important. If their infants were exposed to a lot of hyperoxia prior to the intervention then reducing this alone could have explained most of the change in levels of ROP. Alternatively, reducing the variability may have been more important.

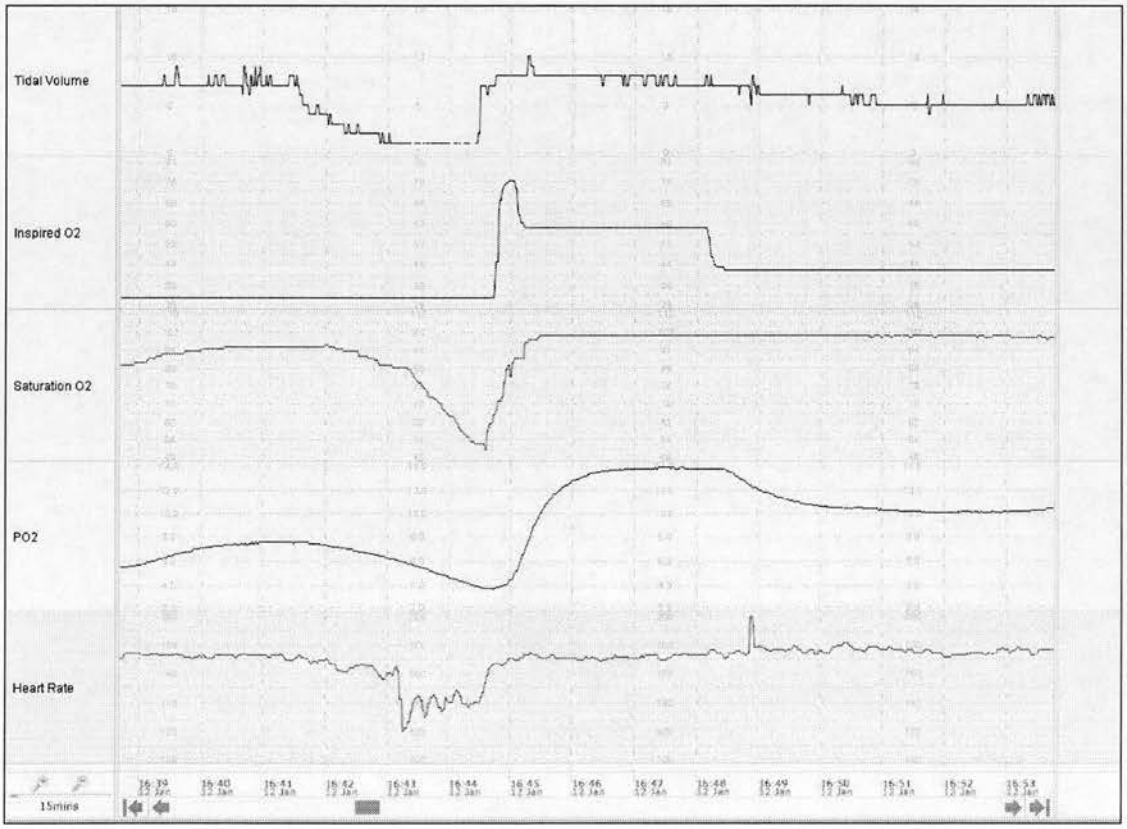
Adherence to oxygen saturation targets can never be 100%. Infants have previously been shown to spend a substantial amount of time above upper saturation targets in a potential hyperoxic state[133-135]. Some babies are more unstable than others but a

substantial degree of the variability in a baby might be determined by the clinical decisions made by the caregiver and the approach that they take to adjusting supplemental oxygen. Different carers attempt to maintain the oxygen saturation levels in different ways. Some turn inspired oxygen levels up and down much more readily than others. Some make larger or smaller adjustments than others. There is no definitive guidance of what patterns of adjustment are most effective. This is likely to depend on the nature of the problem causing the derangement in oxygen saturation.

Ventilated infants often have episodes of desaturation that give rise to adjustments in their inspired oxygen concentration. Bolivari et al, Hummler et al and Esquer et al showed that most hypoxemic episodes in preterm infants undergoing mechanical ventilation were triggered by active expiratory effort that reduces tidal volume of mechanical breaths and produces a large decrease in lung volume[116-118] Bolivari theorised that this reduction in lung volume probably leads to closure of small airways and the development of intrapulmonary shunts, which would explain the rapid development of hypoxemia. In ventilated infants it is also likely that reduced alveolar oxygen pressure caused by the reduction in tidal volumes would lead to desaturation because, with saturations typically in the low 90's, ventilated preterm infants are already operating on the steep part of the oxyhaemoglobin saturation vs inspired oxygen curve (Figure 8)[181 230]. Thereby a small decrease in alveolar oxygen pressure will lead to a much larger change in measured oxygen saturation. This conversion/artifactual effect may lead to increased instability and is one of the mechanisms whereby the switch from transcutaneous monitoring to oxygen saturation monitoring may have increased instability by increasing nursing interventions following insignificant desaturation events. Desaturations caused by intrapulmonary shunting due to airway closure would not be expected to respond substantially to adjustments in inspired oxygen, whereas reduced alveolar oxygen tension would be expected to respond better.

Figure 22 shows the computerised charts of one of the study infants, including tidal volume, oxygen saturation, inspired oxygen, transcutaneous oxygen and heart rate. This exemplifies the problem. In response to a significant desaturation event that is likely to have been triggered by active expiratory effort that produced a large decrease in lung tidal volume[116 117], the nurse increased the inspired oxygen by 48%. This in turn led to a prolonged period of hyperoxia, during which 100 % saturations were achieved and a $TcPO_2$ of 14 kPa was present for over 2 minutes before the oxygen was turned down. It took several minutes before the saturations returned to the target range. It is also clear that the infant's tidal volumes had begun to improve and saturations were already improving before the inspired oxygen was increased.

Figure 22: The computerised charts of one of the study infants



The aim of Study 3 was to explore whether inspired oxygen adjustment practices may influence oxygen stability and adherence to oxygen saturation targets, over and above the baby's general condition in preterm ventilated infants. We separated out the variation in oxygen stability attributable to the condition and behaviour of the baby from that attributable to the nursing staff practices, and so were able determine the extent to which oxygenation patterns are influenced by the nursing staff. The study also investigated how nursing seniority affected oxygen control practices and outcome.

2.3.3. Method

2.3.3.1. Setting

This study took place in the Neonatal Intensive Care Unit of the Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh during the period August 2004 to July 2005. The study was approved by the local ethics advisory committee. As this was principally a study of nursing practices rather than babies, a small number of clinically unstable, chronically ventilator dependent infants were studied, each of whom was cared for by a series of different nurses whose practices could be compared.

Infants were eligible for inclusion in the study if they remained ventilated (SLE 2000, SLE Ltd, Surrey, UK) for a minimum of at least six 12-hour nursing shifts. 13 infants were eligible during the period of study and 195 shifts were identified for these infants where appropriate data was available. According to clinical policy the nursing staff attempted to maintain oxygen saturation within the range 86%-94%. Each infant had continuous respiratory function monitoring using a Florian respiratory monitor (Acutronic Medical Systems, Zug, Switzerland). The physiological stability of the infants was monitored using a Siemens SC 7000 multi-parameter patient monitor (Draeger Medical, Inc). Heart rate, oxygen saturation (SpO_2), and FiO_2 data points were downloaded from the monitoring devices every

second to a cot-side computer and displayed graphically at the cot-side by a computerised patient data management system (Badger Patient Data Management System, Clevermed, Edinburgh, UK) as part of routine clinical practice. The downloaded data were analysed later. Saturation readings where the heart rate measured by the saturation monitor differed from the simultaneous ECG heart rate by more than 10 beats per minute were excluded as artifact from all monitored shifts in order to minimise any motion artifact. It is a long established routine practice in the Simpson Neonatal Unit to download continuously the real time inspired oxygen levels (where possible) and saturation values of all patients in the neonatal intensive care unit and to display them at the cot side in the form of trend charts. The nursing staff were therefore aware that inspired oxygen and saturation data was being downloaded. The data analysis of nurse oxygen adjustment practices was retrospective and the nursing staff were not aware that it would take place. The identities of the individual nurses were anonymised prior to analysis so that the identities of the staff could not be determined after the analysis. The seniority grade (d-h) of the nurse looking after the infant during each 12 hour nursing shift was also documented.

2.3.3.2. Analysis of nurses' oxygen adjustment practices

For this analysis the oxygen adjustment practices related to control of oxygen therapy were studied in a group of 24 trained neonatal nurses whilst they cared for the 13 clinically unstable ventilator dependent infants. Only nursing staff who did at least 4 shifts with the study infants were included. The resulting analysis contained a total of 133 nursing shifts during which 13 infants were cared for by a total of 24 trained neonatal nurses.

(a) Describing the overall respiratory stability of the infants

First the overall respiratory stability of the 13 infants during the 133 nursing shifts was described. This may reflect a combination of the intrinsic stability of the infant

and the way that the individual nurses adjusted the FiO_2 during each shift. For each infant during each 12 hour nursing shift the mean SpO_2, the variability (standard deviation) of SpO_2, the time that the infant spent with SpO_2 >94% whilst receiving supplemental oxygen, and the time spent with SpO_2 <86% were calculated. Three oxygen stability measures were then defined, the variability (standard deviation) of SpO_2 (saturation variability), the percentage of time that the infant spent with SpO_2 >94% whilst receiving supplemental oxygen (hyperoxia time) and the percentage of time spent with SpO_2 <86% (hypoxia time). The mean FiO_2 of the infant, the variability (standard deviation) of FiO_2, the number of FiO_2 increases per shift and the size of each FiO_2 increase during the shift were also determined.

(b) Separating the characteristics of the infants from the effect of nurses' oxygen adjustment practices

In order to separate the contribution to instability in oxygenation that may be attributable to nursing oxygen adjustment practices from the underlying intrinsic instability of the infants, a second more focussed analysis that incorporated the anonymised individual nurse identities and the overall stability of the individual infants that they care for was performed.

The respiratory stability data from all of the shifts studied for each of the 13 infants, for each of our three stability measures (saturation variability, hyperoxia time and hypoxia time) was used to calculate a summary value for the average stability of the individual infant by each of these three measures across all the studied shifts for that infant. Then, each individual nurse's data was analysed. For each shift during which each nurse had cared for a study infant, the stability of the infant during that shift was determined. This stability was then compared to the average stability for that baby during all of that baby's studied shifts and classified the individual nursing shift as being one during which the baby was more stable than its own average or less stable. This enabled determination of the proportion of all of the shifts studied for each

nurse during which their infant was more stable than that infant's average or less stable than that infant's average.

The oxygen adjustment practices of the nurses for whom, on more than 50% of their studied shifts, the infant was more unstable than its own average, were compared to the practices of the remaining nurses, for each of our three stability measures. The oxygen control practices that were compared between nurses were the number of FiO_2 increases per shift, the mean size of FiO_2 increase, the mean FiO_2 variability, and the mean FiO_2 administered and the mean SpO_2 maintained.

2.3.3.3. Nursing seniority/experience

Oxygen adjustment practices and oxygen stability data were examined in a cohort of 34 nurses who looked after one of the 13 infants for 3 or more shifts (total number of shifts 164) to examine the effect of different levels of nursing experience. The overall stability of the 13 infants during the 164 nursing shifts and the oxygen adjustment practices and oxygen stability achieved by each of the 34 nurses was first described. Additionally, a further measure of hypoxia was compared, namely percentage of time spent saturated below 80%. Oxygen control practices and oxygen stability data was averaged over all shifts each nurse did for each infant. Average oxygen control practices (number of FiO_2 increases per shift, the mean size of FiO_2 increase, the mean FiO_2 variability, the mean FiO_2 administered and the mean SpO_2 maintained) and the three oxygen stability measures were compared between E grade nurses (junior) and F and G grade nurses (senior). Neither D nor H grade nurses cared for one of the 13 infants for 3 or more shifts during the study.

2.3.3.4. Statistics

The independent samples t-test and chi-squared test were used to compare the difference in nurse oxygen control practices between the nurses whose babies displayed high and low instability, and between nurses of different seniority.

2.3.4. Results

2.3.4.1. Infant characteristics

The characteristics of the 13 infants studied are given in Table 9.

Table 9: Infant characteristics. Data are mean (SD) or number (%).

N	13
Gestation at birth (weeks)	25.9 (1.8)
Birth weight (g)	901 (249)
Mean age of infant at start of 12 hr shift under study (days)	12.1 (8.4)
Reason for prolonged ventilation	Extreme prematurity: 6 infants Sepsis 4 infants Following bowel surgery 3 infants (one NEC, one spontaneous perforation, one incarcerated inguinal hernia)

2.3.4.2. Analysis of nurses' oxygen adjustment practices

(a) Unadjusted oxygen stability data

Oxygenation stability patterns were analysed for data from a total of 133 12-hour nursing shifts during which the 13 studied infants were cared for by a total of 24 different neonatal nurses.

The mean (range) number of shifts for which data were available for each infant was 10.2 (3-19). The percentage of time for which downloaded inspired oxygen fraction data were available was 91.2%. The percentage of time for which downloaded SpO_2 data were available for was 91.9%. The percentage of time for which both inspired oxygen and oxygen saturation data were available was 85.1%. The mean (range) number of shifts carried out by each nurse was 5.4 (4-14).

Table 10: Basic stability data of the 13 infants during 133 shifts. Data are mean (SD).

Mean (SD) inspired oxygen concentration (%)	32.3 (7.5)
Mean (SD) variability in inspired oxygen concentration	5.7 (1.4)
Mean (SD) number of inspired oxygen changes per shift	23.9 (10.7)
Mean (SD) size of FiO_2 increase (%)	9.32 (3.2)
Mean (SD) oxygen saturation (%)	91.2 (2.4)
Mean (SD) oxygen saturation variability for each infant	5.43 (1.4)
Mean (SD) proportion of time spent below 86% saturation (%)	11.9 (5.7)
Mean (SD) proportion of time spent saturated above 94% while receiving supplemental oxygen (%)	18.8 (9.6)

(b) Separating the characteristics of the infants from the effect of nurses' oxygen adjustment practices

The oxygen stability data for the 13 infants are summarised in Table 11. The oxygenation stability data for the 24 nurses who cared for one or more of the 13 infants during these 133 shifts are summarised in Table 12.

Table 11: Oxygenation stability data for the infants during these 133 shifts

Infant	Number of shifts	Mean SpO_2 (%)	Mean SpO_2 variability	Mean % time with SpO_2 >94 in O_2 (%)	Mean % time with SpO_2 < 86 (%)
1	17	90.2	5.7	18.6	13.9
2	5	89.9	7.9	30.1	21.1
3	19	90.7	6.4	30.2	15.9
4	3	95.9	4.9	27.9	2.6
5	7	91.6	4.1	22.9	6.9
6	11	89.5	6.6	16.1	16.7
7	4	91.2	4.8	13.9	10.0
8	18	89.9	6.4	16.7	14.4
9	4	91.2	6.8	32.9	15.9
10	4	96.6	3.7	10.7	1.9
11	17	89.3	4.4	6.5	12.7
12	17	89.9	5.6	15.9	14.8
13	7	89.5	3.4	1.5	8.5
Mean	10	91.2	5.4	18.8	11.9

Table 12: Oxygen adjustment practices of the 24 nurses during these 133 shifts

Nurse number	Number of shifts	Mean FiO_2 used (%)	Mean FiO_2 variability	Mean number of FiO_2 increases per shift	Mean size of FiO_2 increase (%)	Mean oxygen saturation (%)	Mean (SD) oxygen saturation variability	Mean % time with SpO_2 >94 in O_2	Mean % time with SpO_2 < 86
1	6	28.2	4.0	22	7.3	91.4	5.1	28.6	11.9
2	4	33.7	5.1	35	7.4	89.9	5.9	15.7	14.8
3	7	37.0	5.7	22	8.1	90.2	3.7	7.6	8.2
4	5	33.9	5.5	27	7.3	90.4	5.2	19.1	14.0
5	14	37.9	6.9	29	9.2	90.0	5.1	15.9	12.9
6	4	31.2	5.1	20	7.2	91.3	6.1	14.7	13.5
7	5	36.9	3.4	14	6.8	90.2	5.0	14.5	11.4
8	6	33.9	5.2	26	6.7	91.1	5.0	11.8	14.2
9	5	41.3	8.3	25	9.1	89.8	6.7	16.8	15.3
10	5	37.9	8.1	24	11.1	90.7	6.7	24.1	13.8

11	10	35.0	5.1	23	5.8	90.5	5.7	15.8	14.6
12	5	33.0	6.3	48	8.0	90.1	7.2	29.2	19.8
13	4	43.7	8.7	33	9.7	90.3	7.0	24.2	15.0
14	5	36.9	6.5	21	8.4	88.8	7.8	18.7	21.2
15	4	34.8	5.4	12	15.9	93.7	5.4	37.0	6.5
16	5	52.3	7.6	39	7.6	88.2	8.5	25.6	26.5
17	5	32.3	7.6	25	14.6	92.6	6.1	29.9	11.4
18	5	30.7	6.2	22	8.9	90.6	4.7	20.8	11.7
19	4	27.6	6.4	17	11.5	91.8	3.5	11.4	3.4
20	4	36.7	5.8	27	6.7	89.6	5.7	12.9	16.4
21	7	41.7	6.1	19	8.4	89.6	5.5	11.5	12.9
22	4	41.4	4.1	15	7.6	90.5	4.4	9.1	8.2
23	4	31.1	4.2	18	7.2	90.7	4.0	11.5	6.6
24	6	32.2	6.3	25	7.1	90.0	5.6	14.8	14.1
Mean	5.5	35.9	6.0	24	8.6	90.5	5.7	18.4	13.3

Variability There were 11 nurses (high oxygen variability group) for whom, for more than or equal to 50% of their shifts, their infant showed more variable oxygenation (standard deviation of SpO_2) than its own average. The 11 were compared with the remaining 13 nurses (low oxygen variability group). The results are given in Table 13. The high oxygen variability group of nurses made significantly more inspired oxygen increases during each 12hr shift than the low oxygen variability group of nurses. There was no significant difference between the mean size of the FiO_2 increase between the groups. When cared for by nurses in the high oxygen variability group infants had a slightly lower mean saturation and spent more time with saturations <86%, but did not spend significantly more time with saturations greater than 94% whilst receiving oxygen. There was no significant difference in nursing seniority between the two groups.

SpO_2 >94% There were 11 nurses (increased hyperoxia group) for whom, for more than or equal to 50% of their shifts, their infant showed more time with SpO_2>94% whilst receiving supplemental oxygen than its own average. The 11 were compared with the remaining 13 nurses (decreased hyperoxia group). The data are shown in Table 14. Nurses in the increased hyperoxia group made significantly larger individual increases in FiO_2, compared to nurses in the decreased hyperoxia group. There were no other significant differences in oxygen adjustment practices between the groups. When cared for by nurses in the increased hyperoxia group infants had slightly higher mean saturation, although this was not statistically significant). They spent no more time with saturation <86%. There were significantly more senior nurses in the decreased hyperoxia group.

Table 13: Comparison of oxygen adjustment practices between high and low variability nursing groups

		High oxygen variability nurses n=11	Low oxygen variability nurses n=13	p
Nurse oxygen adjustment practice	Mean FiO_2 administered (%)	38.0	34.1	0.09
	FiO_2 variability	6.4	5.7	0.22
	Number of FiO_2 increases per shift	28.4	21.2	0.03
	Mean size of FiO_2 increase (%)	8.1	9.1	0.29
Infant outcomes	Mean saturation maintained (%)	90.0	90.9	0.04
	Saturation variability	6.5	4.9	<0.001
	Percentage time above 94% saturated in supplemental oxygen	18.9	17.9	0.75
	Percentage time below 86% saturated	16.5	10.5	0.001
Nursing grade	Junior/Senior	2/9	6/7	0.15

Data are means or fractions

Table 14: Comparison of oxygen adjustment practices between Increased and decreased hyperoxia nursing groups

		Increased hyperoxia nurses n=11	Decreased hyperoxia nurse n=13	p
Nurse oxygen adjustment practice	Mean FiO_2 administered (%)	35.4	36.3	0.71
	FiO_2 variability	6.4	5.7	0.22
	Number of FiO_2 increases per shift	25.6	23.6	0.57
	Mean size of FiO_2 increase (%)	9.9	7.6	0.02
Infant outcomes	Mean saturation maintained (%)	90.9	90.2	0.15
	Saturation variability	5.9	5.4	0.37
	Percentage time above 94% saturated in supplemental oxygen	23.6	13.9	0.001
	Percentage time below 86% saturated	13.2	13.3	0.98
Nursing grade	Junior/Senior	7/4	1/12	0.004

Data are means or fractions

SpO_2 <86% There were 12 nurses (increased hypoxia group) who for more than or equal to 50% of their shifts their infant spent more time with SpO_2 <86% than the overall average for that infant and they were compared with the remaining 12 nurses (decreased hypoxia group) (Table 15). Nurses in the increased hypoxia group made significantly more frequent FiO_2 changes compared to decreased hypoxia group. There was no significant difference in amount of change, FiO_2 mean or FiO_2 variability. When cared for by nurses in the increased hypoxia group infants showed greater SpO_2 variability and spent more time with SpO_2 >94%. There was a non significant trend to higher fraction of senior nurses in the increased hypoxic group.

Table 15: Comparison of oxygen adjustment practices between increased and decreased hypoxia nursing groups

		Increased hypoxia nurses n=12	Decreased hypoxia nurses n=12	p
Nurse oxygen adjustment practice	Mean FiO_2 administered (%)	37.2	34.6	0.25
	FiO_2 variability	6.4	5.6	0.21
	Number of FiO_2 increases per shift	29.2	19.8	0.003
	Mean size of FiO_2 increase (%)	7.7	9.2	0.15
Infant outcomes	Mean saturation maintained (%)	90.1	90.9	0.06
	Saturation variability	6.4	4.9	0.002
	Percentage time above 94% saturated in supplemental oxygen	20.2	16.6	0.25
	Percentage time below 86% saturated	16.5	10.1	<0.001
Nursing grade	Junior/Senior	2/10	6/6	0.08

Data are means or fractions

2.3.4.3. How nursing seniority affects oxygen adjustment practices and Infant outcome

For these analyses, oxygenation stability patterns were analysed for data from a total of 164 12-hour nursing shifts during which the 13 studied infants were cared for by a total of 34 different neonatal nurses. The oxygen stability data for the 13 infants who were included in the study are summarised in Table 16. The oxygenation stability data for the 34 nurses who cared for one or more of the 13 infants during these 164 shifts are summarised in Table 17.

Table 16: Oxygenation stability data for the infants during the 164 shifts

Infant	Number of shifts	Mean SpO_2 (%)	Mean SpO_2 variability	Mean % time with SpO_2 >94 in O_2 (%)	Mean % time with SpO_2 < 86 (%)
1	19	90.3	5.7	19.4	13.6
2	5	89.9	7.9	30.1	21.1
3	19	90.7	6.4	30.2	15.9
4	6	95.4	4.4	20.0	2.7
5	10	91.7	4.0	20.7	6.2
6	18	89.7	5.9	14.8	14.5
7	7	91.1	4.5	14.0	9.4
8	19	89.8	6.4	16.7	14.8
9	4	91.2	6.8	32.9	15.9
10	5	96.7	3.4	8.7	1.5
11	20	89.2	4.5	6.6	12.9
12	17	89.9	5.6	15.9	14.8
13	14	89.1	3.7	1.6	11.5
Mean	12.5	91.1	5.3	17.8	11.9

Table 17: Oxygen adjustment practices of the 34 nurses during the 164 shifts

Nurse number	Number of shifts	Mean FiO_2 used (%)	Mean FiO_2 variability	Mean number of FiO_2 increases per shift	Mean size of FiO_2 increase (%)	Mean oxygen saturation (%)	Mean oxygen saturation variability	Mean % time with SpO_2 >94 in O_2	Mean % time with SpO_2 < 86
1	6	28.2	4.0	21.6	7.3	91.4	5.1	28.6	11.9
2	4	33.7	5.1	34.8	7.4	89.9	5.9	15.7	14.8
3	7	37.0	5.7	22.8	8.1	90.2	3.7	7.6	8.2
4	5	33.9	5.5	26.4	7.2	90.4	5.2	19.1	14.0
5	14	37.9	6.9	28.8	9.2	90.0	5.1	15.9	12.9
6	3	27.8	3.3	21.6	12.9	92.8	5.2	20.6	8.7
7	4	31.2	5.1	19.2	7.2	91.3	6.1	14.7	13.5
8	5	36.9	3.4	13.2	6.8	90.1	5.0	14.5	11.4
9	6	33.9	5.1	26.4	6.7	91.1	5.0	11.8	14.1
10	5	41.3	8.3	25.2	9.1	89.7	6.7	16.8	15.3
11	5	37.9	8.1	24	11.1	90.7	6.7	24.1	13.8
12	10	35.0	5.1	22.8	5.8	90.5	5.7	15.8	14.6
13	5	33.0	6.3	48	8.0	90.1	7.2	29.2	19.8
14	4	43.7	8.7	33.6	9.7	90.2	7.0	24.2	14.9
15	5	36.9	6.5	21.6	8.4	88.8	7.8	18.7	21.2

16	4	34.8	5.4	12	15.9	93.7	5.4	37.0	6.5
17	5	52.3	7.6	38.4	7.6	88.2	8.5	25.6	26.5
18	5	32.3	7.6	25.2	14.6	92.6	6.1	29.9	11.4
19	5	30.7	6.2	21.6	8.9	90.6	4.7	20.8	11.7
20	3	23.8	4.2	8.4	19.8	93.5	3.3	6.9	3.3
21	3	40.6	7.6	13.2	7.8	90.5	4.7	10.0	17.3
22	3	39.4	6.0	12	6.7	90.9	5.0	21.0	11.1
23	4	27.6	6.4	16.8	11.5	91.8	3.5	11.4	3.4
24	3	31.5	3.7	22.8	6.8	90.4	4.7	11.6	10.8
25	3	28.2	6.7	16.8	10.3	90.0	4.0	7.6	6.7
26	4	36.7	5.8	26.4	6.7	89.5	5.7	12.9	16.4
27	7	41.7	6.1	19.2	8.4	89.6	5.5	11.5	12.9
28	3	52.4	7.0	15.6	6.6	88.7	4.7	3.6	15.1
29	3	24.7	5.1	18	8.7	91.1	4.1	14.2	8.5
30	4	41.4	4.1	15.6	7.6	90.5	4.3	9.1	8.2
31	3	52.2	7.1	24	7.4	88.7	5.4	8.0	19.3
32	5	30.9	4.7	19.2	7.8	90.6	4.6	14.7	9.4
33	6	32.2	6.3	25.2	7.1	90.0	5.6	14.8	14.1
34	3	30.9	4.8	9.6	11.3	90.0	3.3	2.3	4.2
Mean	4.8	35.7	5.9	22.1	9.0	90.5	5.3	16.2	12.5

Comparisons by t-tests showed that senior nurses maintained significantly higher mean FiO_2 (38.1 vs 30.5%, p=0.002) than more junior nurses, and the size of the individual oxygen level increases was significantly smaller (7.8 vs 11.5, p=0.001) (Table 18). There was no difference between the nurses of different seniority in the number of increases in FiO_2 per shift (22.1 vs 21.9, p=0.8) or FiO_2 variability (5.9 vs 5.8, p=0.8). Infants looked after by the senior nurses had significantly lower oxygen saturations, spent significantly less time saturated above 94% while in supplemental oxygen, but significantly more time spent saturated below 86 %. There was no difference between oxygen variability levels or percentage of time spent saturated below 80 %.

Table 18: Unadjusted oxygen control practices of the 34 nurses, looking after the 13 infants during 164 shifts, comparing nursing seniority

		Junior E Grade n=11	Senior ≥ F Grade N=23	p
Nurse oxygen adjustment practice	Mean FiO_2 administered (%)	30.5	38.1	0.002
	FiO_2 Variability	5.8	5.9	0.81
	Number of FiO_2 increases per shift	21.9	22.1	0.81
	Mean size of FiO_2 increase (%)	11.5	7.8	<0.001
Infant outcomes	Mean saturation maintained (%)	91.6	90.0	<0.001
	Saturation variability	5.1	5.4	0.55
	Percentage time above 94% saturated in supplemental oxygen	20.3	14.2	0.03
	Percentage time below 86% saturated	10.1	13.7	0.047
	Percentage time below 80% saturated	3.2	4.8	0.11

Data are mean of each nurse's mean value

2.3.5. Discussion

The results of Study 3 show that, after controlling for the intrinsic instability of the infant, the way that supplemental oxygen is adjusted by nursing staff is significantly associated with the stability patterns achieved by the infant. Large changes in FiO_2 contribute to greater time spent in a hyperoxic range. Frequent changes in FiO_2 contribute to increased variability in oxygenation and to greater time spent in a hypoxic range. Senior nurses, despite looking after the sicker infants as shown by their higher FiO_2 but lower mean saturation maintained, make significantly smaller oxygen changes meaning that their infants spend significantly less time in the hyperoxic range. Since the time spent with hyperoxia and the degree of oxygen variability contribute to the risk of adverse outcome this information might make a useful contribution to clinical care.

Chow et al described how a new oxygen management policy designed to reduce the repeated episodes of hypoxia-hyperoxia in very low birth weight infants, was associated with a dramatic decrease in retinopathy of prematurity[37]. The new policies on monitoring included avoidance of repeated increases and decreases of FiO_2, and minimisation of "titration" of FiO_2, both of which this study has demonstrated to be associated with hyperoxia and oxygen variability. In a similar study by Wright et al[139], the incidence of threshold ROP in infants 500-1500 grams fell from 7.3 to 1.3% ($p < 0.05$), following the introduction of a reduced oxygen saturation protocol and training to minimize fluctuations in SpO_2 and to adjust FiO_2 in small increments.

Others have reported the oxygenation patterns of preterm infants and have demonstrated that there is variation between nurses in the instability that their babies demonstrate. However, as far I am are aware, this is the first study to attempt to control for the intrinsic instability of the infant and to have incorporated measurements of the way that the inspired oxygen was adjusted. This is also the first

study to investigate the relationship between nursing experience, oxygen adjustment practices and oxygen stability maintained.

Nursing experience

In the analysis of the effect of nursing experience on oxygen adjustment behaviour and stability of oxygenation, there was no adjustment for the intrinsic stability of the infants that the nursing staff were caring for, because in some cases there would have been too few shifts to permit this. It is likely that, to some extent, infants that are more unwell or unstable tend to be looked after more often by senior members of nursing staff. This was suggested by the fact that during the shifts analysed that were undertaken by more senior nurses the babies had higher mean FiO_2 but lower mean saturation. Despite this, the more senior nurses made significantly smaller oxygen changes and their infants spent less time with saturation greater than 94% whilst receiving supplemental oxygen. Whether the increase in time the infants spent saturated below 86 % for the senior nurses was due to sickness of the infants or that the senior nurses allowed the infants to spend more time in the hypoxic range prior to increasing inspired oxygen, is difficult to determine. Whatever the mechanism, senior nurses do not let the infants spend significantly more time below 80% so it is probably not significant in terms of infant exposure to hypoxia.

During this study, the size and number of each oxygen concentration decrease was not analysed. For the purposes of this study we were particularly interested in nursing practices that might lead to more hyperoxia and we focused on increases in FiO_2. A study looking at decreases in FiO_2 would also be interesting as these would also have an affect on the oxygen patterns achieved by infants. The fact that junior nursing staff administered lower mean inspired oxygen levels despite making larger oxygen concentration increases suggests that they must be making larger oxygen concentration decreases as well.

In the AVIOx study[134], compliance with saturation policy was monitored in 84 infants born at less than 28 weeks of gestation in 14 centres. Compliance was measured during a 72 hour period in each of the first 4 weeks of life in infants who were in oxygen. The proportion of time spent within the intended saturation range varied from 16-64% between centres. Most non-compliance was above the intended target range with 20-74% of time spent above intended range. Their mean level of modifiable hyperoxia (saturations above upper saturation limits while in supplemental oxygen) 36% compares unfavourably with our figure of 18.8 %. However firstly the alarm limits used in some of the units from this study were quite narrow, which was associated with reduced compliance as expected. Secondly our study more accurately excludes non-modifiable time. In AVIOx monitoring periods were included as modifiable if the infant spent less than 20% of the time in supplemental oxygen. Therefore infants could have non-modifiable hyperoxia for up to 20% of time included as modifiable time. Rasmussen et al[135] studied 20 haemodynamicaly stable preterm infants who were receiving positive pressure support. Their target saturation range was 88-92%, which is again a tighter alarm limit and they found that their infants spent 49% of their time with saturations above 93%, although there was no comment as to whether this was modifiable or not in the abstract (ie whether the infants were in supplemental oxygen for all of this time). Sun et al[133] studied the ability of 35 nicu nurses caring for 10 ELBW infants to keep infants within a target range of 80-92%, and found that their infants spent 9% of their time saturated above 95%. Again, however, they did not mention if this included non-modifiable time.

Computerised control of inspired oxygen concentration my provide an effective alternative to nurse adjustment. Bhutani et al[141] described three protocols for adjusting inspired oxygen in a group of infants with bronchopulmonary dysplasia, and found that infants spent significantly more time (81%) within their set oxygen limits when using a computerised adaptive control delivery system, than when standard caregiver control (54%) or close bedside control by a single researcher

(69%) was used. Claure et al[142] in a group of ventilated infants who presented with frequent episodes of hypoxemia, found a significant increase in duration of normoxemia (75% of time within range) when using closed-loop control to maintain SpO_2 within a target range compared with continuous manual FiO_2 adjustments by a nurse (66% of time within range). Urschitz et al[143] found in a population of preterm infants receiving nasal CPAP and oxygen, automatic closed-loop oxygen control was associated with more time spent within target range 90.5% than routine manual oxygen control 81.7%. The frequency of manual oxygen adjustments was also lowest in automatic control (Friedman's test: $p=0.001$). Closed loop or adaptive controlled inspired oxygen concentration may be the way forward for reducing some of the burden of alarms placed on nursing staff and allowing them more time to carry out more of their ever extended role when looking after the extreme preterm neonate.

In this analysis, it was assumed that a single nurse looks after a single infant for their whole 12 hr shift. Clearly this is not always the case and does not take into account nursing breaks and influence of other medial staff etc. This would be expected to weaken any difference found between the groups but the analysis has still shown practices that were significantly associated with stability outcomes. These infants were selected deliberately as they remained ventilator dependent for a series of nursing shifts and they are likely to be more unstable than the average preterm infant who is now only ventilated for a relatively short time. The infants in this study at first seem older than the infants in some other studies such as AVIOx, being on average 12.1 days old at start of each studied shift, but most infants were studied repeatedly from within 2-3 days of birth for a large number of 12 hr shifts.

When examining infant oxygen stability of ventilated preterm infants, this study has not looked into any of the infant interaction with ventilation that might have influenced stability. Clearly this type of information would be very interesting to explore as well. It was not possible to download inspired oxygen concentrations or other ventilation parameters during use of CPAP.

Infants were ventilated using SLE 2000 ventilators, which are conventional pressure controlled, time cycled ventilators. It is possible that volume support or guarantee modes of ventilation on other ventilators may contribute to better stability in this population of infants. However, most research to date on these modes of ventilation has concentrated on tidal volumes, rate of weaning and rates of lung disease. There is little evidence that these modes of ventilation lead to more stable oxygenation, or better compliance to target range[231 232].

Adubakar et al[140] found that assist control with volume guarantee (AC + VG) mode was associated with less variability of SpO_2 than synchronised intermittent mandatory ventilation with volume guarantee (SIMV + VG). However, the mean saturation achieved during AC+VG was significantly higher (95% vs 91%), which suggests that they must have permitted much higher levels of modifiable hyperoxia during this method of ventilation given that their target range was 88-92%. They did not deal with this issue in their discussion.

Hummler et al[117] found that infants with frequent hypoxemic episodes spent significantly less time above their upper oxygen saturation target of 92% when volume controlled synchronised intermittent mandatory ventilation (SIMV) was used rather than pressure-controlled SIMV. The volume controlled infants tended to have less deep desaturation events (not significant), better preserved tidal volumes during desaturation events and fewer associated bradycardias. This probably meant that the nurses made less major adjustments to inspired oxygen concentrations, which in turn led to less hyperoxia. However, they failed to show a significant difference in their primary outcome of percentage of time spent with hypoxemia. This in part may reflect the nature of the desaturation events in ventilated preterm infants, which are due to active expiratory effort by the infants and therefore not completely correctable by this type of intervention. Although volume control could preserve tidal volume, it may not abolish the loss of end-expiratory lung volume that occurs with active

expiratory efforts. This area needs further research with measurement of inspired oxygen changes.

In conclusion, the results of this study suggest that the average number of FiO_2 increases per 12 hr nursing shift in unstable ventilated preterm infants was more than 20. After controlling for the intrinsic instability of the infant the results suggest that large changes in FiO_2 contribute to greater time spent in a hyperoxic range and that frequent changes in FiO_2 contribute to increased variability in oxygenation, and more time spent in a hypoxic range. Senior nurses looking after more sick infants are able to avoid hyperoxia more successfully than less experienced nurses and this may be because they make smaller oxygen changes. Since the time spent with hyperoxia and the degree of oxygen variability contribute to the risk of adverse outcome, this information might make a useful contribution to clinical care if these observations can be incorporated more widely into practice.

2.4. Study 4: Non-invasive measurement of reduced ventilation-perfusion ratio and shunt in infants with bronchopulmonary dysplasia; a physiological definition of the disease

2.4.1. Abstract

Introduction

An objective definition of bronchopulmonary dysplasia (BPD) is required to interpret trial outcomes and provide a baseline for prognostic studies. Current definitions do not quantify disease severity. The cardinal measures of impaired gas exchange are a reduced ventilation/perfusion ratio (V_A/Q) and increased right to left shunt. These can be determined non-invasively by plotting oxygen saturation (SpO_2) against inspired oxygen pressure (PIO_2).

Aims

To describe the reduced V_A/Q and shunt in infants with BPD and evaluate these as graded measures of pulmonary dysfunction.

Methods

21 preterm infants with BPD were studied. PIO_2 was changed stepwise to vary SpO_2 between 86% and 94%. Pairs of PIO_2 and SpO_2 data points for each infant were plotted and analysed to derive reduced V_A/Q and shunt.

Results

In every infant the SpO_2 vs PIO_2 curve was shifted to the right of normal because of a reduced V_A/Q. The mean (SD) shift was 16.5 (4.7) kPa (normal 6kPa). Varying degrees of shunt were also present but these were less important in determining SpO_2 within the studied range. The degree of shift was strongly predictive of the PIO_2 required to achieve any SpO_2 within the range 86-94% ($R^2>0.9$), permitting shift and V_A/Q to be determined from a single pair of PIO_2 and SpO_2 values in this range.

Conclusions

The predominant gas exchange impairment in BPD is a reduced V_A/Q described by the right shift of the SpO_2 vs PIO_2 relationship. This provides a simpler method for defining BPD that grades disease severity.

2.4.2. Introduction

Despite great improvements in the survival of infants born prematurely, there continues to be a large number of infants who develop bronchopulmonary dysplasia (BPD). This causes them to remain in hospital longer, prolongs their requirement for supplemental oxygen, and is associated with long-term morbidity and an increased risk of mortality. Reducing BPD remains a major focus of clinical and research activity.

An objective definition of BPD is required to allow reliable interpretation of clinical trial outcomes and to serve as a baseline in prognostic studies. Yet an ideal definition has been elusive. Definitions based on the infant having a requirement for supplemental oxygen at 28 days of life[233] or at 36 weeks corrected gestational age[175] have been used widely, but their usefulness is severely limited by the marked variation between clinicians in their criteria for oxygen supplementation[162]. A definition based on the use of oxygen therapy alone gives wide variations in the incidence of disease that reflect little more than clinician variation and have little relevance to the severity of any underlying pathology[163]. Recently a physiological definition has been proposed that aims to eliminate this bias by defining BPD as a requirement for supplemental oxygen to maintain an oxygen saturation of 90% at 36 weeks corrected gestational age[163]. This is undoubtedly an advance. However, healthy preterm and term infants have saturations around 97% in air[48 49] and saturations lower than this in air must reflect a degree of gas exchange impairment, even if supplemental oxygen is not always deemed necessary. Present approaches to defining BPD classify these infants as disease free.

It is possible, by non-invasive measurements of PIO_2 and SpO_2, to quantify the severity of gas exchange impairment in a graded fashion and to partition this between the contribution made by reduced ventilation/perfusion ratio (V_A/Q) and that due to right to left shunt[177-182]. The aim of Study 4 is to apply this method to analyse the gas exchange abnormalities in infants with BPD, and to use the observations to model an improved approach to the definition of BPD that measures the severity of the gas exchange impairment.

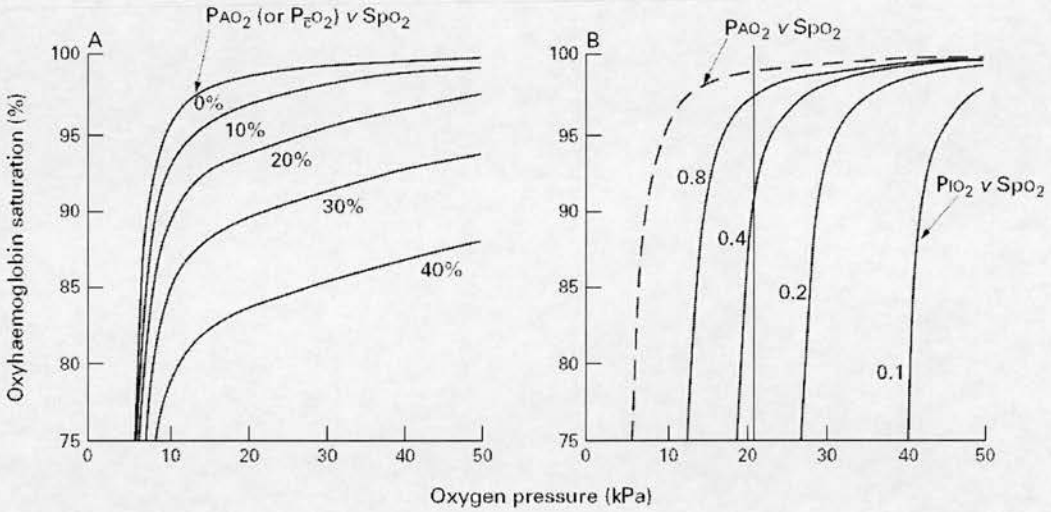
2.4.3. Methods

2.4.3.1. Underlying physiology

Reduced V_A/Q and increased shunt have different effects on the relationship between inspired oxygen pressure (PIO_2) and arterial oxygen saturation (SpO_2). A reduced V_A/Q causes a fall in alveolar and arterial oxygen tension (PO_2) and a rise in alveolar and arterial carbon dioxide tension (PCO_2). Increasing PIO_2 restores the alveolar PO_2 and SpO_2 to normal, overcoming the effect of the reduced V_A/Q. Increased shunt does not raise PCO_2 but reduces arterial oxygen saturation because the shunted blood is not exposed to alveolar oxygen. Increasing PIO_2 can compensate for only a small amount of shunt because the non-shunted blood is already almost fully saturated and does not carry much more oxygen other than small amounts in solution when PIO_2 is increased. These independent effects on gas exchange can be represented in the form of plots of oxygen saturation (SpO_2) against inspired oxygen pressure (PIO_2)[177 179-183], as shown in Figure 23.

Figure 23: Plots of oxyhaemoglobin saturation % (SpO_2) vs inspired oxygen pressure in kPa (PIO_2)[181].

(A) Increasing shunt from 0 to 40% lowers the position of the upper part of the curve. (B) Reducing V_A/Q from 0.8 to 0.1 shifts the curve to the right. The right shift of each PIO_2 vs SpO_2 curve from the position of the dissociation curve (dashed line) is the $PIO_2 - PAO_2$ difference in kPa, which includes $PaCO_2/R$. The 0.8 curve represents the normal adult curve which intercepts a PIO_2 of 21 kPa (vertical line) at 97% SpO_2.

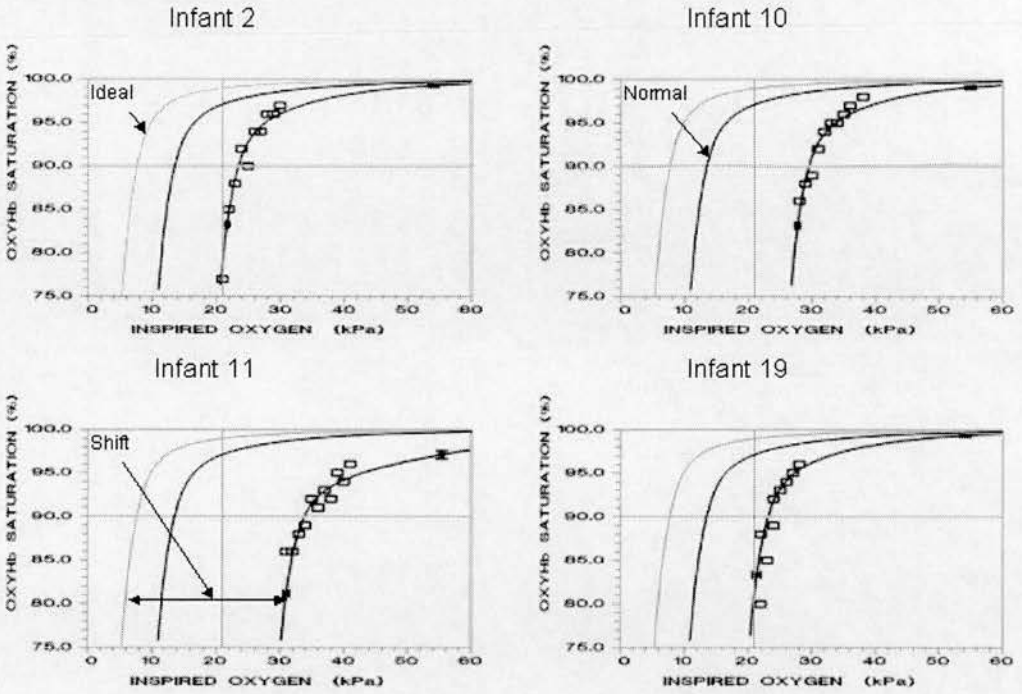


At sea level (one atmosphere) the inspired oxygen pressure (PIO_2) in kPa is the same as the inspired oxygen percentage. The curve relating alveolar (mixed capillary) PO_2 to oxygen saturation in the ideal lung represents the shape of the oxy-haemoglobin dissociation curve. Increasing shunt displaces the top part of the curve downwards (Figure 23A) as the maximum SpO_2 obtainable falls. In contrast, reducing V_A/Q shifts the whole curve to the right (Figure 23B). The degree of right shift, using the oxygen dissociation curve as a reference, is determined by the reduction in V_A/Q and rise in alveolar PCO_2. The normal curve is shifted to the right of the haemoglobin-oxygen dissociation curve by 6kPa, which is largely PCO_2/R (where R is the

respiratory gas exchange ratio). Additional right shift compared to normal represents the increase in PIO_2 that will be required to restore the mixed capillary PO_2 to normal levels and thereby permit normal arterial saturation. If multiple pairs of PIO_2 and SpO_2 values are obtained from the same patient then a single pair of shunt and shift values can be derived. This can be done graphically[177-180] by moving a set of shunt curves like those in Figure 23A laterally over the plot of PIO_2 vs SpO_2 data points until one of the shunt curves superimposes the data points. The degree of shift can then be read off the axis of the graph and the shunt determined by which shunt curve most closely fits the data. Alternatively, the shift and shunt can be calculated using a computer algorithm that derives confidence intervals for the shunt and shift values and coefficients of determination (R^2) for the fit of the data to the shunt and shift model[179-181].

Figure 24: Plots of oxyhb saturation % (SpO_2) vs inspired oxygen (PIO_2) in kPa for infants 2,10,11 and 19.

Reference grid lines are added at a SpO_2 of 90% and a PIO_2 of 21kPa. The haemoglobin oxygen dissociation curve (ideal lung) is the reference point for derivation of shift. The normal SpO_2 vs PIO_2 curve is also included for comparison.



2.4.3.2. Procedure

Twenty-one preterm infants who were considered to have BPD on the basis of a continuing requirement for supplemental oxygen at 36 weeks corrected gestational age, were studied. The study was approved by the institutional ethics advisory committee and written informed consent was obtained from the parents in all cases. This was a convenience sample. Infants were included if they were receiving supplemental oxygen, but not other support at the time of study. According to the

unit policy oxygen was being administered as required to maintain oxygen saturation in the target range 86-94%. All infants were being cared for in the neonatal unit of the Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh between January 2002 and March 2005. All data were collected within two weeks of the infant reaching 36 weeks corrected gestational age.

At the time of the study, all infants were receiving oxygen via nasal cannulae. To permit measurement and control of the inspired oxygen pressure, the infants were placed in a neonatal intensive care incubator with oxygen under servo control (Draeger 8000IC). The oxygen analyser was calibrated at the start of each study. Functional arterial oxygen saturation (SpO_2) was measured using either a Siemens SC7800 or a Philips M3046A multiparameter patient monitor, depending on which nursery the infant was being nursed in. Studies began at least 30 minutes after a feed and were conducted with the infant lying supine. PIO_2 was reduced in increments of 1-2% (1-2kPa) and then increased again to vary SpO_2 between 94% and 86%. At each PIO_2 value the infant was allowed to stabilise for around 5 minutes before a pair of SpO_2 and PIO_2 values was recorded. Values were recorded only if there was a good pulse waveform on the oximeter and the infant was not displaying gross body movements.

Sleep state was not standardised. PIO_2 was never reduced below 21 kPa, and oxygen administration to saturation greater than 94% was minimised as per unit policy. The pairs of PIO_2 and SpO_2 data points obtained from each infant were plotted and analysed using a computer algorithm which gave a curve representing a single solution for shunt and shift (the difference between PIO_2 and mixed capillary PO_2) for each subject's data set[179-181]. If the data pairs obtained did not describe the plateau of the oxyhaemoglobin dissociation curve, the algorithm was sometimes unable to calculate the shunt and shift values. Under these circumstances the data were plotted manually and shunt and shift were determined from the graphs directly using the method described above.

Because right shift is due to the combined effects of raised $PaCO_2$ and reduced V_A/Q we determined the contribution of these two variables using a mathematical model of gas exchange described by Olszowka and Wagner[183]. PIO_2 vs SpO_2 curves were constructed for V_A/Q values from 0.9 to 0.15 and the predicted $PaCO_2$ value was calculated from the model. From this we related the shift value in each subject to a particular V_A/Q and compared the subject's most recent $PaCO_2$ measurement with the predicted $PaCO_2$.

2.4.4. Results

The clinical characteristics of the 21 infants are described in Table 19. All were receiving supplemental oxygen at the time of study. There was wide variation between the infants in the length of time that each had been ventilated or supported with CPAP. Some were still cycling on and off CPAP.

The main finding was that, in every infant, the PIO_2 vs SpO_2 curve was shifted to the right of the oxygen dissociation curve, mean shift (SD) 16.5 (4.7) kPa (Table 20). The normal PIO_2 vs SpO_2 curve is shifted 6 kPa to the right of the dissociation curve and is identical to the V_A/Q 0.8 curve shown in Figure 23B. This intercepts the vertical line at 21kPa PIO_2 at a SpO_2 of about 97%. Figure 24 shows the data plots of infants 2, 10, 11 and 19 in relation to the oxy-haemoglobin dissociation (ideal) curve and the normal adult PIO_2 vs SpO_2 curve. Table 20 shows the values for shunt and right shift for all 21 infants, with 95% confidence intervals and R^2. In 3 infants (5, 8 and 18) the range of paired values of PIO_2 and SpO_2 obtained did not describe enough of the plateau of their PIO_2 vs SpO_2 relationship to enable the algorithm to calculate shunt and shift values. Their data points were plotted and the shunt and shift values were determined manually from the graphs as described above. These 3 infants all had $SpO_2 \geq 90\%$ breathing air.

Table 19: Characteristics of the infants studied

Infant	Gestation at birth (weeks)	Corrected gestation at time of study (weeks)	Birth weight (kg)	Weight at time of study (kg)	Nasal cannula O_2 flow rate (l/min)	Total days ventilated	Total days of CPAP
1	25.6	37.7	0.640	2.330	0.03	27	55
2	25	36.4	0.870	3.000	0.03	19	33
3	27	37.7	0.670	2.200	0.02	6	16
4	25.9	37.3	0.965	2.705	0.1	2	50
5	28	38	0.590	1.940	0.01	11	70
6	26	36.6	0.970	2.535	0.1	45	70
7	27.4	36.4	0.800	2.300	0.04	1	44
8	28	37.3	0.890	2.650	0.02	2	40
9	27.3	37.9	0.750	2.130	0.08	1	31
10	26.7	37	0.965	2.600	0.02	16	63
11	24	37.9	0.520	2.100	0.15	50	68
12	27.3	36.3	0.490	1.530	0.03	2	81
13	25.4	36.3	0.650	2.195	0.02	4	15
14	26.7	37.4	1.110	2.910	0.02	1	40
15	26.1	37.1	0.690	2.040	0.05	4	70
16	26.1	36.1	0.610	1.790	0.07	14	76
17	29	37.4	1.060	2.350	0.125	0	0
18	23.7	36.9	0.630	1.960	0.01	50	74
19	28	38	0.570	2.250	0.05	4	33
20	26.7	37.6	0.950	2.440	0.03	11	65
21	23.7	37.6	0.530	2.380	0.08	41	77
Mean	26.4	37.2	0.758	2.302	0.052	14.8	51
SD	1.45	0.62	0.192	0.359	0.040	17.3	23.3

Table 20: Shunt, right shift of the SpO_2 vs PIO_2 curve, R^2 for the fit to the model and V_A/Q.

Infant	Shunt (%)	Shift (kPa)	R^2	Shunt (%) 95% C.I.	Shift (kPa) 95% C.I.	V_A/Q
1	10.3	15.0	0.55	2.7	0.6	0.33
2	6.7	15.0	0.94	1.5	0.3	0.34
3	4.2	12.7	0.78	1.1	0.4	0.41
4	9.2	19.0	0.65	1.7	0.8	0.26
5	5.6	12.9				0.4
6	14.8	28.5	0.56	3.2	1.1	0.16
7	5.1	13.5	0.61	5.1	0.5	0.38
8	5.0	11.5				0.45
9	11.6	18.0	0.38	1.0	0.4	0.28
10	6.0	20.9	0.90	1.6	0.4	0.23
11	14.3	24.2	0.81	1.5	0.5	0.2
12	10.0	18.7	0.66	2.1	0.7	0.26
13	13.8	13.5	0.58	4.3	0.7	0.38
14	9.7	12.2	0.66	3.6	1.0	0.43
15	10.0	18.0	0.64	4.1	0.4	0.28
16	7.3	18.6	0.83	2.6	0.5	0.27
17	11.1	22.5	0.81	2.6	0.4	0.21
18	7.5	9.0				0.6
19	6.4	14.6	0.82	1.7	0.7	0.35
20	13.3	12.7	0.64	2.7	0.6	0.41
21	5.1	15.4	0.81	1.1	0.9	0.33
Mean	8.9	16.5	0.69	2.4	0.6	0.33
SD	3.4	4.7	0.15	1.2	0.2	0.10

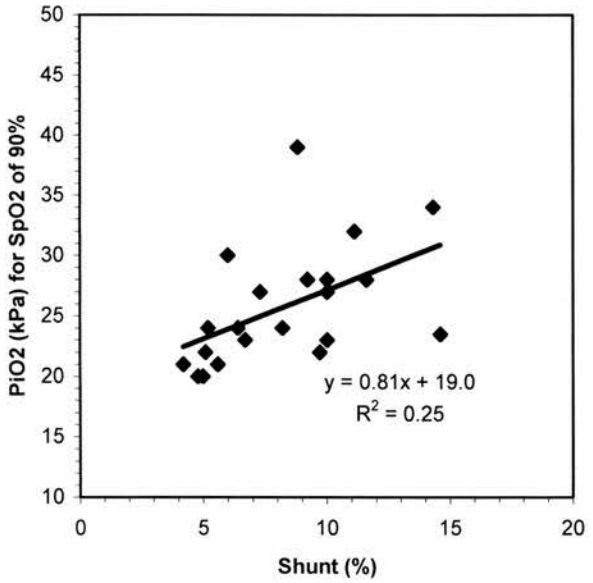
Because a significant right shift of the PIO_2 vs SpO_2 curve occurred in every case, and was a sensitive measure of reduced V_A/Q, we looked for an index of right shift that might obviate the need to produce a range of different PIO_2 values in each case. In every infant, the 90% SpO_2 value fell on the steep part of the dissociation curve so

that the PIO_2 needed to produce 90% SpO_2 might be a candidate marker of right shift. Figure 25 shows plots of the degree of shunt and shift in each infant against the PIO_2 required to achieve a SpO_2 of 90%. At this SpO_2, the relationship between PIO_2 and shift was highly significant and linear, whereas the relationship between PIO_2 and shunt was weak, indicating that shift was the main determinant of reduced SpO_2 in these infants.

Plots of shift against the PIO_2 required to achieve SpO_2s 86-94% were constructed, suggesting linear relationships between shift and PIO_2 at all SpO_2s in this range with all R^2 values greater than 0.9 (Table 21). The consistency of the relationship between shift and PIO_2 within this range was such that multiple data pairs in each infant were not required to derive shift. A single pair of PIO_2 and SpO_2 values in the SpO_2 range 86-94% was sufficient to predict the shift that would be derived from the whole data series. The mean (SD) difference between the shift calculated from individual data pairs and the entire data series for each infant was 0.24 (1.25) kPa.

Figure 25: (A) PIO_2 required to achieve SpO_2 of 90% vs Shunt. (B) PIO_2 required to achieve SpO_2 of 90% vs shift.

(A)



(B)

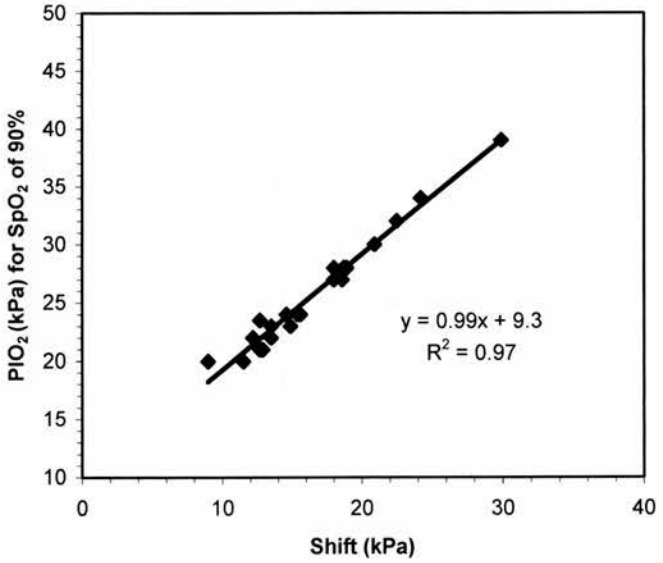


Table 21: Results of plots including R^2 values, slope, intercept and predicted PIO_2 at each saturation that would predict that an infant would maintain a $Sp0_2$ of 90% in air

Saturation	R^2	Slope	Intercept	PIO_2 at each saturation that would predict that an infant would maintain a SpO_2 of 90% in air
86	0.98	0.97	8.30	19.8
87	0.98	0.97	8.56	20.0
88	0.98	0.98	8.67	20.2
89	0.98	0.99	8.92	20.6
90	0.98	1.01	9.08	21
91	0.97	1.04	9.19	21.5
92	0.96	1.07	9.31	21.9
93	0.94	1.13	9.37	22.7
94	0.90	1.22	9.37	23.8

To permit others to derive shift from a single pair of SpO_2 and PIO_2 values, shift was calculated from the results of this study for the range of PIO_2s and saturations that are likely to be observed in infants with BPD at 36 weeks corrected gestational age and the results are given in Table 22.

The PCO_2 predicted by the model of Olszowka and Wagner[183] for the degree of reduced V_A/Q in each infant was linearly related to measured PCO_2 ($y=0.68x+3.2$, $R^2 = 0.6$). This is only a consistency check on the model because in many cases the most recent PCO_2 value available was obtained several days or more from the time of the study (median days 7.5, IQR 1-19). Median

When this analysis was restricted to the 6 infants with PCO_2 values obtained within 1 day of the study the correlation was close ($y=0.88x+1.5$, $R^2 = 0.99$).

Table 22: Right shift (kPa) of the SpO_2 vs PIO_2 relationship for different pairs of PIO_2 and SpO_2 values, calculated from the values in Table 21

PIO2	Mean saturation achieved for given PIO2								
	86	87	88	89	90	91	92	93	94
21	13.09	12.80	12.53	12.19	11.82	11.40	10.89	10.29	9.53
22	14.12	13.83	13.55	13.20	12.81	12.37	11.82	11.18	10.35
23	15.15	14.85	14.57	14.20	13.80	13.33	12.75	12.07	11.17
24	16.18	15.88	15.58	15.21	14.79	14.30	13.69	12.95	11.99
25	17.21	16.91	16.60	16.22	15.78	15.27	14.62	13.84	12.81
26	18.24	17.94	17.62	17.23	16.77	16.23	15.55	14.72	13.63
27	19.27	18.97	18.63	18.24	17.76	17.20	16.48	15.61	14.45
28	20.30	20.00	19.65	19.25	18.76	18.16	17.41	16.49	15.27
29	21.33	21.03	20.67	20.26	19.75	19.13	18.34	17.38	16.09
30	22.36	22.06	21.69	21.26	20.74	20.09	19.28	18.26	16.91
31	23.40	23.09	22.70	22.27	21.73	21.06	20.21	19.15	17.73
32	24.43	24.12	23.72	23.28	22.72	22.03	21.14	20.03	18.55
33	25.46	25.15	24.74	24.29	23.71	22.99	22.07	20.92	19.37
34	26.49	26.17	25.75	25.30	24.70	23.96	23.00	21.80	20.20
35	27.52	27.20	26.77	26.31	25.70	24.92	23.94	22.69	21.02
36	28.55	28.23	27.79	27.32	26.69	25.89	24.87	23.57	21.84
37	29.58	29.26	28.80	28.33	27.68	26.85	25.80	24.46	22.66
38	30.61	30.29	29.82	29.33	28.67	27.82	26.73	25.34	23.48
39	31.64	31.32	30.84	30.34	29.66	28.78	27.66	26.23	24.30
40	32.67	32.35	31.85	31.35	30.65	29.75	28.59	27.12	25.12

2.4.5. Discussion

Series of paired values of SpO_2 and PIO_2 were used in preterm infants with BPD to show, non-invasively, an increase in shunt and a reduction in V_A/Q. The latter was the dominant gas exchange defect causing a significant right shift of the SpO_2 vs PIO_2 curve in all these infants. The right shift of the curve explained the need for an

increased PIO_2 and there was a highly significant linear relationship between the degree of shift and the PIO_2 required to achieve any chosen saturation in the range 86-94%. The consistency of this was such that a single measurement of PIO_2 to achieve any SpO_2 in the range 86-94% was sufficient to derive shift. There is presently no definition of BPD in use that provides both a robust physiological threshold for diagnosis and a continuous scale of severity that is based on the degree of gas exchange impairment. The authors believe that the degree of right shift of the relationship between SpO_2 and PIO_2 provides such a measure. This could be expressed as either the shift in kPa or as the PIO_2 required to maintain a saturation of 90%. Such information has previously required more invasive methods to derive it.

This non-invasive method of partitioning gas exchange impairment has been applied in sick infants[181], and in healthy and sick adults[177 179 180 182] and the results showed a good fit between the model and the clinical data in all age groups and disease states studied. Kjaergaard et al[182] obtained almost identical results non-invasively using saturation measurements to those obtained from simultaneous more invasive measurements.

Iles et al[66] showed that measures of gas exchange impairment derived from arterial blood gases sampled around term predict the prognosis of BPD and that infants with low saturation are at higher risk of acute life threatening events[69].

The recent NICHD network consensus definition of BPD[77] categorises infants as no BPD, mild, moderate or severe BPD according to the amount of oxygen supplementation and ventilatory support required up to 36 weeks gestation. These categories predict later respiratory morbidity[184], but they are not physiologically based and later respiratory problems are also seen in a substantial number of infants not identified to have BPD by this definition. Infants with BPD have reduced numbers of alveoli, enlarged airspaces, interstitial fibrosis and variable degrees of

small airway narrowing[185]. Defining the degree of physiological impairment associated with this pathology is likely to be more informative than quantifying the preceding exposure to therapies. Like the Walsh test[163], the NICHD network definition[77] is likely to permit infants with saturations lower than those observed in healthy infants to be categorised as no BPD. Measurement of reduced V_A/Q in terms of shift permits the degree of gas exchange impairment to be determined in all infants, including those who are stable in air, and may provide a more detailed description of study outcomes and serve as a more informative baseline for studies of the prognosis of BPD.

The Walsh test[163] cannot properly be considered a threshold test because many infants fail it during the 30-minute observation period after having adequate saturation to begin with. In a recent study infants with saturation of >96% with an effective FiO_2<23% had a positive predictive value of 66% for passing the Walsh test[234]. As can be seen in Figure 22 of our study, this reflects the fact that an oxygen saturation around 90% lies on the steep part of the dissociation curve where reducing the PIO_2 by 1% is associated with changes in saturation of ≥2-3% and small changes in alveolar ventilation will therefore cause considerable desaturation.

Using our method, a mean saturation value obtained at a fixed PIO_2 during a brief observation period whilst an infant was lying supine and free from gross body movements could be used to determine whether the infant would have a saturation of 90% in air. We have not measured the day to day variability of this test within patients. Infants with BPD are better clinically on some days than on others. We have also not studied the effect of sleep state on V/Q. It is possible that V/Q may vary with sleep state if resting lung volume changes. The accuracy of the test is dependent on the accuracy of the measurement of PIO_2 and SpO_2. The issue of PIO_2 measurement can be eliminated if SpO_2 is determined with the infant breathing air. Current SpO_2 monitors are accurate to 1-3% in the range studied[235]. On the steep part

of the dissociation curve, changes in SpO_2 of this magnitude have a small effect on shift.

The saturation values used to derive the models in the methods described above were derived from the normal adult haemoglobin oxygen dissociation curve[236]. Newborn infant curves may differ slightly in the presence of varying amounts of fetal haemoglobin. However, by the time of study, the infants in our study were around 11 weeks old. Beresford et al[5] demonstrated that healthy one week old and 6 month old preterm infants have mean saturation values of around 97% in air and Parkins et al[49] showed similar values in healthy term infants at 3 months of age so there is unlikely to be important bias from using the normal adult curve as a reference point for calculating shift. The model assumes a fixed arteriovenous oxygen gradient of 5ml per 100ml. Any variation of this within or between individuals affects the position of the plateau of the oxygen dissociation curve but has little effect on its shape and should not therefore have much effect on calculations of shift[180]. Similarly estimations of shunt are more sensitive to haemoglobin level than estimations of shift[180].

This method could be used to categorise disease severity using a cut-off approach as with current methods for defining BPD or a more physiological approach could be adopted, considering that there is a continuum of impaired gas exchange from normal to severely abnormal. A series of cut offs could be used to categorise disease severity or populations such as trial groups could be compared according to their mean shift or V/Q.

In conclusion, we have shown that the contribution of reduced V_A/Q (shift) and shunt to impaired gas exchange can be derived very simply from non-invasive measurements of SpO_2 and PIO_2 in infants with BPD. The degree of right shift of the SpO_2 vs PIO_2 curve provides a readily accessible continuous measure of the

severity of gas exchange impairment due to reduced V_A/Q, which was a more dominant contributor than shunt. This measure could be used to define BPD as an outcome in studies and to categorise infants in prospective studies of BPD prognosis.

3. Chapter 3: Summary and Conclusion

3.1. Study 1

Study 1 showed, in a randomised cross-over design, that within the target ranges specified in the protocol, controlling oxygen therapy on the basis of transcutaneous PO_2 monitoring is more affective at limiting high and low oxygen tensions and variability in oxygen tension or saturation than controlling oxygen therapy on the basis of saturation monitoring. When the oxygen treatment was adjusted on the basis of $TcPO_2$ the infants spent more time with high SpO_2 than when control was based on SpO_2 but this was not statistically significant and a high SpO_2 is unlikely to be harmful if it is not associated with increased oxygen tension. Healthy infants can have saturations of 97% or more breathing air[48 49].

Randomised trials of different saturation target ranges are under way, but this and other studies[98 134] suggest that there may be more to the oxygen jigsaw than merely what level of oxygen to aim for, as magnitude of saturation range, lower and upper oxygen saturation limits may all have affects on oxygen stability and therefore outcome. It will be important for the interpretation of current oxygen level trials to gather detailed information about the oxygenation patterns that are actually achieved in the different groups. Further work is required to identify the most effective strategies for minimising the risks of oxygen toxicity.

One of the mechanisms which may explain the findings in this study, is that with saturations typically in the low 90's, ventilated preterm infants are already operating on the steep part of the haemoglobin-oxygen dissociation curve.[181] Therefore a small decrease in arterial oxygen pressure may lead to a much larger change in measured oxygen saturation. This may lead to increased instability by increasing nursing interventions following insignificant hypoxia events, when infants are monitored using saturation monitors.

This leads to a number of further research questions: how does the width of oxygen saturation target range affect oxygenation; do tight or lax limits lead to more time in desired oxygen range, more time spent in a hyperoxic and hypoxic ranges; how does oxygen saturation target range width affect caregiver reaction to desaturation events, in terms of the number and size of each FiO_2 change? The questions could be investigated in two or more time periods when on a ventilator, when on support modes of ventilation (CPAP, BiPAP) and when on simple supplemental oxygen.

Although present trials of oxygen saturation target ranges underway are designed to determine what are the best oxygen saturation levels to run infants at to minimise morbidities of prematurity, it may be that upper and lower oxygen saturation limits independently affect resulting oxygenation and outcomes.

Various papers and neonatal networks have used a range of different oxygen control policies in order to reduce morbidities of prematurity with varied success. These policies should be researched in a systematic way. How does reducing the frequency and size of inspired oxygen fraction increments affect oxygenation patterns in preterm infants? How does an education program affect behaviour of nursing oxygen adjustments? How does nursing staff workload affect oxygenation patterns and compliance achieved?

As a large cohort of infants are currently being studied as part of Boost II UK, it would be very interesting to examine how the target limits affect oxygen saturations achieved, hyperoxia events (saturation above 95%), hypoxia events (saturation below 80%), bradycardia episodes, size and frequency of inspired oxygen changes. These questions should be studied over at least two periods - early on during the first few weeks and later when infants are older and sometimes more unstable.

3.2. Study 2

Study 2 described the range of oxygen tensions likely to be achieved in the first three weeks of life in a population of high risk preterm infants at currently targeted oxygen saturation values[38 208]. In the first week of life the SpO_2 range 85-95% (investigated in NeOProM) results in a range of PaO_2s that is much lower than the range recommended in published clinical guidelines based on oxygen tensions and indicates that a shift towards lower oxygen tensions has taken place with current care practices based on saturation targeting[203]. If lower saturation targets are accepted as safe by further research then lower PaO_2 targets will also be safe. Current controlled trials of oxygen saturation target ranges are targeting oxygenation levels that are likely to achieve mean PaO_2 levels between 3.8-8.9 kPa (28.5-66.8 mmHg) for 95 % of the time, if corrected for ideal pH, $PaCO_2$ and temperature the confidence intervals would be 3.6-8.7 kPa (27-65.3 mmHg).

This study found no significant association between infants Hb affinity, or fraction of fetal Hb and out comes BPD, ROP, mortality or combined outcome when gestation, birthweight and birthweight z score, were included in the mutilogistic regression analysis.

Permissive ventilation strategies used in contemporary practice result in infants with more hypercapnia and lower pH[209-214]. Physiology predicts that this would result in a reduction in haemoglobin oxygen affinity (Bohr effect). Lower oxygen affinity in turn requires a higher oxygen tension to achieve any given saturation and increases the amount of oxygen given up in end organs. This may potentially lead to increased tissue hyperoxia. Despite this, the current study failed to find an association between infants intrinsic oxygen affinity and outcome. This may, in part, be because modern oxygen saturation targets tend to achieve lower oxygen tensions, as we have shown.

3.3. Study 3

Study 3 showed that, after controlling for the intrinsic instability of the infant, the way that supplemental oxygen is adjusted by nursing staff is significantly associated with the stability patterns achieved by the infant. Since the time spent with hyperoxia and the degree of oxygen variability contribute to the risk of adverse outcome this information might make a useful contribution to clinical care.

Upton et al (in preterm infants median birth weight 1120g and gestation 29 weeks) and Renolleau (full term lambs) have shown that apnoea in spontaneously breathing infants is central 58%, mixed 35.5%, or obstructive 6.5%[114 237]. Airway closure (glottic closure) is noted in 47-90% of apnoeas both central and mixed and appears to be important in the pathophysiology, there is evidence that this helps to maintain absolute lung volume, limiting oxygen desaturation and likely functions to aid autoresuscitation. This suggests that increasing oxygen during these episodes is possibly not the answer, and that potentially early identification and stimulation may be more beneficial.

It seems that the physiology of desaturation/apnoea events occurring with and without an ET tube are different, potentially requiring different treatments. When there is an ET tube present a rapid decrease in lung volume occurs because any protective laryngeal reflex activity that could have narrowed or closed the glottis so as to brake the expiration and preserve lung volume is prevented by the presence of the endotracheal tube[238 239].

Computerised control of inspired oxygen concentration may provide an effective alternative to nurse adjustment. Volume control/guarantee modes of ventilation may also prove to be affective in reducing oxygen associated morbidity, but have so far had a limited success in abolishing the loss of end-expiratory lung volume that occurs with active expiratory efforts.

Further research is required into the physiology of "splinting events" and what is occurring during apnoea/desaturation/bradycardia events on and off ventilators or CPAP, in extreme preterm infants and what ventilation strategies and or oxygen control policies are most useful in maintaining physiological stability during these events. It is only by understanding the underlying physiology that we can treat the cause in the best way rather than reaching for that oxygen dial. This will necessitate the measuring of lung mechanics on CPAP and BiPAP devices to monitor physiological parameters during their use.

During the most severe events in the most severely affected infants, it is sometimes clear that the infants undergo hypoxic seizure events. With the advent of simple EEG monitoring devices it would be interesting to investigate what levels of oxygen would potentially affect brain activity in these infants.

Cross et al showed a significant response to a single breath of 100% oxygen, reducing minute ventilation in preterm infants by 40%, this third study shows that nursing staff make average inspired oxygen adjustments of 10%, which is clearly then left for several breaths and sometimes adjustments up to 50 % are made[129]. Large inspired oxygen increases are associated with significant increases in $TcPO_2$, (see Figure 21). It would be interesting to explore whether hyperoxia might be associated with reduction in respiratory stability through central or chemoreceptor activity, be this through a reduction of minute ventilation, apnoea or periodic breathing. Lofaso et al clearly showed a reduction in minute ventilation using only 30% oxygen given to rat pups, which was not attenuated by repeated exposure as was the case if 100% oxygen was given. It is possible that high oxygen concentrations given to some of our sick unstable infants may actually worsen any instability that it is designed to reduce[131]. Further research might explore whether there is a threshold of saturation or $TcPO_2$ levels after which respiratory activity on and off a ventilator is affected.

3.4. Study 4

Study 4, the final study, showed that the contribution of reduced V_A/Q ratio (shift) and shunt to impaired gas exchange can be derived very simply from non-invasive measurements of SpO_2 and PIO_2 in infants with BPD. The degree of right shift of the SpO_2 vs PIO_2 curve provides a readily accessible continuous measure of the severity of gas exchange impairment due to reduced V_A/Q ratio, which was the dominant gas exchange impairment, in our infants with BPD at 36 weeks CGA. Right shift of PIO_2 vs Sat curve and therefore reduced VA/Q ratio can be calculated by a single pair of PIO_2 vs Sat data points in the saturation range (86-94%). This provides a graded physiologically objective measure of the severity of the gas exchange impairment in infants with BPD and may prove useful as a clinical trial outcome measure, and serve as a baseline for prognostic studies.

Infants with BPD have reduced numbers of alveoli, enlarged airspaces, interstitial fibrosis and variable degrees of small airway narrowing[185]. Defining the degree of physiological impairment associated with this pathology is likely to be more informative than quantifying the preceding exposure to therapies.

Previous definitions like the Walsh test[163], and the NICHD network definition[77] is likely to permit infants with saturations lower than those observed in healthy infants to be categorized as no BPD. Measurement of reduced VA/Q in terms of shift permits the degree of gas exchange impairment to be determined in all infants, including those who are stable in air, and may provide a more detailed description of study outcomes and serve as a more informative baseline for studies of the prognosis of BPD.

We noted an association, as predicted by Olszowka & Wagner's[183] model, between reduced V_A:Q ratio in each infant and PCO_2. This fits in well with data from Kovesi et al[240] who noted a significant association between PCO_2 (obtained shortly before or

after discharge from NICU) and risk of both severe adverse event (defined as pulmonary hypertension, death, or subsequent reintubation or tracheostomy for respiratory illness), and readmission to hospital for respiratory causes. Iles et al[66] also noted that $PaCO_2$ level of greater than 7 kpa predicted a $MSaO_2$ of less than 90% in room air at 1 year of age (specificity of 0.78 and a sensitivity of 0.88). Subsequently to our publication Kaempf et al[241] have also found an association between PCO_2 at 36 weeks corrected gestational age and severity of BPD. Kaempf also found that $PaCO_2$ was inversely correlated with room air saturation at this gestation.

It will be important to carry out a larger study to examine whether this simple test (the degree of right shift of the SpO_2 vs PIO_2 curve), or simple blood gas measure such as PCO_2, may predict longer term pulmonary outcome, in a large series of infants such as in the population of infants in Boost II UK. Important outcome measures would be admission rates, length of home oxygen, use of respiratory medication and lung function measures over at least the years till adulthood. It would be important to see what the day to day variation and inter observer bias of such a test was, and whether there was any correlation between the result and overnight sleep study. It might be that, although this measures everyday V/Q mismatch, it does not clearly delineate everyday variability or airway pulmonary hyperactivity. It would also be interesting to see how prone and supine positioning affect the right shift of the SpO_2 vs PIO_2 curve and therefore V/Q mismatch.

3.5. Conclusion

In conclusion, the studies suggest that the way in which oxygen levels are monitored, our response to monitoring and the oxygen dissociation characteristics of these infants have a big effect on oxygen levels achieved. It is plausible that these effects are more important to longterm morbidity than the proposed small changes in oxygen level targets made in studies such as NeOPRoM. A simple test that might better

grade disease severity of BPD has been defined. These studies will be important in assisting further research, and in helping clinicians to keep compliance to oxygen targets once these have been elucidated.

There is increasing evidence that Priestley was right when he so eloquently warned about the hazards of his new air, later named oxygen. "Research rarely leads to final answers, but often to better questions".[242]

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Appendix A - Published Articles

1. Quine D, Stenson BJ. Does the monitoring method influence stability of oxygenation in preterm infants? A randomised crossover study of saturation versus transcutaneous monitoring. *Arch Dis Child Fetal Neonatal Ed Sep 2008; 93 (5), F347-50.*

2. Quine D, Stenson BJ. Arterial oxygen tension (PaO_2) values in infants <29 weeks of gestation at currently targeted saturations. *Arch Dis Child Fetal Neonatal Ed Jan 2009; 94: F51 - F53.*

3. Abstract: Quine D, Stenson BJ. Contribution of nurse oxygen adjustment behaviours to stability of oxygenation in preterm infants. *Arch Dis Child Fetal Neonatal Ed Nov 2008; 93: p10.*

4. Quine D, Wong CM, Boyle EM, Jones JG, Stenson BJ. Non-invasive measurement of reduced ventilation:perfusion ratio and shunt in infants with bronchopulmonary dysplasia: a physiological definition of the disease. *Arch Dis Child Fetal Neonatal Ed Nov 2006; 91(6):F409-14.*

Consent has been obtained from joint authors, and from publishers of all the above journals, to include copies of each paper as appended.

Fantoms

Martin Ward Platt, *Deputy Editor*

Checking normal babies: NICE work or redundant ritual?

The NICE guidance on postnatal care, especially with regard to neonatal care, was greeted with some surprise by many paediatricians so we felt the subject deserved closer scrutiny and perhaps an alternative view. Even more recently the UK Newborn Screening Programme Centre has started to take an interest in the neonatal examination, so Green and Oddie's review could not be more timely. Readers may be interested in their assessment of the use of pulse oximetry—should it be routine, or reserved for babies with heart murmurs? They also point out that even the individual components of the examination are not good "screening tests" in any rigorous sense of the word, but that the examination as a whole has a value that goes beyond hips, heart and eyes. So it's a qualified thumbs up, so long as we don't pretend it can do things that it can't. ***See page F389***

Putting the tension back in oxygenation

Those of us brought up on transcutaneous oxygen monitoring ($TcPO_2$), in the days before the universal adoption of pulse oximetry, have noticed the different behaviours among doctors and nurses that the use of each of these modalities generates. It is not just about the babies, it is about the adjustments to the oxygen dial that are made in response to the information. And since the saturations and transcutaneous tensions are obtained in radically different ways, it is of considerable interest to try to understand this better since it may bear on the question of how best to reduce the incidence of retinopathy. Quine and Stenson's randomised controlled trial addresses the short-term outcome of variability in oxygenation: they found that variability was more pronounced when monitoring relied on pulse oximetry rather than TcP02 monitoring. Poets and Bassler, in their linked perspective, point out that we need to look at end points (such as retinopathy) before the saturation monitors are consigned to the bin of outmoded equipment; however, astute observers will notice that the BOOST II trial (comparing different oxygen saturation targets, with retinopathy as an important outcome variable) costs a lot of money and is a huge multi-centre enterprise. Quine and Stenson did their informative study on a shoestring in their own unit. ***See pages F330 and F347***

Does a bigger head hold a better brain?

Head growth usually means brain growth, but quantity is not the same as quality: in the end, it will take longer-term follow-up data than just one year to answer the question that Tan and Cooke posed in their randomised controlled trial of hyperalimentation for preterm babies. As others have found, it is really, really difficult to feed seriously preterm babies adequately in their first month, and deficits tend to be cumulative. They found that better nourished babies do seem to have better head and brain growth, even though there were no group differences in head circumference, brain size or developmental outcome between the two arms of the study. Sadly, the power of their trial was severely limited by the loss of half the subjects from follow up. ***See pages F337 and F342***

The non-smoking, smoke exposed fetus

There are many reasons to welcome the smoking bans now mandated in many countries. Here's another. The interesting thing about Leonardi-Bee's paper is that the magnitude of the effect of environmental tobacco smoke on the fetus of a non-smoking mother is surprisingly large when compared with that of having a smoking mother—an average loss of 33 g birth weight instead of 200 g. This seems to be a consequence of the fact that sidestream smoke contains more toxins even though it is more dilute than directly inhaled smoke, so that in terms of population attributable damage, the fetuses of non-smokers as a group have at least as much to gain by the ban as the fetuses of smokers. Such a shame that the authors did not present data on head circumference. Perhaps that will be the subject of a different paper. ***See page F351***

Measuring the milk

One of the many disadvantages of being a tiny premature baby is that you get force fed. Even if you are lucky enough to get your mother's milk, you can't co-regulate your intake with her in a normal way, and you can end up seriously short-changed nutritionally. How can we help? Some knowledge of the fat and protein content of a mother's milk should in principle be an advantage, since milk that is dilute can be fortified, but to do this we need an easy-to-use method for evaluating milk quality in the nursery itself. Corvaglia *et al* report the use of near-infrared reflectance as just such a simple tool for this purpose, and compare it with the standard laboratory methods for estimating fat and protein. This looks like a really useful step forwards, but we now need to be able to show that the combination of measurement, and fortification if needed, is actually superior to seeing if a baby grows with the milk provided, and fortifying the milk empirically if she doesn't. ***See page F372***

Stool-gazing in the newborn

Sometimes the simplest ideas are the best. Everyone talks about "delayed passage of meconium", but no one knows exactly what they mean because we didn't know what is normal—until now. Bekkali *et al* have done a great service by simply describing the time to first passage of meconium and analysing it by gestation. That prematurity is associated with delay in the first passage of meconium is no surprise, nor that morphine slows it too (also described by Menon *et al* in this edition). What did surprise me was that almost a fifth of term babies first passed meconium later than 48 hours, so that this degree of delay is hardly abnormal. And I was also surprised by the clearly J-shaped relation between gestational age and mean time to pass meconium. ***See page F376***

Perspective

Providing stability in oxygenation for preterm infants: is transcutaneous oxygen monitoring really better than pulse oximetry?

Christian F Poets, Dirk Bassler

Non-invasive monitoring of blood gases has become standard procedure in neonatal intensive care units (NICU).[1] In particular, continuous monitoring of oxygenation is now considered indispensable to prevent retinopathy of prematurity (ROP) and brain damage that can result from too much or too little oxygen,[2–4] despite randomised trials never having shown continuous monitoring to have an effect on clinically meaningful outcomes.[5 6]

Two standard techniques are used to monitor oxygenation continuously in the NICU: transcutaneous monitoring of the partial pressure of oxygen ($TcPo_2$) measures the amount of oxygen dissolved in tissue (which corresponds reasonably well to arterial oxygen tension (Pao_2) when the skin underneath the sensor is heated to 44°C); and pulse oximetry, which measures the proportion of haemoglobin molecules in arterial blood that are loaded with oxygen. $TcPo_2$ monitoring was introduced in the early 1970s, but was soon replaced by pulse oximetry after that technique became available. Many factors influence the precision and accuracy of $TcPo_2$ monitoring, including skin thickness, sensor site and temperature, amount of contact gel used and state of peripheral perfusion. It may cause skin burns and requires frequent re-siting and calibration.[7] In contrast, pulse oximetry, introduced into the NICU in the 1980, was much easier to do but was prone to motion artefact. There were also considerable differences between brands in their measurement bias and precision, at least until a new generation of more motion-resistant instruments became available about 10 years ago. Ideally both monitoring techniques should be used in combination, particularly in critically ill preterm neonates, although this is costly and time consuming.[7] However, the question arises whether it is justified to rely on just one technique for the continuous monitoring of oxygenation in the NICU.

In this issue of the *Archives*, Quine and Stenson report a randomised crossover study of 19 preterm infants with a mean weight of 1 kg in which they compared saturation versus transcutaneous monitoring. They identified a potentially important advantage of $TcPo_2$ monitoring, namely that it is associated with less fluctuations in blood or tissue oxygen levels, and, thereby, a higher proportion of time spent with these levels within target range. Displaying either $TcPo_2$ or Spo_2, they found that Spo_2 monitoring was associated with 10 times more time spent hyperoxaemic and three times more time spent hypoxaemic than $TcPo_2$ monitoring.[8]

Shall we now throw away our pulse oximeters and in future solely rely on $TcPo_2$ monitoring? We do not think so, for the following reasons.

- First, it is possible that much of the reduction in extreme values (either hypoxic or hyperoxic) in the above study[8] was due to differences in averaging and/or response times. $TcPo_2$ monitors respond to changes in Pao_2 only with a delay of approximately 15–30 s.[9] This will dampen any variability in their readings considerably if Pao_2 fluctuates, as also acknowledged by the authors. No information is given on the averaging time of the pulse oximeter used in their study, but it most likely was considerably shorter than that of the $TcPo_2$ monitor.
- Second, we are not informed on how motion resistant their pulse oximeter was. Excluding readings only if pulse and heart rate differ by more than 10 beats per minute (which happened to be the case for only 0.5% of recording time in their study) might not exclude artefacts sufficiently reliably. Thus, it is possible that the actual fluctuations in *arterial* Po_2 were similar with both monitoring techniques, but resulted in a higher proportion of pulse oximeter readings that were too high or too low because the oximeter responded much faster to these fluctuations, or was more likely to display erroneous readings during motion than the $TcPo_2$ monitor. It is equally possible, however, that the shorter averaging time of the pulse oximeter resulted in over-adjustments in fraction of inspired oxygen (Fio_2) by nursing staff, in response to spontaneous or induced variations in tissue or blood oxygen levels, thereby causing the wider fluctuations in these levels. To separate between these potential explanations would have required to download data on Fio_2, which was not possible in their setting. In any case, to overcome this potential problem would require better staff education, not necessarily different types of monitor.

Perspective on the paper by Quine and Stenson (see p F347)

- Third, although one might expect $TcPo_2$ monitors to be better suited to detect hyperoxaemia than pulse oximeters, given the shape of the oxygen dissociation curve, this has not been confirmed by previous studies.[7] These studies analysed the sensitivity and specificity of $TcPo_2$ and Spo_2 monitors in detecting hyperoxaemia and hypoxaemia (for a review, see Poets and Southall[7]). The average sensitivity of $TcPo_2$ monitors for hyperoxaemia detection was 87% versus 93–97% with pulse oximeters, depending on instrument brand and alarm threshold.[7 10] These findings, relying on arterial blood gases as the reference, measured during steady state, are different from those reported by Quine and Stenson.[8] The explanation for these differences may lie in the methodological issues raised above.
- Fourth, to ensure optimal agreement between $TcPo_2$ and Pao_2, transcutaneous monitoring requires frequent blood sampling for arterial blood gases, either from an arterial line or repeated arterial puncture. Neonatologists might consider this too invasive

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for routine monitoring in daily practice, and survey data from Germany suggest that in only 8% of NICUs *arterial* blood gases are obtained to validate the transcutaneous measurements.[11] However, relying on values based on capillary or venous blood gases might further impair the accuracy of transcutaneous monitoring.

What we need before deciding on the best technique for oxygen monitoring in the NICU are data on how best to prevent ROP and other oxygen-related disorders—that is, whether the absolute level of PaO_2, fluctuations in this level, or both, are relevant to the development of ROP. Currently, the question "which is the best baseline level for SpO_2" is being addressed in large randomised trials in Australia as well as in Canada and Europe. Fluctuations in PaO_2 levels, however, may be equally important, but have yet only been addressed in retrospective studies.[12] One way to reduce such fluctuations in PaO_2 would be an automated control of oxygen supply, which is now within reach.[13 14] However, a randomised controlled trial is required to show that an increased stability in oxygenation will minimise the incidence of ROP. Until such data become available it might be too early yet to decide on the best method of monitoring stability of oxygenation in preterm infants.

Competing interests: None

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Original article

Does the monitoring method influence stability of oxygenation in preterm infants? A randomised crossover study of saturation versus transcutaneous monitoring

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See Perspective, p F330

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ABSTRACT

Introduction: Hyperoxia and variable oxygenation are associated with morbidity in preterm infants. The optimal range of oxygen tensions is not known. This study aimed to determine whether care based on transcutaneous oxygen tension ($TcPo_2$) or saturation (Spo_2) monitoring is associated with less time spent with high oxygen tension and less variability of oxygenation.

Methods: Spo_2 and $TcPo_2$ were measured simultaneously during two 3-h study periods allocated in random order. During one period supplemental oxygen was adjusted according to $TcPo_2$ (target range 6.0–9.0 kPa) and during the other according to Spo_2 (target range 86–94%). During each period, readings from the second monitor were not displayed. Both $TcPo_2$ and Spo_2 were downloaded every second. For each period the mean level and the variability (standard deviation) of Spo_2 and $TcPo_2$ and the percentage of time spent above and below target range were calculated and compared.

Results: 19 infants, 13 ventilated and 6 on continuous positive airway pressure, were studied at mean corrected gestational age of 27.2 weeks and mean postnatal age of 6.8 days. Their mean fraction of inspired oxygen at the start of the study was 0.34. Care based on Spo_2 monitoring was associated with more time spent with high oxygen tension (median increase 2.62%, $p = 0.01$), more time with low oxygen tension (median increase 17.41%, $p = 0.01$), more variability in oxygen tension (median increase 0.28 kPa, $p = 0.02$) and more variability in oxygen saturation (median increase 0.82%, $p = 0.01$) than care based on $TcPo_2$ monitoring.

Conclusion: Within the target ranges studied Spo_2 monitoring was associated with significantly more variable oxygenation than $TcPo_2$ monitoring.

What is already known on this topic

- Oxygen saturation (Spo_2) monitoring is now used more frequently than transcutaneous oxygen tension ($TcPo_2$) monitoring to guide oxygen therapy in preterm infants in neonatal units.
- Neither monitoring method is clearly superior in reducing morbidity and the optimal target ranges are unknown.

What this study adds

- Within the target ranges studied, the use of $TcPo_2$ monitoring was associated with less variability in oxygen tension and saturation and less time spent with low and high oxygen tension than the use of Spo_2 monitoring.

Hyperoxia and variability of oxygenation have been linked with increased risk of morbidity in preterm infants.[1–5] Oxygen saturation (Spo_2) and transcutaneous oxygen tension ($TcPo_2$) monitors are used to monitor oxygen levels in preterm infants. Oxygen therapy is usually adjusted with the aim of keeping the infant's oxygenation within a target range. Specific target ranges vary from unit to unit because there remains uncertainty over the optimal levels.[6 7] Randomised trials are in progress, examining different target ranges. Although both types of monitoring device are used, oxygen saturation and oxygen tension are not linearly related to one another. Neither monitoring method is clearly superior in terms of minimising adverse outcome but comparative studies have not been done.

Saturation monitors are non-invasive, easy to use and do not require calibration or cause heating of the skin. They have a relatively high rate of false alarms,[8–10] often caused by poor signal resulting from motion. Because of the shape of the haemoglobin-oxygen dissociation curve small changes in oxygen saturation above 95% can mask large increases in oxygen tension so that saturation monitoring may not be reliable in preventing hyperoxia.[8 9 11–13] Transcutaneous monitors require calibration and this can lead to periods of time when no oxygen level is being measured. They are sometimes inaccurate.[9 14–16] They need to be re-sited regularly to avoid skin damage from heating and can cause skin burns if left on too long. These issues make them more cumbersome and deter some from using them, particularly in more immature infants. The relative convenience of using saturation monitors may be one reason why saturation monitoring has become the predominant method of monitoring oxygenation in the USA and in the UK, and why more recent studies have focused on saturation monitoring.[17 18]

We aimed to determine whether infants are exposed to more cumulative hyperoxia or hypoxia or to more variable oxygen tension when oxygen therapy is controlled on the basis of transcutaneous Po_2 monitoring or oxygen saturation monitoring.

Table 1 Infant characteristics at the time of enrolment in the study

	Mean (SD)
Weight (g)	1003 (416)
Corrected gestational age (weeks)	27.2 (2.5)
Age (days)	6.8 (9.5)
Fractional inspired oxygen concentration	0.34 (0.12)

METHODS

We conducted the study at the neonatal unit of the Simpson Centre for Reproductive Health, Edinburgh, between February 2004 and January 2005. Preterm infants who were more than 24 h old, had an arterial line in situ and were receiving supplemental oxygen, were eligible for inclusion in the study if they were considered unlikely to require a major handling procedure such as intubation during the next 6 h. Infants with known duct-dependent congenital heart disease were excluded. Written informed parental consent was obtained in all cases and the study was approved by an ethics advisory committee.

Each infant was monitored simultaneously with an Spo_2 monitor and a $TcPo_2$ monitor. Data from both monitors were downloaded continuously in real time to a cot-side PC for later analysis. The sites of attachment of these monitors were left up to the nursing staff and not standardised among infants as we wished to study the real-life implementation of these technologies and this is often limited by the presence of lines and dressings. Functional oxygen saturation was measured using a Siemens Infinity SC 7000 multiparameter patient monitor (Siemens Medical Systems, Inc, Danvers MA). This monitor uses Siemens' Oxisure pulse oximetry technology and Nellcor Oximax (Nellcor Puritan Bennett, CA, USA) saturation probes and incorporates ECG to reduce motion artefact. The normal averaging mode for this monitor was used in all cases. This reflects 90% of a Spo_2 change within 30 s. The same multiparameter monitor measured transcutaneous Po_2 using a Radiometer sensor (Radiometer, Copenhagen, Denmark). Although both methods of monitoring were attached to the patient throughout, at any given time information was only displayed from one monitor. During two consecutive 3-h periods allocated in random order by the opening of a sealed opaque envelope, nursing staff adjusted the oxygen therapy for the first 3 h on the basis of one of the monitors and for the subsequent 3 h on the basis of the other. The transcutaneous oxygen sensor was maintained at a temperature of 43.5°C. The sensor was sited shortly before the start of the first monitoring period and monitoring commenced once the transcutaneous Po_2 reading had stabilised. The sensor was re-sited for the second monitoring period. During the $TcPo_2$ monitoring period the nursing staff adjusted the fraction of inspired oxygen (Fio_2) to maintain the infant's $TcPo_2$ within the range 6.0–9.0 kPa. At the start of the study a blood gas sample was obtained from the arterial line of each infant to ensure that there was close agreement between $TcPo_2$ and the arterial oxygen tension (Pao_2). Where there was a difference of 1 kPa or more between the two values the $TcPo_2$ alarm limits that were set by the nurse were adjusted by the difference between Pao_2 and $TcPo_2$ to the nearest kPa. The downloaded $TcPo_2$ data in these infants were adjusted by the same amount prior to data analysis so that the final data reflected as closely as possible the likely Pao_2 of the infants. During the Spo_2 monitoring period the nursing staff adjusted the Fio_2 to maintain the infant's Spo_2 within the range 86–94%. For each of the two periods alarms were only enabled for the monitor under investigation. The infants were cared for by the nursing staff throughout as normal, with no intervention from study personnel.

Downloaded data for $TcPo_2$, Spo_2, saturation derived heart rate and ECG derived heart rate were analysed using SPSS version 12.0. Saturation readings where the heart rate measured by the saturation monitor differed from the simultaneous ECG heart rate by more than 10 beats per minute were excluded as artefact from both monitoring periods in order to minimise any motion artefact. For each infant and for each period of monitoring we calculated: the mean $TcPo_2$; percentage of time spent with $TcPo_2$ >9.0 kPa; percentage of time with $TcPo_2$ <6.0 kPa; variability (standard deviation) of $TcPo_2$; mean Spo_2;

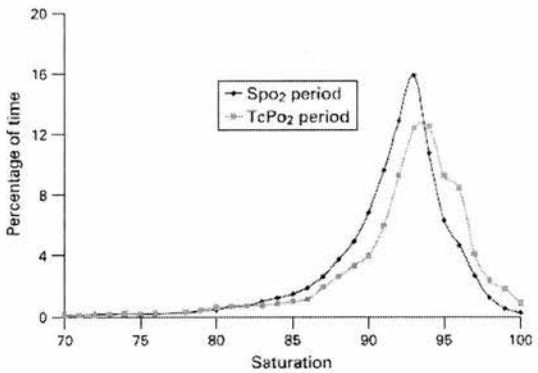

Figure 1 Percentage of time spent at each oxygen saturation according to the method of monitoring in clinical use. Combined data from all of the study infants.

Table 2 Summary data for stability of oxygenation

	Monitor on display to clinical staff		Median difference within patients (Spo_2 period minus $TcPo_2$ period)	Significance (p value)
	$TcPo_2$	Spo_2		
Mean $TcPo_2$ (kPa)	6.91 (6.34 to 7.48)	6.41 (5.54 to 7.20)	−0.33 (−1.1 to −0.03)	0.09
% time with $TcPo_2$ >9.0 kPa	0.14 (0.48 to 3.33)	1.57 (0.31 to 9.53)	2.62 (0.12 to 13.24)	0.01
% time with $TcPo_2$ <6.0 kPa	11.3 (3.94 to 15.4)	31.3 (10.4 to 60.12)	17.41 (3.15 to 40.20)	0.01
Variability (SD) of $TcPo_2$ (kPa)	0.79 (0.41 to 1.00)	1.07 (0.58 to 1.27)	0.28 (0.01 to 0.64)	0.02
Mean Spo_2 (%)	92.8 (90.6 to 94.5)	91.7 (90.3 to 92.1)	−1.16 (−3.24 to 0.71)	0.06
% time with Spo_2 >94%	16.1 (7.07 to 55.47)	12.1 (4.15 to 29.14)	−1.71 (−34.78 to 0.22)	0.06
% time with Spo_2 <86%	0.43 (0 to 7.91)	4.50 (1.34 to 12.35)	1.53 (−0.75 to 5.61)	0.23
Variability (SD) of Spo_2 (%)	2.75 (1.44 to 4.04)	3.33 (1.98 to 4.61)	0.82 (−0.02 to 1.89)	0.01

Data are median (interquartile range).

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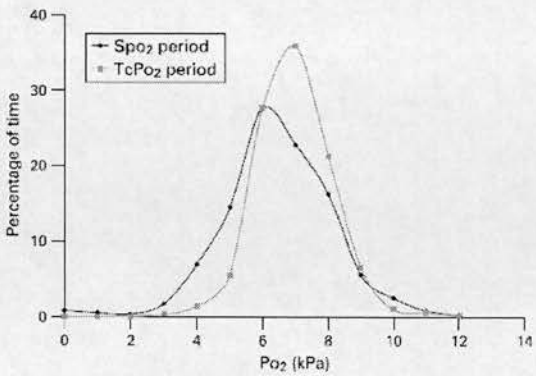

Figure 2 Percentage of time spent at each oxygen tension according to the method of monitoring in clinical use. Combined data from all of the study infants.

percentage of time with Spo_2 >94%; percentage of time with Spo_2 <86%; and variability (standard deviation) of Spo_2. Transcutaneous Po_2 probes required re-siting during two studies, which led to a period where saturation readings were unblinded until transcutaneous Po_2 readings were available again. These periods were included in the analysis on an intention-to-treat basis. Because the variables showed non-normally distributed data the two methods of monitoring were compared using non-parametric two related samples test (Wilcoxon test).

RESULTS

A total of 19 infants were enrolled in the study; 11 were conventionally ventilated, 2 received high-frequency oscillatory ventilation and 6 were on nasal continuous positive airway pressure (CPAP). Table 1 gives the characteristics of the infants. None of the infants was paralysed at time of study.

The Spo_2 probe site was postductal in 15 infants and preductal in 4 infants. The $TcPo_2$ probe site was postductal in 15 infants and preductal in 4 infants. In 9 infants the first monitoring period was Spo_2 and in 10 infants the first period was $TcPo_2$. Saturation data were excluded as artefact for a total of 695 s (0.3%) and 608 s (0.3%) from the $TcPo_2$ and Spo_2 monitoring periods, respectively. $TcPo_2$ data were not available from one 3-h monitoring period in an infant during the time when the clinical care was based on Spo_2 readings because the $TcPo_2$ monitor was not attached. $TcPo_2$ data were available for a total of 94% of the time when $TcPo_2$ was the monitor displayed to the clinical staff. The transcutaneous Po_2 data of four infants was adjusted by the difference between $TcPo_2$ and Pao_2 obtained on the arterial blood gas taken at the start of the study. In one case the adjustment was 1 kPa and in three cases the adjustment was 2 kPa.

Table 2 summarises the outcome data. Figures 1 and 2 show the cumulative data from all of the infants for the percentage of time spent at different Spo_2 and $TcPo_2$, according to the method of monitoring being displayed to the clinical staff.

DISCUSSION

We have shown in a randomised study that within the target ranges specified, controlling oxygen therapy on the basis of transcutaneous Po_2 is more effective in limiting high and low transcutaneous oxygen tensions and variability in transcutaneous oxygen tension or saturation than controlling oxygen therapy on the basis of saturation. There was no significant difference in the amount of time spent with low oxygen saturations between the two monitoring methods. When the oxygen treatment was adjusted on the basis of $TcPo_2$ the infants spent more time with high Spo_2 than when control was based on Spo_2, but this was not statistically significant. Also, a high Spo_2 is unlikely to be harmful if it is not associated with increased oxygen tension. Healthy infants can have saturations of 97% or more breathing air.

These results have important implications for practice. There has been a trend recently to reject transcutaneous monitoring in favour of saturation monitoring. Survival of preterm infants has increased but similar improvements in morbidity have not been observed.[19–21] No randomised trials have compared the two methods of monitoring. Epidemiological studies and case series suggest that high oxygen tensions or saturations and increased variability of oxygenation may be harmful[2 22] and that limiting these exposures may be associated with improved outcomes.[4 5] The differences in oxygen tension variability observed in this study were large enough to be relevant to the risk of developing retinopathy of prematurity.[2 4] Using only saturation monitoring as the basis for administering oxygen might not be the most effective clinical strategy. There are practical difficulties associated with using transcutaneous monitoring that make saturation monitoring more straightforward but these can generally be overcome in all but the most fragile infants. However, it cannot be assumed that these results, obtained in a research setting, would be replicated fully in everyday use. Randomised trials of different saturation target ranges are under way. It will be important for the interpretation of these trials to gather detailed information about the oxygenation patterns that are achieved.

There are several reasons that the oxygenation of infants may be more stable when they are nursed on the basis of $TcPo_2$ rather than Spo_2. Depending on the set averaging time, saturation monitors respond to change more rapidly than transcutaneous monitors. Brief desaturations that trigger the saturation alarms could prompt caregivers to adjust the inspired oxygen, whereas the relatively damped signal obtained with $TcPo_2$ might not show such fluctuation or bring about these adjustments. This may be the main explanation of the differences in stability shown. Movement artefact can lead to loss of signal from saturation monitors, trigger low saturation alarms and cause inappropriate adjustment of the oxygen, with consequent hyperoxia. These issues may be reduced by intensive staff education.[4] Saturation monitors incorporating technology that reduces motion artefact, such as Masimo SET may also reduce this problem.[23] To minimise bias attributable to motion artefact we excluded saturation data from both monitoring periods where there was a difference in heart rate of more than 10 beats per minute between the ECG and oximeter derived heart rates.

The Spo_2 probe and the transcutaneous probe were postductal in 15 of 19 infants. As this was a clinical study, the site of the monitors was left up to the clinical staff. Because few babies have remarkable right-to-left shunts beyond the first few hours after birth, we suspect that most units do not vary their target ranges according to whether their monitors and lines are preductal or postductal. This is unlikely to have had an important effect on the results.

With the limits that we specified, infants spent substantially more time with $TcPo_2$ <6 kPa when oxygen was controlled on the

basis of SpO_2 than when it was controlled on the basis of $TcPO_2$. The mean $TcPO_2$ and saturation of the infants were also slightly lower, although these differences were not statistically significant. Other studies have shown that episodes of apnoea occur less frequently in infants with higher mean PO_2 and sleep architecture and pulmonary hypertension may also be affected.[24 31]

Because saturation and PO_2 are not linearly related it would be expected that the two measures would result in different care being delivered. Even though the target ranges overlap, some infants with $TcPO_2$ approaching 9.0 kPa will have saturation greater than 94% and some with saturation of 86% will have $TcPO_2$ less than 6.0 kPa. There is broad consensus that high oxygen tensions should be avoided. Our data suggest that using saturation monitoring with an upper alarm limit of 94% is slightly less effective in this respect than using a $TcPO_2$ limit of 9.0 kPa. However, oxygen tensions greater than 11.0 kPa were seldom observed in either group (fig 2). There is far less agreement over how low oxygen tension or saturation should be allowed to go. Infants in this study spent considerably more time with lower oxygen tension when controlled on the basis of SpO_2, but no more time with low saturation. This may not be important, provided that haemoglobin and cardiac output are adequate. Fetal haemoglobin permits satisfactory blood oxygen content and tissue oxygen delivery at lower saturation than 86% and oxygen tensions far lower are observed in the healthy fetus. Preliminary data describing 10-year follow-up of infants cared for with lower saturations do not demonstrate increased adverse outcome.[22 32] Deulofeut *et al*[34] observed a reduction in bronchopulmonary dysplasia and retinopathy of prematurity and better mental development index scores at 18 months in infants with birth weight ⩽1250 g when they adopted lower saturation targets. Long-term outcome data from the ongoing randomised trials of different saturation ranges will be capable of showing even modest differences between groups in neurodevelopmental outcome.

We could not download information about the inspired oxygen concentration that the infants were exposed to, as some intensive care equipment do not have the necessary data ports. This should be addressed by manufacturers when developing new equipment.

The target ranges employed in this study simply reflected practice in our unit and are not necessarily the ideal. They are within the range of accepted oxygen targets that have been described. Although some may feel that a lower saturation alarm limit of 86% is quite low, other neonatal units use much lower levels.[4 7 22 34] All of the infants in the study were monitored with a single type of oxygen saturation monitor. There is variation in the saturation readings obtained with monitors produced by different manufacturers.[6]

In conclusion, we have shown in a randomised crossover study that the method of monitoring used to control oxygen therapy in preterm newborn infants has a significant effect on the oxygenation patterns that result. This could have an important effect on the risk of adverse clinical outcome and is worthy of further study.

Competing interests: None.

Ethics approval: The study was approved by a local ethics advisory committee.

Patient consent: Obtained.

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Fantoms

Martin Ward Platt, *Deputy Editor*

After Nuffield

When the Nuffield Council on Bioethics published *"Critical care decisions in fetal and neonatal medicine: ethical issues"*,[1] it challenged professional institutions to produce some sensible guidance for practitioners of fetal, intrapartum and neonatal care on the management of fetuses and neonates at the borderline of viability. Then in September we published a leading article by Ahluwalia *et al*, which posed some important questions that emerged from the Nuffield document: *"Decisions for life made in the perinatal period: who decides and on which standards?"*[2] Finally, in this month's edition we have if not all the answers at least a coherent statement of best practice that has been produced in a multi-collegiate fashion under the auspices of the British Association for Perinatal Medicine by Wilkinson *et al*. This is an important document that will, for some time to come, be a touchstone for practice; though produced in the UK it will no doubt be read with interest in Europe and beyond, and it will be compared with the guidance from the American Academy of Paediatrics in the USA. ***See page F2***

Bacteria, mycoplasmas, fungi and viruses – take your pick

This edition of *Fetal & Neonatal* is particularly strong on infections as it has material on four classes of pathogen. Modi *et al* suggest a workable definition that could be used to provide more international standardisation in relation to describing bacterial infections. This will be important epidemiologically as well as clinically, and recognises that the sensitivity of blood culture for "proving" infection is not all that good. Along with this, there are the differential effects of chorioamnionitis and funisitis: Lahra *et al* present evidence that inflammation, especially on the fetal side, may be good for the neonatal lung in term of less respiratory distress syndrome (but we must not forget that it is bad for the neonatal brain). In contrast, Oue *et al* find that exposure to pathogens at birth, especially mycoplasmas, is associated with long-term harm to the lungs in terms of bronchopulmonary dysplasia. Fungal infection is addressed in a review by Brecht *et al*, who warn that well meaning strategies to protect babies from candidal infection by using anti-fungal prophylaxis might yet have unwanted consequences in terms of selecting organisms resistant to anti-fungal agents. Finally, postnatal cytomegalovirus virus infection is discussed, again in a review, by Luck and Sharland. They conclude that postnatal infection is not always benign, but although pre-emptive treatment at a threshold of viral load may be justified, a lot of work needs to be done to find out if such a threshold exists, and if it does, what treatment might be justifiable. ***See pages F8, F13, F17 and F58***

The continuum of disadvantage

There have been many studies that have attempted to unpick the various factors that are associated with pre-term delivery, and it is well known that as with so many other conditions, premature birth is associated with social deprivation. But deprivation is a slippery concept, and Jansen *et al* have made an important contribution to this literature by trying to pin down some of the components of deprivation by focusing on maternal educational achievement and some of its covariates. They found that poor maternal educational status was associated with a two-fold increase in the risk of preterm delivery, and that much of this increase was related to a variety of other factors that included maternal body mass index and psychosocial stress. ***See page F28***

Congenital anomaly registers

In a previous Perspective in *Archives*,[3] I have banged the drum for population based congenital anomaly registers. I make no apology for doing so again, this time in relation to the paper by Savva and Morris who used Down syndrome as a marker condition to calibrate the performance of congenital anomaly registers, and found that the high performance of the regional registers contrasted with the poor ascertainment of the national congenital anomaly reporting system. Congenital anomaly remains a major cause of death and disability. Yet the existence of the registers remains precarious through uncertainties about their funding, while their importance in monitoring the potential teratogenic effects of everything from drugs, through environmental agents, to (potentially) artificial reproductive technologies, has never been greater. My competing interest: as Clinical Director of the northern Regional Maternity Survey Office, I have responsibility for the Northern Congenital Anomaly Survey (NorCAS). ***See page F23***

Oxygen tensions and oxygen saturations – again

Did you know that when a standard pulse oximeter reads 90%, this is compatible with a PaO_2 value of anything from 3 (or less) to 10 kPa? No, I thought not. Neither did I. Discerning readers may remember that in the September 2008 issue, we carried a paper by Quine and Stenson[4] on the stability of oxygenation in babies, depending on whether the babies were monitored using transcutaneous oxygen tensions or pulse oximetry. This time these authors correlate pulse oximetry values with simultaneous directly sampled arterial PO_2 values from a blood gas analyser. The relevance of this relates in part to the current trials of oxygen saturation targets (such as BOOST II), in part to the relative paucity of data on this relationship in the literature, and in part to the level of trust that we place in pulse oximetry monitoring. Indeed, their data beg the question as to whether oximetry might not be the more "correct" way to monitor oxygenation in as much as oxygen availability to the tissues is a function of its dissociation from haemoglobin, and this is related more to haemoglobin saturation than to blood oxygen tension. ***See page F51***

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Short report

Arterial oxygen tension (Pao_2) values in infants <29 weeks of gestation at currently targeted saturations

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ABSTRACT

Background: Oxygen saturation (Spo_2) monitors are commonly used to determine the need for supplemental oxygen. We aimed to describe the range of arterial oxygen tensions (Pao_2) observed in preterm infants at saturation levels targeted in current trials.

Methods: In a cohort of 98 consecutive infants born at <29 weeks' gestation, the Pao_2 from each arterial blood gas result during the first week of life (n = 2076) was matched to the Spo_2 at time of sampling. The mean (95% CI) Pao_2 was calculated for each saturation.

Results: The 95% CI of Pao_2 for the Spo_2 range 85–95% was 3.8 to 8.9 kPa. The mean (95% CI) Pao_2 at a saturation of 85% was 5.3 (3.8 to 6.8) kPa and at a saturation of 95% it was 7.2 (5.5 to 8.9) kPa.

Conclusion: Saturations within the range 85–95% largely exclude hyperoxia in preterm infants <29 weeks' gestation but permit Pao_2 values far lower than those recommended in traditional guidelines.

Oxygen saturation measurements made by pulse oximetry have become the most widely used method for monitoring the oxygenation of preterm infants. Control of oxygenation is achieved by maintaining saturation within a target range, usually by setting alarm limits. No studies have definitively determined which oxygen saturation levels or oxygen tensions are ideal. Consequently, the recommended oxygen saturation limits in routine clinical use vary considerably among units.[1]

High oxygen tensions increase the risk of retinopathy of prematurity,[2] and have been linked to other morbidities such as bronchopulmonary dysplasia,[3] necrotising enterocolitis,[4] and adverse neurological outcome.[5] Yet there is a concern that inappropriately low oxygen tensions might also increase morbidity.

Several large, prospective multicentre randomised controlled trials of oxygen saturation target ranges for extremely preterm infants are under way around the world. The investigators have agreed on common saturation target ranges to facilitate a prospective meta-analysis of the results with optimum power to determine the effects of these policies on long-term outcome. This collaboration is called NeOProM (neonatal oxygen prospective meta-analysis). The outcomes of preterm infants who are targeted to maintain saturations in the range 85–89% are being compared with those of infants targeted to maintain saturations in the range 91–95%. This reflects the broad range of saturation targets that are in general clinical use for preterm infants.

There has been surprisingly little information published describing the ranges of arterial oxygen tension (Pao_2) observed in contemporary extremely preterm infants over the full range of pulse oximeter saturations at which they are currently cared for.[6–8] We therefore aimed to describe the range of oxygen tensions achieved in the first week of life in a population of high-risk preterm infants at currently targeted pulse oximeter saturation (Spo_2) levels.

METHODS

The infants in this study were cared for in the neonatal unit of the Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, between October 2002 and October 2004. We retrospectively studied a group of 98 consecutively admitted premature infants, born at <29 weeks' gestation, who had arterial lines inserted and at least one arterial blood gas taken during the first week of life while their oxygen saturation was being monitored. Blood gases were measured on a Radiometer ALB700 series analyser (Radiometer Medical ApS, Copenhagen, Denmark). Functional pulse oximetry was performed using a Siemens Infinity SC 7000 multiparameter patient monitor (Siemens Medical Systems, Inc, Danvers, MA, USA). This monitor uses Siemens' Oxisure pulse oximetry technology and Nellcor Oxinax (Nellcor Puritan Bennett, CA, USA) saturation probes. This is a multiparameter monitor and in real-time, values of saturation, heart rate and blood pressure were downloaded every second to a cot-side patient data monitoring system for graphical display as part of routine practice (Badger, Clevermed).

The Pao_2 from each blood gas result was matched to the pulse oximeter saturation at the time of sampling. This could be determined accurately on inspection of the graphs of the downloaded data by the presence of an interruption to the continuous arterial blood pressure trace at the time of sampling. To exclude blood gas samples taken when there was motion artefact affecting the saturation values, data pairs were only included if the heart rate derived from the saturation trace was stable and differed from the heart rate determined from the arterial blood pressure trace by less than 10 beats per minute. All paired saturation and Pao_2 values were documented for each infant during the first week of life.

The number of blood gas results available for each infant depended on the duration of invasive arterial blood pressure monitoring. For each

Table 1 Infant characteristics

Number	98
Gestation (weeks)	26.7 (1.56)
Birth weight (g)	869 (214)
Male gender	52 (53)
At least one dose antenatal steroid	87 (90)

Data are mean (SD) or number (%).

individual infant, the mean PaO_2 at each saturation point in the 80–100% saturation range was calculated. The individual infant mean arterial oxygen tensions at each saturation point were then combined to calculate a population mean PaO_2 with 95% CI (mean (2 SD)) for each saturation value.

As this was a study of routinely collected clinical data performed by the team caring for the babies, with no intervention and there was no intention to publish individual confidential patient information, the local ethics advisory committee decided that formal review by the committee was not required.

RESULTS

Table 1 gives the characteristics of the 98 infants who were studied. A total of 2076 arterial blood gas samples were taken from these infants in the first week of life at times when the saturation trace was free of artefact and the saturation value was ≥80%. The mean (SD) number of samples from each infant was 21.4 (15.4).

Figure 1 shows a scatter plot of all of the data points. The shaded boxes show the 95% CI for PaO_2 that will probably be achieved in the higher (91–95%) and lower (85–89%) oxygen saturation target ranges currently under investigation in the NeOProM meta-analysis, and the range of PaO_2 values recommended in published clinical guidelines (6.7–10.7 kPa).[9 10] The 95% CIs of PaO_2 (mean (2 SD)) for the higher and lower NeOProM saturation ranges were 4.6 to 8.9 kPa and 3.8 to 7.15 kPa, respectively. The 95% CIs for PaO_2 for the saturation range 85–95% were therefore 3.8–8.9 kPa. If corrected for ideal pH, PcO_2 and temperature, the CI would be 5.6 to 8.7 kPa.

DISCUSSION

We have described the range of oxygen tensions achieved in the first week of life in a population of high-risk preterm infants at currently targeted oxygen saturation levels. The SpO_2 range 85–95% permits a range of PaO_2 that is much lower than has been recommended in published clinical guidelines based on targeting oxygen tensions,[9 10] suggesting that the move towards saturation monitoring and away from transcutaneous PO_2 monitoring that has taken place is resulting in infants being cared for at lower oxygen tensions than before. The upper 95% CI for PaO_2 at a saturation of 95% of 8.9 kPa indicates that provided that infants stay within the targeted range during supplemental oxygen therapy, serious hyperoxia is unlikely.

We studied pulse oximeter data rather than co-oximeter data because it is the pulse oximeter that is used to guide clinical care. We did not have a record of whether the saturation probe and/or arterial line were preductal or postductal in individual cases but this varies in clinical practice. Most babies do not have remarkable right-to-left shunts, and it is not common for neonatal units to have different saturation target ranges according to the site of the saturation probe or arterial line. We have presented the unmodified blood gas analyser results as these are what tend to be used in clinical decision making. Disturbances in acid–base balance and temperature can alter the haemoglobin-oxygen affinity. Correcting the results for these effects has a small effect on the 95% CI of the oxygen tensions achieved within the studied range.

There are variations between saturation monitors, particularly between monitors that monitor functional or fractional saturation. Most monitors, including Siemens Oximart and Masimo (used in the NeoProM collaboration) now measure functional saturation. Differences between functional oximeters within the studied range are small.[11] Emond *et al*[5] used co-oximetry to measure the P90 of blood from a population of preterm infants with mean gestation 26.4 weeks, and obtained a mean P90 of 40.8 (3.6) mm Hg (5.4 (0.5) kPa), which is similar to the mean PaO_2 of 5.9 kPa at a saturation of 90% from our data.

In summary we have described the range of arterial oxygen tensions achieved in the first week of life in a population of

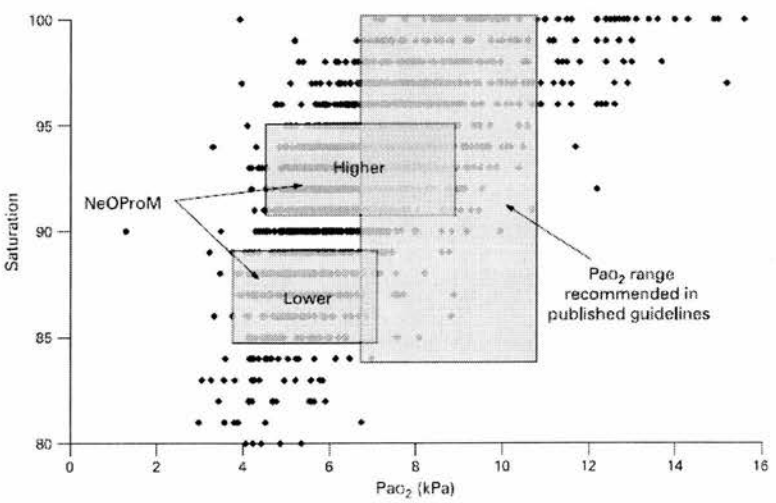

Figure 1 Plot of saturation (%) versus Pao_2 (kPa), 2076 data pairs from 98 preterm infants <29 weeks' gestation during the first week of life. The shaded boxes outline the 95% CI of Pao_2 for the saturation ranges 85–89% and 91–95%, and the recommended Pao_2 ranges from published guidelines.[9 10]

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high-risk preterm infants at currently targeted oxygen saturation values. This is lower than the range recommended in published clinical guidelines based on oxygen tensions and indicates that a shift towards lower oxygen tensions has taken place with current care practices based on saturation targeting. The results of the NeOProM meta-analysis will provide the long-awaited, high-quality information about the effect of different oxygen targeting policies on clinical outcome.

Competing interests: None.

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CONTRIBUTION OF NURSE OXYGEN ADJUSTMENT BEHAVIOURS TO STABILITY OF OXYGENATION IN PRETERM INFANTS

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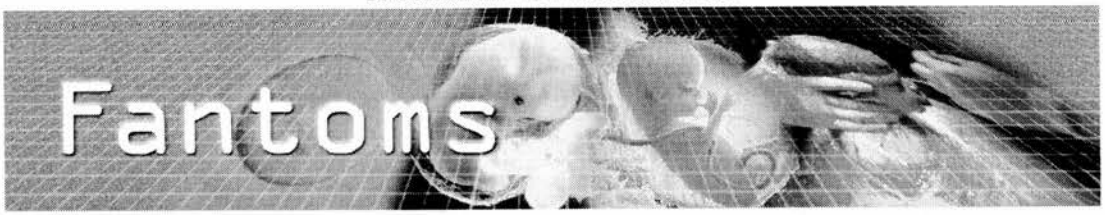
Objective: To explore the contribution of nurse oxygen adjustment behaviours to the stability of oxygenation in preterm infants, by controlling for infants' intrinsic instability.

Methods: Oxygen adjustment behaviours of 24 trained neonatal nurses while caring for 13 ventilated infants during 133 nursing shifts were studied. Average time per shift that each individual infant spent with saturation (SpO_2) >94% in supplemental oxygen (hyperoxic), the variability (SD) of SpO_2 and time spent with SpO_2 <86% were calculated. The oxygen adjustment behaviours of the nurses who for ⩾50% of their shifts the infant in their care was more unstable by these measures than the average for that infant, were compared with the behaviours of the remaining nurses. Behaviours compared were mean number FiO_2 increases, mean size FiO_2 increase, mean FiO_2 variability, mean FiO_2 and mean SpO_2 maintained. Independent samples t-tests were used for comparisons.

Results: Nurses whose babies spent more time hyperoxic than average (24% vs 14%) made larger increases in FiO_2, (9.9% vs 7.6%, p = 0.02) but not more frequent increases. Nurses whose babies showed greater than average variability in SpO_2 increased the FiO_2 more frequently (28 vs 21 times per shift, p = 0.03) but not in larger steps. Nurses whose babies spent most time with SpO_2 <86% (16% vs 10%) also made more frequent (29 vs 20 times per shift, p = 0.003) but not larger increases in FiO_2.

Conclusion: After controlling for the intrinsic instability of the infant we found that larger and more frequent changes in FiO_2 contribute to instability of oxygenation.



Martin Ward Platt, *Associate Editor*

NITRIC OXIDE AND THE BRAIN

Just as we have all been getting used to nitric oxide as a compound with desirable vaso-active properties when given by inhalation; and just as we have been considering promoting its production pharmacologically with new drugs such as sildenafil; along comes a new family of compounds that inhibit nitric oxide synthase. These may become important in neonatal care because the production of locally toxic nitric oxide appears to be a mediator of the damage caused by ischaemia and reperfusion injury in the brain, so inhibiting nitric oxide synthase may be a useful strategy following severe birth asphyxia. Nitrotyrosine is a compound formed when nitric oxide combines with oxygen, forms peroxynitrite, and reacts with tyrosine. Groenendaal *et al* have demonstrated that nitrotyrosine was widely distributed in the brains of babies who died following perinatal asphyxia, but not in the brain of a control infant who died with spinal muscular atrophy. Interestingly, the distribution of nitrotyrosine in the brains of the asphyxiated infants was wide and variable, with hippocampal damage as well as "watershed" and basal ganglia damage. Although the authors do not highlight this, it would be consistent with the suggestion that asphyxia might sometimes damage later cognitive function more than motor function in certain babies.

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ASPHYXIA AND COGNITIVE FUNCTION

It is timely, in the light of the above paper, that Gonzalez and Miller should review impaired cognitive function, without cerebral palsy, as a complication of perinatal asphyxia. Certainly the received wisdom is that disordered motor function is the dominant long-term complication, and that learning difficulties may or may not accompany serious (four limb) cerebral palsy, but it is plausible that in some infants the asphyxial insult may selectively affect parts of the brain predominantly related to cognitive rather than motor function. Readers may take issue with reading too much into the short-term outcomes of the recently published randomised controlled trials of hypothermia (using Bayley MDI scores at 18 months), but the published data using cognitive instruments at school entry are harder to dismiss, even though these data are mostly from case control or cohort studies.

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PERINATAL DATA FROM BEFORE THE DAWN OF PAEDIATRICS

What can data from up to 200 years ago tell us about perinatal care? Quite a lot, as Woods shows us in his thought-provoking paper. The lessons I drew were first, that the very fact of introducing systems for auditing stillbirths was a catalyst to drive public health change. Second, the introduction of quality assured midwifery, prioritising those areas with the highest stillbirth rates, was the single most important common factor in bringing down the highest rates in scandinavian countries in the 19th century. And third, one of the key participants with responsibility for recording the stillbirths was not medical: it was the clergy, who were presumably already used to recording adult marriage and death, and who in relation to recording stillbirth were perhaps most likely to be impartial in their work.

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MEASURING BEHAVIOUR IN EX-PREMS AT SCHOOL ENTRY...

Trying to get a handle on some of the "difficult" outcomes of survivors of premature birth is a particular challenge, because it is tempting to attribute to "prematurity" outcomes that may in fact have been predestined by other factors that are themselves associated with prematurity. Behaviour is one such "difficult" outcome, and the contribution of Reijneveld *et al* to the literature is to ascertain behavioural status at the age of 5 years (school entry), as this may subsequently track through the school years. They have the enormous advantage of a high quality control group consisting of contemporaneous national cohort data, so the findings should certainly be taken seriously. But one cannot help noticing that the mothers of the premature babies were of lower educational attainment than the controls, and one cannot help but wonder what other unmeasured factors about these children's family backgrounds might have been the "real" causes of their behaviour patterns.

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...AND MEASURING BRONCHO-PULMONARY DYSPLASIA

Just as we all know what we mean by behaviour, but it is quite hard to measure, so we all know broncho-pulmonary dysplasia (BPD) when we see it, but again it is quite hard to measure. Quine *et al* have just made it a lot easier, using apparatus available to us all rather than complex and temperamental technology. This may be a real step forward, since it is meaningless to ascertain rates of "oxygen dependency at 36 weeks", or "in oxygen at discharge", if we do not distinguish properly between the baby in a small trickle who will be off within 3 months, and the baby in half a litre who will have severe and prolonged respiratory disability. Furthermore, their method could be implemented routinely in any unit that wanted to introduce a higher level of sophistication into their audit of respiratory morbidity, as well as being potentially useful in randomised controlled trials with long-term oxygen dependency as an outcome.

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ORIGINAL ARTICLE

Non-invasive measurement of reduced ventilation:perfusion ratio and shunt in infants with bronchopulmonary dysplasia: a physiological definition of the disease

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See end of article for authors' affiliations

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Background: An objective definition of bronchopulmonary dysplasia (BPD) is required to interpret trial outcomes and provide a baseline for prognostic studies. Current definitions do not quantify disease severity. The cardinal measures of impaired gas exchange are a reduced ventilation:perfusion ratio (V_A:Q) and increased right to left shunt. These can be determined non-invasively by plotting arterial oxygen saturation (Spo_2) against inspired oxygen pressure (PIo_2).
Aims: To describe the reduced V_A:Q and shunt in infants with BPD and evaluate these as graded measures of pulmonary dysfunction.
Methods: 21 preterm infants with BPD were studied. PIo_2 was changed stepwise to vary Spo_2 between 86% and 94%. Pairs of PIo_2 and Spo_2 data points for each infant were plotted and analysed to derive reduced V_A:Q ratio and shunt.
Results: In every infant, the Spo_2 versus PIo_2 curve was shifted to the right of the normal because of a reduced V_A:Q. The mean (SD) shift was 16.5 (4.7) kPa (normal 6 kPa). Varying degrees of shunt were also present, but these were less important in determining Spo_2 within the studied range. The degree of shift was strongly predictive of the PIo_2 required to achieve any Spo_2 within the range 86–94% (R^2>0.9), permitting shift and V_A:Q to be determined from a single pair of PIo_2 and SpO_2 values in this range.
Conclusions: The predominant gas exchange impairment in BPD is a reduced V_A:Q, described by the right shift of the Spo_2 versus PIo_2 relationship. This provides a simpler method for defining BPD, which can grade disease severity.

Despite great improvements in the survival of infants born prematurely, there continues to be a large number of infants who develop bronchopulmonary dysplasia (BPD). This causes them to remain in hospital longer, prolongs their requirement for supplemental oxygen, and is associated with long-term morbidity and an increased risk of mortality. Reducing BPD remains a major focus of clinical and research activity.

An objective definition of BPD is required to enable reliable interpretation of clinical trial outcomes and to serve as a baseline in prognostic studies. Yet, an ideal definition has been elusive. Definitions based on the infant having a requirement for supplemental oxygen at 28 days of life[1] or at 36 weeks' gestation[2] have been used widely, but their usefulness is severely limited by the marked variation among clinicians in their criteria for oxygen supplementation.[3] A definition based on the use of oxygen treatment alone gives wide variations in the incidence of disease, which reflect little more than clinician variation and have little relevance to the severity of any underlying pathology.[4] Recently, a physiological definition has been proposed that aims to remove this bias by defining BPD as a requirement for supplemental oxygen, to maintain an oxygen saturation of 90% at 36 weeks' gestation.[5] This is undoubtedly an advance. However, healthy preterm and term infants have saturations around 97% in air,[6 7] and saturations lower than this in air must reflect a degree of gas exchange impairment, even if supplemental oxygen is not always deemed necessary. Present approaches to defining BPD classify these infants as disease free.

By non-invasive measurements of PIo_2 and Spo_2, it is possible to quantify the severity of gas exchange impairment in a graded fashion and to partition this between the contribution made by reduced ventilation:perfusion ratio (V_A:Q) and that made by right to left shunt.[8–11] We have applied this method to analyse the gas exchange abnormalities in infants with BPD and used these observations to model an improved approach to the definition of BPD, which measures the severity of gas exchange impairment.

METHODS

Underlying physiology

A reduced V_A:Q ratio and an increased shunt have different effects on the relationship between inspired oxygen pressure (PIo_2) and arterial oxygen saturation (Spo_2). A reduced V_A:Q ratio decreases alveolar and arterial oxygen tension (Po_2) and raises alveolar and arterial carbon dioxide tension (Pco_2). Increasing PIo_2 restores the alveolar Po_2 and Spo_2 to normal, overcoming the effect of the reduced V_A:Q ratio. Increased shunt does not raise Pco_2 but reduces Spo_2 because the shunted blood is not exposed to alveolar oxygen. Increasing PIo_2 can compensate for only a small amount of shunt, because the non-shunted blood is already almost fully saturated and does not carry much more oxygen than small amounts in solution when PIo_2 is increased. These independent effects on gas exchange can be represented in the form of plots of Spo_2 against PIo_2 (fig 1).[8–12]

Abbreviations: BPD, bronchopulmonary dysplasia; Pco_2, arterial carbon dioxide tension; Po_2, arterial oxygen tension; PIo_2, partial pressure of inspired oxygen; Spo_2, arterial oxygen saturation; V_A:Q, ventilation:perfusion ratio

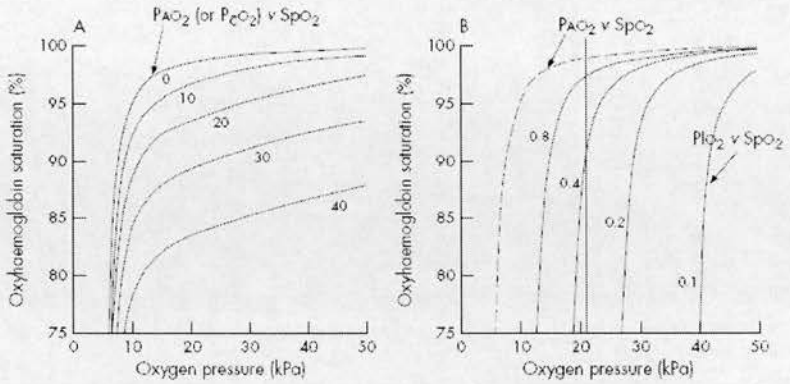

Figure 1 Plots of oxyhaemoglobin saturation (Sp_{O_2}, %) against inspired oxygen pressure (P_{IO_2}, kPa).[10] (A) Increasing shunt from 0% to 40% lowers the position of the upper part of the curve. (B) Reducing ventilation:perfusion ratio (V_A:Q) from 0.8 to 0.1 shifts the curve to the right. The right shift of each P_{IO_2}–Sp_{O_2} curve from the position of the dissociation curve (dashed line) is the P_{IO_2}–P_{aO_2} difference (kPa), which includes P_{aCO_2}/R. The 0.8 curve represents the normal adult curve, which intercepts a P_{IO_2} of 21 kPa (vertical line) at 97% Sp_{O_2}. R, respiratory gas exchange rate.

At sea level (1 atm), P_{IO_2} (kPa) is the same as the inspired oxygen percentage. The curve relating alveolar (mixed capillary) P_{O_2} to oxygen saturation in the ideal lung represents the shape of the oxyhaemoglobin dissociation curve. Increasing shunt displaces the top part of the curve downwards (fig 1A) as the maximum Sp_{O_2} obtainable falls. In contrast, reducing the V_A:Q ratio shifts the whole curve to the right (fig 1B). The degree of the right shift, using the oxygen dissociation curve as the reference, is determined by the reduction in the V_A:Q ratio and a rise in alveolar P_{CO_2}. The normal curve is shifted to the right of the haemoglobin–oxygen dissociation curve by 6 kPa, which is largely P_{CO_2}/R (where R is the respiratory gas exchange ratio). An additional right shift compared with the normal represents the increase in P_{IO_2} that will be required to restore the mixed capillary P_{O_2} to normal levels and thereby permit normal arterial saturation. If multiple pairs of P_{IO_2} and Sp_{O_2} values are obtained from the same patient, then a single pair of shunt and shift values can be derived. This can be done graphically[7–9] by moving a set of shunt curves such as those in fig 1A laterally over the plot of P_{IO_2}–Sp_{O_2} data points until one of the shunt curves superimposes the data points. The degree of shift can then be read off the axis of the graph, and the shunt can be determined by selecting the shunt curve that most closely fits the data. Alternatively, shift and shunt can be calculated using a computer algorithm that derives confidence intervals for the shunt and shift values, and coefficients of determination (R^2) for the fit of the data to the shunt and shift model.[8 10]

Procedure

We studied 21 preterm infants who were considered to have BPD on the basis of a continuing requirement for supplemental oxygen at 36 weeks' gestation. The study was approved by the institutional ethics advisory committee and written informed consent was obtained from the parents in all cases. This was a convenience sample. Infants were

Table 1 Characteristics of the infants studied

Infant	Gestation at birth (weeks)	Corrected gestation at time of study (weeks)	Birth weight (kg)	Weight at time of study (kg)	Nasal cannula O_2 flow rate (l/min)	Total days on ventilator	Total days of CPAP
1	25.6	37.7	0.640	2.330	0.03	27	55
2	25	36.4	0.870	3.000	0.03	19	33
3	27	37.7	0.670	2.200	0.02	6	16
4	25.9	37.3	0.965	2.705	0.1	2	50
5	28	38	0.590	1.940	0.01	11	70
6	26	36.6	0.970	2.535	0.1	45	70
7	27.4	36.4	0.800	2.300	0.04	1	44
8	28	37.3	0.890	2.650	0.02	2	40
9	27.3	37.9	0.750	2.130	0.08	1	31
10	26.7	37	0.965	2.600	0.02	16	63
11	24	37.9	0.520	2.100	0.15	50	68
12	27.3	36.3	0.490	1.530	0.03	2	81
13	25.4	36.3	0.650	2.195	0.02	4	15
14	26.7	37.4	1.110	2.910	0.02	1	40
15	26.1	37.1	0.690	2.040	0.05	4	70
16	26.1	36.1	0.610	1.790	0.07	14	76
17	29	37.4	1.060	2.350	0.125	0	0
18	23.7	36.9	0.630	1.960	0.01	50	74
19	28	38	0.570	2.250	0.05	4	33
20	26.7	37.6	0.950	2.440	0.03	11	65
21	23.7	37.6	0.530	2.380	0.08	41	77
Mean	26.4	37.2	0.758	2.302	0.052	14.8	51
SD	1.45	0.62	0.192	0.359	0.040	17.3	23.3

CPAP, continuous positive airway pressure.

included if they were receiving supplemental oxygen but not other support at the time of study. According to our unit policy, oxygen was being given as required to maintain oxygen saturation in the target range 86–94%. All infants were being cared for in the neonatal unit of the Simpson Centre for Reproductive Health, Royal Infirmary of Edinburgh, Edinburgh, UK, between January 2002 and March 2005. All studies were carried out within 2 weeks of the infant reaching 36 weeks' gestation.

At the time of study all infants were receiving oxygen via nasal cannulae. To enable measurement and control of PIo_2, the infants were placed in a neonatal intensive care incubator with oxygen under servo control (Draeger 8000IC, Draeger Medical AG & Co KGaA, Lübeck, Germany). The oxygen analyser was calibrated at the start of each study. Functional Spo_2 was measured using either a Siemens SC7800 (Siemens Medical Systems Inc, Danvers, MA, USA) or a Philips M3046A multiparameter patient monitor (Agilent Technologies, Boblingen, Germany), depending on which nursery the infant was being nursed in. Studies began at least 30 min after a feed and were conducted with the infant lying supine. PIo_2 was reduced in increments of 1–2% (1–2 kPa) and then increased again to vary Spo_2 between 94% and 86%. At each PIo_2 value, the infant was allowed to stabilise for about 5 min before a pair of Spo_2 and PIo_2 values was recorded. Values were recorded only if there was a good pulse waveform on the oximeter and the infant was not displaying gross body movements.

Sleep state was not standardised. PIo_2 was never reduced below 21 kPa, and oxygen administration to saturation >94% was minimised as per unit policy.

The pairs of PIo_2 and Spo_2 data points obtained from each infant were plotted and analysed using a computer algorithm that gave a curve representing a single solution for shunt and shift (the difference between PIo_2 and mixed capillary Po_2) for each infant's dataset.[8–10] If the data pairs obtained did not describe the plateau of the oxyhaemoglobin dissociation curve, the algorithm was sometimes unable to calculate the shunt and shift values. Under these circumstances the data were plotted manually, and shunt and shift were determined from the graphs directly using the method described above.

As right shift is due to the combined effects of raised Pco_2 and reduced V_A:Q ratio, we determined the contribution of these two variables using a mathematical model of gas exchange described by Olszowka and Wagner.[11] PIo_2–Spo_2 curves were constructed for V_A:Q values from 0.9 to 0.15, and the predicted $Paco_2$ value was calculated from the model. From this we related the shift value in each infant to a particular V_A:Q and compared the child's most recent Pco_2 measurement with the predicted Pco_2.

RESULTS

Table 1 describes the clinical characteristics of the 21 infants. All infants were receiving supplemental oxygen at the time of study. There was wide variation among the infants in the length of time that each had been on a ventilator or supported with continuous positive airway pressure. Some were still cycling on and off continuous positive airway pressure.

The main finding was that in every infant the PIo_2 versus Spo_2 curve was shifted to the right of the oxygen dissociation curve. The mean (standard deviation (SD)) shift was 16.5 (4.7) kPa (table 2). The normal PIo_2–Spo_2 curve is shifted 6 kPa to the right of the dissociation curve and is identical to the V_A:Q 0.8 curve shown in fig 1B. This intercepts the vertical line at 21 kPa PIo_2 at an Spo_2 of about 97%. Figure 2 shows the data plots of infants 2, 10, 11 and 19 in relation to the oxyhaemoglobin dissociation (ideal) curve and the normal adult PIo_2 versus Spo_2 curve. Table 2 shows the values for shunt and right shift for all 21 infants, with 95% confidence interval (CI) and R^2. In three infants (5, 8 and 18), the range of paired values of PIo_2 and Spo_2 obtained did not describe enough of the plateau of their PIo_2 versus Spo_2 relationship to enable the algorithm to calculate the shunt and shift values. Their data points were plotted, and the shunt and shift values were determined manually from the graphs as described above; data of these infants do not therefore include CI or R^2. All three infants had Spo_2 ≥90% breathing air.

Table 2 Shunt and right shift of the arterial oxygen saturation versus partial pressure of inspired oxygen curve, R^2, for the fit to the model and ventilation:perfusion ratio

Infant	Shunt (%)	Shift (kPa)	R^2	Shunt (%) 95% CI	Shift (kPa) 95% CI	V_A:Q
1	10.3	15.0	0.55	2.7	0.6	0.33
2	6.7	15.0	0.94	1.5	0.3	0.34
3	4.2	12.7	0.78	1.1	0.4	0.41
4	9.2	19.0	0.65	1.7	0.8	0.26
5	5.6	12.9				0.4
6	14.8	28.5	0.56	3.2	1.1	0.16
7	5.1	13.5	0.61	5.1	0.5	0.38
8	5.0	11.5				0.45
9	11.6	18.0	0.38	1.0	0.4	0.28
10	6.0	20.9	0.90	1.6	0.4	0.23
11	14.3	24.2	0.81	1.5	0.5	0.2
12	10.0	18.7	0.66	2.1	0.7	0.26
13	13.8	13.5	0.58	4.3	0.7	0.38
14	9.7	12.2	0.66	3.6	1.0	0.43
15	10.0	18.0	0.64	4.1	0.4	0.28
16	7.3	18.6	0.83	2.6	0.5	0.27
17	11.1	22.5	0.81	2.6	0.4	0.21
18	7.5	9.0				0.6
19	6.4	14.6	0.82	1.7	0.7	0.35
20	13.3	12.7	0.64	2.7	0.6	0.41
21	5.1	15.4	0.81	1.1	0.9	0.33
Mean	8.9	16.5	0.69	2.4	0.6	0.33
SD	3.4	4.7	0.15	1.2	0.2	0.10

V_A:Q, ventilation:perfusion ratio.
The results for infants 5, 8 and 18 were derived manually and do not therefore have CI or R^2 values.

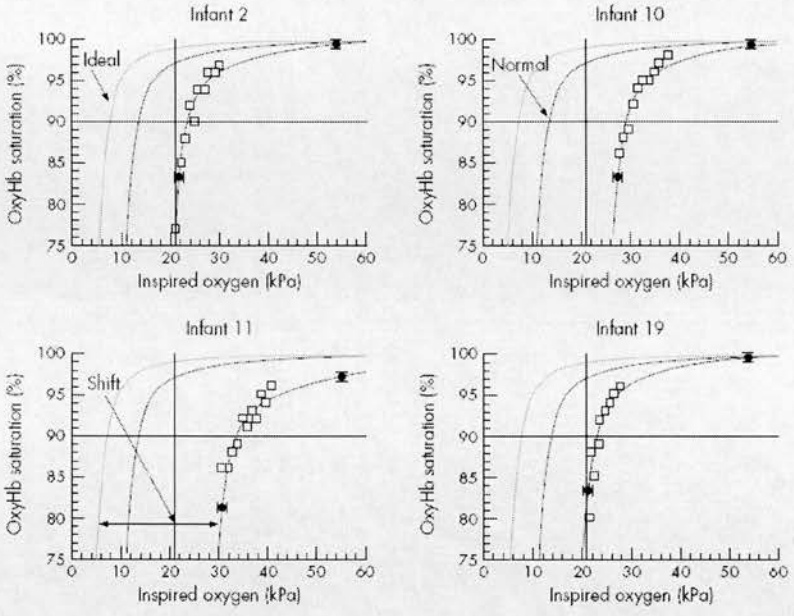

Figure 2 Plots of oxyhaemoglobin (OxyHb) saturation (Spo_2, %) versus inspired oxygen (PIo_2, kPa) for infants 2, 10, 11 and 19. Reference grid lines are added at an Spo_2 of 90% and a PIo_2 of 21 kPa. The haemoglobin oxygen dissociation curve (ideal lung) is the reference point for derivation of shift. The normal Spo_2–PIO_2 curve is also included for comparison.

As a significant right shift of the PIo_2 versus Spo_2 curve occurred in every case, and was a sensitive measure of a reduced V_A:Q ratio, we looked for an index of right shift that might obviate the need to produce a range of different PIo_2 values in each case. In every infant, the 90% Spo_2 value fell on the steep part of the dissociation curve so that the PIo_2 needed to produce 90% Spo_2 might be a candidate marker of right shift. Figure 3 shows plots of the degree of shunt and shift in each infant against the PIo_2 required to achieve 90% Spo_2. At this Spo_2, the relationship between PIo_2 and shift was highly siginificant and linear, whereas that between PIo_2 and shunt was weak, indicating that shift was the main determinant of reduced Spo_2 in these infants.

We constructed plots of shift against the PIo_2 required to achieve each saturation in the range 86–94% Spo_2, and found linear relationships between shift and PIo_2 at all of the Spo_2 values in this range, with all values of $R^2>0.9$. The consistency of the relationship between shift and PIo_2 in this range was such that multiple data pairs in each infant were not required to derive shift. A single pair of PIo_2 and Spo_2 values in the Spo_2 range 86–94% was sufficient to predict the shift value that would be derived from the whole

Table 3 Right shift (kPa) of the arterial oxygen saturation (Spo_2) versus partial pressure of inspired oxygen (PIo_2) relationship for different pairs of PIo_2 and Spo_2 values

	Spo_2 (%)								
PIo_2 (kPa)	86	87	88	89	90	91	92	93	94
21	13.1	12.8	12.5	12.2	11.8	11.4	10.9	10.3	9.5
22	14.1	13.8	13.6	13.2	12.8	12.4	11.8	11.2	10.4
23	15.2	14.9	14.6	14.2	13.8	13.3	12.8	12.1	11.2
24	16.2	15.9	15.6	15.2	14.8	14.3	13.7	13.0	12.0
25	17.2	16.9	16.6	16.2	15.8	15.3	14.6	13.8	12.8
26	18.2	17.9	17.6	17.2	16.8	16.2	15.6	14.7	13.6
27	19.3	19.0	18.6	18.2	17.8	17.2	16.5	15.6	14.5
28	20.3	20.0	19.7	19.3	18.8	18.2	17.4	16.5	15.3
29	21.3	21.0	20.7	20.3	19.8	19.1	18.3	17.4	16.1
30	22.4	22.1	21.7	21.3	20.7	20.1	19.3	18.3	16.9
31	23.4	23.1	22.7	22.3	21.7	21.1	20.2	19.2	17.7
32	24.4	24.1	23.7	23.3	22.7	22.0	21.1	20.0	18.6
33	25.5	25.2	24.7	24.3	23.7	23.0	22.1	20.9	19.4
34	26.5	26.2	25.8	25.3	24.7	24.0	23.0	21.8	20.2
35	27.5	27.2	26.8	26.3	25.7	24.9	23.9	22.7	21.0
36	28.6	28.2	27.8	27.3	26.7	25.9	24.9	23.6	21.8
37	29.6	29.3	28.8	28.3	27.7	26.9	25.8	24.5	22.7
38	30.6	30.3	29.8	29.3	28.7	27.8	26.7	25.3	23.5
39	31.7	31.3	30.8	30.3	29.7	28.8	27.7	26.2	24.3
40	32.7	32.4	31.9	31.4	30.7	29.8	28.6	27.1	25.1

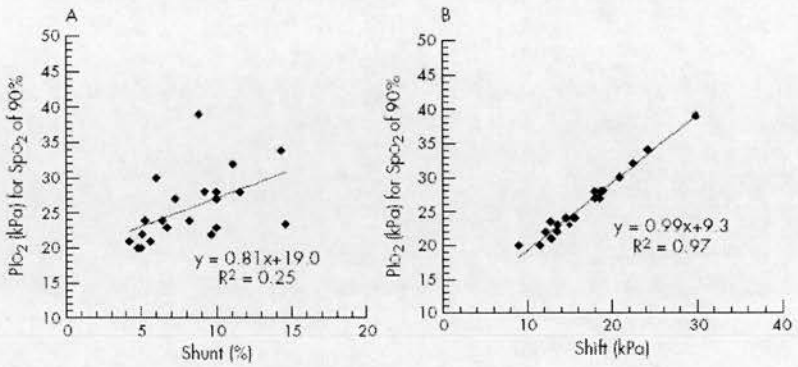

Figure 3 (A) Partial pressure of inspired oxygen (PIO_2) required to achieve an arterial oxygen saturation (SpO_2) of 90% versus shunt. (B) PIO_2 required to achieve an SpO_2 of 90% versus shift.

data series. The mean (SD) difference between shift calculated from individual data pairs and that calculated from the entire data series for each infant was 0.24 (1.25) kPa.

To enable others to derive shift from a single pair of SpO_2 and PIO_2 values, shift was calculated from the results of this study for a range of PIO_2 and SpO_2 values that are likely to be observed in infants with BPD at 36 weeks' gestation. Table 3 shows the results.

PCO_2 predicted by the model of Olszowka and Wagner[12] for the degree of a reduced V_A:Q ratio in each infant was linearly related to measured PCO_2 ($y = 0.68x+3.2$, $R^2 = 0.6$). This is only a consistency check on the model, because in many cases the most recent PCO_2 value available was obtained several days or more from the time of the study. When this analysis was restricted to the six infants with PCO_2 values obtained within 1 day of the study, there was a close correlation ($y = 0.88x+1.5$, $R^2 = 0.99$).

DISCUSSION

Series of paired values of SpO_2 and PIO_2 were used in preterm infants with BPD to show, non-invasively, an increase in shunt and a reduction in the V_A:Q ratio. The reduced V_A:Q ratio was the dominant gas exchange defect causing a major right shift of the SpO_2 versus PIO_2 curve in all these infants. The right shift of the curve explained the need for an increased PIO_2, and there was a strong linear relationship between the degree of shift and the PIO_2 required to achieve any chosen saturation in the range 86–94%. The consistency of this finding was such that a single measurement of the PIO_2 required to achieve any SpO_2 in the range 86–94% was sufficient to derive shift. Presently, no definition of BPD exists that provides both a robust physiological threshold for diagnosis and a continuous scale of severity that is based on the degree of gas exchange impairment. We believe that the degree of right shift of the relationship between SpO_2 and PIO_2 provides such a measure. This could be expressed either as the shift in kPa or as the PIO_2 required to maintain a saturation of 90%. Such information has previously been derived by more invasive methods.

This non-invasive method of partitioning gas exchange impairment has been applied in sick infants,[10] and in healthy and sick adults.[8 9 11] The results showed a good fit between the model and the clinical data in all age groups and disease states studied. Kjaergaard *et al*,[13] using saturation measurements non-invasively, obtained results almost identical to those obtained from simultaneous more invasive measurements. Iles and Edmunds[13] showed that measures of gas exchange impairment derived from arterial blood gases sampled around term predict the prognosis of BPD, and that infants with low saturation are at higher risk of acute life-threatening events.[14]

The recent National Institutes of Health workshop consensus definition of BPD[15] categorises infants as having no BPD, or with mild, moderate or severe BPD according to the amount of oxygen supplementation and ventilatory support required up to 36 weeks' gestation. These categories predict later respiratory morbidity,[16] but they are not physiologically based; and respiratory problems are also seen later in life in a substantial number of infants not identified to have BPD by this definition. Infants with BPD have reduced numbers of alveoli, enlarged air spaces, interstitial fibrosis and variable degrees of small airway narrowing.[17] Defining the degree of physiological impairment associated with this pathology is likely to be more informative than quantifying the preceding exposure to treatment. Similar to the Walsh test,[4] the National Institutes of Health network definition[15] is likely to permit infants with saturations lower than those observed in healthy infants to be categorised as having no BPD. Measurement of the reduced V_A:Q ratio in terms of shift enables the determination of the degree of gas exchange impairment in all infants, including those who are stable in air, and may provide a more detailed description of study outcomes and serve as a more informative baseline for studies on the prognosis of BPD.

The Walsh test[4] is not really a threshold test, because many infants fail it during the 30-min observation period after having adequate saturation to begin with. In a recent study, infants with a saturation of >96% with an effective fraction of inspired oxygen ≤23% had a positive predictive value of 66% for passing the Walsh test.[18] This reflects the fact that an oxygen saturation around 90% lies on the steep part of the dissociation curve, where reducing the PIO_2 by 1% is associated with changes in saturation of ≈2–3%, and small changes in alveolar ventilation will therefore cause considerable desaturation (fig 2). Using our method, a mean saturation value obtained at a fixed PIO_2 during a brief observation period while an infant was lying supine and free from gross body movements could be used to determine whether the infant would have a saturation of 90% in air.

We have not measured the day-to-day variability of our test within patients. The accuracy of the test is dependent on the accuracy of the measurement of PIO_2 and SpO_2. The issue of PIO_2 measurement can be eliminated if SpO_2 is determined with the infant breathing air. Current SpO_2 monitors are accurate to 1–3% in the range studied.[19] On the steep part of

What is already known on this topic

Present definitions of bronchopulmonary dysplasia have limited capacity to describe disease severity.

What this study adds

Reduced ventilation:perfusion ratio can be quantified non-invasively and may provide a simple, objective method for defining bronchopulmonary dysplasia that can grade disease severity.

the dissociation curve, changes in Spo_2 of this magnitude have a small effect on shift.

The saturation values used to derive the models used in the methods described above were derived from the normal adult haemoglobin oxygen dissociation curve.[20] Curves of newborn infants may differ slightly in the presence of varying amounts of fetal haemoglobin. However, by the time of our study, the infants were around 11 weeks old. Beresford *et al*[5] showed that healthy 1-week-old and 6-month-old preterm infants have mean saturation values of around 97% in air, and Parkins *et al*[6] showed similar values in healthy term infants at 3 months of age; so there is probably no major bias from using the normal curve in adults as a reference point for calculating shift by the time these infants reach 36 weeks' gestation. The model assumes a fixed arteriovenous oxygen gradient of 5 ml/100 ml. Any variation in this within or between individuals affects the position of the plateau of the oxygen dissociation curve but has little effect on its shape, and should not therefore have much effect on calculations of shift.[8] Similarly, estimations of shunt are more sensitive to haemoglobin level than estimations of shift.[8]

In conclusion, we have shown that the contribution of reduced V_A:Q (shift) and shunt to impaired gas exchange can be derived easily from non-invasive measurements of Spo_2 and PIo_2 in infants with BPD. The degree of right shift of the Spo_2 versus PIo_2 curve provides a readily accessible continuous measure of the severity of gas exchange impairment due to a reduced V_A:Q ratio, which is a more dominant contributor than shunt. This measure could be used to define BPD as an outcome in studies and to categorise infants in prospective studies on BPD prognosis.

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Appendix B – Boost 2 Study protocol-Outlining NeOProM study.

1.2 Global collaboration

The outcome of this study will have a major worldwide impact on one of the most important, and least well understood, elements of the care given to babies born before retinal vascularisation is complete. However, even a trial involving more than a thousand babies would have limited capacity to show that clear short term benefits were not associated with some increase in adverse long term outcomes.

Therefore similar trials are now being planned or are funded in several countries (see Table 1).

Table 1 Similar trials of oxygen saturation from around the world

Country	Chief Investigator	Sample size
Australia	William Tarnow-Mordi	1,200
New Zealand	Brian Darlow	320
USA	Neil Finer	1,310
UK	Peter Brocklehurst	1,200
Canada	Barbara Schmidt	1,200
Potential NeOProM Total		**5,230**

Because of this the Chief Investigators planning these trials have all pledged their support for a prospective meta-analysis of individual participant data from each of these studies, Neonatal Oxygenation Prospective Meta-analysis (NeOProM). This will be undertaken by Dr Lisa Askie (the lead investigator of BOOST)[14] under the supervision of Professor RJ Simes in Sydney, Australia, who is the world's leading authority on this recent development in controlled-trial strategy[32,33].

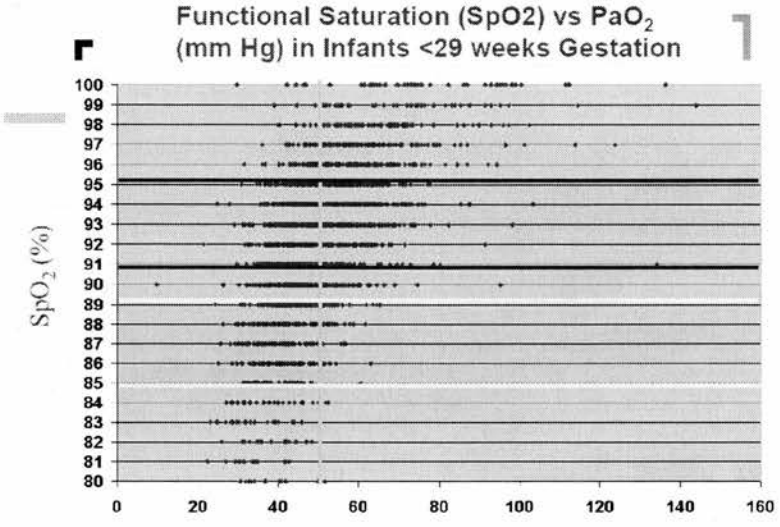
The UK trial will provide information to such a prospective meta-analysis. Without such an overview clinicians around the world will never be able to show that short term benefits are not being 'bought' at the expense of a worse long term outcome. It took clinicians 20 years to realise that the short term benefits achieved by giving dexamethasone soon after birth in these babies to limit lung damage increases the risk of a worse long term outcome[34]. The same could easily be true of oxygen – the one therapeutic agent that almost every preterm baby receives.

Appendix C - Boost 2 Study protocol

This is an appendix from a freely available web published protocol to show that the current research has already been helpful in designing further research studies.

Which oxygen saturation level should we use for very premature infants? A randomised controlled trial

APPENDIX C



Unpublished data supplied by courtesy of B Stenson, Simpson Memorial Maternity Pavilion, Edinburgh.

These simultaneous measurements of SpO2 and oxygen tension were obtained in stable infants with normal blood pressure and blood lactate less than 3 mmol/ L. They illustrate the broad scatter of values of oxygen tension at any given value of SpO2. It is therefore unlikely that the BOOST II trial would become unmasked by knowledge of simultaneous values of oxygen tension.

However, imposing an arbitrary lower limit of oxygen tension of 50 mm Hg would, in a substantial proportion of cases, make it impossible to achieve actual SpO2 targets of 85 – 89% or 91 – 95%. It may be helpful to remember that the normal fetal reference range (95% CI) for umbilical venous oxygen tension has a lower limit of about 22 -33 mm Hg at 23 weeks gestation, and a lower limit of about 18 - 23 mm Hg at 32 weeks gestation. [30, 31]

Appendix D: SPSS workings for study 2.

T-Test

Group Statistics

	BPD	N	Mean	Std. Deviation	Std. Error Mean
Gest	y	49	26.6268	1.40813	.20116
	n	36	27.0913	1.48703	.24784
zscore	y	49	-.8030	1.01468	.14495
	n	36	-.4346	.94024	.15671
fhb	y	49	82.6735	4.82350	.68907
	n	36	82.0833	7.67696	1.27949
BW	y	49	835.2041	207.35426	29.62204
	n	36	944.0000	202.49233	33.74872
P50	y	49	18.5687	1.72897	.24700
	n	36	18.0595	2.17106	.36184

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Gest	Equal variances assumed	.613	.436	-1.467	83	.146	-.46445	.31652	-1.09400	.16510
	Equal variances not assumed			-1.455	73.155	.150	-.46445	.31920	-1.10059	.17170
zscore	Equal variances assumed	1.236	.269	-1.706	83	.092	-.36839	.21600	-.79799	.06122
	Equal variances not assumed			-1.726	78.573	.088	-.36839	.21347	-.79332	.05655
fhb	Equal variances assumed	1.876	.175	.434	83	.665	.59014	1.35863	-2.11213	3.29240
	Equal variances not assumed			.406	54.881	.686	.59014	1.45325	-2.32238	3.50265
BW	Equal variances assumed	.344	.559	-2.414	83	.018	-108.79592	45.06998	-198.438	-19.15354
	Equal variances not assumed			-2.423	76.566	.018	-108.79592	44.90480	-198.221	-19.37093
P50	Equal variances assumed	2.714	.103	1.203	83	.232	.50924	.42318	-.33244	1.35092
	Equal variances not assumed			1.162	64.935	.249	.50924	.43811	-.36573	1.38422

T-Test

Group Statistics

	ROP	N	Mean	Std. Deviation	Std. Error Mean
Gest	y	16	25.2411	1.49532	.37383
	n	69	27.1905	1.17667	.14165
zscore	y	16	-.3003	.96510	.24128
	n	69	-.7274	.99142	.11935
fhb	y	16	80.2500	9.57427	2.39357
	n	69	82.9275	5.02733	.60522
BW	y	16	767.8125	198.79612	49.69903
	n	69	907.5942	206.43959	24.85241
P50	y	16	19.1829	1.91639	.47910
	n	69	18.1606	1.89883	.22859

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Gest	Equal variances assumed	1.815	.182	-5.664	83	.000	-1.94940	.34416	-2.63393	-1.26488
	Equal variances not assumed			-4.876	19.528	.000	-1.94940	.39977	-2.78460	-1.11421
zscore	Equal variances assumed	.012	.913	1.560	83	.123	.42705	.27379	-.11751	.97160
	Equal variances not assumed			1.586	22.936	.126	.42705	.26918	-.12988	.98398
fhb	Equal variances assumed	11.166	.001	-1.581	83	.118	-2.67754	1.69403	-6.04689	.69182
	Equal variances not assumed			-1.085	16.964	.293	-2.67754	2.46890	-7.88730	2.53222
BW	Equal variances assumed	.002	.967	-2.456	83	.016	-139.78170	56.90453	-252.963	-26.60089
	Equal variances not assumed			-2.516	23.121	.019	-139.78170	55.56650	-254.697	-24.86686
P50	Equal variances assumed	.429	.514	1.937	83	.056	1.02234	.52776	-.02736	2.07204
	Equal variances not assumed			1.926	22.351	.067	1.02234	.53084	-.07755	2.12223

T-Test

Group Statistics

	rip	N	Mean	Std. Deviation	Std. Error Mean
Gest	y	13	25.7582	1.97552	.54791
	n	85	26.8235	1.45179	.15747
zscore	y	12	-.6411	1.09135	.31505
	n	85	-.6470	.99509	.10793
fhb	y	12	76.3333	11.49967	3.31967
	n	85	82.4235	6.15935	.66807
BW	y	13	789.6154	225.02279	62.41009
	n	85	881.2824	211.13501	22.90081
P50	y	13	18.9885	3.31538	.91952
	n	85	18.3530	1.93293	.20966

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Gest	Equal variances assumed	4.077	.046	-2.342	96	.021	-1.06529	.45478	-1.96802	-.16255
	Equal variances not assumed			-1.869	14.051	.083	-1.06529	.57009	-2.28760	.15702
zscore	Equal variances assumed	.169	.682	.019	95	.985	.00587	.31045	-.61045	.62219
	Equal variances not assumed			.018	13.709	.986	.00587	.33302	-.70982	.72155
fhb	Equal variances assumed	5.834	.018	-2.825	95	.006	-6.09020	2.15551	-10.36942	-1.81097
	Equal variances not assumed			-1.799	11.906	.097	-6.09020	3.38623	-13.47458	1.29419
BW	Equal variances assumed	.213	.646	-1.446	96	.152	-91.66697	63.40878	-217.532	34.19847
	Equal variances not assumed			-1.379	15.409	.188	-91.66697	66.47907	-233.037	49.70283
P50	Equal variances assumed	4.850	.030	.990	96	.325	.63543	.64171	-.63836	1.90921
	Equal variances not assumed			.674	13.275	.512	.63543	.94312	-1.39778	2.66863

T-Test

Group Statistics

	var00001	N	Mean	Std. Deviation	Std. Error Mean
Gest	y	66	26.3853	1.60923	.19808
	n	32	27.2946	1.27669	.22569
zscore	y	65	-.6933	1.04742	.12992
	n	32	-.5507	.90926	.16074
fhb	y	65	81.0769	7.78883	.96609
	n	32	82.8750	5.90107	1.04317
BW	y	66	829.3939	210.37972	25.89595
	n	32	951.0625	200.88673	35.51209
P50	y	66	18.6931	2.16615	.26663
	n	32	17.9098	2.06413	.36489

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Gest	Equal variances assumed	1.950	.166	-2.796	96	.006	-.90936	.32524	-1.55496	-.26376
	Equal variances not assumed			-3.028	75.725	.003	-.90936	.30029	-1.50747	-.31125
zscore	Equal variances assumed	2.191	.142	-.657	95	.513	-.14258	.21691	-.57319	.28804
	Equal variances not assumed			-.690	70.218	.493	-.14258	.20668	-.55475	.26960
fhb	Equal variances assumed	1.836	.179	-1.152	95	.252	-1.79808	1.56072	-4.89650	1.30035
	Equal variances not assumed			-1.265	78.875	.210	-1.79808	1.42180	-4.62818	1.03202
BW	Equal variances assumed	.802	.373	-2.724	96	.008	-121.66856	44.66783	-210.333	-33.00363
	Equal variances not assumed			-2.768	64.091	.007	-121.66856	43.95121	-209.469	-33.86833
P50	Equal variances assumed	.002	.961	1.704	96	.092	.78328	.45963	-.12908	1.69564
	Equal variances not assumed			1.733	64.213	.088	.78328	.45193	-.11949	1.68605

Logistic Regression

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	85	100.0
	Missing Cases	0	.0
	Total	85	100.0
Unselected Cases		0	.0
Total		85	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
n	0
y	1

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			BPD		Percentage Correct
			n	y	
Step 0	BPD	n	0	36	.0
		y	0	49	100.0
	Overall Percentage				57.6

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	.308	.220	1.973	1	.160	1.361

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Gest	2.149	1	.143
		zscore	2.878	1	.090
		fhb	.193	1	.661
		BW	5.576	1	.018
		P50	1.458	1	.227
	Overall Statistics		7.149	5	.210

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	7.546	5	.183
	Block	7.546	5	.183
	Model	7.546	5	.183

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	108.293[a]	.085	.114

a. Estimation terminated at iteration number 4 because parameter estimates changed by less than .001.

Classification Table[a]

			Predicted		
			BPD		Percentage Correct
	Observed		n	y	
Step 1	BPD	n	13	23	36.1
		y	12	37	75.5
	Overall Percentage				58.8

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Gest	-.778	.731	1.134	1	.287	.459
	zscore	-1.189	1.094	1.183	1	.277	.304
	fhb	.024	.038	.401	1	.526	1.025
	BW	.004	.006	.468	1	.494	1.004
	P50	.063	.131	.233	1	.629	1.065
	Constant	13.544	14.300	.897	1	.344	762290.1

a. Variable(s) entered on step 1: Gest, zscore, fhb, BW, P50.

Logistic Regression

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	85	100.0
	Missing Cases	0	.0
	Total	85	100.0
Unselected Cases		0	.0
Total		85	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
n	0
y	1

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			ROP		Percentage Correct
			n	y	
Step 0	ROP	n	69	0	100.0
		y	16	0	.0
	Overall Percentage				81.2

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-1.462	.277	27.743	1	.000	.232

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Gest	23.697	1	.000
		zscore	2.421	1	.120
		fhb	2.484	1	.115
		BW	5.761	1	.016
		P50	3.677	1	.055
	Overall Statistics		25.763	5	.000

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	27.338	5	.000
	Block	27.338	5	.000
	Model	27.338	5	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	54.883[a]	.275	.444

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification Table[a]

			Predicted		
			ROP		Percentage Correct
	Observed		n	y	
Step 1	ROP	n	65	4	94.2
		y	6	10	62.5
	Overall Percentage				88.2

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Gest	-1.494	1.057	1.998	1	.157	.224
	zscore	-.352	1.487	.056	1	.813	.704
	fhb	-.038	.047	.666	1	.414	.962
	BW	.004	.009	.205	1	.651	1.004
	P50	.183	.196	.871	1	.351	1.200
	Constant	33.668	20.537	2.688	1	.101	4.2E+14

a. Variable(s) entered on step 1: Gest, zscore, fhb, BW, P50.

Logistic Regression

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	96	98.0
	Missing Cases	2	2.0
	Total	98	100.0
Unselected Cases		0	.0
Total		98	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
n	0
y	1

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			rip		Percentage Correct
			n	y	
Step 0	rip	n	85	0	100.0
		y	11	0	.0
	Overall Percentage				88.5

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-2.045	.320	40.721	1	.000	.129

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Gest	3.777	1	.052
		zscore	.008	1	.930
		fhb	6.319	1	.012
		BW	1.712	1	.191
		P50	3.155	1	.076
	Overall Statistics		10.768	5	.056

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	9.425	5	.093
	Block	9.425	5	.093
	Model	9.425	5	.093

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	58.925[a]	.094	.184

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Classification Table[a]

			Predicted		
			rip		Percentage Correct
	Observed		n	y	
Step 1	rip	n	83	2	97.6
		y	10	1	9.1
	Overall Percentage				87.5

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Gest	-1.238	1.030	1.446	1	.229	.290
	zscore	-1.357	1.542	.774	1	.379	.257
	fhb	-.074	.039	3.667	1	.055	.928
	BW	.008	.009	.740	1	.390	1.008
	P50	.116	.183	.406	1	.524	1.123
	Constant	26.836	20.681	1.684	1	.194	4.5E+11

a. Variable(s) entered on step 1: Gest, zscore, fhb, BW, P50.

Logistic Regression

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	96	98.0
	Missing Cases	2	2.0
	Total	98	100.0
Unselected Cases		0	.0
Total		98	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
n	0
y	1

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			var00001		Percentage Correct
			n	y	
Step 0	var00001	n	0	32	.0
		y	0	64	100.0
	Overall Percentage				66.7

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	.693	.217	10.250	1	.001	2.000

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	Gest	7.216	1	.007
		zscore	.414	1	.520
		fhb	1.155	1	.282
		BW	6.811	1	.009
		P50	3.945	1	.047
	Overall Statistics		10.328	5	.066

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	11.064	5	.050
	Block	11.064	5	.050
	Model	11.064	5	.050

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	111.147[a]	.109	.151

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Classification Table[a]

			Predicted		
			var00001		Percentage Correct
	Observed		n	y	
Step 1	var00001	n	8	24	25.0
		y	9	55	85.9
	Overall Percentage				65.6

a. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Gest	-.438	.701	.389	1	.533	.646
	zscore	-.272	1.052	.067	1	.796	.762
	fhb	-.030	.040	.577	1	.447	.970
	BW	.000	.006	.001	1	.977	1.000
	P50	.124	.132	.889	1	.346	1.132
	Constant	12.358	13.901	.790	1	.374	232913.1

a. Variable(s) entered on step 1: Gest, zscore, fhb, BW, P50.