Respiratory Support Of Newborn Infants In The Delivery Room and Neonatal Intensive Care

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MB BS FRCPCH FRACP

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Doctor of Medical Science

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ABSTRACT

Background

Many newborn infants have respiratory difficulties from birth. The newborn infant’s lung is vulnerable to injury from interventions provided in the delivery room (DR) and the neonatal intensive care unit (NICU). Some of the possible techniques to assess, stabilise and manage infants with respiratory difficulty whilst minimising harm have been explored in this thesis.

Aims

The aims of this thesis were to

1. investigate the clinical utility of pulse oximetry in the DR
2. document observations on pressures and tidal volumes from a respiratory function monitor in spontaneously breathing infants and those receiving assisted breaths
3. document difficulties encountered whilst intubating infants
4. investigate the effects of inspiratory times on the morbidity of ventilated infants in the NICU
5. Determine the utility of a spontaneous trial of breathing to predict successful extubation.

Methods and Subjects

1. Human studies of newborn infants born at or admitted to The Royal Women’s Hospital, Melbourne, including observational studies in the DR and NICU, and randomised controlled studies in the DR.
2. Bench top studies of simulated neonatal resuscitation using manual ventilation devices and face masks
Results

Major results from my studies of pulse oximetry include the following: 1) The technique of sensor application can affect the time to obtain data and the quality of data on oxygen saturations in the NICU and DR. 2) Newborn infants not receiving any respiratory support in the first five minutes after birth commonly have oxygen saturations much lower than those targeted in the NICU and that the values increase gradually with time. 3) Clinical evaluation of heart rate is unreliable and inaccurate, whilst pulse oximetry is accurate and precise in measuring infant heart rate compared with electrocardiography.

Major results from my studies of video recordings of neonatal resuscitation include the following: 1) Intubation is difficult and often unsuccessful. 2) It is feasible to measure tidal volumes in spontaneously breathing infants and those receiving assisted inflations. 3) Tidal volumes can be measured in infants with congenital diaphragmatic hernia receiving assisted ventilation in the DR.

Major results from my bench top studies of positive pressure ventilation include the following: 1) Using a round silicone mask, there are large leaks from masks, inflating pressures are a poor proxy for delivered tidal volumes but improved techniques of face mask application can be taught and retained by adult learners.

Major results from my studies in the NICU include the following: 1) Short (< 0.5 seconds) inspiratory times reduce the risk of air leak in infants with hyaline membrane disease. 2) A three minute trial of spontaneous breathing prior during endotracheal continuous positive airway pressure has high positive and negative predictive values for predicting extubation success.
Conclusion

Major conclusions arising from my work include the following: 1) Pulse oximetry in the DR can be used as an adjunct to clinical assessment to help determine the need for providing respiratory support with objectivity. 2) Lung injury may be avoided by monitoring tidal volumes in the DR, using short inspiratory times and improving rates of successful extubation.
DECLARATION

This is to certify that

i. this thesis comprises only my original work towards the Doctor of Medical Science except where indicated in the Preface

ii. due acknowledgement has been made in the text to all other material used

iii. the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

Camille Omar Farouk Kamlin
PREFACE

This thesis is a collection of published papers resulting from my efforts within the respiratory research group at the Royal Women’s Hospital. My contribution and the contributions of my collaborators are detailed in the individual descriptions of each study.

The work is the result of work carried out in the delivery rooms and neonatal intensive care unit of the Royal Women’s Hospital between 2003 and 2009.

During this time period, my research activities were conducted with my colleagues Dr Colm O’Donnell, Dr Arjan tePas, Ms Jennifer Dawson, Dr Georg Schmoelzer, Dr Liam O’Connell, Dr Fiona Wood, Dr Kevin Wheeler, Dr Louise Owen, Professor Peter Davis and Professor Colin Morley.

The collaborative work and resulting articles included in this thesis have also been included in higher degrees in which my colleagues were enrolled. The tables below and overleaf identify the studies and resultant publications that I have been involved with and data from which were included, at least in part, in the theses submitted for examination by my colleagues.

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This registration date for the DMedSci was July 2009. The dates of publication for each manuscript are detailed in the main text and in the individual papers collated in the appendix.
Relative contribution by Dr COF Kamlin to each of the published articles included in this thesis

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This thesis could not have been completed without the infectious energy and enthusiasm of the respiratory research team at the Royal Women’s Hospital. Initially led by Professor Colin Morley and latterly by Professor Peter Davis, I was helped along the way by the vision and wit of Dr Colm O’Donnell, the gentle questioning presence of Dr Arjan tePas and the organisational skills of Ms Jennifer Dawson. It was for the encouragement of the whole team and the above mentioned individuals collectively, that the work was finally completed.

Without the help and support of my family this thesis would not have come to fruition. My parents especially my father, Mo who supported my relocation to Melbourne to pursue my dream of becoming a researcher; I am deeply indebted to their lifelong support - they have been my greatest teachers. To my wife Maryam and our recent arrival, Humza – they have been a constant source of patience, love support and encouragement – thank you.

I would like to thank my supervisors Professors Peter Davis, Lex Doyle and Colin Morley for their mentorship and sharing their considerable combined clinical and research experiences with me; they are all true leaders and exceptional teachers.

Many thanks to the babies and their parents – I have and continue to appreciate the altruism shown by parents who provide consent for research on their newly born children during one of the most intense times of their lives. Without them this work would not have been possible.

Many thanks to the staff at the Royal Women’s Hospital, Melbourne for their support.

The studies presented in this thesis have been supported by a Program Grant from the National Health and Medical Research Council and a Postgraduate Scholarship from the Royal Women’s Hospital.
ABBREVIATIONS

BPD bronchopulmonary dysplasia
bpm beats per minute
CDH congenital diaphragmatic hernia
CI confidence interval
CNRG Cochrane Neonatal Review Group
CO₂ carbon dioxide
CPAP continuous positive airway pressure
DR delivery room
ECG electrocardiogram
ELBW Extremely Low Birth Weight
FiO₂ fraction of inspired oxygen
FRC functional residual capacity
H₂O water
Hb haemoglobin
HR heart rate
ILCOR International Liaison Committee on Resuscitation
IPPV intermittent positive pressure ventilation
IQR interquartile range
IT inspiratory time
min minutes
MV  mechanical ventilation
NICU  neonatal intensive care unit
NRP  neonatal resuscitation program
O₂  oxygen
PEEP  positive end expiratory pressure
PPV  positive pressure ventilation
PSANZ  Perinatal Society of Australia and New Zealand
RCT  randomised controlled trial
RR  relative risk
RWH  The Royal Women’s Hospital
SBT  spontaneous breathing trial
sec  seconds
SpO₂  peripheral oxygen saturation
STINT  stylet for intubation of newborn infants
VLBW  Very Low Birth Weight
V_T  tidal volume
V_Te  expiratory tidal volum
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CHAPTER 1. INTRODUCTION

1.1 AN INTRODUCTION TO THE WORK AND PAPERS PRESENTED IN THIS THESIS

There have been significant improvements in the provision of care provided to newborn term and preterm infants in the last five decades leading to dramatic improvements in the survival rates of very immature infants. These gains have been attributed to improved perinatal care, including the use of corticosteroids antenatally, better environments for caring for high risk pregnancies and newborn infants in regionalised perinatal centres, use of postnatal surfactant in respiratory distress syndrome, and the development of invasive and non-invasive forms of ventilator support.

However, the improvements in survival appear to have plateaued recently with an epidemiological survey showing minimal change (from 84% to 85%) in survival rates of very low birth weight infants between two epochs of data (1995-1997 and 1997-2002). These were collected from the National Institute of Child Health and Human Development Neonatal Research Network.

Rather disappointingly the rate of survival without common neonatal morbidities (including bronchopulmonary dysplasia, intraventricular haemorrhage and necrotising enterocolitis) between these two epochs was also static at 70% \(^1\). Improving the rates of these morbidities in preterm infants remains a high priority for researchers in perinatal medicine. Minimising lung injury from assisted ventilation is the major focus of this thesis.

This thesis presents 19 research papers in two themes. Firstly, investigating the respiratory management of infants in the delivery room (DR) and secondly, investigating aspects of ventilation in the neonatal intensive care unit (NICU).
An integral part of providing respiratory support is clinical evaluation. Guidelines on neonatal resuscitation (assessment, intervention and equipment needed) are contained in the advisory statement issued by the Neonatal Subcommittee of the International Liaison Committee on Resuscitation (ILCOR). ILCOR recommend that the newborn be assessed clinically in the DR, with particular emphasis placed on the assessment of the infants’ respiration, heart rate and colour. The studies in the DR in this thesis are focused on the feasibility and clinical utility of pulse oximetry as an adjunct to clinical assessment.

In this thesis I provide an introduction and summary for each of the research papers published. My role and that of my collaborators are detailed in the preface and in each chapter where the papers are discussed.

In keeping with the two themes, Chapter Two focuses on delivery room care of newly born infants transitioning from an intra-uterine to extra-uterine environment. These include studies investigating the utility of pulse oximetry in the DR and the NICU, a literature review on using pulse oximetry in the DR. Pulse oximetry can be used to monitor oxygen saturations (SpO₂) and heart rate (HR). A major observational study of mine was to define the normal range of oxygen saturations during the first minutes of life in infants not receiving any assistance with breathing or supplemental oxygen. The accuracy and precision of pulse oximetry in measuring infant heart rate is described as well as the accuracy of clinical estimation of heart rate against the gold standard, electrocardiography. One paper describes the changes in oxygen saturation and heart rate of infants < 30 weeks gestation resuscitated in two historical eras. In the first cohort the standard of care was to resuscitate infants, including those born very prematurely, with 100% oxygen. In the latter cohort, following a change in hospital guidelines, the initial gas for resuscitation was changed to air. The change in management was in response to accumulating evidence demonstrating the harmful effects of oxidative injury linked to oxygen administration in the delivery room. This study was a natural progression from the feasibility studies of pulse oximetry and was one of the first descriptions in the literature highlighting the utility of
pulse oximetry in titrating the inspired concentration of oxygen during neonatal resuscitation in the delivery room.

The provision of positive pressure inflations manually via a face mask and/or endotracheal tube are common interventions in the DR, especially for the extremely premature infant. The latter sections of Chapter One describe bench top studies designed to optimise techniques of face mask ventilation and using a respiratory function monitor to document the observations of spontaneous breathing patterns of premature infants and the tidal volumes used to ventilate a subgroup of infants extremely vulnerable to lung injury; infants with congenital diaphragmatic hernia. Finally, the difficulties encountered during intubation of infants in the DR and a case report on the limitations of exhaled carbon dioxide (CO₂) detectors in confirming correct placement of the endotracheal tube are described. In addition, the results from a recently completed randomised controlled trial (manuscript not published so not included in this thesis) comparing the use of a stylet with no stylet to improve rates of successful endotracheal intubation are briefly described.

Chapter Three describes studies of assisted ventilation in the NICU. A systematic review of long (> 0.5 secs) versus short (<0.5 secs) inspiratory times to ventilate newborn infants is presented using the established methods of the Cochrane Neonatal Review Group (CNRG). This is followed by two reports describing a spontaneous breathing trial (SBT) to assist clinicians on the optimal time to extubate very low birth weight infants. If infants are extubated too early this may lead to re-intubation, potentially causing laryngeal trauma and leading to a longer duration of ventilation. On the other hand, if physicians are reluctant to extubate and delay extubation, this may lead to nosocomial infections, laryngeal trauma and may contribute to the pathogenesis of bronchopulmonary dysplasia (BPD). Using an objective assessment of readiness for extubation such as the SBT or a combination of pulmonary function tests may be clinically important in reducing common neonatal morbidities. The clinical outcomes of using the SBT compared to a historical cohort are described in the second paper.
In Chapter Four, I draw conclusions from the papers presented, reflect on the nature of the studies, the results and discuss which direction future studies may be undertaken to minimise morbidity associated with providing assisted ventilation to the preterm infant.
The nature of the inter-relationships of the individual studies is shown in Figure 1.

Figure 1. Schematic of a hypothetical patient journey of a newly born infant; assessment of respiratory status and specific interventions provided in the DR and NICU to assist ventilation. Superscript numbers relate to papers presented in this thesis.
2.1 NEONATAL RESUSCITATION

“In relation to resuscitation in the delivery room, it is now clear that it is not only important to do the ‘right thing’, but to ask ourselves: Are we doing ‘things right?’”

Augusto Sola, Richard Deulofeut & Marta Rogido

During the first few minutes after birth, traditional assessment of the newly born infant is subjective and may be inaccurate. As a consequence the infant may be exposed to a number of potentially harmful interventions or therapies including a higher concentration of inspired oxygen than appropriate, unnecessary intubation and ventilation, inappropriately high or low tidal volumes, and a lack of a positive end expiratory pressure, all of which can cause lung injury.

Preterm birth is the main contributor to perinatal mortality and morbidity. The incidence of NICU admission and duration of hospital stay are inversely related to gestational age. There has been a great deal of research into the management of infants born preterm once they have been admitted to the NICU. However, the number of clinical studies investigating the management of preterm infants in the DR is limited. Large parts of international and national neonatal resuscitation guidelines have been based on historical dogma and consensus opinion, rather than research. It is possible that the lungs of the most immature infants are injured during the first few minutes after birth, well before they enter the NICU and this predisposes them to ongoing problems.

The studies of neonatal resuscitation presented in this thesis investigated and clarified some of the recommendations for assessment and treatment of infants in the DR. The aim was to improve the ways in which infants are stabilised and resuscitated.
**Figure 2.** Research trolley with respiratory function monitor, computer, pulse oximeter juxtaposed to a resuscitation trolley where a webcam is mounted. A flow sensor is placed in the circuit between the manual ventilating device (here self inflating bag) and proximal to the face mask.

In figure 2, the equipment used to conduct these studies is shown. The research trolley housing a desktop computer installed with dedicated respiratory data acquisition and analysis physiology software program, Spectra (Grove Medical, London, UK) is connected to a power supply. The pressures and gas flow in ventilator circuit are measured using the Florian (Acutronic Medical Systems, Zug, Switzerland) respiratory function monitor. It uses a flow sensor to detect gas flow and calculates the volume of gas passing through the sensor by integration of the flow signal. An oxygen analyser is also connected to the ventilator circuit to measure the inspired concentration of oxygen. The output from the Florian and analyser is transferred to the computer via an analog-digital converter. Digital data from the pulse oximeter and the webcam are
directly transferred to the computer and integrated into the Spectra software such that it is possible to record in real-time video images of a resuscitation with measurements of inspired oxygen, tidal volumes, pressures delivered to the infant with continuous monitoring of oxygen saturations and heart rate, coupled with webcam video footage.

2.2 STUDIES OF PULSE OXIMETRY

Pulse oximetry measures oxygen saturations (SpO₂) and heart rate (HR) continuously and non-invasively, without the need for calibration and correlates closely with arterial oxygen saturation.

These studies have investigated the use of a pulse oximeter on newly born infants in the DR.

Pulse oximetry, a technique for monitoring HR and SpO₂ is ubiquitous in modern emergency and intensive care settings. Pulse oximeters were introduced into neonatal care more than 30 years ago with the aim of avoiding periods of hypoxia and hyperoxia. They were not routinely used in the DR to assist clinicians in the assessment of the newly born infant at that time because of limitations of the technology.

Improvements in pulse oximetry technology enabled me to examine the feasibility of using oximetry immediately after birth and how this can monitor the changes in SpO₂ and HR measurements during the transition from fetal to neonatal life.

Pulse oximetry is based on two principles; firstly that oxy- and deoxyhaemoglobin differ in their relative absorption of two wavelengths of light, red and infra-red. Using a photo detector to measure the absorption of light emitted from a diode, the pulse oximeter determines the amount of oxyhaemoglobin in pulsatile or arterial blood and expresses it as a percentage of haemoglobin capable of binding oxygen, the oxygen saturation (SpO₂). The second principle is that only values from pulsatile flow are used in the final analyses and from this heart rate is determined.
In 2005, the Neonatal Subcommittee of the International Liaison Committee on Resuscitation noted the paucity of information on SpO$_2$ for healthy term and preterm infants during the first minutes of life$^2$. The optimal concentration of oxygen to use at neonatal resuscitation was unknown and it has been suggested that pulse oximetry may be used to titrate supplemental oxygen according to the infant’s SpO$_2$ $^4$$^5$. However before the optimal inspired oxygen concentration could be determined, more data were needed on the changes in SpO$_2$ as healthy infants undergo postnatal transition.

Pulse oximetry, having established itself as a tool for monitoring desaturation episodes and low SpO$_2$ values, is now being used to identify and limit the deleterious effects of hyperoxia. Concerns about even the briefest exposure to hyperoxia have been extended to the delivery room in recent years$^6$$^7$. Historically, the benefits of high concentrations of oxygen during neonatal resuscitation were unchallenged, as illustrated in the following quote:

“Oxygen is vital, not just useful. One breath of oxygen is worth five breaths of air in this situation.”

Ainley-Walker, 1975$^8$

Although well established in the NICU, the limiting factors for using pulse oximetry in the DR were its reliability and ability to get accurate readings in a time frame that would be clinically useful. Historically conventional pulse oximeters took several minutes to register any data and in the earliest clinical study evaluating a new generation technology Masimo oximeter, a median of 2.3 minutes from birth was reported for acquisition of data in infants less than 30 weeks’ gestation$^9$. With assessment of the infant and resuscitation interventions required in the first two minutes after birth, these delays suggested pulse oximetry would be impractical.

My first study, designed and conducted with Dr Colm O’Donnell, was to determine the optimal technique for placing the oximeter on an infant. We were interested in defining the fastest method for obtaining accurate data to reflect the rapid changes in cardio-
respiratory physiology during neonatal transition. Earlier publications documenting trends in \( \text{SpO}_2 \) in the newly born infant in the DR have highlighted the difficulties encountered in obtaining oximetry data using older conventional oximeters\(^{10}\).

Paper 1


**Role:** Patient enrolment, data collection and writing/editing the manuscript. This work has also been included in Dr CPF O'Donnell's PhD thesis, University of Melbourne 2006

This study was designed after a discussion with Professor Neil Finer at the annual conference of the Perinatal Society of Australia and New Zealand (PSANZ) in Sydney (2004) who described a method of placing the sensor first on the patient before connecting the sensor to the cable/oximeter\(^{11}\). Our findings confirm that the best method for obtaining data from the Masimo Radical pulse oximeter from stable infants in the nursery is having the oximeter switched on and applying and securing the sensor on the right limb before connecting the sensor to the oximeter cable\(^{11}\). We focused on reporting heart rate data as this parameter is of paramount importance for making decisions in the DR.

Role: Patient enrolment, data collection and assistance with writing manuscript. This work has also been included in Dr CPF O'Donnell's PhD thesis, University of Melbourne 2006

This study based on our observations from videotaping high risk resuscitations in the DR, confirms this technique of application was effective when used on infants in the DR\textsuperscript{12}. The reduction in the time for oximetry data acquisition was much greater than those obtained in the NICU and further confirmed the feasibility of using this technology in the DR. The time taken from sensor application to a digital display of data was considerably shorter (mean difference 36 seconds) if the sensor was applied to the infant first compared with connecting it to the oximeter then the infant. This difference was greater than that seen in paper one where the mean difference was only 10 seconds. This study used historical controls (an earlier method of application of the sensor) to compare with the method identified in paper one and it may be argued that the improvements seen were a result of continuing experience gained over time using this method. The algorithms used by the oximeters were identical and the differences may reflect the relative difficulties of applying a sensor in a wet mobile limb of a newly born infant compared with stable infants in the NICU, and may also reflect the changes and fluctuations of peripheral perfusion in a transitioning infant.

The major limitations of using early pulse oximeters were that ambient light, blood flow, movement artefact, decreased blood volume and venous stasis from excess pressure on the tissues from the sensor may interfere with its ability to provide accurate data. Following our findings from both these studies using a Masimo Radical oximeter, this method of applying pulse oximeters in the DR is now taught to medical and nursing personnel attending deliveries at the Royal Women’s Hospital and is being used in many other centres around the world (personal communications).
2.2.1 Oxygen Saturations In The Delivery Room

Paper 3


Role: Study design, patient enrolment, data collection and analysis, writing the manuscript. This work has also been included in Dr CPF O'Donnell's PhD thesis, University of Melbourne 2006.

In the delivery room, the newly born infant undergoes a series of complex physiological changes involving gradual aeration of the lungs, concurrent with circulatory changes. The changes in oxygenation accompanying aeration of the newly born lung in healthy newborn infants, although reported earlier, were not previously well documented and were limited by the technology available at the time. The objective of my study was to document trends in SpO\_2 immediately after birth using pulse oximetry in healthy newborn infants in the delivery room who did not require any medical intervention. Earlier reports described term infants only delivered vaginally\textsuperscript{13}, infants who were resuscitated or received supplemental oxygen\textsuperscript{10 14 15} or who were monitored with technology that has been superceded\textsuperscript{10 13 16 17}.

Harris and colleagues placed an oximeter probe around the tendo-achilles within 15 seconds of cord clamping in 76 term infants\textsuperscript{17}. All the mothers received supplemental oxygen and 44 infants were delivered by caesarean section. The mean SpO\_2 at one and seven minutes were 61% and 82% respectively. This was one of the first studies to show that post ductal oxygen saturations, measured by pulse oximetry, were low and that levels less than 82% occurred in normal infants in the first seven minutes after birth.

In 1987, House et al, published data from 100 infants weighing between 850g and 5,230g using two machines measuring functional (Nellcor) and fractional (Ohmeda)
saturations respectively\textsuperscript{15}. Functional saturation measures haemoglobin (Hb) available to carry oxygen whereas fractional saturation calculates a value by incorporating all Hb types namely fetal Hb, methaemoglobinaemia and carboxyhaemoglobinaemia. In the context of dysphaemoglobinaemia, a condition rarely seen in neonates, a normal functional saturation reading may mislead the clinicians. Sixty two infants were delivered by caesarean section, 42 under general anaesthesia. All infants had pre-ductal (right upper limb) measurements and the mean SpO\textsubscript{2} at 1 and 5 minutes was 59\% and 82\% respectively. These data are difficult to interpret as half the infants received supplemental oxygen. The authors said that having oximetry data was useful in objectively judging the adequacy of resuscitative efforts and identifying cyanosed infants. They suggested that pulse oximetry may be used as an adjunct to clinical assessment.

In 2002, Toth and colleagues studied 50 term infants and demonstrated from a combination of pre and post ductal readings that healthy term infants took more than 12-14 minutes to achieve saturations >95\%. They found that preductal values rose faster than post ductal readings\textsuperscript{13}. Their findings were in general agreement with those of Harris et al\textsuperscript{17}.

In the time between these early publications and my study of oxygen saturations in healthy infants immediately after birth, there were several publications from controlled studies and meta-analyses implicating increased mortality risk if term asphyxiated infants were initially resuscitated using 100\% oxygen compared with 21\%\textsuperscript{7,14,18,23}. In the Resair2 study\textsuperscript{10}, Rao and Ramji published data on SpO\textsubscript{2} values at 1, 5 and 10 minutes, as did Vento and colleagues for term and near term asphyxiated infants resuscitated with either air or 100\% oxygen\textsuperscript{10,23,24}. The striking result of these studies, especially the latter where the resuscitators were blinded to the inspired concentration of oxygen, was that the use of 21\% or 100\% oxygen for resuscitation had little effect on the change in SpO\textsubscript{2} in the first 10 minutes after birth. I felt it appropriate to use new generation technology to establish normal SpO\textsubscript{2} levels in the first few minutes of life. Having normative data would form the basis of any recommendations on titrating the inspired
oxygen concentration with blenders in the DR, thereby potentially avoiding unnecessary oxygen exposure and minimising harm from either hypoxia or hyperoxia. In order to be in a position to do so, “normoxia” in the first few minutes from birth had to be defined.

The study was conducted prospectively at the Royal Women’s Hospital and I attended 205 births of term and preterm infants and collected data from a Masimo Radical pulse oximeter placed on the right upper limb. After exclusions for either technical reasons or the need for resuscitation, 175 infants (121 term and 54 preterm) were recruited. I found the median SpO$_2$ at 1, 2, 3, 4 and 5 minutes to be 63%, 70%, 77%, 84% and 90% respectively. My findings suggested that immaturity and absence of labour slowed the rise in SpO$_2$ in healthy infants. Maternal analgesia and anaesthesia did not influence the rate of rise of SpO$_2$ after birth.

Before this study was undertaken, normal values of SpO$_2$ were not well described and the appropriate target ranges for sick term and preterm infants were also unknown. With the data I have published showing the median values and interquartile ranges in the form of box plots one could use the 25$^{th}$ quartile as a cut off for providing supplemental oxygen to those infants who fail to achieve SpO$_2$ at this level. Of note from these box plots are the long tails that demonstrate many healthy newborns have oximetry values less than 70%; the lower limit of industry calibration. Whilst the true values cannot be verified in the newly born subject by means of blood sampling, the trends are valuable in informing birth attendants that newly born infants’ SpO$_2$ take minutes to reach the “normal” adult range. Using this approach of potentially targeting an SpO$_2$ in a newly born infant, assumes that trends in SpO$_2$ of healthy infants also apply to sick preterm and term infants. More data on high risk deliveries are needed. However, I believe the study provides data on which to base informed decisions when attempting to avoid both hypoxia and hyperoxia, guiding clinicians on how much supplemental oxygen to use during transition after birth. Two recent randomised controlled studies were published assessing the feasibility of titrating oxygen concentrations during resuscitation of preterm infants in the DR. Compared with either
100% or 90% oxygen (high oxygen), attainment of target \( \text{SpO}_2 \) was more successful using 30% oxygen compared with 21% oxygen (low oxygen) as the initial admixture\(^{25, 26}\). These authors suggest that 30-40% oxygen may be the optimal concentration of gas at the start of a resuscitation of a very preterm infant. These studies, although not designed or powered to demonstrate safety or superiority of using a lower initial inspired oxygen concentration compared with 100% oxygen as recommended by national and international resuscitation guidelines, have highlighted the need for pulse oximeters, blenders and a source of compressed air in the DR to avoid hyperoxia from 100% oxygen in the first minutes after birth.

Paper 4


**Role:** Literature search, analysis and contributing author. Date from this paper have also been included in Ms Jennifer Dawson's PhD thesis, University of Melbourne 2010

This paper is a review of the use of pulse oximetry in the DR co-authored with Ms Jennifer Dawson with my involvement being assistance with the literature review, analyses and a contribution to the writing of the manuscript. The paper summarises data on the history and feasibility of pulse oximetry in the DR and compared and contrasted the reported \( \text{SpO}_2 \) values from each study. We conclude that studies need to be designed to show that pulse oximetry in the DR actually improves patient outcomes.
2.2.2 Heart Rate Assessment In The Delivery Room

Pulse oximetry, in addition to providing data on a patient’s SpO\textsubscript{2}, also displays pulse rate continuously. International resuscitation guidelines recommend providing respiratory assistance to newly born infants based on infant heart rate. Positive pressure ventilation is recommended if the heart rate (HR) falls below 100 bpm, and external cardiac massage if the heart rate is less than 60 bpm. Bradycardia is considered a sign of inadequate ventilation and the maintenance of a normal heart rate is an important sign indicating successful ventilation. Two methods of clinical assessment of heart rate are recommended by the neonatal resuscitation guidelines; auscultation of the heart and palpation of the umbilical cord.

Paper 5


Role: Study design, data collection and analysis, writing manuscript.

In this study we asked two health professionals attending the birth of infants delivered by elective caesarean section to assess the HR (count for 6 seconds and multiply by 10) by both auscultation and palpation of the umbilical pulse. Accuracy of both methods was compared against the gold standard, electrocardiography (ECG). I found that auscultation was more reliable (cord pulsations were not palpable in 20% of infants compared with auscultation which provided a HR in all infants), and that both methods underestimated the true HR by a range of 14 to 22 bpm. If the inaccuracies seen in our study were to occur with infants in the delivery room, we speculate that therapies based on clinical measurements of heart rate may be administered excessively.

Both clinical methods require the attention of one operator and can interrupt ventilation if the heart rate cannot be heard. Heart rate measured by a pulse oximeter or
electrographic monitor provides the resuscitation team with a continuous display and provides immediate feedback about the resuscitation. I sought to investigate the accuracy and precision of the Masimo Radical pulse oximeter against the gold standard, ECG.

Paper 6


Role: supervising medical student (JKS) project, patient recruitment, data collection and analysis, editing manuscript

Paper 7


Role: Study design, patient recruitment, data collection and analysis, drafting manuscript

Prior to evaluating the accuracy of the Masimo Radical pulse oximeter in monitoring HR in the DR, I first wanted to confirm the accuracy and precision of this oximeter in stable patients in the NICU. I found that the accuracy and precision of the Masimo were clinically acceptable and better in the NICU compared with the DR. This was not surprising as these infants were quiet and had less variability in the heart rate. Nevertheless, the results from this study were encouraging and highlighted a potential
role for using pulse oximetry in the DR where the infants were wet, cool, often more active, and where rapid changes in heart rate were anticipated. A scatter plot in this paper demonstrates the almost linear relationship between heart rate measured by pulse oximetry with electrocardiography. Importantly, for the true bradycardias (HR <100 bpm) measured by the ECG monitor, the oximeter displayed only 26 false negative data points from a total of 232 data points. In other words over 90% of readings were in agreement with ECG when HR was less than 100 bpm. This study showed that the pulse oximeter accurately identified low heart rates. I concluded that the pulse oximeter is a very useful adjunct to clinical evaluation of newly born infants at risk of resuscitation.

These two studies suggest that in the DR, pulse oximetry offers significant advantages over the intermittent and inaccurate clinical assessment of HR. In addition, a pulse oximeter probe is easier to apply than ECG leads which may damage the fragile skin of an extremely preterm infant. Studies evaluating the accuracy and precision of the pulse oximeter for monitoring heart rate during resuscitation are needed.
Observational Studies Of Pulse Oximetry In The Delivery Room – A Discussion

To summarise, these studies have shown that there is an optimum method of Masimo pulse oximeter sensor application that results in the fastest display of accurate data. We have shown that it is feasible to use pulse oximetry in the delivery room. The technique is acceptable to the resuscitation team and provides a continuous display of both oxygen saturations and pulse rate, allowing the effectiveness of the interventions to be assessed. I have shown it is possible to quantify the range of SpO\textsubscript{2} values seen in healthy newborn infants. This could be used as a reference range to titrate the inspired oxygen in the DR. Although the design of this study was similar to earlier reports; my study was one of the first to obtain preductal SpO\textsubscript{2} data using modern oximetry technology. However, whether these data can be used to determine the optimal SpO\textsubscript{2} targets in sick infants and those born extremely premature (where normative data are hard to gather) is yet to be determined.

Kopotic and Lindner examined the role of the Masimo pulse oximeter in making clinical decisions in a prospective uncontrolled observational study of extremely preterm (< 30 weeks’ gestational age) infants born at a single centre (University Hospital of Ulm). The resuscitation protocol at that hospital included a sustained controlled inflation of 20-30 cm H\textsubscript{2}O for 15 seconds delivered by a ventilator through a nasopharyngeal tube with the purpose of establishing sufficient pulmonary functional residual capacity. The initial resuscitation was conducted with 100% oxygen and the concentration was adjusted using a blender to maintain a target SpO\textsubscript{2} within a range of 80-92%. Criteria for intubation included bradycardia (<100 bpm or an FiO\textsubscript{2} > 0.6 at 15 minutes of age). Only 68% (15/22) of infants were studied – exclusions included major malformations (2), second twin (3) and technical difficulties in obtaining data (2). Of the 15 infants studied, the median gestational age and birth weight were 26 weeks and 880 g respectively. Clinical decisions were made on two infants (immediate intubation for apnoea and no intervention because of adequate spontaneous respiration). Of the remaining 13 infants, pulse oximetry was used as an adjunct to clinical assessment to guide interventions; 5 infants were commenced on CPAP because of a HR >100 bpm and an acceptable SpO\textsubscript{2} (>80%) and 8 were intubated for meeting the above criteria for

(20)
intubation and early rescue surfactant therapy. This was also one of the first studies to
describe weaning FiO₂ in the DR with the assistance of pulse oximetry from 1.0 to a
mean of 0.4. However, the small number of infants in this study, delays in acquiring
data (median 2.3 minutes for HR and SpO₂) and an apparent failure rate of acquiring
data of almost 10% were major limitations. Before a change in practice could be
recommended further evidence was needed to assess the feasibility and utility for the
routine use of pulse oximetry data in the DR.

In a later study, Finer et al, compared the use of a T piece manual ventilation device
providing positive end expiratory pressure (PEEP) with a self inflating bag (no PEEP).
Across five centres, 104 infants were randomised of which 69 had pulse oximeters to
monitor SpO₂ and HR. Decisions to intubate and treat with surfactant in the DR were
based on both SpO₂ and HR readings.

As a result of accumulating evidence from other centres and our own series of studies,
the use of pulse oximetry in the DR has become the standard of care at the Royal
Women's Hospital. Pulse oximeters, for neonatal use, are available in every birthing
area. Oximetry has been used to monitor patients in randomised controlled trials in the
DR providing useful data for the caregiver and researcher alike. I believe there is an
important role for pulse oximetry in the management of the transition of a high risk
infant, such as an extremely preterm infant. Pulse oximetry is essential for the safe
titration of supplemental oxygen to avoid hypoxia and hyperoxia. Compared with
clinical examination, pulse oximetry is convenient and accurate, and it has the
advantage of allowing the resuscitator to continue stabilising the infant whilst providing
continuous SpO₂ and heart rate data. This enables the clinician to determine the need
for and the effectiveness of resuscitative interventions without the interruptions
necessary to assess heart rate.

In the next study, our research group report our findings on newly born premature (<
30 weeks) infants' SpO₂ levels before and after a change in DR policy in administering
supplemental oxygen.
2.2.3 The Future – Titrating Oxygen In The Delivery Room Using Pulse Oximetry

Paper 8


Role: Data collection, analysis and writing the manuscript. This work has also been included in Ms Jennifer Dawson’s PhD thesis, University of Melbourne 2010

In this paper we reported our hospital’s experience after a change in clinical practice. The change in policy of beginning resuscitation with 100% to beginning with 21% oxygen was compared using downloaded oximetry data. For resuscitations starting with 21% oxygen, the new hospital guidelines stipulated that this could only be changed to 100% oxygen if the SpO\textsubscript{2} was <70% at 5 min of life, if the HR was <100 bpm after 60 s of ventilation or if chest compressions were initiated. Of the 106 preterm infants started with 21% oxygen, 97 (92%) infants were given supplemental oxygen at some point in the resuscitation. The median SpO\textsubscript{2} for these infants at 2 and 5 min of life was 31% and 54%, respectively, and increased to 81% at 6 min of life, once 100% oxygen was administered. Conversely, the 20 infants evaluated before the practice change (resuscitated with 100% oxygen) had median SpO\textsubscript{2} values of 84% and 94% at 2 and 5 min of life, respectively. The nine infants successfully resuscitated with 21% oxygen had median SpO\textsubscript{2} 87% at 5 min of life. This study showed that whilst preterm infants frequently require assistance with ventilation due to pulmonary immaturity, the need for supplemental oxygen is not universal. 100% oxygen was associated with inappropriately high SpO\textsubscript{2} values, whereas 21% was associated with oxygen levels for the first five minutes that sometimes did not increase above fetal levels. Although the long-term consequences of such differences in oxygenation are not known it appears likely that neither 21% oxygen nor 100% oxygen is optimal. This study, in addition to the
randomised trials of Wang et al\textsuperscript{25} and Escrig and colleagues\textsuperscript{26}, shows that a policy of titrating oxygen concentration levels to saturation targets in the first minutes of life is both sensible and practical. These randomised studies have used starting points of 21\%, 30\%, 90\% and 100\% oxygen and an alternative and superior starting point to the conventional (21\% or 100\%) remains to be identified. In both trials, most infants received supplemental oxygen with an average FiO\textsubscript{2} of 0.5 at 5 minutes. More normative data on the SpO\textsubscript{2} in the immediate transition period will help define SpO\textsubscript{2} targets which avoid the potential side effects of both hypoxia and hyperoxia.

Until we have more studies using oximetry to titrate oxygen in the DR, it remains unclear whether the pulse oximeter offers any benefit to these infants during immediate transition. It must be acknowledged that at the Royal Women’s Hospital, pulse oximetry in the DR has become the standard of care without rigorous evaluation from a randomised controlled study. It is appropriate to point out that the almost universal use of oximetry in the intensive and special cares nurseries of the world is also not based on randomised controlled trial data.

Whilst pulse oximetry technology has improved, with algorithms in the most modern devices compensating for low perfusion states, ambient light and motion of the limb, it remains to be determined whether pulse oximetry in the DR increases survival, minimises oxygen toxicity and/or the effects of “hypoxia”, reduces or increases unnecessary interventions or reduces the costs of care.
2.3 POSITIVE PRESSURE VENTILATION IN THE DELIVERY ROOM

2.3.1 Bench Top Manikin And Face Mask Studies

Providing adequate ventilation is a pillar to effective neonatal resuscitation. International consensus statements and agreed guidelines from national bodies recommend giving positive pressure ventilation (PPV) with manual devices using face masks as an interface. From recent international surveys, there appears to be a clear preference for round cushioned silicone masks. The technique for “bag and mask” ventilation is commonly taught using a manikin. Teaching and assessment of these techniques using manikins are a part of neonatal resuscitation courses. In these courses, participants are taught to assess adequacy of ventilation by assessing the degree of chest excursion. According to consensus statements, most newly born infants can be adequately ventilated with a bag and mask although there is very little evidence to support this. Of the few infants studied in the DR, tidal volumes conventionally thought to be adequate for tidal ventilation were rarely delivered via a face mask. However the tidal volumes and measurements of leak around the face mask have never been reported in very low birth weight and preterm infants.

Paper 9


Role: Assistance with bench top design and work. Writing and editing manuscript. This work has also been included in Dr CPF O'Donnell's PhD thesis, University of Melbourne 2006

In this study, Dr Colm O'Donnell and I modified a standard resuscitation manikin so that we could measure the flow of gas passing through the face mask and the resultant tidal volume delivered to the test lung during simulated neonatal resuscitation. In a leak free system, this
model showed that when a flow sensor (pneumotachometer) is placed between the manual ventilation device and face mask, the volume of gas returning to mask from the manikin is a good estimate of the tidal volume entering and leaving the lung. This model was set up with the aim of measuring tidal volume and leak measurements noninvasively. Such data should be useful in providing feedback to resuscitators using a manikin during training sessions with the goal of improving PPV techniques. In addition this system would permit us to make real time measurements of tidal volume during spontaneous breathing as infants undergo transition independently and judge when PPV is needed to provide respiratory support for preterm infants in the DR. Using a Florian respiratory function monitor (Acutronic Medical Systems, Ag, Switzerland), a computer running a dedicated neonatal physiology program, Spectra (Grove Medical, UK), and a video camera I was able to record respiratory physiology, download oximetry data, and video-record over 170 high risk resuscitations. The data collected from these series of observations on infant colour, agreement between observers on Apgar scoring, were published and form part of Dr Colm O'Donnell's PhD thesis. Physiological data obtained from recordings of spontaneously breathing infants and those infants with antenatally diagnosed congenital diaphragmatic hernia are also presented in the current thesis.

Paper 10


Paper 11


Role: Study design, data analyses and editing manuscript, for both articles
In this series of bench top studies, we report our results after subjecting medical and nursing staff to an evaluation of teaching methods and techniques of holding a face mask. In these two studies, my involvement was helping with the design, recruitment of participants and editing the manuscript.

In the first study, health professionals trained in neonatal resuscitation were asked to provide positive pressure ventilation to a modified Laerdal Resuscibabe™ manikin using a T-piece ventilator (Neopuff Infant Resuscitator™) with two masks in random order; a standard silicone round mask and a new Fisher and Paykel (FP) round mask. None of the participants had used the FP mask before. The techniques used to hold the mask and the expertise of participant were noted. We identified three common holds (stem, two point top and “OK” hold) and found the degree of leak on average to be greater than 50% irrespective of operator experience or technique. There was no difference in leak between the two masks.

In the next paper we identified the optimal hold for round face masks on a neonatal manikin and investigated which teaching methods led to the best retention of a taught practical skill. Rolling the face mask from the chin to cover the nose and mouth followed by two point top hold in conjunction with jaw lift was identified as the optimal technique by three experienced neonatologists. When participants were provided written instruction on technique followed by a demonstration, face mask leak was reduced by 24%. In both studies operators were unaware of the magnitude of the leak around the mask when providing PPV. This study has shown that neonatal staff can improve and retain a skill when combining written instruction with a demonstration. Such methods are already used in established neonatal life support courses but without studies looking at face mask technique in the delivery room.
2.3.2 Respiratory Function Monitoring In The Delivery Room


Role: Study design, patient recruitment, data collection and analysis, drafting and editing of manuscript

This study investigated respiratory physiological parameters recorded during the stabilisation of infants with antenatally diagnosed congenital diaphragmatic hernia (CDH). Mortality and morbidity rates from this condition are related to the degree of pulmonary hypoplasia, size of defect and the presence of associated anomalies. Recent improvements in survival have been attributed to the adoption of gentle ventilation strategies and encouraging spontaneous breathing in the NICU. However, recommendations on how to manage these infants in the DR are derived solely from expert opinions. Tidal volumes used to ventilate infants with CDH have not been described previously.

We studied 12 infants and witnessed spontaneous breathing in 11. Although most breathed at birth, only a small proportion of these breaths coincided with a manual inflation. We also noted larger tidal volumes with spontaneous breaths compared with mandatory inflations putting infants at risk of both volutrauma and insufficient aeration of these hypoplastic lungs. The compliance of the respiratory system is affected by the severity of pulmonary hypoplasia and fluid shifts during aeration of the lungs in the transitional period such that having a fixed peak inflating pressure and non synchronised inflations may put infants with CDH at risk of early ventilation-induced lung injury. Although this study is limited by the small number of infants, the paper highlights the feasibility of using a respiratory function monitor to titrate the PIP in order to avoid volutrauma when ventilating high risk infants in the DR.
In this context, I am, as part of the Neonatal Resuscitation Research Team, at the Royal Women’s Hospital, currently investigating the use of a respiratory function monitor in the DR. In a randomised controlled study, resuscitators have the monitor either visible or masked during PPV. If the monitor is visible, the clinician may use the information to minimise mask leak, adjust the PIP to achieve estimated optimal tidal volumes. The results from this RCT will be available in 2010. There is also a growing number of experts who recognise the limitations of using a fixed peak inflating pressure as a proxy for delivering an appropriate tidal volume during neonatal transition, with some also encouraging manufacturers to incorporate displays of tidal volume delivered on resuscitation trolleys.\textsuperscript{34}
2.4 SPONTANEOUS BREATHING PATTERNS OF NEWBORN INFANTS

Dr Arjan tePas and I have also used the flow sensor placed proximal to the face mask to monitor the spontaneous breathing patterns of preterm and term infants.

Paper 13

Spontaneous breathing patterns of very preterm infants treated with continuous positive airway pressure at birth. te Pas AB, Davis PG, Kamlin CO, Dawson J, O'Donnell CP, Morley CJ. Pediatr Res 2008; 64(3):281-285

Paper 14


Role: Patient recruitment, data collection and editing manuscript, for both articles. This work has also been included in Dr AB tePas' PhD thesis, University of Leiden 2009

These two studies explored the spontaneous breathing patterns of newly born infants in the DR. International guidelines on providing positive pressure support for infants in the DR are based on studies conducted more than 30 years ago on a small number of spontaneously breathing term infants. Both preterm and term infants encounter difficulties in transitioning but the mechanisms are likely to differ and as such the methods used to resuscitate term infants may not be applicable to preterm infants. Our aim was to describe the respiratory patterns of very premature infants breathing spontaneously to provide an insight on how they may aerate their lungs. This is not previously described and may clarify for the physician which infants are likely to
respond to nasal continuous positive airway pressure (CPAP) support in the DR and NICU.

Using physiological data recorded from the resuscitations of 12 very preterm infants there were 792 suitable breaths for analysis. Continuous positive airway pressure (CPAP) was provided to these infants using a Laerdal round mask attached to a Neopuff Infant Resuscitator. The inspiratory time with a mean duration of 0.36 seconds was similar in all analysed breaths. In contrast, there were distinct patterns to the expiratory flow waveforms; 1) an expiratory breath hold, 2) crying, 3) grunting, 4) panting and 5) normal flow. With the exception of normal flow and panting all the other patterns had a prolonged expiratory phase, presumably to defend lung volumes. Expiratory braking has been previously described as a mechanism to prevent loss of lung volume in term\(^{37, 38}\) and preterm infants\(^{39}\). The most frequently encountered pattern was crying and this occurred with equal frequency in term and preterm infants as described in the second study (paper 14). Preterm infants use significantly more expiratory breath holds than term infants. However, the number of infants studied and number of breaths analysed may bias the frequencies and patterns of breathing we observed. The application of a mask on the infant’s face may influence the breathing pattern by stimulating respiratory reflexes. Thus it would be wrong to assume that all preterm infants have similar breathing patterns. Further research is needed to see if recognising the prevalence and frequency of expiratory braking can guide clinicians on how best to support the infant in the DR. This may involve increasing CPAP pressures, synchronising manual inflations with spontaneous breaths or anticipating the need to intubate the infant.

In summary these studies on PPV have included bench top studies evaluating face mask technique, focusing on measurements of leak around the face mask to assess efficacy of ventilation. These findings will inform trainers and give encouragement to the organisers of neonatal resuscitation programs that such skills can be taught and retained over a period of time. The human studies have been observational. Using face masks, I have recorded the tidal volumes generated during different patterns of

(30)
spontaneous breathing including the first descriptions of crying as a means of defending lung volumes in the DR. These observations need confirmation in a larger sample size of infants and may assist clinicians in determining the optimal method of providing support in the first minutes after birth.
2.5 ENDOTRACHEAL INTUBATION

Endotracheal intubation of infants is a mandatory competence skill for paediatric trainees in the UK, Australia and North America. There are fewer opportunities for trainees to acquire this skill in the DR and we sought to document the number and duration of attempts, success rates and adverse effects during endotracheal intubation in the DR. In addition, the success rates of more experienced operators (consultant neonatologists) have not been reported before.

Paper 15


Role: Study design, patient recruitment, data collection and analysis, editing manuscript. This work has also been included in Dr CPF O'Donnell's PhD thesis, University of Melbourne 2006

In this study we identified all infants where intubation was attempted and captured on a video recording in the DR. All infants had pulse oximetry data and many of the infants had pulmonary mechanics measured during PPV using the Florian respiratory function monitor (Acutronic, Zug, Switzerland). A time limit on the duration of attempts is not enforced at the Royal Women’s Hospital. Intubation was attempted a total of 60 times in 31 infants. Success rates for residents, fellows and consultants were 24%, 78% and 86% respectively. The average duration of attempts was 38, 36 and 28 seconds for residents, fellows and consultants respectively. A quarter of the successful intubations took longer than 30 seconds and infant deterioration (as measured by oximetry) was more common when HR and SpO2 were low before the attempt.

With the difficulties encountered by paediatric trainees intubating infants in the DR, as reflected by the poor success rates, I was interested in improving the methods used to train physicians. International guidelines state the use of an introducer (or stylet) as
being optional to assist with neonatal intubation. A stylet offers extra rigidity which may facilitate the passage of the endotracheal tube into the laryngeal inlet. There is no evidence to demonstrate safety or efficacy of the stylet in neonatal orotracheal intubation.

I designed a randomised controlled trial comparing the use of a stylet with no stylet for orotracheal intubation (STINT study) of infants in the DR and NICU. The study was recently completed after 302 intubations. Operators were trainees (residents or fellows) and intubations were randomised only if an endotracheal tube was required for ventilatory support. Residents performed 76% of intubation attempts and the overall success rate was 55%, much higher than we observed beforehand. This may reflect the ongoing training provided before and during the study. We found that overall success rates were not improved by the use of a stylet, irrespective of grade of trainee, age or size of infant, or use of premedication. In keeping with earlier observations, the durations of attempts were rarely within the time suggested by NRP. However, the stylet appears to be safe. The results of the STINT study will be published in 2010.

Paper 16


**Role:** Direct patient involvement, literature search and writing manuscript.

End tidal carbon dioxide detectors are increasingly used for verification of correct endotracheal placement. Semi-quantitative colorimetric end tidal carbon dioxide (CO₂) detectors such as the PediCap™ are user friendly, correctly identifying exhaled CO₂ within 5 manual inflations. In this study, we report a previously unrecognised cause of false negative reading from such detectors. An extremely preterm infant remained
apnoeic and bradycardic after mask PPV and what was thought to be successful intubation by an experienced neonatologist (CJM). Inflating pressures were increased on the Neopuff Infant Resuscitator but the PediCap™ did not show any change in colour. The infant was re-intubated, but in spite of the inflating pressures being increased further, there was no change in the PediCap™ colour until after five very high (unrecorded pressure) inflations from a self-inflating bag with the pop off valve occluded. We concluded that in some very preterm infants with very stiff lungs or airway obstruction, high inflating pressures are needed to initiate alveolar ventilation and until then, there will be no ventilation and hence no exhaled CO₂. Finer and colleagues have also reported the utility of using the PediCap™ to improve face mask ventilation with lack of colour change alerting the resuscitator to adjust mask position or perform airway opening manoeuvres to correct for obstruction⁴².
CHAPTER 3. STUDIES IN THE NEONATAL INTENSIVE CARE UNIT

3.1 TIME CYCLED PRESSURE LIMITED VENTILATION

Paper 17


**Role:** Literature search, extracted and performed meta-analysis of the data, wrote the report

Infants are commonly intubated for respiratory failure and / or surfactant therapy. Once ventilated, physicians choose a mode of ventilation, and set an inspiratory time, peak inflating pressure, positive end expiratory pressure (PEEP) and rate. One of my first projects as a research fellow at the Royal Women’s Hospital was to write a systematic review for the Cochrane Neonatal Review Group (CNRG) comparing long inspiratory (>0.5 seconds) times with short (< 0.5 seconds) inspiratory times. The CNRG is a voluntary group of medical, nursing and allied health professionals who perform systematic reviews of the literature to identify risks and benefits of medical interventions. I wrote the protocol for the review and performed this systematic review with help from Professor Peter Davis. Data from studies identified by our search strategy were analysed using a standardised software program (Review Manager) in accordance with established methods of the CNRG. Although the only eligible studies were found in the pre-antenatal corticosteroid and pre-surfactant eras and before modern ventilation modes such as volume targeting and synchronised ventilation were available, my review showed that a long inspiratory time was associated with an increased risk of developing air leaks. Most of the infants studied had respiratory distress syndrome with poorly compliant lungs and short time constants. A long inflation time during square wave ventilation increased the mean airway pressure applied, facilitating alveolar expansion leading to improved oxygenation. In resource-
limited settings where both antenatal corticosteroids and postnatal surfactant are not readily available to mothers and infants, this review provides data on how clinicians may reduce the risk of air leak. Whilst these results may not be applicable to infants being cared for in resource rich settings with advanced ventilators, for the most commonly used modes (assist control or synchronised intermittent mandatory ventilation), the clinician is still required to set the inflation time. A longer inflation time may be reasonable for infants with pathophysiology associated with long time constants such meconium aspiration syndrome and those infants with normal lungs and ventilated for surgery or sepsis. No studies have been performed to evaluate inflation times during mechanical ventilation of these patients. In conclusion, given the increased rates of air leak (Relative Risk 1.56) with 95% confidence interval (1.25, 1.94), and death (RR 1.26 (1.00, 1.59), infants with poorly compliant lungs should be ventilated with a short (<0.5 seconds) inflation time.
3.2 WEANING INFANTS FROM MECHANICAL VENTILATION IN THE NICU

The lung as an organ of gas exchange is reliant on a pump (rib cage, respiratory muscles and central controller). Respiratory failure due to the inadequacy of the gas exchanger (lung) can commonly be distinguished from failure of the pump. Whilst the physiological criteria to intubate and initiate mechanical ventilation may vary slightly between clinicians and centres, it is often the severity of an infant's parenchymal lung disease and the maturity of its ventilatory pump that determines the duration of such support. The adverse effects of prolonged endotracheal intubation include bacterial colonisation, sepsis, tracheal trauma and bronchopulmonary dysplasia\textsuperscript{13-44}

Weaning is the process of reducing the support given by the ventilator to the infant. Quicker weaning may reduce the risk of infants acquiring the adverse effects listed above, but premature extubation may precipitate ventilator pump failure, especially in the extremely low birth weight infant\textsuperscript{45}. It has been suggested that applying continuous positive airway pressure (CPAP) following extubation preserves functional residual capacity of the lung by reducing alveolar or lobar atelectasis and/or retained secretions or central apnoea\textsuperscript{46}. However, up to 40\% of extremely low birth weight infants (<1000g) infants fail their first extubation attempt when weaned onto nasal CPAP\textsuperscript{47}.

Weaning infants from mechanical ventilation can be challenging and is perceived to be as much of an art (which comes with increasing clinical experience) than science\textsuperscript{48}. Several studies have explored the utility of using predictive indices based on different physiologic parameters of the respiratory system (pulmonary mechanics and function tests) as an adjunct to clinical decision making\textsuperscript{49-54}. However unlike adult studies, these studies remain an investigative tool as threshold values that can differentiate between success and failure of extubation have not evolved. In an attempt to objectify extubation decision making I described a spontaneous breathing trial (SBT) during endotracheal CPAP.

Role: Study design, patient enrolment, data collection and analysis, writing manuscript

In this study, once the clinicians had made a decision to extubate an infant, physiological recordings (tidal and minute volumes, SpO$_2$ and HR) were made during three minutes of spontaneous breathing while still intubated. Infants who were able to maintain their SpO$_2$ >85% and HR >100 bpm were judged to have a successful (or pass) SBT. The test was found to be highly accurate in predicting extubation success and also identified infants for whom extubation was most likely to fail (a high negative predictive value). Compared with earlier described tests/indices, the SBT is very simple, does not require specialised equipment, is not time consuming, and is a pragmatic assessment of an infant's respiratory drive. Although the SBT was associated with high positive predictive and negative predictive values for successful extubation, it was only used in infants who were going to be extubated. Nevertheless, as a result of these encouraging findings, the SBT was incorporated into clinical practice at the Royal Women's Hospital as an adjunct to clinical decision making. Therefore, the next study I conducted was designed to audit this change in policy on the timing and success of extubation of very low birth weight infants.
Paper 19


Role: Study design, patient enrolment, data collection and analysis, writing manuscript

With this study, I collected data prospectively, over 13 months, from ventilated infants in whom the SBT was performed with a view to extubating the infant based on a successful SBT. These data were compared with a cohort of VLBW infants admitted to our hospital in 2002, two years before the SBT became standard clinical practice. I found that in comparison to the era when clinicians decided to extubate on clinical grounds alone, the SBT did not lead to prolonged duration of mechanical ventilation or a higher rate of extubation failure. There was no reduction in the rate of BPD when the SBT was used. The study also highlighted changes in ventilator duration during the two time periods thereby limiting the strength of recommendation for using the SBT. Whether the use of the SBT may reduce the duration of all respiratory support, BPD and length of stay can only be addressed in the context of a large multicenter randomised controlled study.
CHAPTER 4. CONCLUSIONS AND FUTURE DIRECTIONS

“Since intubation and positive pressure were first recommended by Flagg in North America in 1928 and by Blaikley and Gibberd at Guy's Hospital in 1935, a pattern of resuscitation has evolved based on extrapolation and assumption rather than clinical measurement. There can be few areas of medicine where the potential benefit is so great but which have been subjected to so little evaluation.”

A.D Milner 1991

In spite of a growing number of researchers performing studies of neonatal resuscitation, the paucity of evidence for the equipment and techniques used allows almost every aspect of current practice to be a potential area of investigation.

Stabilisation of preterm infants in the delivery room is a very common activity for neonatologists around the world. Research to determine the best practice for vulnerable infants in the first few minutes after birth should remain a high priority.

Basic scientists can assist clinical researchers by testing specific hypotheses on animal models thereby guiding future human trials. An example of this has been the recent completion of a randomised trial by our group in the delivery room comparing a T-Piece Resuscitator versus a self inflating bag. This study was designed after Probyn and colleagues in a newborn lamb model suggested that a PEEP of 8 cmH₂O improved oxygenation by maintaining end expiratory lung volumes in the creation of a functional residual capacity. The International Liaison Committee on Resuscitation does not recommend the routine use of PEEP for newly born infants in need of PPV.

The optimal tidal volumes, use and length of sustained inflations and standard inflations and rate of ventilation to provide infants receiving PPV during transition to establish FRC are not known. There is increasing acceptance that not all newly born
preterm infants require resuscitation but rather stabilisation during transition. A focus of future research should examine how best to provide support to a spontaneously breathing infant. I am confident that with close collaboration with basic scientists, physiologists and clinicians the evidence will be generated on how best to stabilise the most immature infants in the DR including data on long term (neurodevelopmental) outcomes.

I am currently comparing two interfaces in a randomised controlled trial; a single nasal tube with a Laerdal silicone round mask. Recruitment is in progress and, at the time of writing, 25 infants have been randomised.

Other technologies which I would like to investigate further include the use of neonatal ventilators for providing support in the DR, use of humidified warm gases of varying flow rates, caring for infants on a standard resuscitation trolley with a modified incubator (Giraffe) that can be used to transport infants to the NICU. I would also like to follow up the STINT study by investigating the utility of a video laryngoscope for intubation of infants by paediatric trainees. I would like to use pulse oximetry in the DR to titrate the inspired oxygen to set targets determined from centile charts our resuscitation group have developed. Future clinical trials are required to address how well the use of this technology in the DR improves clinical care and outcomes including the safer and more effective use of oxygen. Such clinical studies are about to start and can only succeed with collaborative support from other centres.

In the NICU, modifications to currently used weaning modes in combination with the three minute SBT may increase the number of infants successfully extubated. To show a reduction in respiratory morbidity (duration of all forms of assisted ventilation) and length of stay, large trials with multicentre study collaboration will be necessary. For example a randomised trial to assess the effectiveness of a spontaneous breathing trial in reducing the extubation failure rate from 25% to 15%, with 80% power and an alpha error of 0.05 would require a total recruitment of 500 very low birth weight infants in both the intervention and control arms.
Summary

In summary, in this thesis I have investigated the ventilatory support neonatologists provide to infants in the DR and in the NICU. The evidence base which we draw upon to refine our techniques is continuing to grow. My personal priorities are to

1. Determine the best interface to use to provide manual PPV in the DR.
2. Determine the need for and duration of sustained inflation to assist in the aeration of a lung in an infant in the DR who has either never breathed or is struggling to breathe.
3. Use a blender and an oximeter with data on the changes in SpO₂ during neonatal transition, I would like to titrate FiO₂ according to SpO₂ targets judged by the best available evidence in both preterm and term infants in the DR. These studies should incorporate long term follow up before a protocol can be deemed safe and effective.
4. Improve clinical training in neonatal resuscitation, in particular neonatal intubation.
5. Examine weaning protocols and further refinements of the SBT which reflect diaphragmatic dysfunction as a cause of extubation failure.
REFERENCES


weeks’ gestation with air or 100% oxygen. *Arch Dis Child Fetal Neonatal Ed* 2009; 94(2):F87-91.


APPENDIX

Compilation of publications resulting from the body of work submitted for DMED SCI
Obtaining pulse oximetry data in neonates: a randomised crossover study of sensor application techniques
C P F O’Donnell, C O F Kamlin, P G Davis, C J Morley

Pulse oximetry may be useful during neonatal resuscitation. A randomised crossover study was performed to determine the most efficient method of applying the sensor. Applying it to the infant before connecting to the oximeter resulted in quickest acquisition of accurate heart rate. This technique should be preferred during resuscitation.

The need for and response to neonatal resuscitation is determined clinically.1 Auscultation and palpation of heart rate (HR) are subjective, intermittent, and of questionable accuracy.2-4 Assessment of colour (a proxy for oxygen saturation, \(\text{SpO}_2\)) is subjective. Pulse oximetry, routinely used in intensive care, gives continuous, accurate measures of HR and \(\text{SpO}_2\). Although not routinely used during neonatal resuscitation, it is potentially useful in determining HR. Also, although debate continues about whether air or oxygen should be used, a role for oximetry in titrating oxygen concentrations during resuscitation has been suggested.5 Difficulties in obtaining oximetry data during resuscitation have been reported.6 Newer generation oximeters are more reliable than others in intensive care.

After patient sensor application, a delay in obtaining data ensues while the oximeter recognises the pulse waveform and calculates HR and \(\text{SpO}_2\); both values are then displayed simultaneously. During resuscitation, HR is of primary importance in determining need for intervention—for example, intubation, chest compressions. Thus prompt acquisition of accurate HR is ideal. The sensor can be applied in a number of ways. We sought to determine which resulted in the quickest display of accurate HR.

METHODS
We conducted a randomised crossover study of infants in our intensive and special care nurseries. All were stable and monitored with oximetry and electrocardiography (ECG). Measurements were taken in the supine position via a sensor applied to the right wrist (infants <1500 g) or palm (≥1500 g). The sensor was secured using Coban wrap (3M Health Care, St Paul, Minnesota, USA).

We studied the Masimo Radical (Masimo Corporation, Irvine, California, USA) oximeter (fig 1, A), using an averaging interval of two seconds with maximal sensitivity. This oximeter has a patient cable (B) to which the sensor (C) is attached. The manufacturers recommend connecting the sensor to the cable and to the patient before switching the oximeter on. We wished to avoid the delay incurred switching on the machine. Thus, with the machine switched on, we applied the LNOP Neo-L sensor to each infant on three occasions using the following methods:

1. Sensor connected to cable, then applied to infant;  
2. Sensor connected to cable, applied to investigator’s finger, then to infant;  
3. Sensor applied to infant, then connected to cable.

The investigator applying the sensor and the order of these methods were allocated randomly. The times taken to apply the sensor, to display data, and to display accurate HR—that is, that matched the ECG—were recorded with a stopwatch. The number of accurate first displayed HRs for each method was noted. Data were analysed using SPSS. Means were compared using paired t tests.

RESULTS
We studied 40 babies of various weight (mean (SD) 1659 (991) g), gestational age (29 (4.8) weeks) and postnatal age (22 (31) days).

The time taken to apply the sensor using method 3 compared with method 1 was slightly longer but this was not significant (table 1). The time taken by the oximeter to display the correct HR using method 3 was significantly shorter (mean (SD) difference 10 (20) seconds, \(p = 0.004\)) (table 1). Combining these time periods gave the time for accurate HR data to be displayed. The quickest method was 3, followed by 2, then 1. The difference between methods 1 and 3 was significant (mean (SD) difference 7 (20) seconds, \(p = 0.047\)); the difference between methods 2 and 3 was not. The proportion of accurate first displayed HRs was 80%, 28%, and 93% for methods 1, 2, and 3 respectively. Thus method 3 gave the quickest, most accurate HR data.

Abbreviations: ECG, electrocardiography; HR, heart rate; \(\text{SpO}_2\), oxygen saturation
**DISCUSSION**

This study does not specifically address the question of which method of sensor application most rapidly obtains an accurate SpO₂. We believe that HR monitoring is more important than SpO₂ in effectively guiding neonatal resuscitation; thus it was the focus of this study.

An oximeter switched on with the sensor connected will immediately try to calculate data. If the sensor is not applied to a person, the oximeter tries to interpret environmental stimuli and may generate artificial signal. This delays the display of data when the sensor is subsequently applied to an infant (method 1). When the sensor is first applied to an investigator (method 2), data are acquired more quickly. Data from the investigator are initially averaged, however, and this often leads to the display of an erroneous initial HR. The subsequent delay in displaying the correct HR is variable (mean (SD) 9 (7) seconds here). The display of incorrect HR during resuscitation is concerning as it may prompt inappropriate intervention or inaction; thus, in the absence of an ECG to assess accuracy of the oximeter HR, we advise against using method 2.

A seven second difference in obtaining data, although not large, may be clinically important during resuscitation. This study assessed stable infants who were not being resuscitated. It is possible that it may take longer to apply a sensor and obtain data during delivery room resuscitation. The algorithms used by the oximeter, however, do not change. The differences observed may thus become greater and more clinically important.

We assessed the Masimo Radical oximeter; this study should be repeated for other oximeters to confirm the superiority of this method of sensor application.

**CONCLUSION**

In intensive and special care settings, applying the sensor to the right hand or wrist before connection to the pulse oximeter results in quicker acquisition of accurate HR data in infants compared with other techniques. This method of application should be preferred during resuscitation.

**ACKNOWLEDGEMENTS**

We thank Professor Neil Finer whose original observation prompted this study. CPF O'D is supported in part by the Royal Women's Hospital Postgraduate Degree Scholarship. PGD is supported by an NHMRC Practitioner Fellowship.

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**REFERENCES**


FEASIBILITY OF AND DELAY IN OBTAINING PULSE OXIMETRY DURING NEONATAL RESUSCITATION

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Application of the sensor to newly born infants before connection to a pulse oximeter increases the reliability and speed with which data are displayed. Data are available in most infants within 90 seconds of birth. Oximetry may be useful in guiding interventions during resuscitation. (J Pediatr 2005;147:698-9)

Consensus statements advise that newborn’s need for and response to resuscitation be determined clinically.1 Sparked by debate on the optimal oxygen concentration for neonatal resuscitation,2,3 a role for pulse oximetry has been suggested.4,5 It is not known how often or how quickly pulse oximetry data may be obtained from newborns anticipated to need resuscitation. Since January 2004, we have made observational studies of delivery room (DR) resuscitation at our hospital with endorsement from our Research and Ethics Committee. Techniques used included pulse oximetry. From January to March 2004, we connected the sensor to the oximeter before applying the sensor to the infant. In April 2004, we found that applying the sensor to infants in our intensive and special care nurseries before connecting it to the oximeter yielded an accurate heart rate more quickly.6 We thus changed to this method of sensor application in the DR at this time.

The objectives of the present study were to evaluate newborns anticipated to need resuscitation in the DR to determine (1) how often pulse oximetry data are obtained, (2) the success rates and delays in obtaining data associated with different methods of sensor application, and (3) the success rates in very low birth weight (VLBW) infants (< 1500 g) compared with heavier infants.

METHODS

When available, 1 of 2 investigators attended deliveries and made detailed recordings. A digital video camera was mounted above the resuscitation cot to acquire a clear view of the infant. An L-NOP Neo-L sensor of a Masimo Radical (Masimo Corporation, Irvine, Calif) pulse oximeter was placed on the infant’s right hand or wrist as soon as practicable after delivery and secured with Coban wrap (3M Healthcare, St. Paul, Minn). The oximeter was set to acquire data with maximal sensitivity and to average data over 2 seconds.

To assess how often and how quickly data were obtained, we reviewed all videos and identified those in which pulse oximetry was used. The infant’s gestational age and birth weight, as well as the method of sensor application, were noted. The times taken to apply the sensor, for the oximeter to display data, and from birth to data display were recorded. These time intervals were compared for cohorts before and after the change in the method of sensor application and for VLBW and heavier infants. Data were analyzed using SPSS software (SPSS Inc., Chicago, Ill).

RESULTS

Pulse oximetry was used in 115 of the 122 videos obtained. The mean (standard deviation, range) gestational age and birth weight of these infants were 32 (6, 23 to 42) weeks and 1830 (1064, 495 to 4930) g, respectively. Of the 115 infants, 60 (52%) were VLBW. The maximal respiratory support given to these infants was as follows: none in 29, supplemental oxygen in 9, mask continuous positive airway pressure (CPAP) or
positive-pressure ventilation (PPV) in 19, nasal CPAP in 28, and endotracheal PPV in 30. A Neopuff (Fisher and Paykel, New Zealand) delivering 100% oxygen was used for respiratory support. No infant received cardiac massage or medications, and all survived beyond the DR.

Oximetry data were obtained from 105 of the 115 (91%) infants. Data were always recorded if the sensor was applied to the infant before it was connected to the oximeter (see Table). The time from sensor application to data display (ie, how long it took the machine to interpret signals) was substantially shorter if the sensor was applied to the infant first (see Table). Applying the sensor to the infant first produced a data display by 92 seconds of life in 90% of infants. Data were always obtained from VLBW infants irrespective of how the sensor was applied. Response time was not affected by the use of respiratory support.

### DISCUSSION

The findings of the present study demonstrate that it is possible to obtain pulse oximetry data during neonatal resuscitation. When an oximeter is switched on with a sensor connected, it immediately attempts to generate data. If the sensor is not applied to an infant, then it will interpret environmental “noise” and generate an artifactual signal. When the sensor is then applied, the oximeter averages this artifactual signal with the true signal detected from the infant, leading to a delay in data display. This problem can be avoided by first applying the sensor to the infant, because then the oximeter immediately interprets signals from the infant. The superior reliability and speed in data display with this method of sensor application suggest that it should always be used in the DR.

We did not prospectively compare sensor application techniques in a randomized fashion; thus it is possible that the improvement associated with the change in method of sensor application was due to experience gained in the use of pulse oximetry over time. If this were true, then it should be reflected in an improvement in the time taken to apply the sensor, the human element in obtaining these data. This time did not differ appreciably between the 2 periods, however.

Data were always obtained from VLBW infants irrespective of how the sensor was applied. We believe that this reflects the difficulties sometimes encountered in opposing the emitter and detector windows of the sensor around the wrist or palm of larger infants.

We investigated only a single pulse oximeter, and do not know whether our results are applicable to other models. Also, although we have demonstrated the feasibility of pulse oximetry in the DR, the effectiveness of this technique remains unproven. There is currently insufficient information to define normal and abnormal oxygen saturation levels in the first few minutes of life, or the values that should be targeted for infants resuscitated in the DR. Until these values are defined, we believe that pulse oximetry during neonatal resuscitation is most useful in providing a continuous, objective display of heart rate.

We thank Professor Neil Finer, whose observation prompted this study.

### REFERENCES

OBJECTIVE

Because the optimal concentration of oxygen (FiO₂) required for stabilization of the newly born infant has not been established, the FiO₂ is commonly adjusted according to the infant’s oxygen saturation (SpO₂). We aimed to determine the range of pre-ductal SpO₂ in the first minutes of life in healthy newborn infants.

STUDY DESIGN

We applied an oximetry sensor to the infant’s right palm or wrist of term and preterm deliveries immediately after birth. Infants who received any resuscitation or supplemental oxygen were excluded. SpO₂ was recorded at 60-second intervals for at least 5 minutes and until the SpO₂ was >90%.

RESULTS

A total of 205 deliveries were monitored; 30 infants were excluded from the study. SpO₂ readings were obtained within 60 seconds of age from 92 of 175 infants (53%). The median (interquartile range) SpO₂ at 1 minute was 63% (53%-68%). There was a gradual rise in SpO₂ with time, with a median SpO₂ at 5 minutes of 90% (79%-91%).

CONCLUSION

Many newborns have an SpO₂ <90% during the first 5 minutes of life. This should be considered when choosing SpO₂ targets for infants treated with supplemental oxygen in the delivery room. (J Pediatr 2006;148:585-9)

The transition from fetus to newborn is a complex physiological process. There is growing interest in the use of pulse oximetry to assess the condition of infants immediately after birth. The subcommittee of the International Liaison Committee on Resuscitation have noted the paucity of information on oxygen saturations (SpO₂) of healthy term and preterm infants during the first minutes of life. They have called for more data before making “evidence-based recommendations on the meaning of pulse oximetry measurements in sick babies at birth.” Previous reports describe term infants delivered vaginally, infants who were resuscitated or received supplemental oxygen (O₂), or who were monitored with technology that is now outdated. The aim of our study was to describe the SpO₂ of healthy newly born preterm and term infants using newer generation pulse oximetry.

METHODS

We conducted a prospective observational study of SpO₂ in newly born infants between May 2004 and April 2005. The study was endorsed by the Human Research and Ethics Committees of the Royal Women’s Hospital, Melbourne, Australia. Verbal parental consent for the study was obtained before delivery. The investigating team was not involved in the care of the infants in the delivery room.

Infants ≥31 weeks gestation who were not anticipated to need resuscitation were studied when an investigator was available to attend their delivery with a pulse oximeter. A stopwatch was started when the cord was clamped. All infants were dried and wrapped with warmed towels. Infants were excluded when they received supplemental O₂ or assisted ventilation, or when we were unable to obtain oximetry data. We used the Masimo Radical (Masimo Corporation, Irvine, Calif) set to detect a signal with maximal sensitivity and averaged it over 2 seconds. The sensor was applied either to the palm of the right hand or to the right wrist to obtain preductal SpO₂ and secured with Coban wrap (3M Health Care, St. Paul Minn). The sensor was then connected to the oximeter, because this leads to the fastest acquisition of data. The times taken to apply the sensor and to display data were noted. SpO₂ was continuously monitored, with values recorded at 60-second intervals from birth for at least 5 minutes and until the SpO₂ was >90%.

<table>
<thead>
<tr>
<th>FiO₂</th>
<th>Concentration of oxygen</th>
</tr>
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<tbody>
<tr>
<td>IQR</td>
<td>Interquartile ranges</td>
</tr>
<tr>
<td>nCPAP</td>
<td>Nasal continuous positive pressure</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Oxygen saturation</td>
</tr>
</tbody>
</table>

See editorial, p 569 and related article, p 590
Where necessary, the sensor remained attached after the infant was given to the parents. The time taken to achieve SpO₂ > 75% and > 90% was noted.

The presence and the quality of the oximetry data were verified by the investigator using the display; thus the caregivers were not masked to the oximetry data. Apgar scores were assigned by the pediatricians or midwives caring for the babies at delivery. The type of delivery, maternal analgesia and method of anesthesia were recorded.

Statistical Analysis

Data are presented as means (SD) and analyzed with 2-tailed t tests when normally distributed. Median and interquartile ranges (IQR) are provided and analyzed with non-parametric tests (2-tailed Mann–Whitney U test) when the distribution of the variable was skewed. Multivariate regression analysis was used to analyze potential confounding variables contributing to the primary end point (time taken for SpO₂ > 90%). A P value of < .05 was considered to be statistically significant. Data were analyzed with SPSS software for Windows (SPSS, Chicago, Ill), version 11.5.

RESULTS

A total of 205 deliveries were attended. Figure 1 shows the characteristics of infants who were excluded (n = 30) and infants who were included (n = 175). Technical difficulties obtaining data occurred in 12 term infants, none of whom was resuscitated or given supplemental oxygen. Patient characteristics and the time taken for sensor application and signal detection are shown in Table I.

The median SpO₂ values (IQR) at 1, 2, 3, 4, and 5 minutes were 63% (53%-68%; n = 92), 70% (58%-78%; n = 164), 76% (64%-87%; n = 172), 81% (71%-91%; n = 174), 90% (79%-91%; n = 175), respectively (Figure 2). For the whole group, the mean (SD) time to achieve SpO₂ > 90% was 5.8 (3.2) minutes (range, 1.3–20.2 minutes). With multivariate regression, the most important determinants of the time to reach SpO₂ > 90% were gestational age and presence of labor ($R^2 = 0.09$ and 0.15; $P < .001$ [analysis of variance]).

Of the 175 infants studied, 63 were admitted to the nursery. Eleven infants (all ≤ 34 weeks) were given supplemental oxygen in the nursery; 8 of these infants were also treated with nasal continuous positive pressure (nCPAP). No infants were intubated or treated for persistent pulmonary hypertension of the newborn. The median (IQR) age at which supplemental oxygen and/or nCPAP was started and duration of therapy were 0.5 (0.3–0.6) hours and 55 (4–74) hours, respectively. The median (IQR) SpO₂ of these 11 infants at 5 minutes in the delivery room was 78% (69%-82%) compared with a median of 91% (81%-91%) in the 164 infants who were not given supplemental oxygen or nCPAP ($P = .001$).

Effect of Mode of Delivery, Prematurity, Analgesia, and Anesthetic on SpO₂

The effect of mode of delivery and gestational age on SpO₂ at 5 minutes are shown as medians (IQR) in Figure 3A and B. The median SpO₂ at 5 minutes was lower after elective cesarean section than after spontaneous vaginal delivery and vacuum extraction (Mann Whitney U test; $P = .013$ and .001, respectively). The median SpO₂ at 5 minutes was significantly lower in preterm infants than term infants ($P < .001$). The time for each group to reach a SpO₂ > 75% and > 90% are shown in Table II. We found no association between SpO₂ and maternal analgesia or anesthesia (Figure 3C and D).

DISCUSSION

The appropriate FiO₂ to use for neonatal resuscitation is subject to debate. It has been suggested that the FiO₂ could be determined by monitoring infants’ SpO₂ by using pulse oximetry. Surveys suggest that many clinicians are already using this approach. There is limited information about infants’ SpO₂ in the minutes after birth. Toth et al measured the pre- and post-ductal SpO₂ of 50 vaginally born healthy term infants with an older generation pulse oximeter. They found SpO₂ at 2 minutes of age as low as 34%, and that these infants took 12 to 14 minutes to reach SpO₂ values ≥ 95%, and that pre-ductal SpO₂ rose more quickly than the post-ductal value. Rao et al used an older oximeter to study the

Figure 1. Profile of infants enrolled.
pre-ductal SpO\textsubscript{2} of 95 infants who were asphyxiated and resuscitated and 30 control infants who were not resuscitated.\textsuperscript{6,6} The resuscitated infants were part of the Resair 2 study,\textsuperscript{17} a multicenter trial comparing air and 100% O\textsubscript{2} for resuscitation of infants with birth weight $>999$ g who had bradycardia and poor respiratory effort at birth. The maturity and mode of delivery of the infants in Rao’s study were not clear.\textsuperscript{18} Data were not obtained from 12 (10%) infants, and it took longer to obtain data from infants who were asphyxiated. In the control group, SpO\textsubscript{2} values as low as 43% were found at 1 minute of age and rose to a mean of 90% by 15 minutes. In infants who were asphyxiated, SpO\textsubscript{2} rose more slowly; however, the results were not reported according to the FiO\textsubscript{2} used, thus the effect of using 21% or 100% oxygen was not clear. Saugstad et al subsequently reported the SpO\textsubscript{2} values from 229 of the 591 infants recruited to Resair 2.\textsuperscript{19} They reported that median SpO\textsubscript{2} rose from about 65% at 1 minute to 90% at 5 minutes and rose equally quickly whether infants were resuscitated with air or 100% oxygen. The oximeter(s) used, site of sensor application, gestational age of the infants, and modes of delivery were not reported.

Using the Masimo SET technology, we measured the SpO\textsubscript{2} of newly born infants who were not resuscitated or given supplemental oxygen. In addition, we examined the effect of preterm delivery, mode of delivery, presence of labor, and maternal analgesia and anesthesia. We did not obtain data from 12 (6%) infants. All were active term babies. We believe that, as has been described, poor alignment of the light emitting diode and detector was responsible.\textsuperscript{20} The SpO\textsubscript{2} in our infants closely resemble those found by others in non-resuscitated term infants\textsuperscript{21,22} and mildly compromised infants resuscitated with either air or 100% oxygen.\textsuperscript{23,24}

Our findings suggest that gestation and the presence of labor have an effect on SpO\textsubscript{2} in the minutes after birth. Like other authors,\textsuperscript{5} we did not demonstrate an effect of either maternal analgesia or anesthesia on SpO\textsubscript{2}. Oximetry data can be obtained within 1 to 2 minutes after birth and gives a continuous, non-invasive measure of SpO\textsubscript{2} and heart rate. Other authors have had difficulties obtaining data with older pulse oximeters\textsuperscript{26}; this may be because of low peripheral perfusion or motion artifact. The Masimo Radical pulse oximeter, uses the same principles as conventional pulse oximetry, but also has signal processing algorithms to reduce “noise” (eg, poor signal in low perfusion states or patient motion).

With a 2-second averaging interval, the oximeter tracked the rapidly changing SpO\textsubscript{2} during postnatal adaptation. We obtained data faster (median, 1.2 versus 2.3 minutes) than an earlier study assessing this oximeter in preterm infants during resuscitation.\textsuperscript{27} This difference may be caused by different methods of sensor application, because we have also obtained data quickly at high-risk deliveries (median, 68 seconds).\textsuperscript{28}

In summary, we have demonstrated the feasibility of
Figure 3. Box plots showing the median, quartiles, range, (1.5 times the quartile on that side) outliers, and extreme values, of SpO2 at 5 minutes from birth by: A, mode of delivery; B, maturity; C, maternal analgesia; and D, maternal anaesthesia. SVD, Spontaneous vaginal delivery; Vacuum, a vaginal delivery assisted by vacuum extraction (Ventouse) delivery; Forceps, a vaginal delivery assisted by forceps; EM.CS, emergency cesarean section delivery; Elect.CS, elective cesarean section delivery; Preterm, delivery before 37 weeks gestation; Term, delivery from 37 weeks gestation; N2O, nitrous oxide analgesia; Opioid, analgesia with narcotic; Spinal, delivery with spinal anesthetic; General, delivery with general anesthetic.

Table II. Comparison of times in minutes (median [IQR]) for infants to attain SpO2 >75% and >90% by mode of delivery, presence of labor and by gestational age (<37 wk versus ≥37 wk)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Time to reach an SpO2 &gt;75% (min)</th>
<th>p*</th>
<th>Time to reach an SpO2 &gt;90% (minutes)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal birth</td>
<td>68</td>
<td>2.4 (1.6–3.7)</td>
<td>.006</td>
<td>4.0 (3.0–6.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Abdominal birth</td>
<td>107</td>
<td>3.5 (2.0–4.8)</td>
<td></td>
<td>5.9 (3.9–7.9)</td>
<td></td>
</tr>
<tr>
<td>Labor</td>
<td>137</td>
<td>2.7 (1.7–4.2)</td>
<td>.004</td>
<td>4.7 (3.2–6.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Not in labor</td>
<td>38</td>
<td>4.1 (2.6–5.4)</td>
<td></td>
<td>7.0 (5.1–10.0)</td>
<td></td>
</tr>
<tr>
<td>GA ≥37 weeks</td>
<td>121</td>
<td>2.5 (1.6–4.0)</td>
<td>&lt;.001</td>
<td>4.7 (3.3–6.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GA &lt;37 weeks</td>
<td>54</td>
<td>4.2 (2.7–6.1)</td>
<td></td>
<td>6.5 (4.9–9.8)</td>
<td></td>
</tr>
</tbody>
</table>

GA, Gestational age.

*Mann Whitney U test used to compare data.
pulse oximetry in the delivery room. We have shown that infants >31 weeks gestation who receive neither assisted ventilation nor supplemental oxygen have a gradual rise in SpO2 during the first 5 minutes of life. This period is slower in premature infants and those born by cesarean section without labor. We did not demonstrate an effect of maternal analgesia or anesthe sia. The range of SpO2 during this time extends well below those currently targeted in our neonatal intensive care units. Despite the similarities in the range of SpO2 seen in our infants and those of term infants who were asphyxiated studied by other groups, caution must be exercised before assuming that the range of SpO2 seen in healthy infants applies to sick preterm and term infants.10,23,29

REFERENCES
Pulse oximetry and newborn infants

Pulse oximetry for monitoring infants in the delivery room: a review
J A Dawson, P G Davis, C P F O’Donnell, C O F Kamlin, C J Morley

During the first few minutes of life, oxygen saturation (saturation by pulse oximetry, \(\text{SpO}_2\)) increases from intrapartum levels of 30–40%. In algorithms for neonatal resuscitation published by the International Liaison Committee for Resuscitation,2 European Resuscitation Council2 and Australian Resuscitation Council,3 clinical assessment of an infant’s colour (a measure of oxygenation) and heart rate are used as major action points. However, studies have shown that clinical assessment of colour during neonatal transition is unreliable.2 O’Donnell et al4 showed that the \(\text{SpO}_2\) at which observers perceived infants to be pink varied widely, ranging from 10% to 100%. Assessing colour is difficult and therefore is a poor proxy for the oxygenation during the first few minutes of life.

Kattwinkel5 suggested pulse oximetry may help achieve normoxia in the delivery room. The American Heart Association6 suggests that “administration of a variable concentration of oxygen guided by pulse oximetry may improve the ability to achieve normoxia more quickly”. Although “normoxia” and an acceptable time to achieve this during neonatal transition have not been defined, Leone and Finer6 advocate a target “\(\text{SpO}_2\) of 85 to 90% from three minutes after birth for all infants except in special circumstances”—for example, diaphragmatic hernia or cyanotic congenital heart disease. International surveys show that oximetry is increasingly used during neonatal resuscitation.10 11

To date, there are no evidence-based guidelines for using oximeter to measure an infant’s \(\text{SpO}_2\) and to guide interventions during neonatal transition after birth. We reviewed the literature to evaluate the evidence on the use of \(\text{SpO}_2\) measurements immediately after birth.

How does pulse oximetry work?
Pulse oximetry measures \(\text{SpO}_2\) continuously and non-invasively, without the need for calibration, and correlates closely with arterial oxygen saturation.12 Pulse oximetry is based on the red and infrared light-absorption characteristics of oxygenated and deoxygenated haemoglobin. A sensor is placed around a hand or foot and two light-emitting diodes send red and infrared light through to a photodetector on the other side. The changes in absorption during the arterial pulsatile flow and non-pulsatile component of the signal are analysed. \(\text{SpO}_2\) is estimated from the transmission of light through the pulsatile tissue bed. With each heartbeat, there is a surge of arterial blood that momentarily increases arterial blood volume. This results in more light absorption during surges. As peaks occur with each heartbeat, heart rate can also be measured.

Can \(\text{SpO}_2\) be successfully measured in the minutes after birth?
Seven studies reported between 20% and 100% success in obtaining \(\text{SpO}_2\) measurements by 1 min after birth.16–18 21–23 By 5 min, the success rate improved to between 63% and 100%.15 16 17–19 21–23 The most common reason for failing to obtain a measurement was motion artefact18 19–22 23; others were the presence of vernix,20 low perfusion,20 oedema,11 high ambient light,16–18 large infants,24 cracked and wrinkled skin,15 or acrocyanosis.15 Artefacts occurred less often in more recent studies where Masimo signal extraction technology (SET) was used.15 21

Where should the oximeter sensor be applied?
In early studies, investigators placed the sensor over the right Achilles tendon,16–18 the forefoot19 or midfoot.20 21 Later studies found that measurements were obtained fastest from the right hand,15 probably owing to better perfusion, higher blood pressure and oxygenation in preductal vessels.21–23 Postdural readings were significantly higher than postdural readings soon after birth (p<0.05).15 22 By 17 min after birth, there was no longer a significant difference between preductal and postdural measurements (p>0.05).15 21 22

How quickly can an \(\text{SpO}_2\) reading be obtained?
A sensor can be applied to a baby within 15–20 s of birth,15–17 with the first data obtained at about 50 s after birth.15 16 21 No studies obtained \(\text{SpO}_2\) data on most infants before 1 min after birth.15 21 22 23 When the Masimo sensor and monitor were used, readings were obtained faster than when the sensor was applied to the infant before connecting it to the oximeter.15

How do \(\text{SpO}_2\) readings change in the first few minutes after birth?
Some studies report the range of \(\text{SpO}_2\) at 1, 5 or 10 min (tables 1 and 2); others report the time taken to reach a predetermined \(\text{SpO}_2\) (table 3). These studies show increases in \(\text{SpO}_2\) from about 60% at 1 min, but the levels vary widely, with some infants taking >10 min to exceed 90%. Therefore, it may not be appropriate to identify specific \(\text{SpO}_2\) levels at certain times after birth, which can be used as a trigger to alter an infant’s treatment.

Does the type of oximeter alter the \(\text{SpO}_2\) results?
Early oximeters had motion artefact.16–18 21–23 This has been improved in newer oximeters.15 21 To determine whether the newer oximeters were more reliable than earlier models in the delivery room, Kopotic compared the Masimo SET to the Nellcor Oxismart, with sensors placed on each foot, in 15 newborns of <30 weeks’ gestation.25 The Masimo SET provided data for 350 of 362 (96%) min, and the Oxismart provided data for 212 of 362 min (59%; p=0.0014).25 Leone and Finer6 recommended that oximeters used during neonatal resuscitation should have “minimal averaging time for the \(\text{SpO}_2\) values coupled with maximum sensitivity”. The combination of these features allows rapid detection of changes in \(\text{SpO}_2\) and improved \(\text{SpO}_2\) measurement during periods of low perfusion.24

Does the type of delivery alter the \(\text{SpO}_2\) after birth?
Harris et al19 found, using an early generation oximeter, that \(\text{SpO}_2\) was much lower in 44 term elective caesarean-section deliveries, when compared with 32 term infants delivered vaginally. The mean (standard error, SEM) \(\text{SpO}_2\) at 1 min was 46% (3%) in the caesarean group and 61% (5%) in the vaginal delivery group (p<0.05), but by 5 min there was no significant difference. They postulated that the difference was due to the increased amount of lung fluid after caesarean section. Kamlin et al30 found that 107 term infants born by elective caesarean section took on average 2 min longer to reach an \(\text{SpO}_2\) >90% than 68 infants born by spontaneous vaginal delivery. Rabi et al31 found a similar difference in a cohort of 115 infants. In infants of >34 weeks’ gestation, the median (interquartile range, IQR) for vaginal births at 5 min was 87% (80–95%) and that for caesarean delivery was 81% (75–83%).31 In contrast, others found no
significant difference in SpO₂ measurements in infants delivered vaginally or by caesarean section, regardless of the presence or type of anaesthesia.¹⁴ ¹⁶

DOES RESUSCITATION WITH AIR OR OXYGEN AFFECT SpO₂ AFTER BIRTH?

Table 4 summarises trials comparing SpO₂ measurements at 1, 3 and 5 min in infants with asphyxia randomised to receive air or 100% oxygen during resuscitation. In the Resair 2 study, which enrolled infants weighing >999 g with apnoea and bradycardia at birth, there were no significant differences in time to reach an SpO₂ of 75%. The median (95% confidence interval) time to reach an SpO₂ of 90% was significantly higher in infants not receiving resuscitation, the time to reach an SpO₂ >90% between the two groups with asphyxia. The striking result of these studies is that resuscitating with air or 100% oxygen had little effect on the change in SpO₂ in the first 10 min after birth.

DOES ALTITUDE AFFECT SpO₂ AFTER BIRTH?

Gonzales and Salirrosas¹⁴ showed that SpO₂ was significantly higher in infants born at sea level (Lima 150 m) than in infants born at a higher altitude (Cerro de Pasco 4340 m) from 1 min to 24 h after birth (p<0.01).

DOES GESTATION AFFECT SpO₂?

There are two reports of SpO₂ measurements in premature infants after birth. In Koptoc and Lindner’s¹² study of 15 infants born at 24–29 weeks’ gestation, the SpO₂ was >80% by 4.4 (1.9–40) min (median (range)). In the study by Kamlin et al.¹⁵ on infants not receiving resuscitation, the time to reach an SpO₂ >90% was significantly longer in 54 preterm infants at 6.5 (4.9–9.8) min (median (IQR)) than in 121 term infants at 4.7 (3.3–6.4) min (median (IQR)) (p<0.001). Other studies including premature infants did not report SpO₂ for different gestational ages.¹⁴ ²²

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**Table 1** Observational studies measuring SpO₂ in the first few minutes of life in the delivery room where no infant received supplemental oxygen

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestation (weeks)</th>
<th>Type of oximeter</th>
<th>Sensor location</th>
<th>SpO₂ (%)</th>
<th>1 min</th>
<th>5 min</th>
<th>10 min</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris et al.</td>
<td>&gt;37</td>
<td>Nellcor N-100</td>
<td>Postductal</td>
<td>32</td>
<td>61 (5)</td>
<td>NA</td>
<td>NA</td>
<td>Vaginal delivery</td>
</tr>
<tr>
<td>Teoh et al.</td>
<td>&gt;35</td>
<td>Nellcor N-300</td>
<td>Postductal</td>
<td>44</td>
<td>46 (3)</td>
<td>NA</td>
<td>NA</td>
<td>C/S</td>
</tr>
<tr>
<td>Reis et al.</td>
<td>&gt;35</td>
<td>Masimo Radical</td>
<td>Postductal</td>
<td>50</td>
<td>78 (42–97)</td>
<td>89 (62–99)</td>
<td>92 (65–99)</td>
<td>2 vacuum extraction, 48 spontaneous deliveries, no significant differences in time to reach an SpO₂ of 75% in the group receiving oxygen (p = 0.27). In this study, the resuscitators were aware of the gas used, whereas Vento et al.¹⁵ blinded resuscitators to the type of gas used to resuscitate infants with asphyxia. He found no significant difference in time to reach an SpO₂ &gt;90% between the two groups with asphyxia. The striking result of these studies is that resuscitating with air or 100% oxygen had little effect on the change in SpO₂ in the first 10 min after birth.</td>
</tr>
<tr>
<td>Kamlin et al.</td>
<td>&gt;31</td>
<td>Masimo Radical</td>
<td>Postductal</td>
<td>175</td>
<td>63 (53–68)</td>
<td>90 (79–91)</td>
<td>NA</td>
<td>51 preterm infants in the first few minutes of life in the delivery room where no infant received supplemental oxygen.¹⁴ ¹⁶</td>
</tr>
<tr>
<td>Gonzalez and Rabi</td>
<td>&gt;37</td>
<td>Nellcor N-100</td>
<td>Postductal</td>
<td>37</td>
<td>42 (2)</td>
<td>NA</td>
<td>NA</td>
<td>Cerro de Pasco (4340 m)</td>
</tr>
<tr>
<td>Gungor et al.</td>
<td>&gt;37</td>
<td>Masimo Radical</td>
<td>Postductal</td>
<td>45</td>
<td>87 (80–95)</td>
<td>NA</td>
<td>NA</td>
<td>No suction</td>
</tr>
<tr>
<td>Gungor et al.</td>
<td>&gt;37</td>
<td>Air-Shields</td>
<td>Postductal</td>
<td>70</td>
<td>69 (70–78)</td>
<td>90 (2)</td>
<td>NA</td>
<td>42% saturation by pulse oximetry.¹⁴ ¹⁶</td>
</tr>
<tr>
<td>Harris et al.</td>
<td>&gt;37</td>
<td>Nellcor N-100</td>
<td>Postductal</td>
<td>32</td>
<td>61 (5)</td>
<td>NA</td>
<td>NA</td>
<td>Vaginal delivery</td>
</tr>
</tbody>
</table>

**Table 2** Observational studies measuring SpO₂ in the first few minutes of life in the delivery room where some infants were treated with 100% oxygen

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestation</th>
<th>Type of oximeter</th>
<th>Sensor location</th>
<th>Resuscitation</th>
<th>n</th>
<th>SpO₂ %</th>
<th>1 min</th>
<th>5 min</th>
<th>10 min</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sordak et al.</td>
<td>Term and preterm</td>
<td>Nellcor N-100</td>
<td>Postductal</td>
<td>No infant received oxygen</td>
<td>25</td>
<td>63 (5)</td>
<td>89 (5)</td>
<td>NA</td>
<td>NA</td>
<td>Vaginal delivery</td>
</tr>
<tr>
<td>Huey et al.</td>
<td>Term and preterm</td>
<td>Nellcor N-100 or Ohmeda Brix 3700</td>
<td>Postductal</td>
<td>19/28 vaginal deliveries and 53/62 C/S received 100% oxygen</td>
<td>100</td>
<td>58 (22)</td>
<td>82 (14)</td>
<td>89 (6)</td>
<td>69 (5)</td>
<td>C/S and oxygen</td>
</tr>
<tr>
<td>Deckard et al.</td>
<td>&gt;37 weeks</td>
<td>Nellcor N-100</td>
<td>Postductal</td>
<td>No infant received oxygen</td>
<td>28</td>
<td>78 (9)</td>
<td>84 (14)</td>
<td>90 (5)</td>
<td>C/S and vaginal deliveries</td>
<td></td>
</tr>
<tr>
<td>Porter et al.</td>
<td>Term</td>
<td>Ohmeda Brix 3700</td>
<td>Postductal</td>
<td>100% oxygen if poor respiratory effort, central cyanosis, or heart rate &lt;100. Number receiving oxygen not indicated</td>
<td>96</td>
<td>77 (11)</td>
<td>84 (7)</td>
<td>89 (6)</td>
<td>C/S and vaginal deliveries</td>
<td></td>
</tr>
<tr>
<td>Rao et al.</td>
<td>Term and preterm</td>
<td>Novametrix 515A</td>
<td>Postductal</td>
<td>Infants with asphyxia randomised to receive air or 100% oxygen during resuscitation. Not reported</td>
<td>95</td>
<td>45 (20)</td>
<td>84 (14)</td>
<td>91 (10)</td>
<td>63 vaginal deliveries</td>
<td></td>
</tr>
<tr>
<td>Doh et al.</td>
<td>Not reported</td>
<td>Ohmeda Brix 3700</td>
<td>Postductal</td>
<td>7 infants received 100% supplemental oxygen</td>
<td>100</td>
<td>72 (6)</td>
<td>83 (6)</td>
<td>91 (5)</td>
<td>63 vaginal deliveries</td>
<td></td>
</tr>
</tbody>
</table>

C/S, caesarean section; IQR, interquartile range; NA, not available; SpO₂, saturation by pulse oximetry.

<sup>1</sup>Mean (SEM); *mean (range); †median (IQR); ‡mean (SD).
CAN OXIMETRY BE USED TO MEASURE THE EFFECT OF RESUSCITATION PRACTICES?

Oximetry has been used to measure the effect of clinical interventions, such as oropharyngeal suction and endotracheal intubation during neonatal transition. Three controlled studies show that suctioning does seem to have a negative effect on oxygenation.21,22 O'Donnell et al.23 measured the effects of attempted endotracheal intubation on SpO2 in the delivery room, and SpO2 often fell during intubation attempts.

COULD OXIMETRY BE USED IN THE DELIVERY ROOM TO IMPROVE OUTCOMES?

There are two studies that evaluate the use of oximetry to guide interventions during neonatal transition. Deckardt et al.24 used SpO2 readings at 5 min after birth to determine whether infants should receive continuous positive airway pressure (CPAP) with a mask and 100% oxygen. CPAP was used only if the SpO2 was <80% at 5 min and stopped once the SpO2 reached 90%. Kopot and Lindner25 studied 50 infants at risk for respiratory failure; 25 infants were managed without oximetry and compared with 25 managed with oximetry. Infants managed with oximetry were less likely to be admitted to the special care nursery (32% vs 52%; p = 0.04). They also observed the effect of oximetry during resuscitation in 15 infants of <30 weeks’ gestation. Initial respiratory care was based on the infant’s clinical state and oximetry measurements. Oxygen was started at 100% and adjusted to achieve an SpO2 between 80% and 92%.26 The authors claim that by using pulse oximetry they were able to reduce the fraction of inspired oxygen (FiO2) from 1.0 to, on average, 0.40. The studies by Kopot and Deckardt, although non-blind and non-randomised, suggest that oximetry can improve short-term outcomes—for example, admission to nursery, the use of oxygen or CPAP. We could find no reports on whether the use of SpO2 measurements immediately after birth alters long-term outcomes.

CONCLUSION

Before oximetry is advocated for routine use in the delivery room, more research is needed to define normoxia, and more importantly, how to interpret and apply SpO2 readings to clinical practice to improve short-term and long-term outcomes. Arch Dis Child Fetal Neonatal Ed 2007;92:F4–F7. doi: 10.1136/adc.2006.102749

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### Table 3: Time (in min) to reach specified SpO2 levels after birth

<table>
<thead>
<tr>
<th>Study</th>
<th>Gestation (weeks)</th>
<th>Type of oximeter</th>
<th>Sensor locations</th>
<th>Resuscitation</th>
<th>SpO2</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toff et al</td>
<td>&gt;35</td>
<td>Nellcor N 3000</td>
<td>Preductal, Postductal</td>
<td>50</td>
<td>No infant received oxygen</td>
<td>NA</td>
</tr>
<tr>
<td>Kamlin et al</td>
<td>&gt;31</td>
<td>Masimo Radical</td>
<td>Preductal</td>
<td>175</td>
<td>No infant received oxygen</td>
<td>NA</td>
</tr>
<tr>
<td>Kopot and Lindner</td>
<td>&lt; 30</td>
<td>Masimo Radical</td>
<td>Preductal</td>
<td>15</td>
<td>Infants initially received 100% oxygen then oxygen adjusted according to SpO2 measurements</td>
<td>NA</td>
</tr>
<tr>
<td>Vento et al</td>
<td>&gt; 37</td>
<td>Not reported</td>
<td>Not reported</td>
<td>22</td>
<td>Control group</td>
<td>NA</td>
</tr>
<tr>
<td>Rao and Rampi</td>
<td>&gt;31</td>
<td>Noninvasive 515A</td>
<td>Preductal</td>
<td>52</td>
<td>Air 100% oxygen</td>
<td>2.0 (0.7)</td>
</tr>
<tr>
<td>Saugstad et al</td>
<td>&gt;31</td>
<td>Not reported</td>
<td>Not reported</td>
<td>103</td>
<td>Air 100% oxygen</td>
<td>1.5 (1.4)</td>
</tr>
</tbody>
</table>

*Mean (range); †median (95% CI).

### Table 4: SpO2 measurements in infants with asphyxia randomised to resuscitation with air or 100% oxygen

<table>
<thead>
<tr>
<th></th>
<th>1 min</th>
<th>5 min</th>
<th>10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air</td>
<td>Oxygen</td>
<td>Air</td>
</tr>
<tr>
<td>Saugstad et al</td>
<td>65 (11)*</td>
<td>61 (14)*</td>
<td>86 (10)*</td>
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<tr>
<td>Saugstad et al</td>
<td>68 (40–82)†</td>
<td>63 (40–82)†</td>
<td>90 (66–95)†</td>
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*Mean (SD); †median (3th–95th centile).
**Controversy**

Neonatal anthropometric charts: what they are, what they are not

E Bertino, S Milani, C Fabris, M De Curtis

Over 40 years have elapsed since Lubchenco et al. proposed an anthropometric classification of neonates based on the so-called intrauterine growth chart—that is, birth weight-for-gestational age charts.

**ARE NEONATAL ANTHROPOMETRIC CHARTS INTRAUTERINE GROWTH CHARTS?**

The use of charts, such as those given by Lubchenco et al., based on the distribution of measurements taken on neonates with different gestational age, should be restricted to the auloxiological assessment of babies at birth. These charts, now called neonatal anthropometric charts, must not be confused with the intrauterine growth charts, which are a tool for monitoring fetal growth, based on ultrasound measurements of anthropometric traits during pregnancy. Preterm births are abnormal events and preterm neonates cannot be equated to fetuses of the same gestational age who will be born at term. When fetal growth studies are longitudinal, both distance and velocity intrauterine growth charts may be traced. Strictly speaking, only charts derived from longitudinal studies should be called growth charts, growth being a process extended over time.

**REFERENCES**


**NEONATAL ANTHROPOMETRIC CHARTS INTRAUTERINE GROWTH RESTRICTED?**

The terms SGA and intrauterine growth restriction (IUGR) are often used as synonyms, although they reflect two different concepts. SGA refers to a statistical definition, based on an auloxiological cross-sectional evaluation (prenatal or neonatal), and denotes a fetus or a neonate whose anthropometric variables (usually weight) are lower than a given threshold value computed on a set of infants having the same gestational age. SGA includes infants who have not achieved their own growth potential, because of maternal, uterine, placental and fetal factors, as well as small but otherwise healthy infants. IUGR refers to a clinical and functional condition and denotes fetuses unable to achieve their own growth potential: a fetus with IUGR would have been larger, without adverse environmental or genetic factors affecting growth. Such a condition can be assessed by ultrasonography during pregnancy by a longitudinal evaluation of fetal growth rate. A neonate identified as SGA by neonatal anthropometric charts is not necessarily a case of IUGR and,

[www.archdschild.com](http://www.archdschild.com)
conversely, a neonate identified as having IUGR during the fetal period by intrauterine growth charts may not be SGA. The current gold standard in neonatal auxological evaluation is based on information obtained from both neonatal anthropometric charts and intrauterine growth charts. Furthermore, Doppler velocimetry can detect altered flow states in the fetal-placental and uterine-placental circulation, and may contribute to the differentiation between a fetus with IUGR and a fetus who is constitutionally SGA. When the prenatal growth pattern is unknown, SGA may be regarded as a proxy of IUGR. An alternative proxy is based on the prediction of birth weight based on early ultrasound assessments of fetal growth: a negative difference between actual and predicted birth weight denotes IUGR. So far, there is insufficient evidence that this alternative method performs better than those based on fetal or neonatal charts.10

WHAT ABOUT RELIABILITY OF ANTHROPOMETRIC AND GESTATIONAL AGE EVALUATIONS?

Weight, length and head circumference at birth are indicators of the quality and quantity of growth; these variables must be evaluated using standardised instruments and following the techniques required for accurate measurements as described by Cameron.11

The validity of neonatal charts is also based on reliable estimations of gestational age, expressed as complete weeks, in accordance with international recommendations.12 Early ultrasound assessment has improved the accuracy of estimation of gestational age,1 and there is general agreement that the best estimation is obtained by a combination of anamnestic—that is, based on reported last menstrual period—and early ultrasound assessment.13 The prior exclusion of neonates with unreliable gestational age seems more sensible than the a posteriori use of any statistical method for detecting biologically implausible birth weight–gestational age pairs.14

SHOULD A NEONATAL CHART BE A REFERENCE OR A STANDARD?
The target population is the population on which the chart is built and to which the chart will apply. A target population is defined by its inclusion criteria—that is, geographical area, ethnic group, sex, single birth, live birth and so on. In the absence of exclusion criteria regarding risk factors for fetal growth, a chart based on such a population is a reference, which describes “how growth actually is” in that population. Centers for Disease Control and Prevention growth charts for the US15 are a reference in the sense that they are explicitly descriptive, although the authors recognise that some compromises were made on developing a true reference.16 The two anthropometric charts elaborated by the Italian Society of Neonatology,17,18 as well as most neonatal charts in use, are essentially descriptive references. Differences between reference charts reflect the different anthropometric characteristics of healthy neonates belonging to different populations and also the different prevalences of risk factors for prenatal growth in those populations. For this reason, by means of reference charts, the differences in the health conditions of two populations, or of one population over time, may be evaluated. On the other hand, the clinical use of a reference raises some methodological problems, as a neonate is compared with a group of peers, also including infants who may have had prenatal growth impairment; therefore, a reference might possess low sensitivity in detecting a neonate with growth anomalies. From a practical viewpoint, when the chart is based on a population with low prevalence of risk factors (such as the populations of developed countries), the clinical use of a reference can be safely accepted. To avoid the methodological weakness of clinical use of a reference, a set of exclusion criteria can be defined, concerning mothers for example, hypertension, diabetes or renal diseases, fetuses (genetic disorders or congenital anomalies), or uterine or placental factors. Highly restrictive criteria aiming to exclude all neonates exposed to any known risk factor for intrauterine growth define the characteristics of infants who fully expressed their growth potential. Such characteristics constitute a model to which a neonate should conform, and a basis for a prescriptive standard or norm that indicates how growth should be.19 However, there is no agreement on which diseases should be taken into consideration, and some of these may even pass unnoticed at birth. Moreover, it is rare to find neonates without IUGR with low gestational age when highly restrictive exclusion criteria are adopted, so that a norm for a severely preterm neonate may be difficult to draw. An example of neonatal standards are the Italian charts based on a multicentre survey carried out between 1973 and 1979.20 Although these charts are the result of a noteworthy (for that time) methodological effort, they overestimate the value of anthropometric traits at low gestational age, where there is a higher probability of including infants with a true gestational age value above that assessed (at that time, ultrasound assessment of gestational age was not common obstetric practice). Even if an accurate neonatal standard were available, its clinical use could be questionable: a large proportion of severely preterm neonates have IUGR a priori, and are expected to be classified as SGA on the basis of such standards. By contrast, the use of a reference, including neonates with different degrees of IUGR, enables the detection of preterm neonates having severe IUGR.

MANY LOCAL REFERENCE CHARTS OR A UNIQUE STANDARD?
A much-debated topic is whether a growth chart should be local, national or international. Strictly speaking, as a reference chart describes the anthropometry of a given population, we need as many reference charts as the number of different populations, no matter whether their anthropometric differences are ascribable to ethnic characteristics or to environmental, nutritional, socioeconomic and health conditions.

Do we really need, however, as many standards as the number of different populations? If the main reason for the differences emerging by comparison between different reference charts is the inequality in health between poor and rich populations, these differences tend to vanish when the restrictive exclusion criteria that define a standard population are adopted. In this case, only one standard could apply to all populations. The new World Health Organization child growth standards are based on such an assumption.21 Even full-term single-born healthy infants of non-smoking mothers from a favourable socioeconomic status show a residual difference in size at birth correlated with ethnicity—for example, 1.4 cm in birth length between Norwegian and Indian neonates. A unique standard is the right or the wrong choice depending on whether such differences are regarded as negligible or not. The extent to which the anthropometric differences between ethnic groups are the result of health, socioeconomic and environmental factors is still debated.22 As asserted by Karlberg et al.,23 clinicians seem to prefer local references when communicating with patients and their parents, and do not seem to take seriously any attempt to establish an international standard. Severely preterm neonates who match the requirements for a standard can hardly be found; thus, neonatal charts can be based only on a local or national reference population.
LEADING ARTICLES

TRADITIONAL POPULATION-BASED OR CUSTOMISED CHARTS?
Establishing neonatal charts adjusted for factors permanently bound to differences in fetal growth such as sex, and single or multiple pregnancy, is indeed useful; such factors are generally taken into account to trace population-based charts. The adjustment for other covariates (the so-called customising features, such as maternal height, weight, and even maternal birth weight and birth weight of previous siblings) is gaining increasing popularity. From a systematic review of the evidence, it seems that customised charts could be suitable to improve the detection of IUGR. Nevertheless, customising features reflect constitutional factors but are also surrogates for a combination of parameters related to the mother, such as socioeconomic level and nutrition86; the available data do not permit confident inferences regarding the extent to which they induce physiological or pathological variations in fetal growth.

HOW TO CHOOSE A CUT-OFF POINT TO DEFINE SGA NEONATES?
A clinically useful threshold value would discriminate neonates with IUGR, who are at high risk of short-term and long-term growth impairment, disease and death, from neonates without IUGR, who are at low risk. On inspection of neonatal morbidity and mortality “risk maps”—that is, a kind of geographical map where prefixed levels of risk are plotted as contours as a function of gestational age (longitude) and birth weight (latitude)—it seems that neonatal risk increases with the decrease in birth weight and gestational age. SGA neonates have long-term risk of auxological deficit,13 neurocognitive impairment,14 metabolic disorders and cardiovascular diseases.15 16 These observations justify the use of neonatal charts, but are of no help in identifying values that best discriminate between infants at high and low risk. An alternative is to adopt statistical definitions instead of clinical ones, although the thresholds based on statistical criteria are only indirectly related to risk. In accordance with the statistical criterion, a neonate is defined to be SGA when his or her weight is below the 10th, 5th or 3rd centile of the neonatal chart or, under assumption of a gaussian distribution, 1.5 or 2 standard deviations below the average (which correspond to the centiles 6.7 and 2.3). The choice of a threshold affects both sensitivity (proportion of SGA neonates among those with IUGR) and specificity (proportion of AGA neonates among those without IUGR): the use of the 3rd centile instead of the 10th centile increases specificity but decreases sensitivity. In the case of a standard based only on neonates without IUGR, setting the cut-off point at the 10th centile is the same as setting the false-positive ratio at 10%—that is, a specificity of 90%. In a case of a reference, the false-positive ratio is expected to be <10%, as the reference set also includes neonates with IUGR. No univocal criterion states that one threshold is better than another, and a general agreement on the centiles to be adopted as cut-off points would be desirable.

SHOULD NEONATAL CHARTS BE UPDATED?
As regards paediatric age range, anthropometric charts should be updated every 5–10 or 15–20 years, in conformity with the intensity of the “secular trend of growth” in the population.17 18 In the past 25 years, developed countries have experienced a secular trend also in birth weight.19 Thus, more frequent updating of neonatal charts has become necessary as a result of changes not only in parity and maternal age and size but also in socioeconomic or environmental conditions, and obstetric or neonatal care.

WHAT MODELS ARE USED TO TRACE NEONATAL CHARTS?
By definition, neonatal charts are based on data from cross-sectional studies: thus, raw non-parametric centiles of the distribution of an auxometric variable conditional on gestational age show an uneven pattern when they are plotted versus age. The need to trace smooth centiles derives from the assumption that somatic growth is a continuous process, at least at a macroscopic level, and pattern irregularity is interpreted not as the expression of an underlying biological phenomenon but rather as a combined effect of measurement error and sampling variability. To trace smooth growth charts, Healy et al20 introduced a class of linear models (Healy Rasbash Yang method), where the value of a given centile at a given age is expressed as polynomial function of age and z score corresponding to the centile—for example, the z score for the 3rd centile is 1.88. As an alternative, Cole21 proposed the LMS method. This sums up the age-dependent changes in the distribution of an auxometric variable by means of three curves that represent the degree of skewness (L(t)), the median (M(t)) and the coefficient of variation (S(t)) at each age (t). This method permits the use of the z score even in the case of non-gaussian variables.

CONCLUSION
The neonatal charts currently in use largely differ as regards inclusion and exclusion criteria, techniques and instruments for measurement, accuracy of assessment of gestational age and methods to compute centiles. Table 1 lists several characteristics that a reliable neonatal chart should possess.

Neonatal charts traced according to the recommendations mentioned in table 1 are of both epidemiological and clinical use. From an epidemiological viewpoint, a reference neonatal chart provides a

Table 1 Characteristics that a reliable neonatal chart should possess to be of both epidemiological and clinical use

<table>
<thead>
<tr>
<th>Type of survey</th>
<th>Pre-planned multicentre ad hoc study</th>
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<tr>
<td>Type of chart</td>
<td>Descriptive reference rather than an ideal prescriptive standard</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Stillbirth, major congenital anomalies</td>
</tr>
<tr>
<td>Target population</td>
<td>Mono-ethnic population living in a given country at a given time</td>
</tr>
<tr>
<td>Subpopulations</td>
<td>Females or males, single or multiple pregnancies, primiparous or multiparous</td>
</tr>
<tr>
<td>Assessment of GA</td>
<td>Last menstrual period confirmed by early ultrasound assessment</td>
</tr>
<tr>
<td>Range of GA</td>
<td>From 42 to 24 weeks or less, to cope with the increasing number of neonates with low GA</td>
</tr>
<tr>
<td>Measurements</td>
<td>Use of standardised instruments and measurement techniques</td>
</tr>
<tr>
<td>Technique to trace charts</td>
<td>HRY method22 or LMS method23</td>
</tr>
<tr>
<td>Sample size</td>
<td>Critical sample size concerns the more external (eg, the 3rd and 97th) centiles at lower GA, therefore, attention should focus on the number of severely preterm neonates, who are more difficult to recruit. Simulation indicates that if 100 neonates are available at 24 weeks, 95% of the HRY or LMS estimates of the 3rd centile are included between centiles 1.3 and 6.3. This range narrows rapidly when GA increases (eg, at 26 weeks is between centiles 2.1 and 4.2) in the case that 100 neonates are sampled at each GA. Several neonates at term have poor effect on the precision of estimates at low GA.</td>
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HRY, Healy Rasbash Yang; GA, gestational age; LMS, lambda (skewness coefficient), mu (median), sigma (coefficient of variation) |
picture of the health status of a population. The comparison of charts referring to different and clearly defined populations living in the same country or in different countries, or to the same population in different periods, is a way of measuring the extent of inequalities in health between populations or to monitor trends over time in response to public health policies.

From a clinical viewpoint, a neonatal chart is essentially a tool to detect neonates at higher risk of neonatal and postnatal morbidity and growth impairment, and to compare neonatal anthropometric conditions with those observed during postnatal growth. A comprehensive auxological evaluation of the neonate should consider not only weight, length and head circumference at birth but also fetal ultrasound biometry and Doppler velocimetry. At present, further clinical studies are needed to reach a consensus on how to combine neonatal and prenatal information to discriminate neonates with IUGR from those without IUGR.
Accuracy of clinical assessment of infant heart rate in the delivery room

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Summary
Heart rate (HR) dictates intervention during neonatal resuscitation. Guidelines recommend that HR be assessed by auscultation or palpation. We compared HRs determined clinically with electrocardiography (ECG) in healthy newborns in the delivery room. Clinical assessment by 23 observers randomly allocated to assess HR by one of two methods in 26 infants, was found to be inaccurate and underestimate ECG HR. The mean difference between HR assessed by auscultation and palpation ECG and HR using methodology recommended by the Neonatal Resuscitation Programme was 14 and 22 beats per minute respectively.

Introduction
International consensus statements recommend that the need for, and response to resuscitation in newborn infants be determined clinically, with the heart rate being the most important sign.1,2 Counting the heart rate (HR) by auscultation of the praecordium with a stethoscope or palpation of umbilical cord pulsations are the recommended techniques.1,3 Auscultation of the HR has been shown to be inaccurate in a model,4 while palpation has been shown to be inferior to auscultation in newborns in the delivery room.5 Neither method has been compared to electrocardiography (ECG) in the delivery room. We wished to determine the accuracy of clinical assessment of HR by comparing it to ECG in the delivery room (DR).

Methods
Approval for this study was obtained from the Human Research and Ethics Committees of the Royal Women’s Hospital. We identified impending low-risk term births and approached parents for consent prior to delivery. Vigorous infants who were
not resuscitated were enrolled. The chest and right thigh were cleaned using Skin-Prep® wipes (Smith & Nephew, FL USA) and three ECG leads (Kitty-cat, Tyco Healthcare, Mansfield, MA, USA) applied. With the infant on the Resuscitator, two leads were applied to the chest and one to the lateral aspect of the right thigh. The leads were connected to a ProPaq 106EL (Protocol Systems Inc., Oregon, USA) monitor. For each infant, two staff members attending the birth were invited to participate in the study once the infant had been dried and stabilised. The two care providers were randomly allocated (by toss of a coin) to assess HR by either palpation (HR\text{palp}) or auscultation (HR\text{ausc}). Participants determined the HR in beats per minute (bpm) by multiplying the number of beats heard or felt in 6 s by 10 s, as recommended in the Neonatal Resuscitation Programme (NRP). Participants simultaneously determined the HR clinically by each method. They were masked to the ECG HR. Each observer recorded the HR on a card, which they gave to the investigator. The HRs assigned by each observer were compared to the HR measured by ECG. Data were analysed using SPSS for Windows (Chicago IL, USA) version 11.5 using paired t tests to compare mean HR.

**Results**

Twenty-three observers (2 consultant neonatologists, 3 neonatal fellows, 7 pediatric registrars, 11 neonatal nurses) assessed 26 infants (mean (S.D.) gestational age and birth weight 38 (2) weeks and 3191 (681) g, respectively). All infants were active and no infant received respiratory support.

Comparison of clinical assessment of HR by auscultation with ECG recordings were performed in all infants. However, cord pulsations were impalpable at the time of assessment in 5 (19%) infants. The mean (S.D.) time from birth to application of ECG leads was 1.9 (0.7) min and the mean ECG HR at the time of clinical evaluation was 168 (21) bpm.

The mean (S.D.) HR from the ECG was 167 (19) bpm compared with HR\text{ausc} \((n = 26)\) of 154 (22) bpm \(p = 0.003\). The mean (S.D.) HR from the ECG was 168 (22) bpm compared with HR\text{palp} \((n = 21)\) of 147 (19) bpm \(p < 0.001\). Clinical assessment underestimated the ECG HR with a mean difference (S.D.) between HR\text{ausc}, HR\text{palp} and ECG HR of \(-14\) (21) and \(-21\) (21) bpm, respectively (Figure 1).

**Discussion**

Immediately after birth the new born infant’s HR guides the need for resuscitation.\(^1\,\text{2}\) The best way to monitor HR at this time has not been determined. This study compared different ways of counting HR in the delivery room in newly born infants who did not require resuscitation. Vigorous new born infants were studied because this was the nearest we could get to investigating the clinical assessment of HR accurately immediately after birth. Although it would have been optimal to study HR in those infants receiving resuscitation it was not possible to do three simultaneous careful assessments of HR during resuscitation.

This study has demonstrated inaccuracy in the counting the HR of newborn infants in the delivery room. Our study did not include infants with HRs <100 bpm, thus we do not know whether clinical assessment is similarly inaccurate at slower HRs. Using a modified infant resuscitation manikin, Theophilosopouls instructed clinicians to determine the heart rate generated by an electronic metronome using the NRP six second method and their own preferred method (duration of listening varied from 5 to 30 s).\(^4\) Both methods were inaccurate at all settings of HR (40, 70, 90 and 120 bpm) but more pronounced when the metronome was set at a HR < 100 bpm, a heart rate at which guidelines suggest interventions for the infant. Our findings in a clinical setting have shown the tendency for delivery room care providers who are counting time and either heart beat or pulsations simultaneously, to underestimate ECG HR across the range of absolute ECG HR. If the inaccuracies seen in our and the manikin study\(^4\) were to occur in non-vigorous infants in the delivery room, it is possible that therapies will be either withheld or administered inappropriately.

![Figure 1](image-url) An error bar chart of the mean difference (95% confidence intervals) between ECG HR and (i) HR\text{ausc} and (ii) HR\text{palp}.
Though ECG provides a continuous measure of HR, obtaining a reading from a wet newborn immediately after birth is slow. This study was designed to compare clinical assessment against ECG HR, the gold standard in an intensive care setting. Whilst it has highlighted the differences between auscultation and ECG HR and the limitations of palpation, costs, access to an ECG on a global scale and time for data acquisition preclude the use of the ECG to monitor an infant’s HR routinely in the delivery room. In contrast, pulse oximetry measures both oxygen saturation and HR and may be superior to the ECG in this setting because the readings are easier to obtain but this comparison has not been assessed. The accuracy of HR assessment by oximetry immediately after birth needs to be determined.

Clinical trials to determine whether different techniques for assessing heart rate, immediately after birth, improve outcomes for resuscitated newborn infants are the gold standard of scientific assessment but they are difficult to organise and expensive to run. In the meantime clinicians need to be aware that the clinical assessment of heart rate in the delivery room may be inaccurate.

Conflict of interest statement
None.

Acknowledgements
COFK and CPFO’D both are in receipt of the Royal Women’s Hospital Postgraduate Degree Scholarship. PGD is supported by a National Health and Medical Research Council Fellowship.

References
Accuracy of pulse oximetry in assessing heart rate of infants in the neonatal intensive care unit

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Aim: To determine the accuracy of pulse oximetry measurement of heart rate in the neonatal intensive care unit.

Methods: Stable preterm infants were monitored with a pulse oximeter and an ECG. The displays of both monitors were captured on video. Heart rate data from both monitors, including measures of signal quality, were extracted and analysed using Bland Altman plots.

Results: In 30 infants the mean (SD) difference between heart rate measured by pulse oximetry and electrocardiography was -0.4 (12) beats per minute. Accuracy was maintained when the signal quality or perfusion was low.

Conclusion: Pulse oximetry may provide a useful measurement of heart rate in the neonatal intensive care unit. Studies of this technique in the delivery room are indicated.

Key words: infant; newborn; pulse oximetry.

Measurement of heart rate (HR) is an important component of the assessment of neonates both in the neonatal intensive care unit (NICU) and in the delivery room (DR). Electrocardiography (ECG) is the accepted ‘gold standard’ method of continuously monitoring HR and has been used in the NICU for decades. However, ECG chest leads may cause breakdown of the fragile skin of extremely preterm infants. Pulse oximetry (PO) has also been used in the NICU for many years and provides a continuous, non-invasive measurement of oxygen saturation and HR.

In the DR, HR is traditionally assessed clinically, either by palpation of the umbilical cord or by auscultation of the heart. Both methods are inaccurate, systematically underestimating HR by an average of 14–21 beats per min (bpm). As all newly born infants are wet, application of ECG monitoring in the DR is technically difficult and time-consuming. With the availability of new generation monitors that cope better with motion artefact, it has been suggested that PO may have a role in the DR to assist both optimising oxygenation and measuring HR. PO monitoring in the DR may be more difficult than in the NICU because of motion of the infant and poor peripheral perfusion in the first minutes of life. New generation pulse oximeters display both a low signal identification and quality indicator (signal IQ), when data may be erroneous because of excessive motion or low perfusion and a perfusion index (PI) which provides a relative assessment of pulse strength at the monitoring site.

The accuracy of PO measurement of HR in the NICU and in the DR is not well studied. If inaccurate in the NICU, it is unlikely that the technique would be useful in the DR. Therefore, in an observational study we sought to determine the accuracy of PO in the NICU and how this varied when the monitor displayed low signal IQ or PI.

Methods

Stable preterm infants who were monitored with ECG in the NICU were eligible for inclusion. Basic demographic data were collected on each baby. A Masimo Radical (Masimo Corporation, Irvine, CA, USA) PO monitor was placed next to the ECG monitor. The PO sensor was placed on the right hand, secured with Coban wrap (3M Healthcare, St. Paul, MN, USA) and then connected to the Masimo Radical PO cable as previously described. The PO sensor was placed on the right hand, secured with Coban wrap (3M Healthcare, St. Paul, MN, USA) and then connected to the Masimo Radical PO cable as previously described. The PO was set to acquire data with maximal sensitivity and average it over 2-s intervals. A Panasonic NVGS200 digital video camera (Matsushita Corporation, Japan) mounted on a Manfrotto Magic Arm (Manfrotto, Italy) was used to record the displays of both monitors.

The videos obtained were reviewed and data were extracted every 2 s on HR, PI and signal IQ. Data extraction began from the time when both PO and ECG data were available and continued for 180 s.

Key Points

1 Pulse oximetry accurately measures heart rate in the NICU.
2 Accuracy is maintained even when signal quality is low.
3 Further studies are required to determine the role of pulse oximetry in the delivery room.

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A Bland Altman plot was constructed to assess the level of agreement between the ECG HR and the PO HR. This method plots the difference between these two values against their average. Two standard deviations around the mean difference represented the limit of agreement. Similar plots were constructed for the subset of Masimo HR values with (i) low PI and (ii) low signal quality. The Human Research and Ethics Committees of The Royal Women’s Hospital, Melbourne, Australia approved the study.

Results

A convenience sample of 30 stable infants in the NICU was studied. The mean (SD) gestational age was 29 (4) weeks and birthweight 1451 (905) g. A total of 2730 pairs of PO and ECG HRs were analysed. The Bland Altman plot showed the mean difference between PO and ECG HR was -0.4 bpm and 2 SD was 12 bpm (Fig. 1). In the subset of PO values with the lowest 5% PI (<0.47) the mean difference was identical to the overall result and 2 SD was 14.4 bpm (Fig. 2). In the subset of readings where the PO displayed low signal quality the mean difference was 0.9 bpm and 2 SD was 28.4 bpm (Fig. 3).

Discussion

Reports of the usefulness of PO to monitor infants in the intensive care unit and under anaesthesia appeared in the 1980s. Case series illustrating its application for monitoring infants in the DR appeared shortly afterwards. These early observational studies noted the limitations of the technique in situations where the infant was moving or had low perfusion. The development of signal extraction technology enabled continuous data to be obtained for a greater proportion of time than older generation oximetry.

Evaluation of PO in both the NICU and DR has focused predominantly on the measurement of oxygen saturation. The ability to measure HR has largely been overlooked. However, Barrington et al. tested a variety of pulse oximeters available in the late 1980s, comparing the HR with ECG. They found that PO HR deviated from ECG HR by more than 10 bpm for 11.9–25% of the time. Hay et al. assessed the accuracy of a new generation signal extraction technology monitor in detecting bradycardic events in the NICU patients and found it to be superior to other monitors. Our study confirms the accuracy of PO measurement of HR in the NICU.

We suggest two novel settings in which measurement of HR by PO may be useful. First, in newborn premature infants with fragile skin who are unable to tolerate conventional ECG
monitoring, PO may be used to measure HR. Second, an alternative to the intermittent, inaccurate measurement of HR by palpation or auscultation in the DR is required. Assessment of the condition of newly born infants and their response to treatment has remained largely unchanged for half a century. PO provides continuous, accurate assessment of HR of stable infants in the NICU, even when PI and signal quality are low. Extension of its use to the DR offers a potential solution to a long-standing problem. Further studies are required before PO is recommended in either setting.

References
Accuracy of Pulse Oximetry Measurement of Heart Rate of Newborn Infants in the Delivery Room

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Objective To determine the accuracy of heart rate obtained by pulse oximetry (HRPO) relative to HR obtained by 3-lead electrocardiography (HRECG) in newborn infants in the delivery room.

Study design Immediately after birth, a preductal PO sensor and ECG leads were applied. PO and ECG monitor displays were recorded by a video camera. Two investigators reviewed the videos. Every two seconds, 1 of the investigators recorded HRPO and indicators of signal quality from the oximeter while masked to ECG, whereas the other recorded HRECG and ECG signal quality while masked to PO. HRPO and HRECG measurements were compared using Bland-Altman analysis.

Results We attended 92 deliveries; 37 infants were excluded due to equipment malfunction. The 55 infants studied had a mean (± standard deviation [SD]) gestational age of 35 (±3.7) weeks, and birth weight 2399 (±869) g. In total, we analyzed 5877 data pairs. The mean difference (±2 SD) between HRPO and HRECG was –2 (±26) beats per minute (bpm) overall and –0.5 (±16) bpm in those infants who received positive-pressure ventilation and/or cardiac massage. The sensitivity and specificity of PO for detecting HRPO <100 bpm was 89% and 99%, respectively.

Conclusion PO provided an accurate display of newborn infants’ HR in the delivery room, including those infants receiving advanced resuscitation. (J Pediatr 2008;152:756-60)

An infant’s heart rate (HR) is used to assess the need for and response to resuscitation.1 HR is determined by auscultating the precordium or palpating the umbilical cord. Intervention is recommended if the HR is <100 beats per minute (bpm).2,3 Clinical assessment of HR in the delivery room is intermittent and often inaccurate.4,5 Pulse oximetry (PO), increasingly used in the delivery room,6 allows titration of oxygen concentrations delivered to infants receiving respiratory support.7 We have demonstrated that HR obtained by PO (HRPO) in the neonatal intensive care setting is accurate compared with HR obtained from 3-lead electrocardiography (HRECG).8 ECG monitoring in the delivery room is difficult due to the infant’s wet skin, is time-consuming,9 and may damage the skin of an extremely preterm infant. Conventional PO is unreliable in the delivery room, where excessive motion and low perfusion can lead to underestimation of true HR.9 Recently developed second-generation pulse oximeters have advanced processing algorithms to adjust for patient motion and poor perfusion states, thereby improving accuracy and precision.10,11 PO data are easily obtained from newborn infants in the delivery room,12 but the accuracy of the HRPO is unknown.

In the present study, we compared HRPO determined by second-generation pulse oximetry with HRECG in newborn infants in the delivery room. Specifically, we sought to evaluate the precision and accuracy of PO across a wide range of HRECG readings and the sensitivity and specificity of PO in detecting HRPO <100 bpm.

METHODS

Two investigators attended the deliveries of a convenience sample of newborn infants between July 2005 and August 2006. Use of the pulse oximeter in the delivery...
room has become a standard of care at our institution, and approval for the study as an audit of practice was obtained from the Royal Women’s Hospital, Melbourne Research, and Human Research Ethics Committees. Verbal consent for video recording of the 2 monitors in the delivery room was obtained from the infant’s parents before delivery.

Immediately after birth, the infant was placed on a resuscitation trolley, where a PO sensor (L-NOP Neo; Masimo Corp, Irvine, CA) was applied to the infant’s right hand/wrist and then connected to a Masimo Radical signal-extraction pulse oximeter. The oximeter was set to acquire data with maximum sensitivity and a 2-second averaging interval.

Simultaneously, another study investigator applied 3 ECG chest leads (Puppydog; Kendall, Mansfield, MA), connected to an Escort II ECG monitor (MDE, Arleta, CA). The HR was based on a measure of the interval between R waves, averaged over 6 complexes. The oximeter and ECG monitor were placed side by side, and both screens were recorded by a video camera. PO and ECG measurements were available to the clinical team responsible for the infant.

Two investigators independently reviewed the videos. The videos were paused every 2 seconds to record data. The starting point for data collection was 10 seconds from the time at which both the HR and PO displays the level of agreement between HR and ECG displayed on the monitor. Data were recorded for a minimum of 3 minutes (90 data points). For an infant receiving advanced interventions (positive-pressure ventilation by face mask or greater), data collection continued until the infant was stabilized.

The relationship between HR and HR was evaluated using Bland-Altman bias analysis; the difference between the measurements was plotted against their average. Two standard deviations around the mean difference represented the upper and lower limits of agreement. The sensitivity, specificity, positive predictive values, and negative predictive values of PO for detecting HR <100 bpm were calculated. The data were analyzed using intercooled Stata version 9.2 (StataCorp, College Station, TX).

RESULTS

We attended 92 deliveries and failed to make recordings at 37 of them, due to 20 ECG, 12 PO, and 5 video camera malfunctions. Consequently, we recorded and analyzed data from 55 infants who had a mean (±standard deviation [SD]) birth weight of 2399 g (±876 g) and a mean gestational age of 35 weeks (±3.7 weeks). The resuscitation administered to these infants is detailed in the Table. The time (median [interquartile range]) taken to acquire HR was 68 seconds (60 to 118 seconds); that to acquire HR was 80 seconds (64 to 104 seconds); and that to the start of data collection was 118 seconds (90 to 155 seconds).

A total of 6475 HR and 6448 HR data points were entered into the spreadsheet; the difference was due to transient loss of HR and/or HR. All of the HR data points were used to determine levels of agreement where the HR was deemed to be of good quality (n = 5877). The HR and HR data for all infants were compared in a Bland-Altman plot (Figure 1A). The mean difference (HR - HR) was –2 bpm, and the 95% limit of agreement (±SD) was ±26 bpm. Figure 1B shows data from 2 active term infants in whom HR significantly underestimated HR. When HR was compared with good-quality HR (ie, presence of signal bars and absence of a “low-signal IQ” message; n = 5143), the mean difference (±SD) was –1 bpm (±20 bpm).

Figure 2 displays the level of agreement between HR and HR for those infants receiving advanced resuscitation. The mean difference (2 SD) for the 5 infants who were intubated (Figure 2A) and the 2 infants who received external cardiac massage (Figure 2B) was 0.2 (±16) and 0.8 (±8) bpm, respectively.

Good-quality signals from both devices (n = 5143) are compared in Figure 3. A strong linear correlation (r = 0.8) can be seen. Dividing this graph into 4 quadrants, above and below a HR of 100 bpm revealed a sensitivity of 89%, specificity of 99%, positive predictive value of 83%, and negative predictive value of 99% of PO to detect a HR <100 bpm. A HR <100 bpm was detected by PO 89% of the time.

### Table. Delivery room interventions received by infants (not mutually exclusive)

<table>
<thead>
<tr>
<th>Delivery room intervention</th>
<th>28 to 31 (n = 12)</th>
<th>32 to 35 (n = 15)</th>
<th>≥36 (n = 28)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4</td>
<td>8</td>
<td>24</td>
<td>36 (65)</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>19 (35)</td>
</tr>
<tr>
<td>Continuous positive airway pressure by mask</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Positive-pressure ventilation by mask</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>12 (22)</td>
</tr>
<tr>
<td>Positive-pressure ventilation by endotracheal tube</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Chest compressions</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

Accuracy of Pulse Oximetry Measurement of Heart Rate of Newborn Infants in the Delivery Room 757
There were 42 data points from 10 infants in which HR\textsubscript{PO} was 100 bpm when HRECG was 100 bpm. One of these 10 infants contributed 16 data points (32 seconds); this infant received positive-pressure ventilation. The other 9 infants each contributed between 1 and 4 data points.

**DISCUSSION**

In this study, we evaluated the accuracy and precision of HR\textsubscript{PO} in the delivery room using a new-generation pulse oximeter. Our results suggest that in the delivery room, HR\textsubscript{PO} is accurate and on average within 2 bpm of HRECG. Overall, the 95% limit of agreement was wider than what we expected, at ±26 bpm. However, in the infants who received the most intervention in our cohort, the level of agreement was ±16 bpm. This compares with the pulse oximeter manufacturer's level of agreement of ±10 bpm when tested on adult subjects with simulated motion.\textsuperscript{14} A weakness of our study is the high number of excluded infants (40%). The most common technical problem was failure to acquire HRECG. The video camera failed during 5 deliveries, due to lack of power or videotape. The pulse oximeter battery failed during 5 deliveries, and in 7 vigorous infants there was poor signal acquisition due to motion artefact. PO failed to acquire data in this setting in 12 of 92 infants (13%). Consequently, we advise caution in the application of this new technology; it may fail or, equally importantly, divert attention away from management of the infant in the stressful environment of the delivery room.

ECG and PO measure HR differently. There are differences in averaging intervals between the 2 devices, and thus it is possible that we have underestimated the true agreement between PO and ECG. With rapidly changing heart rates during neonatal transition, we observed that HR\textsubscript{PO} may lag behind HRECG by a few seconds. Although clinically unim-
important, this lag would introduce differences between the 2 monitors in our data set, as demonstrated by the 26 readings in 5 infants in whom HRPO remained >100 bpm while the HR_{ECG} had dropped to <100 bpm (Figure 3). One infant, of 31 weeks’ gestation, contributed 12 data points in which the ranges of readings from the PO and ECG were 101 to 104 bpm and 96 to 99 bpm, respectively. These recordings are within the margin of error of the devices and are clinically unimportant.

The results on a small number of infants who required advanced resuscitation demonstrate the potential of this technology under these circumstances. Precision and accuracy were slightly improved in this situation (Figure 2). False-positive HRPO readings (ie, where the PO incorrectly identifies an infant as having a low HR, potentially leading to inappropriate intervention) may be a concern. In our sample, 42 data points from 10 infants were noted in which HRPO was <100 bpm and HR_{ECG} was >100 bpm (Figure 3). For all but 1 infant, these readings lasted between 2 and 8 seconds—inconsistently long, we believe, to alter management. In 1 infant who contributed 16 false-positive data points (32 seconds), PO may have led to interventions that were not indicated. However, overtreatment is probably less likely when using HRPO than when using auscultation, which systematically underestimates HR by 17 bpm. We recognize that not every birthing area will have access to PO and that the stethoscope will remain the main instrument for assessing newborn infants worldwide. Based on our findings, we recommend using PO as an adjunct to careful clinical surveillance of infant HR, especially for very preterm infants who may need resuscitation. We have shown that PO can identify with high sensitivity and specificity those infants who require intervention based on current recommendations.

The availability and adoption of PO in the delivery room is increasing worldwide without extensive previous investigation. Kopotic and Lindner examined the feasibility and utility of the Masimo signal-extraction pulse oximeter in the delivery room to titrate the fraction of inspired oxygen to target saturations and assess the need for intervention using HR. In a feasibility study of early continuous positive airway pressure for extremely low birth weight infants in the delivery room, Finer et al used HRPO to guide intervention in all but 1 of 47 infants who were intubated. Other studies have investigated the effects of endotracheal intubation on HR and peripheral oxygen saturation in the delivery room; none of these studies was designed to verify the accuracy of HRPO, however. Our data demonstrate that HRPO is of sufficient accuracy to be of use to clinicians and researchers alike.

The accuracy and precision of this technology have not yet been studied in extremely preterm infants; studies are needed in this patient group. Future studies also should address the question of whether PO used as an adjunct to clinical evaluation improves important patient outcomes in the delivery room.

REFERENCES
50 Years Ago in The Journal of Pediatrics

RECENT ADVANCES IN GENETICS IN RELATION TO PEDIATRICS
Fraser FC. J Pediatr 1958;52:734-57

Five years after Watson and Crick published their hypothesis on the structure of DNA, Fraser opined about the trends in genetics, as well as their potential clinical applications. It is astounding how far the field has come in half a century. We now know that the normal chromosomal complement is 46, not 48, and that DNA is the carrier of genetic information. What is currently called the “central dogma” (DNA→RNA→protein) was a mere “modern concept” 50 years ago. The Human Genome Project, which completed the sequencing of the human genome in 2003, was not even a twinkle in a geneticist’s eye in 1958.

From conceptual foundations to practical applications, the role of genetics in medicine has bloomed. Now, molecular testing is the gold standard for diagnosing a multitude of genetic conditions and is the preferred modality for assessing carrier status. State-coordinated newborn screening programs began in the 1960s with testing for phenylketonuria using a dried blood spot. Recently, many states have expanded their panels to screen for more than 40 conditions as a result of the introduction of tandem mass spectrometry into these programs, which has dramatically improved the ability to diagnose and treat inborn errors of metabolism before symptoms develop.

The first genetic counseling graduate program was established a decade after Fraser noted that “the demand for genetic counseling is growing and there is an increasing need for suitably trained counselors.” There are now more than 2400 board-certified genetic counselors, and the need for these professionals continues to transcend multiple specialties, including pediatrics, adults, prenatal, cancer, cardiovascular, hematologic, and neurology.

Most fascinating is how Fraser’s words still ring true today: “Exciting things have been happening in genetics in the past few years, many of them directly or potentially relevant to the practice of medicine.” This discipline has progressed greatly in the last 50 years, and there is still plenty of excitement to come. Medical Genetics is now a primary specialty with more than 1000 board-certified clinical geneticists, “personalized medicine” is on the horizon, and genetic testing is being marketed directly to consumers. The questions we now face are not just how to identify genes, but rather what can/should we do with this information. It was surely impossible for Fraser to predict that genetics would be so intimately involved in all aspects of health care, as we now know it today.

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REFERENCE
Oxygen saturation and heart rate during delivery room resuscitation of infants <30 weeks’ gestation with air or 100% oxygen

J A Dawson,1,2 C O F Kamlin,1 C Wong,1 A B te Pas,1 C P F O’Donnell,3 S M Donath,4 P G Davis,1,2 C J Morley1,2,5

ABSTRACT

Background: Because of concerns about harmful effects of 100% oxygen on newborn infants, air has started to be used for resuscitation in the delivery room.

Objective: To describe changes in preductal oxygen saturation (SpO2) and heart rate (HR) in the first 10 min after birth in very preterm infants initially resuscitated with 100% oxygen (OX100) or air (OX21).

Patients and methods: In July 2006, policy changed from using 100% oxygen to air. Observations of SpO2 and HR before and after the change were recorded whenever a member of the research team was available to attend the birth.

Results: There were 20 infants in the OX100 group and 106 in the OX21 group. In the OX100 group, SpO2 had risen to a median of 84% after 2 min and 94% by 5 min. In the OX21 group, median SpO2 was 31% at 2 min and 54% at 5 min. In the OX21 group, 92% received supplemental oxygen at a median of 5 min; the SpO2 rose to a median of 81% by 6 min. In the first 10 min after birth, 80% and 55% of infants in the OX100 and OX21 groups, respectively, had an SpO2 >95%. Increases in HR over the first 10 min were very similar in the two groups.

Conclusions: Most very preterm infants received supplemental oxygen if air was used for the initial resuscitation. In these infants, the use of backup 100% oxygen and titration against SpO2 resulted in a similar course to “normal” term and preterm infants. Of the infants resuscitated with 100% oxygen, 80% had SpO2 >95% during the first 10 min. The HR changes in the two groups were very similar.

For many years, 100% oxygen was recommended for delivery room (DR) resuscitation of newborn infants of all gestational ages.1 In recent years, experts have suggested that even a brief exposure to high oxygen concentrations at birth in very-low-birthweight infants is harmful.2 There is also accumulating evidence of oxygen toxicity from animal and in vitro studies.3–5 Several studies have found evidence of oxidative damage in infants after short exposure to 100% oxygen in the DR.6–9 This evidence has led to a change in national guidelines for DR resuscitation, which now advise that 21% oxygen should be considered rather than 100% oxygen during initial resuscitation of all infants.10–11 Very preterm infants appear to be at greatest risk of oxidative damage.9,12 Data from infants born at <30 weeks’ gestation are limited.

The protocol for resuscitation of newborn infants at The Royal Women’s Hospital, Melbourne was changed in line with recommendations of the

What is already known on this topic

- Brief exposure to supplemental oxygen in the delivery room can produce an SpO2 >95%.
- Preductal oximetry measures SpO2 and heart rate within 90 s of birth.
- Using oximetry in the delivery room, clinicians can adjust the FiO2 to the SpO2.

What this study adds

- When very preterm infants are initially resuscitated with air, some will require supplemental oxygen.
- If very preterm infants are initially resuscitated with 100% oxygen, many will rapidly become hypoxic.
- Titrating oxygen administration may reduce the number of very preterm infants with SpO2 measurements >95%.

PATIENTS AND METHODS

In this prospective observational study, the cohorts included infants <30 weeks’ gestation, born at The Royal Women’s Hospital, Melbourne between 12 January 2006 and 31 December 2007, when a member of the research team was available to attend the birth. This included 6 months before (OX100) and 18 months after (OX21) July 2006, when the change in policy and implementation of the new guideline took place.

Immediately after birth, an oximetry sensor (LNOP Neo sensor; Masimo, Irvine, California, USA) was placed on the infant’s right hand and then connected to the oximeter (Radical7 V5; Masimo), as previously described.9,10 SpO2, HR and signal quality were stored by the oximeter every 2 s for at least the first 10 min after birth. We used...
2 s averaging and maximum sensitivity. A member of the research team documented any interventions during resuscitation including adjustments made to the fractional inspired oxygen (FiO₂). In the OX₁₀₀ group, the FiO₂ was not able to be changed because there was no gas blender available until infants were moved into a transport cot for transfer to the neonatal intensive care unit. Infants in the OX₂₁ group were managed according to the 2006 Royal Women’s Hospital DR protocol with oxygen titrated according to SpO₂ measurements (fig 1). If infants reached an SpO₂ >90%, the FiO₂ was reduced in stages of ~10% to target the SpO₂ to 80–90%. Active, spontaneously breathing infants, of any gestation, were started on continuous positive airway pressure (CPAP); infants requiring additional support were intubated and ventilated. This did not change over the time of this study. If free flow oxygen, CPAP or intermittent positive pressure ventilation were required, this was given with a Neopuff (Fisher & Paykel, Auckland, New Zealand) T-piece resuscitation device. In the second time period, a small number of infants were managed using a self-inflating resuscitation device (Laerdal, Stavanger, Norway).

After resuscitation, data from the oximeter (HR, SpO₂ and signal quality) were downloaded to a computer using the NeO₂m program (Dr Girvan Malcolm, Royal Prince Alfred Hospital, Sydney, Australia). The data were analysed with Stata (Intercooled 10). We only analysed measurements where the signal was considered normal, ie, no alarm messages (low IQ signal, low perfusion, sensor off, ambient light).

These observational data are presented to illustrate the effects on SpO₂ and HR of resuscitation with either 100% oxygen or air with backup 100% oxygen if the SpO₂ was <70% at 5 min. The data are presented as numbers and proportions (%) for categorical variables, or means (SD) for normally distributed continuous variables and median (interquartile range) when the distribution was skewed. SpO₂ and HR during the first 10 min are illustrated by group using box plots showing the median, interquartile range (IQR) and range with outliers. We did not define primary or secondary outcomes a priori, therefore inferential statistics have not been used to compare these historical cohorts.

Table 1 Characteristics of infants in the two groups

<table>
<thead>
<tr>
<th></th>
<th>OX₁₀₀ (n = 20)</th>
<th>OX₂₁ (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)*</td>
<td>27 (1.6)</td>
<td>27 (1.6)</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>915 (300)</td>
<td>930 (293)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (65)</td>
<td>67 (64)</td>
</tr>
<tr>
<td>Labour started</td>
<td>3 (15)</td>
<td>51 (48)</td>
</tr>
<tr>
<td>Full course of antenatal steroids</td>
<td>18 (90)</td>
<td>87 (82)</td>
</tr>
<tr>
<td>Apgar score at 1 min†</td>
<td>5 (5–7)</td>
<td>5 (3–7)</td>
</tr>
<tr>
<td>Apgar score at 5 min†</td>
<td>8 (7–9)</td>
<td>8 (6–9)</td>
</tr>
<tr>
<td>Cord pH‡</td>
<td>7.28 (7.25–7.34)</td>
<td>7.3 (7.25–7.34)</td>
</tr>
<tr>
<td>Days in oxygen‡</td>
<td>3.5 (2–35.5)</td>
<td>20 (3–44)</td>
</tr>
<tr>
<td>Days treated with CPAP‡</td>
<td>9 (4–42)</td>
<td>9 (4–34)</td>
</tr>
<tr>
<td>Days treated with ventilation†</td>
<td>9 (3–18)</td>
<td>6 (3–12)</td>
</tr>
<tr>
<td>Died before discharge/transfer</td>
<td>3 (15)</td>
<td>12 (11)</td>
</tr>
</tbody>
</table>

Values are number (%) unless indicated otherwise.

*Mean (SD).
†Median (interquartile range).
‡pH available for eight infants in the OX₁₀₀ group and 77 infants in the OX₂₁ group.
CPAP, continuous positive airway pressure; OX₁₀₀, received 100% oxygen; OX₂₁, received 21% oxygen.

Figure 1 The Royal Women’s Hospital guideline for managing administration and titration of supplemental oxygen in the delivery room. CPAP, continuous positive airway pressure; FiO₂, fractional inspired oxygen; NICU, neonatal intensive care unit; SpO₂, oxygen saturation.

When to give supplemental oxygen in the delivery room?

Consider using 100% oxygen if

- SpO₂ < 70% at 5 min
- OR
- SpO₂ < 90% at 5 min
- OR

HR does not increase above 100 bpm after 60 seconds of effective ventilation
- OR chest compressions are initiated

If oxygen is given the FiO₂ is reduced in stages by 10% every 30 seconds once the oximeter SpO₂ reading is >90%

When to start CPAP?

Consider using mask CPAP if at any time the baby is breathing regularly but has signs of respiratory distress, expiratory grunt or recession.

For transport to the NICU insert a nasopharyngeal prong and use the transport ventilator to provide CPAP.

When to intubate?

Consider intubation if the infant remains apnoeic

- OR
- Infant remains bradycardic

- OR
- The heart rate is not improving with 60 seconds of effective ventilation
In the OX_{100} group, verbal consent was obtained from parents to monitor their infants in the DR. In the later group, parental consent was not obtained to monitor infants, as applying an oximeter sensor for monitoring in the DR was the standard of care for management of infants at “high risk” for receiving active resuscitation in our institution.

RESULTS
A total of 126 infants were studied. Pulse oximeter data were available for 125 infants (sensor failure in one infant in the OX_{21} group). All 20 infants in the OX_{100} group received 100% oxygen before 1 min of age. In the OX_{21} group, 97/105 (92%) were subsequently treated with supplemental oxygen at median (IQR) of 5.05 (4–5.5) min. Eight infants (8%) in the OX_{21} group did not receive supplemental oxygen in the DR. Tables 1 and 2 present the clinical characteristics and DR interventions, respectively. No infants received external cardiac massage.

Changes in oxygen saturation
Figure 2 shows the changes in SpO_{2} values for the two groups over the first 10 min. The median SpO_{2} at 1 min was 60% for the OX_{100} group and 55% for the OX_{21} group. By 2 min, the OX_{100} group had a median SpO_{2} of 84%, which continued to rise steadily to a median of 94% at 5 min and 96% by 10 min. For the OX_{21} group, the median SpO_{2} fell to 31% at 2 min, then rose to a median of 54% at 5 min, followed by a sharp rise to 81% at 6 min, after supplementary 100% oxygen was started, reaching a median SpO_{2} of 91% at 10 min. After 5 min, the median SpO_{2} was very similar in the two groups. In the first 10 min after birth, 80% and 55% of infants in the OX_{100} and OX_{21} groups, respectively, had an SpO_{2} >95%.

The eight infants not receiving supplemental oxygen were similar in gestation to infants in both the OX_{100} and OX_{21} groups, with a mean (SD) gestational age of 27.5 (1) weeks; however, they were slightly larger with a mean (SD) birth weight of 1044 (167) g. Six received CPAP and three received positive pressure ventilation.

The eight infants not requiring resuscitation in the first minutes after birth* had an SpO_{2} of 84%, which continued to rise more quickly. In the OX_{21} group, the median SpO_{2} fell to 31% at 2 min, then rose to a median of 54% at 5 min, followed by a sharp rise to 81% at 6 min, after supplementary 100% oxygen was started, reaching a median SpO_{2} of 91% at 10 min. After 5 min, the median SpO_{2} rose into the “normal” range when they were treated with supplemental oxygen at about 5 min. By 6 min, their median SpO_{2} was 81%. By 7 min, there was a significant difference in the SpO_{2} between the OX_{21} group and the OX_{100} group. Fewer infants in the OX_{21} group had an SpO_{2} >95% in the first 10 min than in the OX_{100} group.

DISCUSSION
Pulse oximetry is increasingly used during neonatal resuscitation with some centres using it to target a specific SpO_{2} range. Several studies report SpO_{2} changes in term or near-term infants not requiring resuscitation in the first minutes after birth. Recent studies used pulse oximeters with algorithms that deal with low perfusion and motion artefact, both of which are common in the DR. These studies reported an SpO_{2} of ~60% at 1 min, with many infants taking at least 10 min to achieve >90%. Data from our very preterm infants initially resuscitated with air and backup 100% oxygen had a similar course. In our very preterm infants resuscitated with 100% oxygen, the SpO_{2} rose more quickly.

When the infants in our study were resuscitated initially with air, the SpO_{2} levels were at the lower end of the normal range for healthy term infants and rose into the “normal” range when they were treated with supplemental oxygen at about 5 min. By 6 min, their median SpO_{2} was 81%. By 7 min, there was little difference in the SpO_{2} between the OX_{21} group and the OX_{100} group. Fewer infants in the OX_{21} group had an SpO_{2} >95% in the first 10 min than in the OX_{100} group.

A systematic review found that air was more effective than 100% oxygen for resuscitation of asphyxiated term infants. SpO_{2} data available for some infants in these trials show no significant difference in SpO_{2} measurements for infants randomised to receive air or 100% oxygen. However, few very preterm infants were enrolled in these studies.

Our hospital changed policy to starting resuscitation in air on the basis of evidence from randomised trials comparing initial DR resuscitation with 100% oxygen or air plus 100% oxygen as needed. When we developed our protocol, there were few data from randomised trials comparing 100% oxygen with an oxygen concentration other than 21% in preterm infants. Two studies had randomised infants to either <100% or >21% oxygen. Lundstrom et al. randomised 70 infants <36 weeks’ gestation to receive air or 80% oxygen in the DR. They hypothesised that cerebral blood flow at 2 h of age might be reduced after a brief period of hyperoxia from 80% oxygen at birth. They found that the cerebral blood flow was significantly (p<0.0001) higher in the group treated with air. They also showed, in a subgroup of infants monitored with oximetry, that the mean SpO_{2} was significantly higher at 3, 5 and 7 min in the 80% oxygen group than the air group. In the air group, 74% did not receive supplemental oxygen. In those who received oxygen, the maximum was 50%. The reasons for the different oxygen requirements from those in our study are that the infants in the study of Lundstrom et al were more mature and clinical methods were used rather than SpO_{2} to titrate oxygen in the air group. We have shown that clinicians’ ability to measure colour or HR in the DR is weak. Harling et al. randomised 63 infants <36 weeks’ gestation to either 50% or 100% oxygen in the DR. They hypothesised that cytokine concentration in bronchoalveolar lavage fluid 12 h after birth would be highest in infants treated with 100% oxygen, but found no significant difference. In infants randomised to receive 50% oxygen, one-third had an FiO_{2} above 50% during resuscitation. They did not measure SpO_{2} in the DR.

One approach to selecting the FiO_{2} to use in the DR is to use SpO_{2} measurements to adjust the FiO_{2}. In the neonatal intensive care unit, targeting a narrow range for SpO_{2} and avoiding hyperoxia is associated with reduced morbidity in

#### Table 2 Delivery room interventions

<table>
<thead>
<tr>
<th></th>
<th>OX_{100}</th>
<th>OX_{21}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal suction</td>
<td>9 (45)</td>
<td>51 (48)</td>
</tr>
<tr>
<td>CPAP</td>
<td>16 (80)</td>
<td>72 (69)</td>
</tr>
<tr>
<td>IPPV</td>
<td>14 (70)</td>
<td>80 (76)</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td>8 (40)</td>
<td>42 (40)</td>
</tr>
<tr>
<td>Surfactant administered</td>
<td>2 (10)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Oxygen administered</td>
<td>20 (100)</td>
<td>97 (92)</td>
</tr>
<tr>
<td>Time oxygen started (min from birth)*</td>
<td>1 (0.86–1.2)</td>
<td>5.05 (4–5.5)</td>
</tr>
</tbody>
</table>

Each infant may have received several interventions. Values are number (%) unless indicated otherwise.

*Median (interquartile range).

CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation.

extremely-low-birthweight infants without a detrimental effect on developmental outcomes. It seems logical that a targeted oxygen delivery approach should be applied during resuscitation. A small observational study titrated FIO2 against targeted SpO2 in 15 infants born at 24–29 weeks. They were initially resuscitated with 100% oxygen and the FIO2 adjusted to maintain the SpO2 between 80% and 92%. The FIO2 was reduced from 100% to ~40%.

There are now three controlled studies on very preterm infants where the FIO2 has been titrated to the SpO2 after birth. Escrig et al38 randomised 28 infants <29 weeks’ gestation to receive 30% or 90% oxygen. The FIO2 was adjusted to achieve an SpO2 of 85%. By 5 min, the SpO2 was just above 90%, with no significant difference between the groups. Wang et al33 randomised infants <32 weeks’ gestation to start resuscitation with 100% oxygen or air. In the 100% oxygen group, the FIO2 was weaned if the SpO2 was >95% at 5 min. In the air group, the FIO2 was increased in 25% steps if the SpO2 was <70% at 3 min or 85% at 5 min, or to 100% if the HR was <100 beats/min for 2 min or <60 beats/min for 30 s at any time. All infants in the air group received oxygen from ~3 min. Infants in the 100% oxygen group had significantly higher FIO2 from 1 to 7 min, but from 8 to 20 min it was similar in the two groups. From 2 to 10 min, the SpO2 was higher in the group initially resuscitated with 100% oxygen.

In the only randomised study to mask clinicians to the SpO2, Rabi et al32 randomised 106 infants <33 weeks’ gestation to three groups. One received 100% oxygen throughout resuscitation, the second received an initial concentration of 100%, which could then be changed, and the third group started with air. In the last two groups, the FIO2 was changed by 20% every 15 s until the SpO2 was between 85% and 92%. The mean time that each group spent in the SpO2 target range was 11%, 21% and 16%, respectively (p<0.01). At the end of resuscitation, the FIO2 was similar in the two targeted groups.

The safe SpO2 range for very preterm infants during resuscitation is undefined. We targeted an SpO2 of 80–90%.
HR is the most important indicator of an infant’s response to resuscitation. Using pulse oximetry in the DR provides clinicians with a continuous display of HR without having to interrupt resuscitation to listen to the HR intermittently. Importantly we found that the HR increased after birth at a similar rate in this group of very preterm infants, regardless of whether the infant was resuscitated with air or 100% oxygen. Our finding and those of other researchers have shown that, even with a low SpO2 during the first few minutes after birth, HR was similar to that achieved by healthy newborn term infants not receiving assistance.

Two important questions cannot be answered by our study but could be addressed in future trials. Does pulse oximetry in the DR improve outcomes for preterm infants? If pulse oximetry is effective, what is the safe SpO2 range for preterm infants in the first minutes after birth?

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Competing interests: None.

Patient consent: Parental consent obtained.

REFERENCES
Background: Neonatal resuscitation is a common and important intervention, and adequate ventilation is the key to success. In the delivery room, positive pressure ventilation is given with manual ventilation devices using face masks. Mannequins are widely used to teach and practise this technique. During both simulated and real neonatal resuscitation, chest excursion is used to assess tidal volume delivery, and leakage from the mask is not measured.

Objective: To describe a system that allows measurement of mask leakage and estimation of tidal volume delivery.

Methods: Respiratory function monitors, a modified resuscitation mannequin, and a computer were used to measure leakage from the mask and to assess tidal volume delivery in a model of neonatal resuscitation.

Results: The volume of gas passing through a flow sensor was measured at the face mask. This was a good estimate of the tidal volume entering and leaving the lung in this model. Gas leakage between the mask and mannequin was also measured. This occurred principally during inflation, although gas leakage during deflation was seen when the total leakage was large. A volume of gas that distended the mask but did not enter the lung was also measured.

Conclusion: This system can be used to assess the effectiveness of positive pressure ventilation given using a face mask during simulated neonatal resuscitation. It could be useful for teaching neonatal resuscitation and assessing ventilation through a face mask.

Materials and Methods

Manual ventilation devices and face masks

The manual ventilation devices used at our hospital are the Neopuff infant resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) and the Laerdal infant resuscitator (Laerdal Medical, Oakleigh, Australia). The Neopuff is a T piece device that requires a compressed gas source. It has a valve on the outlet which allows a positive end expiratory pressure to be set for a given flow rate. Occlusion of this valve generates a predetermined peak inspiratory pressure. The Laerdal Infant Resuscitator is a 240 ml silicone self inflating bag. We routinely use round silicone Laerdal face masks (Laerdal Medical) with both devices at our hospital, and used the appropriate size mask (0/1) for the mannequin in this study.

Abbreviations: PPV, positive pressure ventilation; $V_{\text{mask}}$, volume of gas that, under pressure, distends the mask but does not enter the lung; $V_{T}$, tidal volume; $V_{T,\text{in}}$, inspiratory tidal volume at the mask; $V_{T,\text{ex}}$, expiratory tidal volume at the mask.
Modification of the mannequin

The Laerdal Resusci Baby mannequin (Laerdal Medical) is the most widely used resuscitation mannequin and has been found to be the most realistic for the purposes of simulated PPV. This mannequin is supplied with a bag in its “thorax”. When PPV is given appropriately, this bag inflates and slowly deflates, causing visible “chest” rise and fall. We replaced the bag with a test lung with a baseline volume of 50 ml (Draeger, Lubeck, Germany) and connected it via an airtight seal to the mannequin’s “oropharynx”, so that its inflation and deflation caused “chest” excursion similar to that of the original mannequin. A pressure monitoring line was connected immediately proximal to the test lung. The compliance of this model, calculated by measuring the inspired volume of the whole system when pressurised to 25 cm H₂O, was 0.46 m/cm H₂O, comparable to that of an infant with respiratory distress syndrome.¹⁰

Respiratory monitor

Two Florian Respiratory Monitors (Acutronic Medical Systems, Zug, Switzerland) were used to measure gas flow. This monitor uses a flow sensor with a hot wire anemometer with minimal (<1 ml) dead space to detect gas flow. The monitor calculates the volumes of gas passing through the sensor by integration of the flow signal. The flow sensors from the two monitors were placed in series, and their volume measurement calibrated simultaneously using a fixed volume syringe. The monitors measure airway pressures directly and were calibrated against a column of water. The output from the Florian monitors was acquired using an analogue-digital converter using the Spectra software program (Grove Medical, London, UK). This is a computer program specifically designed for the acquisition and analysis of respiratory signals.

Values measured

We placed one flow sensor (FS1, fig 1) between the manual ventilation device and the face mask. With this sensor, we measured the volume of gas passing from the device through the mask—the inspiratory tidal volume at the mask (VT(mask)₁)—and the volume of gas returning from the mannequin through the mask—the expiratory tidal volume at the mask (VT(mask)₂). We placed the second sensor (FS2, fig 1) in the mannequin’s “airway”, proximal to the test lung. With this sensor we measured the tidal volume (VT) entering and leaving the test lung.

Values calculated

If the volume of gas passing from the device through the mask exceeded that returning from the mannequin through the mask, there was a leak between the mask and the face. This was calculated as their difference expressed as a percentage of the inspiratory tidal volume at the mask:

\[
\text{leak} (%) = \frac{(\text{VT(mask)₁} - \text{VT(mask)₂})}{\text{VT(mask)₁}} \times 100.
\]

If leakage from the mask was detected, we wished to determine whether it occurred during inspiration or expiration.
We hypothesised that if the volume of gas passing from the device through the mask (V_{TE(mask)}) did not equal the volume returning through the mask from the mannequin (V_{TE(mask)}) or the tidal volume measured in the mannequin (V_T), there could be three potential reasons:

(1) Leakage during inflation. In the presence of a poor seal between the mask and face, some of the gas passing through FS1 would escape during inflation and not pass through FS2 at the lung. The volume leaking during inflation would thus contribute to V_{TE(mask)} but not to V_T or V_{TE(mask)}

(2) Leakage during deflation. In the presence of a poor seal between the mask and face, some of the gas leaving the lung through FS2 would escape around the mask during deflation and not pass through FS1, resulting in V_{TE(mask)} underestimating V_T.

(3) Distension of the mask. The mask used is made of distensible silicone; thus we hypothesised that, in the presence of a reasonable seal between the mask and face, gas under pressure would distend the mask but not enter the lung (V_{MASK}). This would pass through FS1 during inflation and back through FS1 during deflation, thus contributing to V_{TE(mask)} and V_{TE(mask)} but not to V_T. This volume was demonstrated by placing the mask flat on a bench top and giving positive pressure inflations (fig 2).

To test this system, we recorded 100 inflations, applied by a consultant neonatologist, with various amounts of leakage at the face mask, with each manual ventilation device. Inflations with a peak inspiratory pressure of 25 cm H_2O and positive end expiratory pressure 5 cm H_2O were given with the Neopuff. With the Laerdal bag a manometer was placed in the circuit and a peak inspiratory pressure of 25 cm H_2O was targeted for inflations. Data were analysed using SPSS for Windows (SPSS Inc, Chicago Illinois, USA). Results are expressed as mean (SD).

RESULTS

The mannequin’s airway and lung were leak free, with a difference between the volume entering and leaving the lung of ~0.2 (0.5)%. There were no significant differences in the V_{TI(mask)}, V_{TE(mask)}, or V_T delivered with each manual ventilation device.

Relationship of V_{TE(mask)} to V_T

The volume returning from the mannequin through the mask (V_{TE(mask)}) was a good estimate of the volume leaving the lung (V_T) (fig 3). When there were large leaks (~51%), V_{TE(mask)} tended to underestimate V_T because some of the gas returning from the lung escaped around the mask during deflation (see under Leak). With smaller leaks, V_{TE(mask)} tended to overestimate V_T because a volume of gas distended the mask but did not enter the lung (see under Volume distending the mask and not entering the lung (V_{MASK})). Overall, V_{TE(mask)} was 100.6 (24.8)% of the lung V_T.

Leak

If the volume of gas passing from the ventilation device through the mask was greater than that returning from the mannequin through the mask—that is, V_{TI(mask)} > V_{TE(mask)}—there was a leak between the mask and the face. When the volume returning from mannequin through the mask (V_{TE(mask)}) was greater than or equal to the volume leaving the lung (V_T), all of the leak occurred during inflation.

When the volume leaving the lung (V_T) was greater than the volume returning from the mannequin through the mask (V_{TE(mask)}), a proportion of the leak occurred in deflation. Leaks during deflation were never seen without a leak during inflation and only seen when total leakage was greater than 51%. When there was a large leak, the proportion occurring during deflation (V_T - V_{TI(mask)})/(V_{TI(mask)} - V_{TE(mask)}) × 100) was 89 (10)%, and the proportion during inflation (V_T - V_{TI(mask)})/(V_{TI(mask)} - V_{TE(mask)}) × 100) was 11 (10)%.

Volume distending the mask and not entering the lung (V_{MASK})

When the volume passing from the device through the mask (V_{TI(mask)}) equated the volume returning from the lung (V_{TE(mask)}), there was no leakage from the mask. During these inflations, V_{MASK} was readily demonstrated, as the volume passing through FS1 was greater than that passing through FS2 and entering the lung. Although this became progressively smaller as the total leak increased, V_{MASK} was seen with leaks up to 51%. This volume was 2.4 (1.4) ml, which represented 18.3 (10.5)% of V_T.

DISCUSSION

Positive pressure ventilation using manual ventilation devices via a face mask is an important skill. It is widely taught and practised using mannequins. We have developed a system that allows estimation of tidal volume delivered and measurement of mask leak during simulated PPV. The pressures used may also be recorded using this system. This system was developed with a view to recording real resuscitations in the delivery room.

Studies of PPV through a mask during resuscitation in the delivery room are few. In a study of term infants, “bag and mask” ventilation seemed relatively inefficient, with tidal exchange substantially less than that seen after intubation and rarely sufficient to produce adequate alveolar ventilation. It is worth noting that the apparatus used to measure expired tidal volumes in this study and other assessments of bag and mask ventilation was similar to ours, in that the flow sensor (pneumotachograph) was placed between the manual ventilation device and mask. Although the mask used for these studies differed from ours and its properties are probably not identical, there was leakage from this mask during inflation. It is thus reasonable to speculate that there may also have been leakage during expiration. It is unclear how the expired tidal volume reported (equivalent to our V_{TE(mask)}) related to the expired tidal volume leaving the lungs.
It remains unclear how effective bag and mask ventilation in the delivery room is as a means of delivering a satisfactory tidal volume, particularly in preterm infants, for which there are no reported studies. Moreover, this technique is not without its complications; bradycardia caused by application of a mask during neonatal resuscitation has been reported.\textsuperscript{11,12} Detailed studies of the efficacy of PPV through a face mask in newborn infants are needed, particularly in preterm infants. Applying a flow sensor between the manual ventilation device and face mask in the delivery room may give valuable insights into the effect of PPV on newborn infants during resuscitation.

**CONCLUSIONS**

We have developed a system for practising and assessing PPV using a face mask. In this model, the volume of gas returning through the face mask from the mannequin is a good estimate of the tidal volume entering and leaving the lung. Most leakage from face masks occurs during inflation, although a small proportion does occur during deflation when the total leakage is large (>51%). With leaks of up to 51%, a volume of gas distends the mask but does not enter the lungs. These data will be useful for further evaluation of resuscitation equipment and techniques in bench top studies and in the delivery room.

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**REFERENCES**

Assessing the effectiveness of two round neonatal resuscitation masks: study 1

Fiona E Wood, Colin J Morley, Jennifer A Dawson, C Omar F Kamlin, Louise S Owen, Susan Donath, Peter G Davis

ABSTRACT

Background: Positive pressure ventilation (PPV) via a face mask is an important skill taught using manikins. There have been few attempts to assess the effectiveness of different face mask designs.

Aim: To determine whether leak at the face mask during simulated neonatal resuscitation differed between a new round mask design and the current most widely used model.

Method: 50 participants gave PPV to a modified manikin designed to measure leak at the face mask. Leak was calculated from the difference between the inspired and expired tidal volumes.

Results: Mask leak varied widely with no significant difference between devices; mean (SD) percentage leak for the Laerdal round mask was 55% (31) and with the Fisher & Paykel mask it was 57% (25).

Conclusion: We compared a new neonatal face mask with an established design and found no difference in leak. On average the mask leak was >50% irrespective of operator experience or technique.

Studies of manikins and infants reveal large leaks from face masks. Available masks are either round or anatomically shaped. Cushioned rimmed masks were advocated, however the silicone Laerdal “round” (LR) mask (Laerdal, Stavanger, Norway) is claimed to be more effective. A new round mask (Fisher & Paykel Healthcare, Auckland, New Zealand) is designed to measure leak at the face mask. Leak was calculated from the difference between the inspired and expired tidal volumes. A modified manikin was used to acquire the output from the Florian respiratory monitor through an A:D converter to a computer. Neither screen was visible to participants.

Setting and participants

Neonatal medical, nursing staff and midwives of the Royal Women’s Hospital, Melbourne, Australia participated. All had received training in neonatal resuscitation.

Face masks

The LR mask is the only design in routine use at our hospital. The size 0/1 Laerdal mask and the Fisher & Paykel (FP) 60 mm round mask were the appropriate sizes for the manikin (fig 1). No participant had previously used the FP mask.

Manual ventilation device

The Neopuff Infant Resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) is a pressure limited T-piece device where the peak inspiratory pressure (PIP) and positive end expiratory pressure (PEEP) are set and displayed. All participants were experienced in its use. The hospital protocol suggested a gas flow of 8 l/min, a PEEP of 5 cm H2O and a PIP of 30 cm H2O.

Modified manikin

A Laerdal Resusci baby manikin (Laerdal, Stavanger, Norway) was modified by removing the lung and stomach bags, and positioning a 50 ml test lung (Dräger, Lubeck, Germany) into the chest so chest excursion mimicked that of an untraltered training manikin. The test lung was connected by non-distensible tubing to the mouth with an airtight seal. A pressure monitoring line was connected to the airway. The system compliance when pressurised to 30 cm H2O was 0.5 ml/cm H2O, with a maximal lung volume of 65 ml.

Results

A Florian respiratory monitor (Acutronic Medical Systems, AG, Switzerland) measured inflating pressures and gas flow through the mask. Airway pressure was calibrated against a column of water; a 10 ml syringe was used to calibrate volume measurement. The flow sensor was placed between the T-piece and mask; tidal volume was calculated by integration of the flow signal. Percentage leak at the face mask was the difference between the inspired and expired tidal volumes, expressed as a percentage of the inspired tidal volume. O’Donnell et al showed this system provides a good estimate of the tidal volumes and leak.

Spectra software (Grove Medical, London, UK) was used to acquire the output from the Florian monitor through an A:D converter to a computer. Neither screen was visible to participants.

Study protocol

Participants ventilated the manikin for 2 minutes at a rate of 40–60 breaths per minute according to the hospital protocol, ensuring chest rise. They knew we were recording tidal volume, mask leak and inflation pressures.

The mean ventilation rate, PIP, PEEP, inspiried and expired tidal volumes and percentage leak were measured for a 2 minute period of ventilation with each mask, excluding the first five inflations.

Observations and participant survey

Mask placement and hold techniques, including the use of jaw lift were recorded. Participants were...
asked “Do you think your average mask leak was large or small?” (five-point Likert scale).

Randomisation, primary outcome and power calculation
The order of assessment of the masks was randomised. The sample size was calculated using the mean percentage leak of 70% (SD 30%) for the Laerdal mask. To detect a 15% difference in mean leak with an alpha value of 0.05 and power of 80%, 34 participants were required.

Statistical analysis
Data were analysed using SPSS. A paired t test compared leak between the two masks, p<0.05 was considered significant. One-way ANOVA assessed the influence of placement-and-hold technique on mask leak.

RESULTS
Participants and years of experience
There were 10 participants in each of the professional categories. The median years of experience were: consultants 18.5 years, fellows (SpR grade) 3.3 years, registrars (SHO grade) 0.1 years, neonatal nurses 9.5 years and midwives 3.5 years. A total of 10 084 inflations were recorded.

Techniques of mask application and holds used to form a seal with the face
Participants held the masks in four ways: (1) stem hold, the thumb and index finger gripping the stem; (2) two-point top hold, applying pressure to two points of the top flat portion of the mask; (3) rim hold, encircling much of the rim of the upper flat portion of the mask; (4) any other hold.

LR mask
Frequencies were: stem hold 24%, two-point top hold 46%, rim hold 28% and other 2%. The mask was rolled onto the face by 14% and the remaining 86% placed the mask directly onto the face. Jaw lift was applied by 50%.
FP mask
Frequencies were: stem hold 26%, two-point top hold 44%, rim hold 28% and other 2%. The mask was rolled onto the face by 10%, with 90% directly placing the mask. Jaw lift was applied by 58%.

PIP, PEEP and ventilation rate
There were no significant differences in PIP, PEEP and ventilation rates between the two masks.

Percentage leak at the face mask
The mean (SD) leak for the LR mask was 55% (31) and FP mask was 57% (25), there was no significant difference between the devices.

Figure 2 shows a box-plot where percentage leak is grouped by professional category for each mask. A large variation in leak was found for all categories. One-way ANOVA analysis showed no significant difference in leak for either mask when grouped by mask hold, placement technique or use of jaw lift.

Participant assessment of mask leak compared with actual leak
Figure 3 shows box-plots for LR and FP percentage leak grouped by self assessed leak for each mask. There was wide variation of actual leak in nearly all of the self-assessed leak categories for both masks. No one thought they had a very large leak with the LR mask, despite many with leaks of 80 to 100%. For either mask, no one who said they had a very small/nil leak had a leak less than 20%.

DISCUSSION
We found mask leak varied widely with both masks from almost zero to 100% with no significant difference between the two masks.

Palme et al.1 studied face mask efficiency by measuring leak indirectly. They reported that the Laerdal mask “leaked” least, suggesting that the other designs must have had considerable leaks.

The techniques of holding the mask on the face, the way the mask was placed on the manikin’s face and the use of jaw lift showed considerable variation, with three distinct hold techniques being used. The technique used made no significant difference to the mask leak.

The set PIP could be achieved despite very large mean leaks (data not shown). This is consistent with findings by O’Donnell et al.1,4 Overall, the participants were unable to accurately self-assess their leak.

CONCLUSION
We compared a new mask with an established design and found no difference in leak. On average the mask leak was >50% irrespective of operator experience or technique. Many operators were unaware of the magnitude of the leak.

Further studies of mask techniques, particularly directed towards detecting and reducing leak, are required to improve effectiveness of PPV.

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Competing interests: None.

REFERENCES
Improved techniques reduce face mask leak during simulated neonatal resuscitation: study 2

Fiona E Wood, Colin J Morley, Jennifer A Dawson, C Omar F Kamlin, Louise S Owen, Susan Donath, Peter G Davis

ABSTRACT
Background: Techniques of positioning and holding neonatal face masks vary. Studies have shown that leak at the face mask is common and often substantial irrespective of operator experience.
Aims: (1) To identify a technique for face mask placement and hold which will minimise mask leak. (2) To investigate the effect of written instruction and demonstration of the identified technique on mask leak for two round face masks.
Method: Three experienced neonatologists compared methods of placing and holding face masks to minimise the leak for Fisher & Paykel 60 mm and Laerdal size 0/1 masks. 50 clinical staff gave positive pressure ventilation to a modified manikin designed to measure leak at the face mask. They were provided with written instructions on how to position and hold each mask and then received a demonstration. Face mask leak was measured after each teaching intervention.
Results: A technique of positioning and holding the face masks was identified which minimised leak. The mean (SD) mask leaks before instruction, after instruction and after demonstration were 55% (31), 49% (30), 33% (26) for the Laerdal mask and 57% (25), 47% (28), 32% (30) for the Fisher & Paykel mask. There was no significant difference in mask leak between the two masks. Written instruction alone reduced leak by 8.8% (CI 1.4% to 16.2%) for either mask; when combined with a demonstration of the identified technique on mask leak for two mask designs following training.
Conclusion: Written instruction and demonstration of the identified optimal technique resulted in statistically reduced face mask leak.

In a study comparing the Laerdal and new Fisher & Paykel round face masks, we found that during simulated neonatal resuscitation mask leak varied widely irrespective of the mask, operator experience or technique of mask application. The average mask leak was greater than 55% and the techniques of mask application varied considerably.

Successful neonatal face mask ventilation requires an airtight seal between the rim of the mask and the face. Achieving this can be difficult. Efficacy of mask ventilation is judged by observing chest rise and an increase in heart rate. Leak at the face mask is a common reason for failure of ventilation and often occurs between the cheek and bridge of the nose at the orbital margin. It is a widespread misconception that using a manometer allows the operator to detect leaks. Even with large leaks, in the presence of a high gas flow into the system, the set pressure is achieved. Many participants in our previous study were unaware of their leak and most were unable to accurately assess the leak during positive pressure ventilation (PPV).

Face mask ventilation is a mandatory skill for staff caring for newborn infants and training employs a variety of educational tools. Recommended techniques of mask placement and hold are variable and have not been formally studied.

Round-shaped masks are the most widely used designs and are more easily cleaned. A correctly sized mask should cover the nose and mouth without extending beyond the chin tip or encroaching on the eyes. Applying excessive pressure may bruise the face and mould the back of the head.

The primary aims of this study were to: (1) identify the technique for placing and holding a face mask which minimised mask leak during simulated neonatal resuscitation; (2) investigate the effect of written instruction and a demonstration of the identified technique on reducing mask leak from a Laerdal round mask and a Fisher & Paykel mask. A secondary aim was to determine whether leak at the face mask differed between the two mask designs following training.

METHODS
Equipment
Face masks
The size 0/1 Laerdal round mask (LR) (Laerdal, Stavanger, Norway) and the 60 mm Fisher & Paykel (FP) (Fisher & Paykel Healthcare, Auckland, New Zealand) ‘round’ neonatal resuscitation mask were the appropriate sizes for the manikin. Participants had used the FP mask once previously and the LR mask is in routine use at our hospital.

Manual ventilation device
The Neonpuf infant resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) was used. It is a continuous flow, pressure limited, T-piece device with a built-in manometer and a positive end expiratory pressure (PEEP) valve. The operator set the gas flow to 8 l/min, the peak inspiratory pressure (P IP) to 30 cm H₂O and PEEP to 5 cm H₂O.

Modified manikin
A Laerdal Resusci baby manikin (Laerdal, Stavanger, Norway) was modified by replacing the original ‘lung’ with a 50 ml test lung (Dräger, Lubeck, Germany) connected by non-dissensible...
tubing to the mouth by an airtight seal. It was positioned so
inflation caused chest rise. A pressure monitoring line was
connected to the airway tubing immediately proximal to the
test lung. The compliance of this whole system when
pressurised to 30 cm H\textsubscript{2}O was 0.5 ml/cm H\textsubscript{2}O, with a maximal
test lung volume at this pressure of 65 ml.

**Respiratory monitor, recording equipment and values measured**

A Florian respiratory monitor (Acutronic Medical Systems, Ag,
Switzerland) was used to measure inflating pressures and gas
flow. The flow sensor was placed between the T-piece and face
mask. The tidal volume passing through the sensor was
calculated by integrating the flow signals and calibrated with
a 10 ml syringe. Percentage leak at the face mask was the
difference between the inspired and expired tidal volumes,
expressed as a percentage of the inspired tidal volume.

\[
\text{Percentage leak} = \left( \frac{(\text{inspiratory tidal volume} - \text{expiratory tidal volume})}{\text{inspiratory tidal volume}} \right) \times 100
\]

Airway pressure was measured directly and calibrated against
a column of water.

Mask leak rather than tidal volume is presented because it is
the best way to compare different techniques and masks with
different volumes and compliance.

The Spectra software programme (Grove Medical, London,
UK) was used to acquire output from the Florian monitor
through an analogue to digital converter onto a dedicated
computer. The Florian monitor and computer screen were not
visible to participants.

**Determining the technique for mask placement and hold that
minimises leak**

Three experienced neonatologists investigated recommended
techniques of positioning and holding face masks\textsuperscript{2-4} to
determine the method that minimised leak. These techniques
included: two ways of positioning a mask on the face; placing it
straight onto the face or rolling it onto the face beginning at the
chin tip.\textsuperscript{2} There were three methods of holding the mask on
the face, which are shown in figure 1: “The stem hold”—where
the mask stem is held between the index finger and thumb.\textsuperscript{13} “The two-point top hold”—the thumb and index finger apply
balanced pressure to the top flat portion of the mask where the
silicone is thickest. The stem is not held and the fingers should
not encroach onto the skirt of the mask.\textsuperscript{13} “The OK rim hold”—
the thumb and index finger form a C shape (as in the “OK”
hand gesture) placed around the top flat portion of the mask
applying an even distribution of pressure to the outer edge and
not encroaching onto the skirt of the mask.\textsuperscript{4} Jaw lift was also
investigated; it was applied by using the third, fourth and fifth
fingers to lift the chin forward\textsuperscript{4} against the downward pressure
on the mask.

The three neonatologists tested the different components of
each technique. They found that rolling the mask upwards onto
the face from the chin tip resulted in more accurate positioning
of the mask and reduced the leak at the orbital margin. Jaw lift
reduced the leak and also reduced the downward pressure onto
the manikin’s head. Rolling the mask onto the face and jaw lift
were subsequently used with each of the three mask holds.
When they were satisfied they had perfected all techniques each
neonatologist ventilated the modified manikin using the three
holds with each mask five times (15 tests in total for each mask
hold combination). Each recording lasted 1 minute. The results
are shown in figure 2, where mean percentage mask leak is
grouped by type of hold for each mask design. The lowest
median leak was found with the two-point top hold for the LR
mask and with the rim hold for the FP mask (fig 3). During this
process two clinical cues, which identified the presence of a
good mask seal, were identified; a whistling/hissing sound from
the PEEP valve during expiration and the maintenance of PEEP
at the set level.

**Figure 1** Photographs of the three hold
types demonstrated on the Laerdal round
neonatal mask.

The stem hold

The two-point top hold

The OK rim hold

**Figure 2** Percentage leak at the face mask for each mask hold type and
mask design (LR dark shading, FP light shading). Box plots show median
values (solid lines), interquartile range (margins of box), range of data,
outliers (circles) and extreme values (asterisk).
Setting and participants
The 50 clinicians from our first study\(^1\) took part in this study. They included consultants, fellows, registrars, neonatal nurses and midwives of the Royal Women’s Hospital, Melbourne, Australia. Their years of neonatal experience were recorded.

Study protocol
The results of our first study\(^1\) provided the baseline percentage mask leak, ventilation rate, PIP and PEEP for both mask designs and for each participant using their usual techniques of mask application before any training; these data are presented in the results as “before instruction.”

Each participant received written instructions containing text and photographs of the techniques the investigators found to have the least leak for each mask. Before each recording, participants were given time to familiarise themselves with the equipment. Participants were asked to ventilate the manikin for 2 minutes at a rate of 40–60 inflations per minute with a PIP of 30 cm H\(_2\)O and a PEEP of 5 cm H\(_2\)O ensuring that they were achieving adequate chest rise. We measured the mean ventilation rate, PIP, PEEP, inspired and expired tidal volumes and percentage leak for 2 minutes with each mask, excluding the first five inflations in each case.

The best technique for each mask was then demonstrated to each participant by one instructor (FEW). The inability to achieve the set PEEP with a large leak was demonstrated; as was the presence of a strong whistling/hissing noise from the PEEP valve of the Neopuff, which occurs with minimal face mask leak. Recordings were then made for 30 seconds of PPV with each mask, excluding the first three inflations in each case. Participants knew face mask leak was being assessed.

Participant survey
At the end of the assessments participants were asked, “Would you now feel more or less confident using this mask to deliver intermittent positive pressure ventilation (IPPV) in a resuscitation situation with the ‘two-point top hold’ for the LR mask and … with the ‘OK Rim hold’ for the FP mask.” There were five possible responses ranging from much more confident to much less confident.

Randomisation and statistical analysis
The order of assessment of the two masks was determined by a computer generated randomisation list. Data were analysed using SPSS version 12.0 and Stata 9.2. Multiple linear regression was used to investigate the difference in face mask leak between the two masks and to assess the influence of technique training on mask leak. The regression analysis uses robust standard errors to allow for the repeated measures. Paired t tests were used to compare other ventilation parameters. A p<0.05 was considered significant. Data are expressed as mean (SD) or percentage unless otherwise stated.

RESULTS
Participants
There were 10 participants in each professional category. The median years of experience were: consultants 18.5 years, fellows (SpR level) 3.3 years, registrars (SHO level) 0.1 years, neonatal nurses 9.5 years and midwives 3.5 years. A total of 10 648 inflations were recorded and analysed.

The effect on mask leak for the three holds and two masks is shown in figure 2. The median percentage leak for the two-point top hold and the rim hold was the smallest and least variable for the LR and FP masks, respectively. These two holds are shown in figure 3. Participants’ usual techniques were presented in our first study.\(^1\)

Inflation pressures and rate
The mean (SD) PIP, PEEP and ventilation rates with the LR mask were 29.3 (2.8) cm H\(_2\)O, 4.0 (0.7) cm H\(_2\)O and 49 (19.8)/min before instruction and 29.7 (2.1) cm H\(_2\)O, 4.0 (0.8) cm H\(_2\)O and 54 (36.9)/min after instruction. With the FP mask they were 29.3 (1.8) cm H\(_2\)O, 3.9 (0.7) cm H\(_2\)O and 52 (38.1)/min before instruction and 29.7 (1.9) cm H\(_2\)O, 4.1 (0.7) cm H\(_2\)O and 49 (13.7)/min after instruction. There was no significant difference between the two masks before or after instruction.

The only significant difference following instruction was for the FP mask where the PEEP increased by 0.2 cm H\(_2\)O (p = 0.038, CI 0.1 to 0.4).

Percentage gas leak at the face mask
The mean (SD) percentage leak before instruction, after instruction and after demonstration of the optimal techniques was 55% (31), 49% (30), 33% (26) and 57% (25), 47% (28), 32% (26) respectively.

![Figure 3](image1.png)

**Figure 3** Photographs of the optimal hold technique for each mask design.

![Figure 4](image2.png)

**Figure 4** Percentage leak at the face mask for each mask design when used before instruction, after written instruction and after demonstration of the techniques (LR dark shading, FP light shading). Box-plots show median values (solid line) interquartile range (margins of box), and range of data. “After demonstration” indicates the combined effect on mask leak of the previous written instruction and following demonstration.
(30) for the LR and FP masks respectively. There was no significant difference between the two masks.

Compared with the mean percentage mask leak of participants before instruction, with either mask, written instruction reduced mask leak by 8.8% (CI 1.4% to 16.2%, \( p = 0.02 \)), the demonstration further reduced leak by 15.3% (CI 9.0% to 22.7%, \( p < 0.0005 \)). The combined effect of written instruction followed by a demonstration reduced leak by 24.1% (CI 16.4% to 31.8%, \( p < 0.0005 \)). Figure 4 shows a box-plot of percentage mask leak for each mask design before and after training.

**Participant survey responses**

For the LR mask using the “two-point top hold,” 32% were much more/more confident, 50% neutral/no change and 18% much less/less confident. For the FP mask with “the OK rim hold,” 56% were much more/more confident, 24% neutral/no change and 20% much less/less confident.

**DISCUSSION**

This study identified techniques of placing and holding neonatal face masks which minimised mask leak. Teaching participants these techniques significantly reduced the leak when they ventilated a modified manikin. There was no significant difference in face mask leak between the two neonatal masks before or after technique training.

With variable and unmeasured mask leaks variable tidal volumes are delivered to the lungs. A large leak may reduce the tidal volume and a small leak, with a fixed inflating pressure, may result in excessive tidal volumes. Successful neonatal resuscitation is dependent on delivering an appropriate tidal volume. Controlling the face mask leak is one part of achieving this.

This study was done using a modified manikin; the results may be different with newborn infants.

A criticism of this study is that the reduction in leak may have resulted from the experience gained by the participants as the studies progressed. If this were the case it is likely that the most experienced clinicians would have lower leaks; however we found a wide and similar variation across all professional categories. This variation in performance irrespective of experience was previously reported.\(^{20}\) If experience was important then we would have expected the leak to be lower with a familiar mask than with a new mask; this was not the case.

Caution should be applied in extrapolating the results of this study. Different devices have different characteristics—for example, self inflating bags without PEEP will have a lower leak. The use of different inflation times (Ti) will also alter leak. We did not measure Ti in our study but it is unlikely that this systematically changed through the different phases of the study.

Clinical skills are best taught in stages and both theoretical knowledge and practical demonstration are important.\(^{3,15,21}\) We have seen that a significant reduction in leak can be achieved with written instruction alone; with a further important reduction in leak after the technique was demonstrated.

It has been shown that the manometer does not reliably identify mask leak unless it is very large.\(^{1,4}\) During face mask ventilation, poor mask application and resultant variable mask leaks affect the tidal volume delivery, which may be inadequate for effective gas exchange.\(^{7,22}\) The delivery of very low tidal volumes as a result of large mask leaks could result in failure to resuscitate an infant. Clinical cues, which suggest mask leak, were identified and used in the education process.

This study has shown that identifying, teaching and demonstrating improved techniques of placing and holding neonatal face masks reduces leak with a modified manikin. This may lead to improvements in the efficacy of face mask ventilation during neonatal resuscitation and hopefully a reduction in the incidence of failed face mask resuscitation.

**CONCLUSION**

There was no significant difference in face mask leak between the Laerdal and Fisher & Paykel neonatal face masks when tested on a modified manikin. Specific techniques of face mask placement and hold reduced leak and were incorporated into educational strategies. There was a significant reduction in face mask leak following written instruction alone and a further reduction following demonstration. Further studies are required to determine whether these techniques prove effective in the delivery room.

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Ventilation and Spontaneous Breathing at Birth of Infants with Congenital Diaphragmatic Hernia

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Objective To describe the interaction of spontaneous breaths, manual ventilation, and tidal volumes ($V_T$) during stabilization of infants with congenital diaphragmatic hernia (CDH) in the delivery room.

Study design We studied infants with CDH receiving respiratory support at birth. Airway pressure, flow, and volume were measured, and each breath or inflation was analyzed. Each $V_T$ was classified as a manual inflation, a spontaneous breath, or a spontaneous breath coinciding with manual inflation on the basis of the timing of the pressure and flow waves.

Results Twelve infants had 2957 breaths suitable for analysis, with spontaneous breathing in 11 infants (92%). The mean (±SD) proportion of manual inflations was 41% (±24%), spontaneous breaths 43% (±25%), spontaneous but coinciding with manual inflation 16% (±12%). $V_T$ was significantly different for spontaneous breaths (3.8 ± 1.9 mL/kg), spontaneous breaths coinciding with manual inflation (4.7 ± 2.5 mL/kg), and manual inflations alone (2.6 ± 1.6 mL/kg).

Conclusions Most infants with CDH breathed spontaneously, and manual ventilation was mostly asynchronous. We observed large differences in tidal volumes between spontaneous breaths, manual inflations, or where these coincided, with manual inflations having the lowest $V_T$. Monitoring the respiratory pattern of these infants could improve respiratory support. (J Pediatr 2009;154:369-73)

Congenital diaphragmatic hernia (CDH) occurs in approximately 1 per 2500 live births. Mortality and morbidity rates from CDH are substantial and are related to the degree of pulmonary hypoplasia, size of diaphragmatic defect, and associated anomalies. Observational studies have demonstrated improvements in patient survival rates with ventilation strategies, which might limit overdistension and barotrauma, that encourage spontaneous breathing. However, no studies have reported detailed measurements of respiratory variables immediately after delivery. Stabilization of infants with CDH in the delivery room is guided by protocols and commentary from experts. The International Liaison Committee on Resuscitation has not made any specific recommendations on the management of infants with CDH in the delivery room.

Guidelines that suggest upper limits of peak inspiratory pressure (PIP) may be inappropriate because lung compliance varies considerably between individual infants and in the same infant in the first minutes of life. Changing the PIP to target a tidal volume ($V_T$) may be more logical, but there are no data indicating the range of tidal volumes for an infant with CDH. In addition, an infant with CDH often breathes at birth and will influence the amount of respiratory assistance required. The aim of this study was to describe the interaction of spontaneous breaths and manual ventilation and to measure tidal volumes during stabilization of infants with CDH immediately after birth.

METHODS

The Royal Women’s Hospital (RWH) Melbourne is a tertiary level perinatal center with approximately 6500 deliveries per year and is a regional referral center for antenatal management of CDH. All live births of infants known to have CDH between February 2004 and August 2007 were eligible for inclusion if a member of the research team was available to attend the delivery. After birth infants were admitted to the neonatal intensive care unit (NICU). Manual ventilation was delivered through a facemask. We studied infants with CDH receiving respiratory support at birth. Airway pressure, flow, and volume were measured, and each breath or inflation was analyzed. Each $V_T$ was classified as a manual inflation, a spontaneous breath, or a spontaneous breath coinciding with manual inflation on the basis of the timing of the pressure and flow waves.

Conclusions Most infants with CDH breathed spontaneously, and manual ventilation was mostly asynchronous. We observed large differences in tidal volumes between spontaneous breaths, manual inflations, or where these coincided, with manual inflations having the lowest $V_T$. Monitoring the respiratory pattern of these infants could improve respiratory support. (J Pediatr 2009;154:369-73)

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intensive care unit and stabilized before being transferred to the regional surgical center (Royal Children’s Hospital, Melbourne).

**Resuscitation Practice**

All staff complete an in-house resuscitation training program based on the Australasian Resuscitation Council guidelines. The resuscitation team attending the birth of an infant with CDH included a consultant neonatologist, a neonatal fellow, a resident, a neonatal nurse, and a member of the Resuscitation Research team.

For manual ventilation we used the Neopuff Infant Resuscitator (Fisher & Paykel, Auckland, New Zealand). This is a manually operated device that delivers gas flow through a T-piece in a mask or endotracheal tube. The T-piece has a valve that controls the positive end-expiratory pressure (PEEP). PIP is generated by occlusion of the valve with a finger. PIP and PEEP are set by the operator and for respiratory support of infants with CDH set at 25 and 5 cm H₂O, respectively.

The delivery room management of infants with CDH was individualized, according to the infants’ condition and response to initial resuscitation and based on expert opinion. When the infant was breathing spontaneously without significant respiratory distress, continuous positive airway pressure (CPAP) via mask was given. When there were signs of respiratory difficulty, infants were intubated orally and manually ventilated at the earliest opportunity. Endotracheal tube position was judged from clinical signs and an exhaled carbon dioxide detector (Pedi-Cap, Nellcor Puritan Bennett, Pleasanton, California). Positive pressure ventilation by mask was avoided if possible. All infants were electively intubated within 10 minutes of age according to protocol. Ventilation was provided with the Neopuff until the infant was transferred to the transport ventilator.

For ductal oximetry with the Masimo Radical (Masimo Corp, Irvine, California) was obtained with a sensor on the infant’s right hand. The oximeter was set to capture heart rate and oxygen saturation with maximal sensitivity and average data over 2-second intervals. Resuscitation was started initially with 100% of oxygen until the RWH policy was changed in 2006 in line with the Australian Neonatal Resuscitation Guidelines. There is accumulating evidence that resuscitation with air is as effective as starting with 100% oxygen and that resuscitation of infants with 100% oxygen increases the mortality rate and delays the onset of breathing. A preductal saturation range of 75% to 85% was targeted. A large-bore nasogastric tube was passed to decompress the stomach. Central arterial and venous access was deferred (unless clinically indicated) until admission to the neonatal intensive care unit and a blood gas reading was performed.

**Recording Respiratory Variables**

Inspiratory and expiratory gas flow, V₄, and pressure were measured with the Florian Respiratory Monitor (Acutronic, Zug, Switzerland). This measures pressure in the respiratory circuit directly (at the gas outlet) and uses a sensor placed between the ventilation device and the endotracheal tube to measure gas flow. The data were recorded and analyzed with Spectra software (Grove Medical, London, United Kingdom), a program designed specifically for the recording and analysis of neonatal respiratory signals. The resuscitation team was not blinded to the Florian display, but the team was not informed of the measured tidal volumes and made their decisions on clinical assessment (heart rate, chest movement and oxygen saturations).

A priori, we decided to limit data collection to 10 minutes after cord clamping. The variation in the amount of data collected were dependent on the duration of ventilation, intubation attempts, confirmation of the endotracheal tube position and the time taken to resite the flow sensor after interventions. Breath-by-breath analysis was performed manually to identify one of 3 respiratory patterns:

**Manual inflation.** This was characterized by an inspiratory flow concurrent with an obvious increase in airway pressure from an inflation, the start of expiratory flow synchronous with end of the inflation and at the same time the airway pressure starts to return to the baseline pressure. In the first example (patient 1), expiratory flow does not return to zero which indicates some air-trapping, however this is not confirmed by the expiratory volume. The second example is of patient 9, despite use of high pressures very little flow and volume are reached. This infant died before transfer to the surgical unit.

**Spontaneous breath.** This was characterized by an inspiratory and expiratory flow in absence of a concurrent pressure...
wave from an inflation. Spontaneous breaths occurred during (endotracheal) CPAP and in between inflations (Figure 2).

**Spontaneous Breath Coinciding with a Manual Inflation.**
This was characterized by a combined pattern with juxtaposed or synchronized spontaneous breath during a manual inflation, characterized by the occurrence of two peak inspiratory flow patterns resulting in one volume wave (Figure 3).

For each pattern, the Spectra program was used to measure expired tidal volumes and minute ventilation. Breaths and inflations were excluded from final analysis if leakage was greater than 20% \((V_{Ti \text{ inspired}} - V_{Te \text{ expired}})/V_{Ti \text{ inspired}} \times 100\).

**Statistical Analysis**
Because no information was available on which to base a sample size calculation, we recruited a convenience sample over a 3.5-year period. Parametric and nonparametric tests were used for normally distributed and skewed data respectively. Tidal volumes of the 3 different types of breaths were compared by use of 1-way analysis of variance and post-hoc comparison was performed by use of the Tukey HSD test. Data were analyzed with SPSS version 15 (SPSS Inc, Chicago, Illinois).

**Ethics**
This study was part of a prospective observational study with recordings of delivery room resuscitations with the endorsement of the Human Research and Ethics Committee at RWH. Antenatal consent was obtained before birth if the mother was not in established labor and if time permitted. Where this was not possible, a waiver of consent was used according to the Australian NHMRC guidelines for studies in emergency medicine, and retrospective consent was sought from the parents to use the recording.

**RESULTS**
Over a 3.5-year period, 31 infants with antenatally diagnosed CDH were born alive at RWH. The research team was able to attend 22 deliveries. At 5 deliveries there was insufficient time to set up the equipment for physiological monitoring, and 5 recordings were excluded for poor quality. The remaining 12 infants formed the study population.

The demographic characteristics of the study group were as follow (expressed as mean [±SD] or median [range] where appropriate): gestational age 39 (±1.0) weeks, birth weight 3.3 (±0.3) kg, 5-minute Apgar score 9 (2-10), caesarean section 60%, left-sided lesion 90%, pulse oximetry at 5 minutes and 10 minutes, respectively, 65% (±29%) and 84% (±23%), heart rate at 5 and 10 minutes, respectively, 138 (±49) and 163 (±29) beats/min, at admission pH 7.19 (±0.23), partial pressure of carbon dioxide in arterial blood of 53 (34-161) mm Hg, and fractional concentration of oxygen in inspired gas of 23% (21%-100%). Ventilation settings in
the neonatal intensive care unit were as follows: volume guarantee 3.8 (±0.5) mL/kg, peak inspiratory pressures measured 29 (±9) cm H₂O and maximum set ventilator rates 50 (±8) min⁻¹. Two infants had an associated anomaly: 1 with talipes equinovarus and another with postnatally diagnosed complex congenital heart disease (Table). Karyotype was normal in all infants tested. No infants received antenatal steroids. Face mask continuous positive airway pressure (CPAP) was provided as initial respiratory support in 4 infants with or without coinciding inflations, compared with manual inflations alone.

**Breathing Patterns**

From the 12 infants, 3547 breaths or inflations were recorded. Leak in excess of 20% was seen in 603 (17%) and these were excluded. A total of 2957 breaths or inflations were recorded. Leak in excess of 20% was seen in 603 (17%) and these patterns in each patient are shown in (Table). From the 12 infants, 3547 breaths or inflations were analyzed, with an average of 237 (85) breaths per patient (Table).

Spontaneous breathing was observed in 11 infants (92%). Overall mean (±SD) proportion of manual inflations was 41% (±25%). Spontaneous breaths accounted for 43% (±25%) and spontaneous breaths that coincided with an inflation accounted for 16% (±12%). The percentages of these patterns in each patient are shown in (Table).

**Respiratory Variables**

In all breaths and inflations of the 12 patients the mean (±SD) respiratory rate was 65 (±24) breaths/min, tidal volume 3.4 (±2.1) mL/kg, minute volume 210 (±129) mL/kg/min, inspiration time 0.41 (±0.20) s, expiration time 0.60 (±0.33) s, peak inspiratory flow 4.1 (2.1) L/min and peak expiratory flow 3.7 (1.8) L/min. The mean (SD) peak inspiratory pressure was 26.1 (2.1) cm H₂O and PEEP was 5.5 (1.7) cm H₂O.

**Tidal Volume**

The mean (±SD) Vₜ during spontaneous breaths was 3.8 (±1.9) mL/kg, during spontaneous breaths that coincided with inflation it was 4.7 (±2.5) mL/kg and during manual inflations it was 2.6 (±1.6) mL/kg. A 1-way analysis of variance showed a statistically significant difference in tidal volume for the 3 groups (*F*[2, 2873] = 2812; *P < .0001). Post-hoc comparison with Tukey HSD test indicated that all groups were significantly different from each other (*P < .0001). The mean Vₜ for each pattern per patient are shown in the Table.

**DISCUSSION**

We reported respiratory patterns and variables during stabilization of infants with CDH at birth. Most infants in our cohort breathed at birth, and only a small proportion of these spontaneous breaths coincided with a manual inflation. Significantly higher Vₜ occurred during spontaneous breaths with or without coinciding inflations, compared with manual inflations alone.

Current guidelines for the management of infants with CDH advise limiting the peak inspiratory pressure (usually not exceeding 25 cm H₂O) and advocate permissive hypercapnia to avoid overdistention.14,15 However, there is a growing appreciation that in preterm infants volutrauma may be more important than barotrauma.16-18 and this may also be pertinent to the management of infants with CDH. The Vₜ delivered when a set pressure is used depends on the compliance of the lung and the spontaneous respiratory effort of the infant. The lung compliance of an infant with CDH is mainly determined by the severity of the lung hypoplasia. In addition,
the mechanical properties of the lung can change quickly as fluid is reabsorbed and the lung aerates. This makes it difficult
to generalize and advise a "safe" range of $V_T$ for all infants
with CDH. Because volumes of both ipsilateral and contralat-
eral lungs of infants with CDH appear to be lower than normal, 19 this makes it likely that the "safe" range of $V_T$
during ventilation is lower than that for normal term infants
(4-6 mL/kg).20 The individual $V_T$ measured during sponta-
neous breathing may represent the "safe" range for a given
infant. From our observations the implication is that using
pressures, as advised by protocol, in most cases the $V_T$
given was too low during a manual inflation and too high during a
synchronized breath. Our speculation is that this could lead to
volutrauma.

Infants with CDH can be severely compromised, but in
most cases their respiratory effort is comparable to healthy
newborn infants. Most infants started breathing at birth, and
most cases their respiratory effort is comparable to healthy
volutrauma.
synchronized breath. Our speculation is that this could lead to

The study is limited by the small number of infants
observed. Therefore the results may not be representative of
all infants with CDH. However, we have shown that it
feasible to monitor respiratory function in infants with CDH
at birth. Most clinicians in CDH centers are familiar with
respiratory function monitoring, and larger observational
studies should be performed to better understand the require-
ments for respiratory support.

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Spontaneous Breathing Patterns of Very Preterm Infants Treated With Continuous Positive Airway Pressure at Birth

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ABSTRACT: There are no data describing how very preterm infants breathe spontaneously immediately after birth. We studied a convenience sample of spontaneously breathing infants ≤32 wk’ gestation treated with facemask continuous positive airway pressure at birth. Airway pressure and flow were measured and each breath analyzed. Twelve infants had 792 breaths suitable for analysis. Results are given as mean (SD). Gestational age and birth weight were 29 (1.9) wk and 1220 (412) g. Recordings were started 159 (77) s after birth. The inspiratory pattern and duration was similar in all breaths at 0.36 (0.11) s. There were five expiratory patterns; most infants had more than one. In 79% of breaths expiratory duration (1.6 (1.1) s) was slowed or held by interruption or braking of expiratory flow. It was braked in 47% to a complete expiratory hold, in 22% by grunting or crying, and in 10% by slow or interrupted expiration. In 21% of the breaths, expiration was not interrupted and lasted 0.53 (0.13) s. Half of these breaths represented a panting pattern (rate >60 /min). Immediately after birth, most very preterm infants, treated with continuous positive airway pressure, frequently prolong their expiration by braking the expiratory flow. (Pediatr Res 64: 281–285, 2008)

Very preterm infants may have difficulty aerating their lungs after birth because of poor respiratory drive, weak muscles, flexible ribs, surfactant deficiency, and impaired lung liquid clearance (1–4). However, many very preterm infants treated immediately after birth with continuous positive airway pressure (CPAP) breathe well and achieve normal blood gases (5,6).

Between 1960 and 1986, observational data were gathered immediately after birth from small numbers of spontaneously breathing term infants and used to inform international guidelines for neonatal resuscitation (7–14). There are no data describing how very preterm infants breathe and aerate their lungs immediately after birth. It may be inappropriate to assume the results of studies of term infants also apply to very preterm infants. The aim of this study was to investigate the spontaneous breathing patterns of very preterm infants treated with CPAP immediately after birth.

PATIENTS AND METHODS

These physiologic studies were approved by the Royal Women’s Hospital Research and Ethics committees. Parental consent for these recordings was obtained.

At the Royal Women’s Hospital, Melbourne, spontaneously breathing newly born very preterm infants with respiratory difficulty are assisted with a facemask CPAP. Between 2004 and 2007, we recorded physiologic parameters during delivery room stabilization of very preterm infants. All recordings of infants born at ≤32 wk’ gestation, who were spontaneously breathing, while treated with CPAP via a face mask, were identified and their breathing patterns in the first 10 minutes of life were analyzed. Our guidelines recommend to start with a CPAP-level set on 8 cmH₂O. Infants were excluded if positive pressure ventilation was given at birth. We only used recordings of infants if there were: a) no signs of mask leak, b) a clean flow signal, not disturbed by secretions or infant movements, and c) no signs of movement of the mask.

Recording equipment. Gas flow in and out of the infant was measured with a hot-wire anemometer (Florian: Acutronic Medical Systems AG, Zug, Switzerland) placed between the T-piece of a resuscitation device (Neopuff Infant Resuscitator, Fisher and Paykel, Auckland, New Zealand) and the facemask. This signal was integrated to derive inspired and expired tidal volume. Airway pressure was measured immediately proximal to the mask. The signals of airway flow, tidal volumes, and airway pressure were digitised and recorded at 200 Hz using a neonatal respiratory physiologic recording program (Spectra, Grove Medical Limited, Hampton, UK).

Data collection. Demographic data were collected from the hospital records. The total number of breaths analyzed for each infant was noted, including their time after birth. Details of the waveforms of pressure, flow, and tidal volume were carefully analyzed to identify the breathing patterns. Breaths of each pattern were analyzed in detail and the following parameters noted (see also Figures): respiratory rate, inspiration pattern and duration, expiratory hold (the time from zero flow at the end of inspiration to the start of the main expiratory flow), expiratory duration, postexpiratory pause (the time from zero flow at the end of expiration to the start of positive flow at the beginning of inspiration), duration of each breath, peak inspiratory flow, peak expiratory flow; inspiratory and expiratory tidal volumes (15).

Data analysis. Data were analyzed with SPSS (SPSS for windows, version 12.0, 2005, Chicago, IL) and presented as mean (SD) or number (%) where appropriate.

RESULTS

Recordings from 103 infants were examined in detail, 91 of these were excluded from analysis for the following reasons: 58 infants were ventilated with mask and bag at the start of resuscitation, 27 recordings showed mask leak and 6 flow signals were disturbed by secretions or movement of the mask. Twelve infants had recordings that were suitable for analysis. Their mean (SD) gestational age was 29 (1.9) weeks, birth weight 1220 (412) g and median (range) of the 5 min Apgar score was 8 (8,9). Eleven received prenatal steroids and seven were born by

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AJP is recipient of a Ter Meulen fund grant for working visits, Royal Netherlands Academy of Arts and Sciences, The Netherlands.
caesarean section. The mean time for the start of recording the analyzed breaths was 159 s (range, 26–301) after birth. None of the infants were intubated in the delivery room.

A total of 792 breaths (range, 17–105 per infant) were analyzed. The pattern of inspiration was similar in all breaths with a duration of 0.36 (0.11) s. There were five different patterns of expiratory flow (Figs. 1–5). Three were characterized by interruption or braking of expiration and were seen in 79% (627/792) of the breaths. They prolonged the expiratory time to 1.6 (1.1) s. The remaining two patterns were seen in 21% (165/792) of the breaths. These showed no evidence of interruption or braking of expiration and had an expiration time of 0.53 (0.13) s. The numbers of breaths of each pattern for each patient are shown in Table 1. In most infants, more than one pattern was observed. The respiratory parameters of each pattern are shown in Table 2.

**Expiratory hold.** In 47% (372/792) of the breaths expiration was braked to a complete hold, postponing the main expiratory flow (Fig. 1). This pattern was characterized by a period of no expiratory flow ending with a single expiratory flow peak or multiple expiratory flow peaks. Expiration was immediately followed by an inspiration, i.e., there was no postexpiratory pause.

**Slow expiration.** In 10% (83/792) of breaths, the expiratory pattern was characterized by an initial low expiratory flow rate ending with a single expiratory flow peak late in expiration and/or frequently interrupted expiratory flow waves (Fig. 2). These were immediately followed by an inspiration.

**Crying/grunting.** In 22% (172/792) of the breaths, expiration was slowed by either grunting or crying (Fig. 3A and B). This pattern was characterized by a large inspiration followed by high frequency interruptions to the expiratory flow wave, observed as a noise signal in the wave. Expiration was then immediately followed by inspiration. We categorized crying and grunting as one pattern as it was difficult in most cases to distinguish between them from the recording and we did not record sound.

**Patterns where expiration was not braked.** In 21% (165/792) of the breaths, an unbraked or normal expiratory pattern was seen (Figs. 4 and 5). This was characterized by uninterrupted expiration with peak expiratory flow early in expiration. Expiration was not prolonged (I:E time approximately 1:1.5) although sometimes the expiratory flow was followed by an expiratory pause before the next inspiration (Fig. 4). In 91/165 of these breaths, the pattern was characterized by a
respiratory rate greater than 60/min by shortening the expiratory time (I:E time to approximately 1:1) and small tidal volumes. In these breaths, there was no postexpiratory pause before inspiration. We named this the panting pattern (Fig. 5).

DISCUSSION

Most of the breaths of these very preterm infants, recorded in the minutes after birth, were characterized by interruption, or braking, of the expiratory flow. This slowed or even stopped the expiration and increased the expiratory time. Slow expiration, grunting/crying, and the expiratory hold pattern each represent different forms of expiratory braking (16–23). These patterns were shown to prevent a loss of lung volume during expiration in older term (16–23) and preterm infants (19,20).

Airflow is controlled throughout the breathing cycle by reflex action of diaphragmatic and laryngeal muscle activity (24–30). These reflexes are present at birth in term and preterm infants and have a crucial role in the control of breathing and lung volume (22,31–37). There are two mechanisms for stopping or slowing expiratory flow and maintaining an elevated lung volume during expiration. The first is diaphragmatic postinspiratory activity, which slows the rate of lung deflation by counteracting its passive recoil (16–20). The second is by closure or narrowing of the larynx (19,21–23). The expiratory noise associated with vocal cord adduction, i.e., grunting has been recognized as a dynamic braking of expiration by the larynx (22,38). In absence of an audible grunt, the larynx still maintains a dynamic role in slowing expiration (27).

The pattern that we most frequently observed, the expiratory hold pattern, has similar characteristics to the first breaths observed in term infants at birth (13,39,40). After inspiration, gas is held in the lung under pressure by laryngeal adduction braking the expiratory flow. This has also been observed in preterm and term infants during spontaneous breathing later in life, but did not occur as frequently as in our study (16–19,22,23,38).

During braked expiration, the closed or narrowed glottis, with increased intra-pulmonary pressure from abdominal muscle contraction, causes the airway pressure to be maintained above atmospheric. This could represent an important force for clearing the fluid from the lung, facilitating distribution of gas within the lung, and splinting the alveoli and airways open (9,10,13,14,22,39).

Another strategy infants can use to increase end-expiratory volume is a high respiratory rate. This was seen in the panting pattern. The shortened expiratory time reduces the time for gas to leave the lung (35).

The spontaneous gas flow patterns we observed are different from those seen when manual inflations are given during neonatal resuscitation (Fig. 6). The neonatal resuscitation guidelines do not mandate any particular ventilation pattern, although they do suggest a rate of 40–60/min (41). Prolonged inflations are mentioned but not mandated for the initial breaths (41). This study demonstrates that very preterm infants have specific mechanisms to inflate their lungs and try to keep them inflated immediately after birth. It is possible that a similar strategy used during the initial resuscitation of a preterm infant who is apnoeic or breathes insufficiently, i.e., inflation followed by a hold and a short expiration, may be more effective than traditional techniques which use a short inspiratory time and no hold.

Making recordings of how very preterm infants breathe immediately after birth is very difficult. Because of the constraints of not interfering with the infant’s care or resuscitation and yet applying a facemask with a pneumotachograph and CPAP device attached, as soon as possible after birth, limited the number of infants that could be recorded in the time available and the number of recordings that could be made. This is an area of research where it is not possible to study large numbers in detail and obtaining a recording of sufficient quality for analysis limited the number of inflations that could be studied. In particular, it caused a large variation in the number of breaths...
analyzed per infant. Analyzing a longer breath sequence over a longer period would have been ideal but was not practical. Future studies should endeavor to achieve this. Similar studies immediately after birth done by Karlberg et al. (39), Milner and Sauders (9), and Mortola et al. (13) also recorded a limited number of breaths in small groups of patients.

Our observation could be biased by the practical difficulties of making respiratory recordings immediately after birth. Our neonatal resuscitation research team has extensive experience in making physiologic recordings and recognized it was very difficult to get long recordings without ventilation, mask leak, movement of the mask or patient, secretions, etc. All recordings with artifacts have been excluded from analysis and as expected, only a minority of recordings was suitable for inclusion in this study. Both small number of recordings and the wide range of analyzed breaths per infant could have led to a bias. Therefore, we cannot assume that the patterns observed in this study represent the patterns of all spontaneously breathing preterm infants. Nevertheless, they are similar to those described in newly born term infants (13,39,40) and in older preterm infants (19,20).

Although a mask on the face is a standard procedure for delivering positive airway pressure to infants after birth it might influence the breathing pattern by stimulating respiratory reflexes and thereby influence the tidal volume and respiratory rate (42,43). However, it is impossible to measure inspiratory and expiratory flows and tidal volumes in this situation without use of face mask (44,45). Previous studies reported no adverse effects of a face mask during the first breaths (7–14). It is possible that the added dead space of the face mask caused carbon dioxide accumulation and influenced the breathing pattern (46,47). However, the wide diameter of the mask reduced rebreathing and firm application of the mask reduced the dead space (15).

In these very preterm infants, it was not appropriate to use a facemask without also providing CPAP. The use of CPAP might have influenced the breathing pattern. However, the patterns we have recorded are similar to some breathing patterns described in term infants at birth without CPAP (13,39,40).

Table 1. Number of each type of breathing pattern for each infant

<table>
<thead>
<tr>
<th>Infant</th>
<th>Gestation (wk)</th>
<th>Expiratory hold</th>
<th>Crying/grunting</th>
<th>Slow expiration</th>
<th>Panting</th>
<th>Unbraked expiration, normal respiratory rate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>49</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>68</td>
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<tr>
<td>2</td>
<td>28</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>32</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>31</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>37</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>58</td>
<td>28</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>104</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>46</td>
<td>0</td>
<td>10</td>
<td>18</td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>5</td>
<td>11</td>
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<td>11</td>
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</tr>
<tr>
<td>9</td>
<td>32</td>
<td>42</td>
<td>16</td>
<td>37</td>
<td>2</td>
<td>1</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>56</td>
<td>22</td>
<td>17</td>
<td>10</td>
<td>0</td>
<td>105</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>10</td>
<td>66</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>7</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>372</td>
<td>172</td>
<td>83</td>
<td>91</td>
<td>74</td>
<td>792</td>
</tr>
</tbody>
</table>

Table 2. Respiratory parameters for each breathing patterns for all infants

<table>
<thead>
<tr>
<th>Parameter mean (SD)</th>
<th>Expiratory hold</th>
<th>Slow expiration</th>
<th>Crying/grunting</th>
<th>Unbraked expiration, normal respiratory rate</th>
<th>Panting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>32 (11)</td>
<td>48 (16)</td>
<td>42 (18)</td>
<td>54 (4)</td>
<td>88 (18)</td>
</tr>
<tr>
<td>Inspiratory time (sec)</td>
<td>0.36 (0.10)</td>
<td>0.34 (0.15)</td>
<td>0.38 (0.14)</td>
<td>0.40 (0.08)</td>
<td>0.34 (0.07)</td>
</tr>
<tr>
<td>Expiratory hold (sec)</td>
<td>1.53 (1.01)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Expiratory time (sec)*</td>
<td>1.85 (1.14)</td>
<td>1.10 (0.90)</td>
<td>1.30 (0.75)</td>
<td>0.65 (0.11)</td>
<td>0.41 (0.14)</td>
</tr>
<tr>
<td>Postexpiratory pause (sec)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.07 (0.03)</td>
<td>0</td>
</tr>
<tr>
<td>Peak inspiratory (ml/min)</td>
<td>32 (16)</td>
<td>29 (130)</td>
<td>63 (37)</td>
<td>22 (9)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Peak expiratory (ml/min)</td>
<td>–42 (30)</td>
<td>–24 (14)</td>
<td>–36 (24)</td>
<td>–19 (15)</td>
<td>–18 (12)</td>
</tr>
<tr>
<td>Tidal volume (ml/kg)</td>
<td>5.8 (4.1)</td>
<td>3.5 (2.3)</td>
<td>7.5 (4.2)</td>
<td>4.2 (1.5)</td>
<td>3.1 (1.7)</td>
</tr>
</tbody>
</table>

* Expiratory time of expiratory hold pattern is time of expiration plus duration of the hold.

Figure 6. Part of a recording of resuscitation of a neonate born at 26 wk gestation showing two inflations with Laerdal mask and bag. Inspiration is immediately followed by expiration, with no expiratory hold or pause.
A nCPAP of 8 cm H\(_2\)O was used for several reasons. Studies show a distending pressure is important for maintaining FRC (48), increasing lung compliance and improving oxygenation, and that 8 cm H\(_2\)O is more effective than a lower pressure (49). Studies have used pressures up to 10 cm H\(_2\)O (50) and Gregory et al. (51) used a nCPAP pressure up to 12 mm Hg. Immediately after birth is the time when most assistance is needed to develop and maintain an FRC because the lungs are fluid filled and the lungs are stiff. It is likely that a relatively high pressure may be necessary in the first few minutes. Animal studies show that a pressure of 8 cm H\(_2\)O improves oxygenation and reduces lung injury better than lower pressures (52,53). The optimum nCPAP pressure for treating individual very preterm infants from birth is unknown.

In conclusion, this is the first study reporting the spontaneous breathing patterns in very preterm infants in the minutes after birth. We frequently observed prolongation of expiration in very preterm infants treated with facemask CPAP immediately after birth, predominantly characterized by a breath hold. This braking of expiration is recognized as an attempt to defend lung volume. Our speculation is that techniques of positive pressure ventilation that mimic expiratory braking might improve the effectiveness of respiratory support in the delivery room.

REFERENCES

8. Saunders RA, Milner AD 1978 Pulmonary pressure/volume relationships during the first breath after birth, predominantly characterized by a breath hold. This braking of expiration is recognized as an attempt to defend lung volume. Our speculation is that techniques of positive pressure ventilation that mimic expiratory braking might improve the effectiveness of respiratory support in the delivery room.
Breathing Patterns in Preterm and Term Infants Immediately After Birth

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ABSTRACT: There is limited data describing how preterm and term infants breathe spontaneously immediately after birth. We studied spontaneously breathing infants ≥29 wk immediately after birth. Airway flow and tidal volume were measured for 90 s using a hot wire anemometer attached to a facemask. Twelve preterm and 13 term infants had recordings suitable for analysis. The median (inter-quartile range) proportion of expiratory braking was very high in both groups (preterm 90 [74–99]%; term 87 [74–94]%; NS). Crying pattern was the predominant breathing pattern for both groups (62 [36–77]% vs. 64 [46–79]%; NS). Preterm infants showed a higher incidence of expiratory hold pattern (9 [4–17]% vs. 2 [0–6]%: \( p = 0.02 \)). Both groups had large tidal volumes (6.7 [3.9] vs. 6.5 [4.1] mL/kg), high peak inspiratory flows (5.7 [3.8] vs. 8.0 [5] L/min), lower peak expiratory flow (3.6 [2.4] vs. 4.8 [3.2] L/min), short inspiration time (0.31 [0.13] vs. 0.32 [0.16] s) and long expiration time (0.93 [0.64] vs. 1.14 [0.86] s). Directly after birth, both preterm and term infants frequently brake their expiration, mostly by crying. Preterm infants use significantly more expiratory braking holds to defend their lung volume. *(Pediatr Res 65: 352–356, 2009)*

Between 1960 and 1986, observational data were gathered on breathing patterns immediately after birth from small numbers of term infants and were used to inform international guidelines for neonatal resuscitation (1–8). These studies demonstrated that the first breaths tend to be deeper and longer than subsequent breaths and are characterized by a short deep inspiration followed by a prolonged expiratory phase. This is known as expiratory braking and helps to develop and maintain functional residual capacity (FRC) during the immediate newborn period when the lung is partially liquid filled and the chest wall is very compliant (9,10). Although this respiratory pattern has also been observed in preterm and term infants later in life (11–15), there are no data describing the breathing pattern of very preterm infants immediately after birth.

Antenatal glucocorticoid treatment has greatly improved postnatal lung function and many preterm infants breathe well and establish an FRC at birth by themselves or with only the support of continuous positive airway pressure (16–20). However, preterm infants have a poor respiratory drive, weak muscles, flexible ribs, surfactant deficiency, and impaired lung liquid clearance, which make it difficult for them to breathe easily at birth (21–24). With these inherent problems, we hypothesized that preterm infants in the minutes after birth will show more expiratory braking than term infants.

The aim of this study was to compare the breathing patterns of preterm and term infants immediately after birth.

METHODS

All inborn infants, term and preterm ≥29 wk gestation, who were expected to require no respiratory support at birth, were eligible for this study. The study was approved by the Royal Women’s Hospital Research and Ethics committees. Written consent was obtained before birth.

Immediately after birth, as soon as the infant was placed on the resuscitation, a facemask (Laerdal round mask, Laerdal Stavanger, Norway) was applied to the face, enclosing the mouth and nose. To ensure that there was no mask leak, a finger was applied around the infant’s chin and held firmly during the recording. A hot wire anemometer (Florian: Acutronic Medical Systems AG, Zug, Switzerland) was attached proximally to the Laerdal mask measuring inspiratory and expiratory gas flow (see also Fig. 1) (25). The flow signal was integrated to provide inspired and expired tidal volume. The signals of airway flow and tidal volumes were digitized and recorded at 200 Hz using a neonatal respiratory physiologic recording program (Spectra, Grove Medical Limited, Hampton, UK).

To eliminate the risk of carbon dioxide retention caused by the mask (26), a bias flow of 2 L/min of air was fed in through the face mask and the anemometer rezeroed (Fig. 1) (26). The dead space of the hot wire anemometers is 1 mL and clinically negligible (27).

To minimize interference with the normal monitoring and stabilization of preterm and term infants at birth, we recorded for only 90 s. If there were signs of respiratory compromise, the study was abandoned and ventilatory support was given according to the Australian Neonatal Resuscitation guidelines (28).

Data collection. The following clinical data were collected: gestational age, birth weight, sex, mode of delivery, and Apgar score. The total number of breaths analyzed for each infant was noted, including their time after birth. Details of the waveforms of pressure, flow, and tidal volume were carefully analyzed to identify breathing patterns. Breaths of each pattern were analyzed in detail by a breath-to-breath analysis and the following parameters were calculated: respiratory rate, inspiration pattern and duration, expiratory hold (the time from zero flow at the end of inspiration to the start of the main expiratory flow), expiratory duration, postexpiratory pause (the time from zero flow at the end of expiration to the start of positive flow at the beginning of inspiration), duration of each breath, peak inspiratory flow, peak expiratory flow; inspiratory and expiratory tidal volumes (29).

Recordings were excluded if: a) there were signs of mask leak, b) the flow signal was disturbed by secretions or infant movements, c) there were signs of movement of the mask, or if ventilatory support was given.

Based on our earlier observations of spontaneous breathing patterns in infants at birth, we divided the breathing patterns by the type of expiration: braked or unbraked. These patterns were defined as follows.

**Expiratory hold.** Expiration is braked to a complete hold, postponing the main expiratory flow (Fig. 2). This pattern is characterized by a period of no expiratory flow ending with a single expiratory flow peak or multiple expiratory flow peaks. Expiration is immediately followed by an inspiration, i.e., there is no postexpiratory pause.

**Slow expiration.** Expiration is characterized by an initial low expiratory flow rate ending with a single expiratory flow peak late in expiration and/or

Abbreviations: FRC, functional residual capacity

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A.B.P. and J.A.D. are recipients of a Royal Women’s Hospital postgraduate scholarship.
frequently interrupted expiratory flow waves (Fig. 3). These are immediately followed by an inspiration.

**Crying.** Expiration is slowed by crying (Fig. 4). This pattern is characterized by a large inspiration followed by high frequency interruptions to the expiratory flow wave, which can be seen in the wave as a noise signal. Expiration is then immediately followed by inspiration. A cry has a higher amplitude and frequency than a grunt.

**Grunting.** Expiration is slowed by grunting (Fig. 5). This pattern is characterized by a large inspiration followed by high frequency interruptions to the expiratory flow wave, which can be seen in the wave as a noise signal. Expiration is then immediately followed by inspiration. In general, a grunt has lower amplitude and frequency than a cry.

**Unbraked expiration patterns.** These are characterized by uninterrupted expiration with peak expiratory flow early in expiration. Expiration is not prolonged (I:E time approximately 1:1.5) although sometimes the expiratory flow is followed by an expiratory pause before the next inspiration (Fig. 6).

The unbraked breathing pattern was called panting when the respiratory rate was greater than 60/min. This is achieved by shortening the expiratory time (I:E time to approximately 1:1) and often small tidal volumes were noted. In these breaths, there was no postexpiratory pause before inspiration (Fig. 7).
Breathing Patterns at Birth

RESULTS

During the period August 2007–February 2008 there were 62 eligible infants. In seven infants, the mothers were not approached because the midwife/doctor considered it would be too stressful for the parents. In ten infants, the parents did not consent. In four infants, no recording was obtained due to technical problems. Forty-one recordings were made in 27 preterm infants and 14 term infants. Of these 16 recordings were excluded from analysis because secretions causing dirty flow signal in one term and one preterm infant and a further 14 preterm infants needed ventilatory support. Thus, there were 25 recordings available for analysis, 12 preterm and 13 term infants. We analyzed 769 breaths in the preterm infants and 749 breaths in the term infants. The characteristics of the infants studied are shown in Table 1.

Patterns of Breathing. The incidence of breaths of each pattern for both groups are shown in Table 2, and examples of each pattern are shown in Figures 2–7.

The median (interquartile range) proportion of expiratory braking patterns was very high in both groups, in preterm infants (0.93 [0.32–0.64] vs. 0.86 [0.50–0.64]; p = 0.001) and a lower peak flow during expiration (3.6 [2.4] vs. 4.8 [3.2] mL/kg; p < 0.001). The average inspiration time was short and not different between the groups (0.31 [0.13] vs. 0.32 [0.16] s; p = 0.5). The average expiration time in both groups was long, but in preterm infants, it was shorter than in term infants (0.93 [0.64] vs. 1.14 [0.86] s; p < 0.001).

The values of the respiratory parameters of both groups when divided into breaths with braked and unbraked expiration are shown in Table 3. In both groups, breaths with braked expiration were characterized by larger tidal volume, larger peak inspiratory flow, longer expiration time, and smaller respiratory rate (see Table 3).

DISCUSSION

We have shown in this study that both term and preterm infants frequently brake their expiration in the first minutes of life. This is achieved most commonly by crying. The crying pattern has not been described in earlier reports (7,30,31).

Table 1. Characteristics of the term and preterm infants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preterm (N = 12)</th>
<th>Term (N = 13)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Gestational age, wk, mean (SD)</td>
<td>32 (2.2)</td>
<td>38.9 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight, g, mean (SD)</td>
<td>2000 (560)</td>
<td>3340 (530)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apgar at 5 min, median (IQR)</td>
<td>9 (9–9)</td>
<td>9 (8–9)</td>
<td>NS</td>
</tr>
<tr>
<td>Time start recording, s, mean (SD)</td>
<td>30 (15)</td>
<td>29 (14)</td>
<td>NS</td>
</tr>
<tr>
<td>Caesarean delivery (%)</td>
<td>33</td>
<td>54</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 2. The proportion of breaths with different expiratory patterns for preterm and term infants

<table>
<thead>
<tr>
<th>Pattern</th>
<th>12 Preterm</th>
<th>13 Term</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. breaths</td>
<td>58 (45–82)</td>
<td>62 (34–73)</td>
<td>0.5</td>
</tr>
<tr>
<td>Braked expiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged</td>
<td>12 (3–17)%</td>
<td>11 (3–18)%</td>
<td>0.9</td>
</tr>
<tr>
<td>Hold</td>
<td>9 (4–17)%</td>
<td>2 (0–6)%</td>
<td>0.02</td>
</tr>
<tr>
<td>Grunt</td>
<td>2 (0–10)%</td>
<td>0 (0–6)%</td>
<td>0.5</td>
</tr>
<tr>
<td>Cry</td>
<td>62 (36–77)%</td>
<td>64 (46–79)%</td>
<td>0.4</td>
</tr>
<tr>
<td>Unbraked expiration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (0–16)%</td>
<td>11 (3–18)%</td>
<td>0.9</td>
</tr>
<tr>
<td>Panting</td>
<td>0 (0–1)%</td>
<td>0 (0–12)%</td>
<td>0.5</td>
</tr>
</tbody>
</table>
lung volume (11,12,14,15,32–35). We were not able to show a difference in breathing between the groups, except that preterm infants use the expiratory breath hold more often than term infants.

This is the first study comparing the breathing patterns of term and preterm infants immediately after birth. Karlberg et al. (30) and Mortola et al. (7) reported the first few breaths in term infants and described similar interruptions in expiration with small or zero flow. These expiratory interruptions or braking were also observed in term infants at 10 min of life (11). They also occur in preterm and term infants later in life during active sleep (15,33).

In newborns, with a very compliant chest wall, it is likely that expiratory braking mechanisms help maintain FRC. There are two mechanisms for stopping or slowing expiratory flow and maintaining an elevated lung volume during expiration. Diaphragmatic postinspiratory activity slows the rate of lung deflation by counteracting its passive recoil (12,14,15,32,33). Closure or narrowing of the larynx increases the resistance to expiration (11,15,34,35). During braked expiration, the closed or narrowed glottis, with increased intrapulmonary pressure from abdominal muscle contraction, causes the airway pressure to be maintained above atmospheric. This helps clear fluid from the lung, facilitate distribution of gas within the lung, and splint the alveoli and airways open (3,4,7,8,11,30).

A cry at birth reassures clinicians that the infant is capable of taking a deep inspiration (36). The sound is produced during forced expiration by vibration of the vocal cords (37). In this study, we have shown that crying is a similar breathing pattern to grunting. It is an interruption of the expiratory flow pattern in term infants is comparable to what has been measured in crying term infants later in life (36). However, we measured a much lower peak expiratory flow, which could indicate more braking occurred at birth than during crying later in life (36).

Making respiratory measurements immediately after birth is very difficult. This is an area of research where it is not possible to study large numbers in detail. We were only able to record more mature preterm infants because we aimed to record only those who were breathing without assistance. To have minimal interference with the monitoring and stabilization of preterm and term infants at delivery, we recorded for only 90 s. It is possible that more differences between the groups would have appeared if more immature preterm infants were studied or if recordings were made for longer periods.

Although using a face mask with a pneumotachometer attached is an accepted and only method for measuring respiratory parameters after birth (37,38), it may have influenced the breathing pattern by stimulating respiratory reflexes and thereby influencing the tidal volume and respiratory rate (39,40). In previous studies, no adverse effects of using a face mask during the first breaths were reported (1,2,7,11). In addition, an open face mask with a small pneumotachograph attached causes less interference to the infants’ breathing than methods used in previous studies (1–6,8).

In conclusion, this is the first report that describes in detail the breathing patterns of preterm and term infants immediately after birth. Both preterm and term infants frequent brake expiration, most often represented by a crying pattern. The crying pattern has not been described before but seems to be a method of breathing that uses expiratory braking and facil-

### Table 3. The respiratory parameters of the braked and unbraked breaths for both groups

<table>
<thead>
<tr>
<th>Respiratory parameters, mean (SD)</th>
<th>Braked expiration</th>
<th>Unbraked expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preterm (N = 652 breaths)</td>
<td>Term (N = 598 breaths)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Tidal volume (mL/kg)</td>
<td>7.2 (3.8)*</td>
<td>6.8 (4.2)*</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Inspiration time (s)</td>
<td>0.32 (0.14)</td>
<td>0.33 (0.16)</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Expiration time (s)</td>
<td>1.03 (0.84)*</td>
<td>1.33 (1.02)*</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Peak flow inspiration (L/min)</td>
<td>6.2 (3.9)*</td>
<td>8.4 (5.2)*</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak flow expiration (L/min)</td>
<td>−3.8 (2.4)*</td>
<td>−4.3 (2.8)*</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiration rate (min⁻¹)</td>
<td>60 (30)*</td>
<td>50 (23)*</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Values of braked vs. unbraked pattern were significantly different in both groups (p < 0.001).
iates lung volume recruitment. We have shown that preterm infants use significantly more expiratory breath holds to defend their lung volume.

REFERENCES
27. Morris MG 1999 A simple new technique to measure the effective dead space of the face mask with a water volumeter in infants. Eur Respir J 14:1163–1166
Endotracheal Intubation Attempts During Neonatal Resuscitation: Success Rates, Duration, and Adverse Effects

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ABSTRACT

OBJECTIVE. Endotracheal intubation of newborn infants is a mandatory competence for many pediatric trainees. The Neonatal Resuscitation Program recommends a 20-second limit for intubation attempts. Intubation attempts by junior doctors are frequently unsuccessful, and many infants are intubated between 20 and 30 seconds without apparent adverse effect. Little is known about the proficiency of more senior medical staff, the time taken to determine endotracheal tube (ETT) position, or the effects of attempted intubation on infants’ heart rate (HR) and oxygen saturation (SpO₂) in the delivery room (DR). The objectives of this study were to determine (1) the success rates and duration of intubation attempts during DR resuscitation, (2) whether experience is associated with greater success rates and shorter time taken to intubate, (3) the time taken to identify ETT position after intubation, and (4) the frequency with which infants deteriorated during intubation attempts and the time at which this occurred.

METHODS. We reviewed videos of DR resuscitations; identified whether intubation was attempted; and, when attempted, whether intubation was attempted by a resident, a fellow, or a consultant. We defined the duration of an intubation attempt as the time from the introduction of the laryngoscope blade to the mouth to its removal, regardless of whether an ETT was introduced. We determined the time from removal of the laryngoscope to the clinicians’ decision as to whether the intubation was successful and noted the basis on which this decision was made (clinical assessment, flow signals, or exhaled carbon dioxide [ETCO₂] detection). We determined success according to clinical signs in all cases and used flow signals that were obtained during ventilation via the ETT or ETCO₂ when available. When neither was available, the chest radiograph on admission to the NICU was reviewed. For infants who were monitored with pulse oximetry, we determined their HR and SpO₂ before the intubation attempt. We then determined whether either or both fell by ≥10% during the attempt and, if so, at what time it occurred.
RESULTS. We reviewed 122 video recordings in which oro-
tracheal intubation was attempted 60 times in 31 in-
fants. We secondarily verified ETT position using flow
signals, ETCO₂, or chest radiographs after 94% of at-
ttempts in which an ETT was introduced. Thirty-seven
(62%) attempts were successful. Success rates and mean
(SD) time to intubate successfully by group were as
follows: residents: 24%, 49 seconds (13 seconds); fel-
loors: 78%, 32 seconds (13 seconds); and consultants:
86%, 25 seconds (17 seconds). Of the 23 unsuccessful
attempts, 13 were abandoned without an attempt to pass
an ETT and 10 were placed incorrectly. The time to
determine ETT position in the DR was longer when
clinical assessment alone was used. Infants who were
monitored with oximetry deteriorated during nearly half
of the intubation attempts. Deterioration seemed more
likely when HR and SpO₂ were low before the attempt.

CONCLUSIONS. Intubation attempts often are unsuccessful,
and successful attempts frequently take >30 seconds.
Greater experience is associated with greater success
rates and shorter duration of successful attempts. Flow
signals and ETCO₂ may be useful in determining ETT
position more quickly than clinical assessment alone.
Infants frequently deteriorate during intubation at-
ttempts. Improved monitoring of infants who are resus-
citated in the DR is desirable.

INTERNATIONAL CONSENSUS STATEMENTS¹ and guide-
lines on neonatal resuscitation²,³ advise that infants
with inadequate respiration and/or bradycardia at birth
be given positive pressure ventilation with a manual
ventilation device with a face mask or endotracheal tube
(ETT). Endotracheal intubation of newborn infants is a
mandatory competence for basic training in pediatrics in
many countries.⁴,⁵ The Neonatal Resuscitation Program
(NRP) recommends that intubation attempts be limited
to 20 seconds.²

A United Kingdom study of the care of preterm in-
fants and its effect on their survival identified difficulties
with intubation and the level of experience of staff
present as the most common concerns about neonatal resuscitation.⁶ In a US study of pediatric residents, none
met the authors’ definition of procedural competence for
intubation (successful at first or second attempt ≥80%
of the time) over a 2-year period.⁷ An additional US
study of delivery room (DR) intubations that were per-
formed mainly by residents and fellows found that few
were successful within 20 seconds and that more infants
were intubated between 20 and 30 seconds without
apparent adverse effect.⁸ Another study from the same
center reported that just over half of all intubation at-
ttempts that were performed by junior doctors were suc-
cessful and that residents there currently have inade-
quate opportunity to become proficient.⁹

There is little information on the success rates or
duration of intubation attempts of more experienced
operators. Also, although adverse effects of endotracheal
intubation in the intensive care setting have been de-
scribed,¹⁰ there is little information on the effects of
intubation attempts on infants’ oxygen saturations
(SpO₂) and heart rate (HR) as determined by pulse oxim-
ery in the DR. Using video recordings, we wished to
determine (1) the success rates and duration of intuba-
tion attempts during neonatal resuscitation at our hos-
pital, (2) whether the success rates and duration of suc-
cessful attempts by staff varied with different levels of
experience, (3) the time taken to identify ETT position
after attempted intubation, and (4) the frequency with
which infants deteriorated during intubation attempts
and the time at which this occurred.

METHODS

Setting
The Royal Women’s Hospital Melbourne is a tertiary-
level perinatal center with ~5000 deliveries per year.
Approximately 450 infants are admitted to the NICU per
year, 100 to 110 of whom have a gestational age of <28
weeks or birth weight of <1 kg. We do not have ad-
vanced neonatal nurse practitioners or respiratory ther-
apists; thus, all infants are intubated by medical staff:
residents, fellows, or consultants. In general, the resi-
dents are pediatric trainees whose first exposure to neo-
natal medicine or intensive care occurs during their
6-month rotation at our hospital. Usually, they have no
previous experience with intubation. The fellows have
variable but at least 18 months’ experience of neonatal
intensive care and thus intubation. Consultants at our
hospital have a range of 5 to 35 years’ experience in
neonatal medicine and extensive intubation experience.

Resuscitation Practice
All staff who attend deliveries at our hospital complete
an in-house resuscitation training program based on
international consensus statements¹ and the NRP.² The
Neopuff Infant Resuscitator (Fisher & Paykel, Auckland,
New Zealand) t-piece and the Laerdal Infant Resuscitator
(Laerdal, Oakleigh Victoria, Australia) self-inflating bag
are the manual ventilation devices used at our hospital.
Peak inflating and positive end-expiratory pressures are
set at 30 and 5 cm H₂O, respectively, on the Neopuff. In
the DR, ETT position is judged from clinical signs as
recommended in international consensus statements¹;
on occasion, an exhaled carbon dioxide (ETCO₂) de-
tector (Pedi-Cap Nellcor Puritan Bennet, Pleasanton, CA) is
used for secondary confirmation. A time limit for intu-
bation attempts is not enforced rigidly at our institution.
Infants who are intubated in our DR are transferred to
the NICU, where they have a chest radiograph to con-
firm ETT position.
Resuscitation Studies
Since January 2004, we have recorded DR resuscitations at our hospital with the endorsement of our Human Research and Ethics Committee. When available, a member of the investigating team attended deliveries for which the need for resuscitation was anticipated and made detailed recordings. When time allowed before delivery, the parents were approached and their permission was sought to record the resuscitation. When time did not allow, the resuscitation was recorded and the parents were approached as soon as practicable thereafter. Their permission then was sought to view the recordings and to use them for data extraction and educational purposes.

We recorded resuscitations using a digital video camera that was mounted above the resuscitation cot and positioned to acquire a clear view of the infant and resuscitative interventions. Sound was audible from these recordings. The sensor of a Masimo Radical (Masimo Corp, Irvine, CA) pulse oximeter was placed on the infants’ right hand or wrist as soon as practicable after delivery. The oximeter was set to capture HR and \(\text{SpO}_2\) with maximal sensitivity and average data over 2-second intervals.

Many of the infants who were videotaped had pulmonary mechanics measured during positive pressure ventilation using the Florian Respiratory Monitor (Acutronic, Zug, Switzerland). This monitor measures pressures in the respiratory circuit directly and uses a sensor placed between the ventilation device and the ETT to measure gas flow. These data were recorded and analyzed using a laptop computer with Spectra software (Grove Medical, London, United Kingdom), a program designed specifically for the recording and analysis of respiratory signals (see Fig 1). Although not usually available to the resuscitation team in the DR, these signals were used occasionally to determine ETT position during the resuscitation. They were used to determine ETT position retrospectively for this study.

Evaluation of Video Recordings
All video recordings were reviewed; those in which intubation was attempted were identified, and the reason for intubation was determined. The number of attempts, the timing of these attempts, and the grade of doctor who performed the procedure were noted. In keeping with previous reports, the duration of an intubation attempt was defined as the time from introduction of the laryngoscope blade into the mouth to the time it was removed, irrespective of whether an ETT was introduced. When an ETT was introduced, we determined the time from removal of the laryngoscope to the decision by the resuscitating team whether the attempt was successful.

For infants who were monitored with pulse oximetry during the procedure, we determined the times of life at which the sensor was applied and oximetry data were available. We determined whether preoxygenation was given before the attempt and the HR and \(\text{SpO}_2\) before and after the attempt. We considered the infants’ condition to have deteriorated when their HR and/or \(\text{SpO}_2\) fell by \(\geq 10\%\) during the procedure and noted the time at which this occurred.

Statistical Analysis
Mean (SD) duration of intubation attempts by different grades of doctors were compared using 1-way analysis of variance and test for linearity. Proportions of successful intubations by different grades of doctors were compared using \(\chi^2\) test and linear-by-linear association. SPSS version 12.0.1 (SPSS Inc, Chicago IL) was used for analysis.

RESULTS
We attended 123 deliveries and were given parental permission to extract data from 122. Intubation was attempted a total of 60 times in 31 infants whose mean (SD; range) gestational age and birth weight were 28 weeks (5; 23–40) and 1227 g (939; 495–3870), respec-
tively. Twenty-one attempts were made by 12 residents, 18 by 6 fellows, and 21 by 10 consultants. All were orotracheal intubation attempts. The mean (SD; range) number of intubation attempts per infant was 2 (1; 1–5). The indications for intubation are shown in Table 1 and included treatment allocation in our randomized trial comparing continuous positive airway pressure with endotracheal intubation and ventilation (the COIN trial).

To be eligible for randomization, infants of 25 to 28 weeks’ gestation had to have regular spontaneous respiration by 5 minutes of age. The infants for whom the indication for intubation was extreme immaturity and/or low birth weight per se had a mean (SD) gestational age and birth weight of 24 weeks (1 weeks) and 681 g (111 g), respectively.

In the DR, ETT position was determined by clinical assessment alone after 46 (76%) attempts and by using flow signals and ETCO₂ on 7 (12%) occasions each. We verified the ETT position retrospectively using flow signals for 32 attempts and by examining the chest radiographs that were taken on admission to the NICU after 6 attempts. We thus secondarily confirmed ETT position using flow signals, ETCO₂, or chest radiograph after 94% (44 of 47) of attempts in which an ETT was introduced.

Successful Attempts
Overall, 37 (62%) intubation attempts were successful. In the DR, ETT position was determined by clinical assessment alone after 26 attempts; flow signals (see Fig 1B) and ETCO₂ were used in addition after 7 and 4 attempts, respectively. Twenty-seven attempts were subsequently verified as successful using flow signals. For the remaining 6 infants who had neither a flow sensor nor an ETCO₂ detector in the circuit in the DR, review of the chest radiographs on admission to the NICU confirmed correct placement of the ETT.

The rates of success and duration of intubation attempts overall and by group are shown in Table 2. The time taken to intubate successfully differed between grades of doctors (P < .01, analysis of variance), with more senior doctors intubating more rapidly (P < .01, test of linear trend; Table 2, Fig 3). Similarly, success rates differed between grades of doctors (P < .001, Pearson χ²), with senior doctors more successful (P < .001, linear-by-linear trend; Table 2). The 2 shortest successful attempts were 8 seconds. Ten (17%) attempts were successful within 20 seconds, an additional 12 (20%) were successful between 20 and 29 seconds, and the remaining 15 (25%) successful intubations took >30 seconds. The longest successful attempt took 70 seconds.

Of note, 1 successful intubation attempt was erroneously thought not to be successful on clinical grounds and on cursory examination of the flow signals. Close retrospective examination of these signals revealed that tiny quantities of gas were passing through the ETT (see Fig 2). In the DR, this correctly placed ETT was removed from this extremely preterm infant. The infant subsequently was reintubated by an experienced fellow who was confident that the ETT was positioned correctly. An ETCO₂ detector was placed in the circuit but did not change color. The ETT was confirmed to be passing through the cords on direct laryngoscopy by a consultant 90 seconds after reintubation. The peak inflating pressure was increased from 30 to 40 cm H₂O, and the HR increased >100 beats per minute at 108 seconds. The infant’s own breathing effort improved at 131 seconds; only then was color change evident on the ETCO₂ detector. This suggests that insufficient exhaled gas and, thus, CO₂ passing through a correctly placed ETT was the reason that the reagent strip did not change color. This is the second such “false-negative” result that we have seen during the resuscitation of a preterm infant with noncompliant lungs.

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**TABLE 1**  Indications for Intubation

<table>
<thead>
<tr>
<th>Indication for Intubation</th>
<th>No. of Infants (% of Total)</th>
<th>No. of Attempts (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradycardia despite mask ventilation</td>
<td>9 (29)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Extreme prematurity and/or low birth weight</td>
<td>10 (32)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Congenital diaphragmatic hernia</td>
<td>3 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Treatment allocation in COIN trial</td>
<td>5 (16)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Apnea/inadequate respiration</td>
<td>2 (7)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Poor respiration and other congenital problem</td>
<td>2 (7)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

**TABLE 2**  Success Rates and Duration of Attempts According to the Grade of Doctor Attempting Intubation

<table>
<thead>
<tr>
<th>No. of attempts</th>
<th>Total</th>
<th>Residents</th>
<th>Fellows</th>
<th>Consultants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of successful attempts</td>
<td>60</td>
<td>21</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Duration of attempts, mean (SD), s</td>
<td>37 (62)</td>
<td>5 (24)</td>
<td>14 (78)</td>
<td>18 (86)</td>
</tr>
<tr>
<td>Duration of successful attempts, mean (SD), s</td>
<td>33 (19)</td>
<td>38 (20)</td>
<td>36 (16)</td>
<td>28 (19)</td>
</tr>
</tbody>
</table>

**FIGURE 2**  Traces recorded at 200 Hz during positive pressure ventilation that was given to an infant who was born at 28 weeks and weighed 1354 g. The flow sensor was placed between the ETT and Neopuff, which delivered a peak inflating pressure of 30 cm H₂O and positive end expiratory pressure of 5 cm H₂O. Minute quantities (0.1 mL) of gas are delivered during inflation and return when inflation stops.
Unsuccessful Attempts

Of the 23 unsuccessful attempts, 13 were abandoned without an attempt to pass the ETT as the vocal cords could not be visualized adequately. Seven attempts were determined to be unsuccessful by clinical assessment alone in the DR. Of these, 4 were verified using flow signals (see Fig 1A) and the infant could be heard to cry after 2 attempts. ETCO$_2$ was used in addition to clinical assessment after 3 attempts. No intubation attempt was determined unsuccessful using flow signals in the DR.

Time to Determination of ETT Position

Overall and excluding the 13 abandoned attempts for which no assessment of tube position was required, the mean (SD; range) time to determine ETT position was 33 seconds (28; 1–127). The mean (SD [range]) time to identify successful and unsuccessful attempts was not significantly different (32 [26] vs. 38 [37]; $P = .55$). The mean (SD; range) time taken for clinical assessment of ETT position ($n = 33$) was 39 seconds (30; 1–127); for flow signals ($n = 7$) and ETCO$_2$ ($n = 7$), it was 19 seconds (16; 8–53) and 17 seconds (20; 4–60), respectively. The time taken to assess tube position exceeded the time taken to intubate the infant on 15 (45%), 1 (14%), and 2 (29%) occasions for which clinical assessment, flow signals, and ETCO$_2$ respectively, were used.

Pulse Oximetry During Intubation Attempts

Twenty-seven infants had pulse oximetry during 51 intubation attempts. The oximetry sensor was applied to the infant at a mean (SD) of 53 (20) seconds of life, and data were displayed at a mean (SD) of 80 (27) seconds of life. The mean (SD; range) time at which intubation was attempted was 253 seconds (135; 86–699).

Overall, infants deteriorated during 25 (49%) of these attempts. Compared with the value just before the intubation attempt, SpO$_2$ alone fell by $\geq 10\%$ in 9, HR alone fell by $\geq 10\%$ in 4, and both fell by $\geq 10\%$ in 12. The time at which infants deteriorated during intubation was variable, ranging from 2 to 55 seconds (mean: 20; SD: 13). Of the 12 attempts that were $< 20$ seconds, no infant deteriorated during the attempt. Infants deteriorated during 4 of the 12 attempts that were between 20 and 29 seconds and 20 of the 27 attempts that were $\geq 30$ seconds. Infants were monitored during 30 successful intubation attempts and deteriorated during 14; during the 21 failed attempts, 11 deteriorated.

As the reasons for intubation varied, so did the infants’ condition before the attempt, eg, infants who were intubated for bradycardia despite mask ventilation had lower HR than infants who were randomly assigned in the COIN trial. Sixteen infants had HR $< 100$ before intubation was attempted; 10 of these infants deteriorated during the attempt. Of the 35 infants who had HR $\geq 100$, 15 deteriorated. The mean SpO$_2$ of the infants at the time intubation was attempted was 70%. Of the 25 infants with SpO$_2$ $< 70$, 17 deteriorated; of the 26 infants with SpO$_2$ $\geq 70$, 8 deteriorated.

DISCUSSION

Endotracheal intubation of the newborn is an important skill that seems to be difficult to acquire and improves with experience. Routine intubation of infants who are born through meconium-stained liquor is no longer recommended; it is no longer acceptable to practice intubation on infants who have died; working hours for doctors in training have been reduced internationally; and, in our hospital at least, there is a reduction in endotracheal ventilation as a result of increasing use of continuous positive airway pressure. These factors mean that the decline in opportunity to learn and practice neonatal intubation and the consequent decline in proficiency that has been described may well continue. This highlights the need for more anatomically suitable and life-like mannequins of premature infants.

This study shows that intubation is successful only $\sim 60\%$ of the time. Even when practitioners with considerable experience attempt intubation, many infants are not intubated within the 20-second limit suggested by the NRP. In addition to fellows who are always present, consultant neonatologists frequently attend high-risk deliveries at our hospital, reflected by the relatively high proportion (35%) of attempts made by this group in our study. Our findings that consultants are more likely to intubate infants successfully and more quickly support the practice of having experienced senior staff present for back-up at high-risk deliveries.

An interval that rarely is considered in the time taken for intubation is the time taken for clinicians to decide whether the ETT is placed correctly. In our study, this frequently took longer than intubation itself when clin-
The use of ETCO\textsubscript{2} flow signals in determining ETT position more quickly than clinical assessment alone was used. Our study suggests that, as has already been suggested for ETCO\textsubscript{2},\textsuperscript{13,14} flow signals may be useful in determining ETT position more quickly than clinical assessment alone. However, as also shown in this study, neither method is fool-proof, and both require additional evaluation.

In our study, infants frequently deteriorated during intubation attempts as determined by pulse oximetry. It seems that the more unwell the infant at the time of intubation, as indicated by the lower HR and Sp\textsubscript{O}\textsubscript{2}, the more likely they were to deteriorate during the procedure. For most of these infants, deterioration was not readily apparent on observation, and it is unlikely that it would have been identified quickly by intermittent assessment of the HR, by either auscultation or palpation. Although infants deteriorated more frequently during longer intubation attempts, the timing of deterioration was highly variable. For example, of the 20 infants who deteriorated during attempts of >30 seconds’ duration, 12 had already done so by 20 seconds. Thus, rather than impose a general time limit for intubation attempts, we advocate improved monitoring of infants in the DR (eg, the use of pulse oximetry) and limiting the duration of intubation attempts according to their individual response.

CONCLUSIONS

Intubation attempts are often unsuccessful, and successful attempts frequently require >30 seconds. Greater experience is associated with greater success rates and shorter duration of successful attempts. The time taken to determine ETT position often exceeds the time taken to intubate and may be reduced by assessing flow signals or ETCO\textsubscript{2}. Infants frequently deteriorate during intubation attempts. Improved monitoring of infants who are resuscitated in the DR is desirable.

ACKNOWLEDGMENTS

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REFERENCES

Clinical assessment and end-tidal carbon dioxide (ETCO₂) detectors are used to verify tracheal intubation in newborn infants. A case is presented in which an ETCO₂ detector was misleading in determining endotracheal tube (ETT) position but useful in determining the efficacy of ventilation in an extremely preterm infant. (J Pediatr 2005;147:547-8)

Extremely preterm infants are frequently intubated for ventilation. Determining whether the trachea has been intubated may be difficult. End-tidal carbon dioxide (ETCO₂) detectors, which indicate the presence of CO₂ in exhaled gas by a color change, are useful for confirming correct endotracheal tube (ETT) placement in adults, children, and neonates. The manufacturers of these detectors express caution about their use in infants weighing <1000 g and in low cardiac output states. We describe a case in which an ETCO₂ detector was misleading in determining ETT position but useful in determining the efficacy of ventilation in an extremely low birth weight infant.

CASE HISTORY

A 32-year-old primigravida with a monochorionic, monoamniotic twin pregnancy presented at 26 weeks gestation. Cardiotocography indicated that 1 twin had died and the other was severely compromised, prompting immediate delivery by caesarean section under general anaesthetic. Twin boys were delivered. One infant was dead; the other was pale, apneic, and bradycardic and weighed 620 g. He was resuscitated by an experienced pediatrician, with the resuscitation videotaped. Mask ventilation was started using the Neopuff infant resuscitator (Fisher & Paykel, Auckland, New Zealand), a flow-driven, pressure-limited T-piece that provides a consistent operator-selected peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP). The flow rate was 8 L/min of 100% oxygen, and the PIP and PEEP were initially set at 30 and 6 cm H₂O, respectively. The infant was ventilated at 60/min. Prolonged inflations were not used. A Masimo Radical pulse oximeter (Masimo, Irvine, Calif) was used to monitor preductal oxygen saturation (SpO₂) and heart rate (HR). At 1 minute of age, the HR was 80 bpm, the SpO₂ was 76%, and chest wall movement was not seen.

The infant was intubated with a 2.5-mm ETT by 2 minutes of age and ventilated using the same pressures. No chest wall movement was seen with inflations, the HR remained < 100 bpm, and SpO₂ was 55%. The infant was then reintubated. His chest wall still did not move, and his condition did not improve with ventilation, so an ETCO₂ detector (Pedi-Cap; Nellcor Puritan, Bennett, Calif) was placed between the ETT and Neopuff to verify the ETT position. No color change was seen, suggesting that the ETT was not in the trachea. At this time, HR was 75 bpm and SpO₂ was 70%. The resuscitator confirmed correct placement of the ETT by direct laryngoscopy, then increased the PIP and PEEP in increments to 70 and 8 cm H₂O, respectively. There was still no chest wall movement with ventilation or color change in the Pedi-Cap.

At age 7 minutes, a 240-mL self-inflating bag (Laerdal, Wappingers Falls, NY) was used with the pop-off valve occluded so that a very high (but unmeasured) PIP was used to inflate the lungs. Within 15 seconds, the Pedi-Cap detected sufficient exhaled CO₂ to cause a color change. The HR then rose above 100 bpm, and chest wall movement was
observed 30 seconds thereafter. Over the next 2 minutes, the SpO₂ rose gradually to 85%. The PIP was reduced to produce shallow but obvious chest wall movement. The infant was transferred to the neonatal intensive care unit receiving 100% oxygen, with PIP and PEEP set at 45 and 8 cm H₂O respectively. No epinephrine, volume expansion, or external cardiac massage was used during the resuscitation.

The infant’s initial hemoglobin was 2.8 g/dL, and a diagnosis of twin-to-twin transfusion syndrome was made. He was subsequently ventilated for 20 days without developing air leaks and then treated with nasal continuous positive airway pressure and a low fraction of inspired O₂.

**DISCUSSION**

Delivery room intubation is difficult, with success rates of <40% in infants <28 weeks gestational age. Signs of correct ETT placement include direct visualization, chest wall movement with inflation, condensation inside the ETT, auscultation of breath sounds, and improvement in HR and color. These observations are subjective, however, and sometimes can produce false-positive impressions of tracheal ventilation.

The pressures required to inflate the newborn lung are variable and unpredictable. They need to be above the airway critical opening pressure and may be >70 cm H₂O. The International Liaison Committee on Resuscitation has stated that visible chest wall expansion is a more reliable sign of appropriate inflation pressures than in-line manometry on the ventilation device. Others suggest that in very preterm infants, visible chest wall movement may represent excessive tidal volumes.

The Pedi-Cap is a colorimetric semiquantitative ETCO₂ detector used to verify correct ETT placement. In the presence of even small amounts of expired CO₂, the indicator turns yellow, which reverses to purple in inspiration when the measured ETCO₂ is <0.5% (4 mm Hg). A persistent purple color is usually due to incorrect ETT placement, but also may be seen in the setting of extremely low pulmonary perfusion. In this case, the ETCO₂ detector did not change color because the infant had extremely noncompliant lungs that could not be ventilated until very high inflating pressures were used.

The ETCO₂ detector gave the false impression that the ETT was not in the trachea, which disagreed with the impression gained from clinical assessment. Such false-negative results are a matter of concern, because they delay appropriate intervention during resuscitation. Once the resuscitator was confident that the ETT was placed correctly, the inflating pressures were increased until ventilation was achieved. The ETCO₂ detector identified gas exchange before the chest wall was seen to move, suggesting that it is more sensitive for assessing adequacy of ventilation. Shortly after exhaled CO₂ was detected by the Pedi-Cap, the HR increased. This sequence suggests that the primary problem was inadequate ventilation rather than low cardiac output leading to poor pulmonary perfusion.

Although evidence for the routine use of expired CO₂ during neonatal resuscitation is limited, these devices are highly sensitive in detecting tracheal intubation, and there appears to be a low likelihood of causing harm. This case illustrates that clinicians need to be aware that failure of the device to change color may be due to inadequate ventilation through a correctly placed ETT.

**REFERENCES**

Long versus short inspiratory times in neonates receiving mechanical ventilation (Review)

Kamlin COF, Davis PG

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Long versus short inspiratory times in neonates receiving mechanical ventilation (Review)

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Long versus short inspiratory times in neonates receiving mechanical ventilation

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ABSTRACT

Background

When intermittent positive pressure ventilation (IPPV) was introduced in newborn infants with hypoxic respiratory failure from hyaline membrane disease (HMD), mortality was high and air leaks problematic. This barotrauma was caused by the high peak inspiratory pressures (PIP) required to oxygenate stiff lungs. The primary determinants of mean airway pressure (and thus oxygenation) on a conventional ventilator are the inspiratory time (IT), PIP, positive end expiratory pressure and gas flow rates. In the 1970s uncontrolled studies on a small number of infants demonstrated a benefit in reducing barotrauma using a long IT and slow rates. This strategy was subsequently widely adopted. Current neonatal ventilators have been designed to minimise lung injury but rates of bronchopulmonary dysplasia (BPD) remain high. It is therefore important that the inspiratory time causing least harm is used.

Objectives

To determine in mechanically ventilated newborn infants whether the use of a long rather than a short IT reduces the rates of death, air leak and BPD.

Search strategy

The standard search strategy of the Cochrane Neonatal Review Group (CNRG) was used. Searches of electronic and other databases were performed. These included MEDLINE (1966 - April 2004) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2003). In order to detect trials that may not have been published, the abstracts of the Society for Pediatric Research, and the European Society for Pediatric Research were searched from 1998 - 2003.

Selection criteria

All randomised and quasi-randomised controlled trials enrolling mechanically ventilated infants with or without respiratory pathology evaluating the use of long versus short IT (including randomised crossover studies with outcomes restricted to differences in oxygenation).

Data collection and analysis

The standard method of the Cochrane Collaboration and its Neonatal Review Group were used. Two authors independently assessed eligibility, and the methodological quality of each trial, and extracted the data. The data were analysed using relative risk (RR) and risk difference (RD) and their 95% confidence intervals. A fixed effect model was used for meta-analyses.
Main results

In five studies, recruiting a total of 694 infants, a long IT was associated with a significant increase in air leak [typical RR 1.56 (1.25, 1.94), RD 0.13 (0.07, 0.20), NNT 8 (5, 14)]. There was no significant difference in the incidence of BPD. Long IT was associated with an increase in mortality before hospital discharge that reached borderline statistical significance [typical RR 1.26 (1.00, 1.59), RD 0.07 (0.00, 0.13)].

Authors’ conclusions

Caution should be exercised in applying these results to modern neonatal intensive care, because the studies included in this review were conducted prior to the introduction of antenatal steroids, post natal surfactant and the use of synchronised modes of ventilatory support. Most of the participants had single pathology (HMD) and no studies examined the effects of IT on newborns ventilated for other reasons such as meconium aspiration and congenital heart disease (lungs with normal compliance). However, the increased rates of air leaks and deaths using long ITs are clinically important; thus, infants with poorly compliant lungs should be ventilated with a short IT.

PLAIN LANGUAGE SUMMARY

Long versus short inspiratory times in neonates receiving mechanical ventilation

Endotracheal intubation and positive pressure ventilation of newborn infants with respiratory failure has revolutionised neonatal intensive care. The majority of infants are ventilated because of lung immaturity and hyaline membrane disease, respiratory difficulties that resolve for most of these infants. Use of ventilators can cause lung inflammation and ventilator-induced lung injury, particularly in the neonate with compliant chest walls, highlighting the importance of protective ventilation strategies. In addition, an infant’s own breathing efforts, when combined with ventilator inflations, can exacerbate lung injury. Managing the mean airway pressure is important to improve oxygenation and not cause excessive airway pressures that can damage the lungs and impede venous return (a factor implied in spontaneous intraventricular haemorrhage in preterm infants). Clinicians still need to set an inspiratory time on the ventilator, making it important to determine whether the use of a long rather than a short inspiratory time reduces the rates of death, air leak and bronchopulmonary dysplasia (BPD, requiring supplemental oxygen at 28 days) in mechanically ventilated newborn infants (term and preterm). The review authors identified five randomised studies reported from 1980 to 1992. These trials recruited a total of 694 newborn infants with acute respiratory failure mainly caused by hyaline membrane disease. A long inspiratory time was associated with a significant increase in air leak from the lungs (NNT 8). There was no significant difference in the incidence of BPD but an increase in mortality before hospital discharge reached borderline statistical significance. Caution should be exercised in applying these results to modern neonatal intensive care because these studies were conducted before the introduction of antenatal steroids, postnatal surfactant and the use of synchronised modes of ventilatory support. Whilst there is increasing use of non-invasive ventilation such as nasal continuous positive airway pressure to avoid ventilator-induced lung injury, mechanical ventilation will continue to have a role in extremely immature infants and those with hyaline membrane disease complicated by apnea.

BACKGROUND

The application of techniques of endotracheal intubation and intermittent positive pressure ventilation (IPPV) for newborns with respiratory failure revolutionised neonatal intensive care. Prior to the introduction of IPPV, the mainstay of early management was supportive care, including the delivery of supplemental oxygen, maintenance of normoglycaemia and correction of metabolic acidosis. These measures had been recognised to reduce morbidity compared to controls (Usher 1963). IPPV was introduced as rescue therapy to treat apnea or correct hypoxaemia and respiratory acidosis in infants likely to die, often after bag and mask ventilation had failed. The techniques applied were initially adapted from those used in adult ventilation and met with limited success when first introduced (D-Papadopoulos 1965, Murdock 1970). The short inspiratory times used in adults to avoid impaired venous return and the fast rates to avoid asynchrony in newborns were not as effective in preterm infants with atelectatic and poorly compliant lungs (Adamson 1968). Gregory 1971 observed dramatic improvements over earlier approaches in neonates with respiratory distress syndrome (RDS) when continuous positive airway pressure (CPAP) was applied through an endotracheal tube. Ventilators were introduced in the early 1970s which used
cuits with continuous gas flow and a timing device to close the expiratory valve allowing the infant to breathe spontaneously and receive intermittent mandatory ventilation (IMV). Cumarausamy 1973 reported improved survival when IMV was combined with the application of positive end expiratory pressure (PEEP), although early experiences in this era document the use of high peak inspiratory pressures (PIP) to achieve adequate oxygenation. The high PIPs which were used reflected the poor compliance of the lung and were associated with high rates of mortality and bronchopulmonary dysplasia (BPD) (Northway 1967).

Alternative strategies were sought to treat infants with HMD using lower inflating pressures. Reynolds 1971 and Herman 1973 noted that alveolar recruitment and hence oxygenation could be improved by using low rates (30 - 40 breaths per minute) and long inspiratory to expiratory (I:E) ratios. In some infants, improvements in oxygenation were seen when inspiratory times exceeded the expiratory times (inverted I:E ratios). In inverse-ratio ventilation the IT is prolonged, thereby increasing mean airway pressures and allowing the use of lower PIP. As neonatal ventilation became more widely used in nurseries in the late 1970s/early 1980s, this strategy was often adopted even though the evidence of efficacy was based on small numbers (less than ten in both studies) with only improved arterial blood gases and indices of oxygenation reported as the primary outcomes.

In assisted ventilation, the ventilator maintains oxygenation by providing an effective mean airway pressure (MAP) exceeding atmospheric pressure and a suitable inspired oxygen concentration. It removes carbon dioxide by passively removing the delivered tidal volume. The tidal volume is the volume of gas moving in and out of the lung in a respiratory cycle. The minute ventilation is the product of tidal volume and respiratory frequency. The alveolar ventilation (minute ventilation minus dead space ventilation) determines the amount of carbon dioxide removed. Ventilator “cycling” refers to the change from inspiration to expiration and may be initiated by time (a pre-determined duration of inspiration), pressure (when a preset pressure is reached) or volume (expiration starts after a preset tidal volume is delivered).

Early pressure limited time cycled (PLTC) ventilators produced a square wave when pressure (on the y axis) was plotted against time (on the x axis). MAP is equal to the integration of the area under the pressure-time curve during a single respiratory cycle. The square wave is dependent on the pre-set inspiratory time, gas flow rate and ventilator frequency. Reynolds 1971 used square wave analysis to hypothesise that prolonging inspiratory time and using slower rates would improve oxygenation by increasing MAP. The longer the IT, the longer the lungs are held distended at the set PIP. Sustained inspiratory pressures may have their greatest incremental effect on non-functioning lung units, thereby improving distribution of the delivered tidal volume. With high frequency positive pressure ventilation (HFPPV; rates >60) changes in the pressure waveform are seen with a shortening of the inspiratory plateau such that the square wave is replaced by a sine wave. Thus any change in IT that accompanies frequency adjustments will change pressure waveforms, thereby altering MAP and oxygenation. Increasing MAP has been shown to improve oxygenation in RDS (Boros 1979). In contrast to early work by Reynolds 1971, Stewart 1981 found that increasing PEEP had the greatest effect on MAP. Whilst a high MAP may be useful in acute RDS, excessive airway pressures in the recovering lung may impede venous return and cause overdistension.

The time required for the lungs to inflate and deflate is determined by the compliance and resistance of the respiratory system which includes the ventilator circuit, endotracheal tube and the patient’s lung. The product of resistance and compliance, the time constant, is a measure of how long it takes for alveolar and proximal airway pressures to equilibrate. It provides a theoretical basis on how best to divide the respiratory cycle into inspiratory and expiratory times. The inspiratory time constant is typically short (approximately 0.05 seconds) in RDS and relatively long (0.25 seconds) in infants with normal lungs. For practical purposes, an expiratory time equivalent to three time constants must be provided to allow 95% of inspired tidal volume to be expelled (Harris 1996). Thus if the expiratory times are absolutely or relatively short (as seen in inverted I:E ratios) there is the potential for gas trapping to occur and the build up of pressure known as inadvertent PEEP (Weigel 1973). Potential complications of inadvertent PEEP include gas trapping, reduced compliance and air leak. This can lead to reduced pulmonary blood flow and central venous return, a factor implied in spontaneous intraventricular haemorrhage in preterm infants (Rennie 1987). Ahluwalia 1994 measured spontaneous inspiratory and expiratory times in newborns ventilated for RDS at a median of 0.3 (range 0.26- 0.34) and 0.46 (0.34-0.66) seconds respectively. RDS, characterised by markedly reduced compliance with very short time constants, can theoretically be managed by using either rapid rates (>60) or slow rates with long inspiratory times providing there is sufficient time for passive exhalation. With HFPPV, the expiratory time may be insufficient to allow for deflation and lung units can become overdistended and further reduce the compliance of the lung.

Meconium aspiration affects mature infants and is characterised by both parenchymal and airway disease. Inhalation of meconium or congenital pneumonias can present as non homogenous lung disease typified by adjacent areas of atelectasis and hyperinflation. Setting ventilator parameters for non homogenous lung disease with different time constants is challenging with the aim being to provide sufficient alveolar ventilation without the development of inadvertent PEEP. The measurement of compliance and resistance in these circumstances is then dependent on the frequency of ventilation. With the limitations of PLTC ventilators, it has been observed that tidal volumes decrease as inspiratory times are
reduced beyond a critical point (less than the time constant of the respiratory system) and that above a certain rate (>75), dead space ventilation increases and minute ventilation is not a linear function of frequency (Boros 1984).

Recent advances in neonatal intensive care may influence the optimal inspiratory time. These include the availability of exogenous surfactant therapy (Soll 2004, Yost 2003) and the advances in ventilator technology that allow synchronisation of ventilator breaths with an infant's spontaneous breathing (Greenough 2004). Surfactant improves oxygenation by increasing functional residual capacity. By stabilising patent airways and with the gradual recruitment of atelectatic regions of the lung, surfactant improves respiratory system compliance and may alter the optimal inspiratory time (Goldsmith 1996). Attempts to achieve synchrony have included the use of muscle relaxation (Greenough 1986) and rapid rates to avoid active expiration against positive pressure inflation (Greenough 2004). Modern neonatal ventilators achieve synchronisation by assisting each spontaneous breath or providing synchronised intermittent mandatory breaths. By measuring lung volumes, tidal volumes, resistance, dynamic and static lung compliance, much of the guesswork of setting ventilator parameters has been eliminated. However, despite these advances in ventilator technology, clinicians still need to set an inspiratory time.

The many variables involved in conventional mechanical ventilation (PIP, PEEP, IT, rate, flow rates) are interdependent making it difficult to assess the effects of changing one variable (IT) whilst holding the others constant. By using stated subgroup analyses (see objectives), the aim of this review is to identify the optimal inspiratory time (or range of times) in newborn infants needing respiratory support on conventional mechanical ventilation.

OBJECTIVES

The primary objective was to evaluate whether, in mechanically ventilated neonates, the use of long inspiratory times compared with short inspiratory times improved short and long term outcomes. These include mortality and the rate of acute lung injury (air leak) and/or chronic lung injury (BPD). For the initial analysis, any definitions of short and long used by the authors of studies were used.

Planned sub-group analyses included:

1. A subgroup of studies defining short IT as less than or equal to 0.5 seconds
2. Subgroup analysis based on the overall ventilator strategy i.e.
   a. Absolute IT set at different (long and short) levels and maintained constant through the infant's treatment
   b. I:E ratios set at different levels and maintained constant so that when rate was altered the IT and expiratory time were adjusted to maintain the I:E ratio
   c. Trials where IT or I:E ratio form only part of the ventilator strategy e.g. when absolute IT and I:E ratios were not prescribed. In these trials an acceptable range of ITs and I:E ratios as defined by the authors would have been used in each arm
3. Underlying pathology (RDS vs other causes)
4. Gestational age i.e. term vs preterm
5. Use of muscle relaxants vs none
6. Surfactant vs no surfactant
7. Mode of ventilation (synchronised vs non synchronised)

METHODS

Criteria for considering studies for this review

Types of studies
All randomised and quasi-randomised controlled trials. Randomised crossover studies were eligible, but only for the assessment of acute effects on oxygenation.

Types of participants
Term and preterm infants less than 28 days of age and requiring conventional mechanical ventilation. No restrictions on underlying pathophysiology were applied.

Types of interventions
Short versus long inspiratory times in conventional mechanical ventilators including time cycled pressure limited ventilators (synchronised and non synchronised) and volume cycled ventilation. Trials using high frequency ventilation (> 150 breaths per minute) were excluded.

Types of outcome measures
Primary
Mortality in the first month of life, and before hospital discharge
Incidence of acute lung injury such as rates of all air leaks (pneumothorax, pulmonary interstitial emphysema, pneumomediastinum, pneumoperitoneum)
Incidence of chronic lung injury (rates of BPD)
• The need for supplemental oxygen at 28 days of life
• The need for supplemental oxygen at 36 weeks postmenstrual age

Secondary
Indices of improved oxygenation including
  • Oxygenation index (OI)
  • Alveolar-arterial oxygen difference (AaDO2)
  • PaO2/FiO2 ratio (P/F ratio)

Lung mechanics (compliance and resistance of either the lung or respiratory system)
Duration of positive pressure respiratory support in days
Duration of supplemental oxygen requirement in days
Radiological evidence of neurologic injury
  • IVH (All grades and severe grades 3 or 4 intraventricular haemorrhage by Papile 1978 classification)
  • Periventricular leukomalacia (PVL)

Long term neurodevelopmental outcomes in childhood (blindness, sensorineural deafness, developmental delay on recognised psychometric testing)

Search methods for identification of studies
See: Cochrane Neonatal Research Group (CNRG) search strategy
The standard search strategy of the CNRG was used. These included MEDLINE (1966 - April 2004) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2003). The MEDLINE search terms used were newborn, neonate, infant, mechanical ventilation, positive pressure respiration and the text phrase “ventilator rate” and text words “inspiratory” or “expiratory”. No language restrictions were applied. The abstracts of the Society for Pediatric Research, and the European Society for Pediatric Research were searched from 1998 - 2003.

Data collection and analysis
The standard methods of the Cochrane Collaboration and the CNRG were used. The methodological quality of each trial was reviewed independently by the two authors for blinding of randomisation, blinding of intervention and outcome measurements as well as completeness of follow up.

The two authors independently assessed eligibility of retrieved studies and extracted data; the results were compared and differences resolved by discussion.

The statistical analysis used the fixed effect model. For categorical data the relative risk (RR), risk difference (RD) and number needed to treat (NNT) with 95% confidence intervals were calculated. Continuous data were analysed using weighted mean difference (WMD). Where data for individual outcomes was incomplete (i.e. did not include all randomised babies), numerators and denominators were those presented in the published manuscript.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
For the summary of the included studies see also table of included studies.

Five published trials (Spahr 1980, Heicher 1981, Greenough 1981, OCTAVE 1991, Pohlandt 1992) recruiting a total of 694 infants were identified. All trials were performed in the pre-surfactant era and when antenatal steroids were not widely used. Three (Spahr 1980, Heicher 1981 and Greenough 1989) were single centre studies whilst OCTAVE 1991 and Pohlandt 1992 involved 6 and 7 centres respectively.

One study (Nilmeier 1995) was excluded. This was a randomised controlled trial in infants with ventilator dependent HMD recruited at two weeks of age, comparing two ITs of 1.0 and 0.4 seconds over a period of seven days. Oxygenation and respiratory mechanics were measured prior to randomisation and compared after a week of the intervention. The results, however were only published in part and were descriptive in nature. Improvements in oxygenation were described as indicated by FiO2 requirement rather than our prespecified indices (AaDO2, PF ratios), and these were only presented for infants randomized to a long IT.

Study Population
The inclusion criteria varied slightly between studies. All the studies except Greenough 1989 recruited infants with acute respiratory failure. Greenough 1989 compared different ITs when weaning infants recovering from HMD. Only Pohlandt 1992 had specific gestational age criteria for inclusion, recruiting infants less than or equal to 32 weeks gestation at birth. Heicher 1981 recruited ventilated infants with a birth weight of greater than 750g. In the study of OCTAVE all ventilated infants less than 72 hours of age were eligible whilst Spahr 1980 recruited all ventilated newborns over a 12 month period. The age at recruitment was not stated in the studies of Heicher 1981 and Spahr 1980. The differences in underlying respiratory pathology between the studies were small. Most infants had HMD although some cases of pneumonia were included. Only OCTAVE 1991 and Heicher 1981 specifically excluded infants with meconium aspiration syndrome (MAS) but no data specific to MAS were provided by any of the included studies.

Interventions
The ventilator strategies and types of ventilator used (see table of included studies) varied with each study.

Once randomised to a long IT or short IT, all infants were ventilated to meet therapeutic range of oxygenation and eucapnia as defined by the authors. All studies allowed adjustments in PIP to correct hypoxia. Ventilation was weaned by decreasing PIP. Where the IT was held constant, weaning of the ventilator rate was achieved...
by lengthening the expiratory time. All studies had a priori failure criteria (see table).

Inspiratory times as defined by the authors were as follows:

- **Spahr 1980** 2.0 vs 1.0 seconds. Both groups were ventilated at a rate of 20 breaths per minute (bpm). This allowed a comparison of I:E ratios (2:1 vs 1:2). IT ratios were held constant throughout whilst rates were allowed to be increased to 40 bpm to correct acidosis and hypercarbia. The range of ITs compared in this study were thus 2.0 - 1.0 (long) vs 1.0 - 0.5 (short) seconds.
- **Heicher 1981** 1.0 vs 0.5 seconds. The ITs were held constant throughout the study period. The long IT group were ventilated at a rate of 20 - 40 bpm and an IT of 1.0 seconds. The rate was increased to correct hypercarbia by reducing expiratory time. The short IT group were ventilated at a rate of 60 bpm and an IT of 0.33 seconds. Both groups were weaned by decreasing PIP and rate by increasing the expiratory time only. I:E ratios were thus not held constant.
- **OCTAVE 1991** 1.0 - 0.75 vs 0.33 seconds. For the long IT group, starting rate was 30 (range 20-40) bpm using an I:E of 1:1 and IT of 1.0 seconds. Whilst weaning the IT was reduced to 0.75 seconds. Thus in the long IT group neither IT or I:E ratio were held constant. The short IT group had an IT of 0.33 seconds, starting rate of 60 bpm, fixing the I:E at 1:2. The IT and I:E ratio was constant throughout in this arm in uncomplicated cases. In the presence of severe hypoxia as defined by the authors, IT could have been increased to 0.5 seconds with the rate unchanged giving an I:E of 1:1 in the short IT group.
- **Pohlandt 1992** 1.0 - 0.66 vs 0.33 seconds. For the long IT group, the starting rate was 30 bpm, an IT of 1 second with I:E of 1:1. The IT was reduced to 0.66 seconds when weaning and rate decreased by increasing expiratory time. Thus in the long IT group neither IT or I:E ratio were held constant. Infants in the short IT group were ventilated with an IT of 0.3 seconds at a rate of 60 bpm, fixing the I:E at 1:2. The IT and I:E ratio was constant throughout in this arm in uncomplicated cases. In the presence of severe hypoxia as defined by the authors, IT could have been increased to 0.66 seconds with the rate unchanged giving an I:E of 1:1 in the short IT group.
- **Greenough 1989** 0.7 -1.0 vs 0.5 seconds. Infants with HMD were recruited if treated with HFPPV and rate had been reduced to 60 bpm. IT for both groups was 0.5 seconds at recruitment. The long IT group were weaned (reduction of respiratory rate) by adjusting both IT and expiratory time and keeping I:E constant at 1:1.2. The IT was increased incrementally to 1.0 seconds. In the short IT group IT was held constant at 0.5 seconds and I:E was variable. Rate was gradually reduced to zero (endotracheal CPAP). A crossover to the other arm was permitted for 30 minutes when rates were weaned to 40 and 20 bpm, allowing a comparison of arterial blood gases at a given rate and I:E ratio using long and short ITs.

**Major Outcomes** The major and secondary outcomes as stated by the authors were as follows.

**Spahr 1980** and **Heicher 1981** - mortality and morbidity (air leak and BPD) and the effect of two different ITs on ventilator settings (MAP, PIP, PEEP and rate compared to baseline). **OCTAVE 1991** - mortality and morbidity (air leak and BPD). This study also followed up surviving premature infants (<33 weeks) recruited to assess the effect of treatment allocation on long term neurodevelopmental outcomes. **Pohlandt 1992** - the incidence of air leak following randomisation. Mortality and the incidence of BPD were recorded as secondary outcomes. In the study of **Greenough 1989** the primary outcome was duration of weaning. Secondary outcomes included rates of air leak, death and the need for re-ventilation.

**Risk of bias in included studies**

The methodological quality of each trial was assessed using the criteria of the Neonatal Review Group. For each trial the following were assessed: concealment of allocation schedule, inclusion in the analysis of all randomised participants and blinding of intervention and outcome measurement.

1. Concealment of allocation schedule
   - **OCTAVE 1991** was a multi-centre trial in which the randomisation was adequately concealed by the use of sealed opaque envelopes held at the co-coordinating centre. Participating centres made a telephone call to the co-coordinating centre when an infant was enrolled and the next sealed envelope opened. Methods of concealing the allocation schedule were not used in the studies of Heicher 1981 and Spahr 1980. Lists were constructed in the study of Pohlandt 1992 such that the numbers treated with either a long or short IT were equal after every second infant enrolled for a particular gestation. These lists were not concealed. The method used in randomising enrolled infants was not described by Greenough 1989 and thus concealment of allocation was unknown.
   - **Generation of allocation sequence**
     - This was not stated for OCTAVE 1991. Pohlandt 1992 used randomisation tables divided into blocks of two for each intervention arm for each of the intended target population (under 28 weeks, 28-30 and 31-32 weeks). Spahr 1980 used a coin toss to determine the treatment allocation sequence. Heicher 1981 quasi-randomised enrolled infants using alternate selection for long and short ITs. The generation of allocation sequence was not stated in the study of Greenough 1989.

2. Inclusion in the analysis of all randomised participants
   All participants were accounted for in the included studies. Pohlandt 1992 used an unusual recruitment and randomisation procedure. Consent was not obtained and all preterm infants less than 32 weeks needing mechanical ventilation were provisionally enrolled and randomised. Infants not meeting secondary enrolment criteria (FIO2 > 0.4) were excluded and replaced by the next preterm infant in the same gestational age category (37 of 181 initially randomised). An additional seven infants were excluded after...
randomisation because they received the alternate form of therapy during transport. Spahrt 1980 excluded five (of 74) patients post randomisation either because of air leaks (one before randomisation, two post PDA ligation), one because of sepsis and one because of use of a muscle relaxant. The remaining three studies had no post randomisation exclusions. OCTAVE 1991 followed a subgroup of enrolled patients (<33 weeks gestation at birth) at a median age of 18 months. Of the 183 surviving eligible infants, 175 (96%) were seen.

3. Blinding of intervention
It was not possible to blind the caregivers in any of the studies.

4. Blinding of outcome assessments
All the primary outcome assessments were unblinded in the five included studies with one exception (Pohlandt 1992), where physicians and radiologists blinded to treatment allocation diagnosed air leak and BPD. In the OCTAVE 1991 study 98% of the long term neurodevelopmental assessments were blinded.

Effects of interventions
Five studies (Spahrt 1980, Heicher 1981, Greenough 1989, OCTAVE 1991, Pohlandt 1992) enrolling 694 infants met the entry criteria and were included in the analysis.

Primary Outcomes

Comparison 01: Long versus short IT as defined by investigators (all trials)

Mortality
Mortality before hospital discharge was reported in all included studies (Table 1). OCTAVE 1991 was the only study to report mortality after hospital discharge. In this study mortality at latest follow up was 30/126 (24%) in the long IT group compared to 36/125 (29%) in the short IT group. In a pooled analysis, there was a trend toward an increased rate of mortality before hospital discharge in newborns ventilated with a long IT that reached borderline statistical significance [typical RR 1.26 (1.00, 1.59), typical RD 0.07 (0.00, 0.13)].

Air Leak
The rates of air leak (acute lung injury) were reported in all included studies (table 2). The studies of Heicher 1981 and Pohlandt 1992 demonstrated statistically significant differences in this outcome favouring the use of a long IT. There were no significant differences in the studies of Greenough 1989, Spahrt 1980. OCTAVE 1991, the largest individual study in this meta-analysis, reported no overall difference in the rates of air leak but when this outcome was compared within a subgroup of infants with HMD, there was a statistically significant difference favouring the use of a short IT (p=0.013). In a pooled analysis, the use of a long IT was associated with a significantly increased rate of air leak [typical RR 1.56 (1.25, 1.94), typical RD 0.13 (0.07, 0.20), NNT 8 (5, 14)].

BPD (Chronic lung injury)
The rates of BPD in all included studies (Table 3) was defined as the need for supplemental oxygen at 28 post natal days. None of the studies reported on this outcome at 36 weeks post conceptual age. No individual study found a significant difference in this outcome and in a pooled analysis, there was no significant difference in the rates of BPD [typical RR 0.91 (0.66, 1.24), RD -0.02 (-0.08, 0.04)]. The trend towards lower rates of BPD using a longer IT in the studies of Spahrt 1980, Heicher 1981 and OCTAVE 1991 is offset by their higher rate of death. For all primary outcomes there was no significant heterogeneity of treatment effect ($I^2 = 0$ for all outcomes)

Secondary Outcomes
Oxygenation
Improvements in oxygenation using our pre-defined criteria (AaDO2, OI, P/F ratios) were not reported when comparing IT greater than 0.5 seconds with shorter IT. Spahrt 1980 provides data for the mean AaDO2 (SD) after 6 hours following the intervention (Table 4). At this early time point, no statistically significant differences were noted. Analysing survivors only, the AaDO2 was significantly lower at 24 and 48 hours in infants ventilated using an IT of 2 seconds versus 1 second.

Duration of mechanical ventilation and oxygen therapy
Data on duration of ventilation in the included studies were either incomplete or presented in a format not permitting a pooled analysis. Pohlandt 1992 and Greenough 1989 did not publish sufficient data to allow a comparison between groups with respect to duration of mechanical ventilation and oxygen therapy. Spahrt 1980 presented data only from survivors in the first week of life and Heicher 1981 excluded more than 10% of babies from the analysis of these outcomes. OCTAVE 1991 reported no significant difference between groups with respect to median age of extubation and median age at weaning from supplemental oxygen.

Neurological injury
No individual study reported the outcomes of IVH or PVL based on ultrasound findings. Spahrt 1980 reported the incidence of IVH through examination at autopsy in those who died and using computed tomography in two survivors. Heicher 1981 described large IVH diagnosed at autopsy but rates of IVH in survivors was not reported. It was the intention of the OCTAVE 1991 group to report on rates of IVH but difficulty was found in retrieving images from all the participating centres and this was replaced by long term neurodevelopmental follow up. In the available data from two trials, no significant effect on this outcome was shown (Table 6).

Patent ductus arteriosus
Symptomatic patent ductus arteriosus (PDA) requiring treatment was reported in the studies of Spahrt and Pohlandt. There was a considerable difference in the rates of PDA, with Spahrt (conducted in 1978) reporting an incidence of 9% in all recruited infants.
and Pohlandt (conducted between 1983 and 1985) reporting an incidence of 35% of all recruited infants. This probably reflects the improvements in echocardiography in the intervening period. In a pooled analysis of these two trials, no significant effect on this outcome was shown (Table 6).

**Developmental delay**

No individual study used formal psychometric testing to assess long term developmental status. The single study reporting long term outcome data (OCTAVE 1991) followed up surviving infants under 33 weeks gestation to a median age of 18 months. The tools used for these assessments were not stated. The outcomes reported were cerebral palsy (Table 7), sensory deficits (impaired hearing or vision; Tables 8 and 9) or global developmental delay. There was an increased rate of cerebral palsy with small numbers (12 versus 4 cases) in infants treated with long IT but this was of borderline statistical significance [RR 2.90 (0.97, 8.65), RD 0.09 (0.00, 0.17).

**Subgroup Analyses**

**Comparison 02: Long (>0.5 seconds) vs Short (<0.5 seconds) IT**

This subgroup analysis involved all the included studies except for Spahr 1980 and resulted in findings similar to the overall analysis. In a pooled analysis of four trials involving 625 infants, mortality before hospital discharge showed a trend disfavouring a long IT which did not reach statistical significance [typical RR 1.24 (0.96, -1.60), typical RD 0.06 (-0.01, 0.13)]. A long IT was associated with a significant increase in the number of air leaks [typical RR 1.56 (1.24, 1.97), typical RD 0.13 (0.07,0.20), NNT 8 (5,14)]. There was no significant difference in rates of BPD [typical RR 0.92 (0.66, 1.28)].

**Analysis based on the overall ventilator strategy**

a. constant IT - only Heicher 1981 maintained IT at 1.0 vs 0.5 seconds in the acute and weaning period.

b. constant I/E ratios - only Spahr 1980 and OCTAVE 1991 aimed to keep I/E ratios constant. It should be noted that the ITs in these two studies are vastly different with the duration of inspiration set in the “short IT” arm of Spahr 1980 equal to that set in the “long IT” arm of OCTAVE 1991. With the vastly different ITs and ventilator rates and thus very different absolute ratios, a subgroup analysis of these two studies was not performed based on ventilator strategy. These two trials were combined using all enrolled infants in Spahr 1980 and those with HMD in OCTAVE 1991 in a pooled analysis of infants with HMD (see below).

c. where both IT and I/E ratios are varied

In all studies the short IT remained unchanged. In most of the studies adjustments of the long IT were permissible when weaning commenced. Variable I/E ratios were seen in the long IT group when rate was either increased or decreased. The ventilator rate ranged between 20 and 40 for Heicher 1981 and OCTAVE 1991 and 30 to 40 for Pohlandt 1992. Thus a subgroup analysis was not performed.

**Comparison 03: Long versus short IT in HMD (subgroup analysis by diagnosis)**

Although the primary respiratory diagnosis was HMD in most infants in the included studies, only Spahr 1980 and OCTAVE 1991 provided published data on outcomes by respiratory pathology. In a pooled analysis of patients with HMD, a significant increase in mortality before discharge [typical RR 1.54 (1.06, 2.23), typical RD 0.12 (0.02, 0.21), NNT 8 (5, 50)] and air leak [typical RR 1.73 (1.17, 2.57), typical RD 0.14 (0.04, 0.24), NNT 7 (4, 25)] was seen in the infants randomised to a long IT.

**Gestational age**

All the trials except for Pohlandt 1992 (infants less than or equal to 32 weeks gestation randomised) had no restrictions on gestational age at recruitment. In this individual study there was a statistically significant increase in air leak in the long IT group. No significant differences were seen in rates of mortality before hospital discharge and BPD.

**Comparison 04: Long versus short IT (subgroup analysis of trials allowing use of muscle relaxants)**

Muscle relaxants were allowed in the trials of Heicher 1981, Pohlandt 1992 and OCTAVE 1991 but not used in Spahr 1980 and Greenough 1989. Data on the extent of use of muscle relaxants were not presented in the report by Pohlandt 1992, and were incomplete in OCTAVE 1991 (published data was sourced from only one of the participating centres). Similar use of muscle relaxants occurred in each arm of Heicher 1981 (13 versus 14). In an analysis confined to the three trials permitting muscle relaxants usage, there was a significant increase in air leak [typical RR 1.56 (1.25, 1.94), typical RD 0.14 (0.07, 0.21), NNT 7 (5, 14)] and an increase in mortality [typical RR 1.26 (0.97, 1.62), typical RD 0.07 (-0.01, 0.14)] which reached marginal statistical significance, in infants managed with a long IT. In the trials where no muscle relaxants were used (Spahr 1980, Greenough 1989), there were no statistically significant differences in air leak or mortality.

**Trials using surfactant**

None of the trials used surfactant in the management of HMD.

**Ventilator mode**

All infants were ventilated using continuous mandatory ventilation. No synchronised modes were used. Ventilator types differed (see table of included studies).

**DISCUSSION**

The goals of mechanical ventilation are to achieve and maintain oxygenation and remove carbon dioxide whilst minimizing the risk of lung injury. These studies were performed at a time when mortality rates for ventilated infants with hypoxic respiratory failure were considerably higher than current rates (Doyle 1999). Ma-
Long inspiratory times used in acute HMD following surfactant replacement may be injurious to the lung. Gas flow rates are usually held constant and the effects of varying gas flow rates on oxygenation and BPD have yet to be investigated. Of all the included studies, only one (Spahr 1980) provided data on the effects of IT on oxygenation in the acute phase of HMD. Whilst the study used ITs in both arms that would be considered “long”, this was a study primarily comparing two I:E ratios. The improvements in oxygenation seen in inverse ratio ventilation can be attained (using the same physiological principles of alveolar recruitment and maintenance of lung volumes) if appropriate PEEP is applied throughout the respiratory cycle. The optimum level of PEEP will vary according to the underlying pulmonary pathophysiology and is yet to be evaluated in a formal clinical trial.

The range of ITs used in the long IT groups in this systematic review was 0.66 to 2.0 seconds. In acute HMD, where the median IT is 0.3 seconds (Ahluwalia 1994), these ITs are likely to cause asynchrony and patient discomfort. If these long ITs were used in surfactant treated infants, the combination of improved compliance and greater likelihood of active expiration against a positive pressure inflation may increase the risk of air leak. Thus using a long IT in acute HMD following surfactant replacement may be an unnecessary strategy unless faced with continuing severe hypoxia. In these situations there are current alternative modes of therapy to improve oxygenation if conventional ventilation is failing, including rescue high frequency ventilation and the use of inhaled nitric oxide in mature infants. Perinatal units are now widely using ventilators that synchronise with the infant’s breathing and target tidal volumes. With synchronised ventilation, square wave ventilation has been replaced by sinusoidal waves so that mean airway pressures are less influenced by the length of the IT.

This review has shown no advantage in using long IT over short IT in the treatment of acute respiratory failure (mainly HMD). Whilst there is increasing use of non invasive ventilation such as nasal continuous positive airway pressure to avoid ventilator induced lung injury in the acute management of HMD, mechanical ventilation will continue to have a role in extremely immature infants and those with HMD complicated by apnea. In institutions where surfactant is unavailable, lengthening the IT may improve oxygenation in the acute phase. However, as compliance improves, the IT should be reviewed regularly as this review demonstrates a significant risk of lung injury (airway leak) with a long IT. The use of a long IT where time constants are longer than acute HMD such as premature infants with BPD, meconium aspiration syndrome and newborns in cardiac failure may be appropriate and is yet to be investigated.

Whilst neonatal respiratory failure is not a single disease entity, relatively recent advances in technology have allowed the bedside display of real time inspiratory and expiratory tidal volumes. Clinicians therefore have the ability to adjust the IT as pulmonary mechanics change during the course of an infant’s illness. These strategies will need to be evaluated in future clinical trials.

AUTHORS’ CONCLUSIONS

Implications for practice
Long inspiratory times when used in acute HMD in a population not exposed to antenatal steroids and postnatal surfactant are associated with higher rates of mortality and morbidity. Stiff lungs with HMD have very short time constants. Mechanically ventilated infants with HMD and especially those treated in institutions where these adjunctive therapies are not available should be ventilated using a short IT.

Implications for research
The availability of real time, continuous measurements of pulmonary mechanics may enhance clinicians’ ability to detect the optimal IT for infants with different underlying pathologies and at different time points in their illness. Future research should examine whether new monitoring equipment and ventilator strategies, including adjusting ITs to match underlying compliance, can...
further reduce the harmful effects of neonatal mechanical ventilation.

REFERENCES

References to studies included in this review

Greenough 1989  {published data only}

Heicher 1981  {published data only}

OCTAVE 1991  {published data only}

Pohlandt 1992  {published data only}

Spahr 1980  {published data only}

References to studies excluded from this review

Nilmeyer 1995  {published data only}
Nilmeyer NL, Hodge GB, Dunn CE, Benitz WE, Ariagno RL. One second inspiratory time improves lung mechanics in preterm infants who are ventilator dependent post respiratory distress syndrome. Pediatric Research 1995; 37:344A.

Additional references

Adamson 1968

Ahuwalia 1994

Boros 1979

Boros 1984

Cumarasamy 1973

D-Papadopoulos 1965

Doyle 1999

Goldsmith 1996

Greenough 1986

Greenough 1987

Greenough 2004

Gregory 1971

Harris 1996
Herman 1973

Murdock 1970

Northway 1967

Papile 1978

Rennie 1987

Reynolds 1971

Soll 1992

Soll 2004
Soll RF, Blanco F. Natural surfactant versus synthetic surfactant for neonatal respiratory distress syndrome. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD000144]

Stewart 1981

Upton 1990

Usher 1963

Weigl 1973

Yost 2003

* Indicates the major publication for the study
## Characteristics of included studies  (ordered by study ID)

### Greenough 1989

| Methods | Conception of allocation: Can't tell - method of randomisation to either long IT (group A) or short IT (group B) not stated.  
Blinding of intervention: No  
Completeness of follow up: Yes for short-term outcomes - all participants accounted for. Blinding of outcome measurement: No  
Single centre study. Method of randomisation not stated. Intervention not blinded. Follow up complete to stated primary outcome (duration of weaning). |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Participants</td>
<td>Single centre study. All infants with RDS (n=40) and ventilated with HFPPV (&gt;60bpm) were recruited when weaning commenced (PIP = 20cm H2O and rate =60bpm).</td>
</tr>
<tr>
<td>Interventions</td>
<td>At recruitment all infants were ventilated using an IT of 0.5 seconds. Weaning then commenced using one of two strategies. In Group A (long IT) (n=20), the rate was reduced by increasing both the IT and ET maintaining a fixed I:E ratio at 1:1.2. Maximum IT in this group was 1 second. In group B (short IT) (n=20), the rate was weaned by keeping the IT fixed at 0.5 secs whilst increasing the expiratory time (ET). Single (Sechrist) type of ventilator.</td>
</tr>
</tbody>
</table>
| Outcomes | Air leak  
Indices of oxygenation (paO2)  
Duration of weaning  
Rate of reintubation |
| Notes | Year of study = 1989. Pre-surfactant. Age at recruitment not specified. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Heicher 1981

| Methods | Conception of allocation: No - quasi-randomised using alternate allocation for long and short ITs  
Blinding of intervention: No  
Completeness of follow up: Yes for short-term outcomes (all outcomes complete for hospital stay)  
Blinding of outcome measurement: No |
<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Participants</td>
<td>All infants &gt;750g and ventilated with abnormal CXR findings (n=102). Infants with gross abnormalities, chromosomal anomalies and meconium aspiration were excluded.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Long IT (n=51) compared with short IT (n=51). Long IT= 1.0 seconds; rates used 20–40bpm. Short IT=0.5 seconds; rate used 60bpm. Single ventilator (Babybird) used in both groups. Criteria for failed treatment and relaxation of allocated ventilator strategy were as follows; 1. Hypoxia - either (i)PaO2 &lt; 50</td>
</tr>
</tbody>
</table>
torr with FiO2 of 1.0 and PEEP of 8 to 10cm H2O or (ii) FiO2 > 0.6 (short IT) or PIP > 30cm H2O (long IT) for 72 hours. 2. Hypercarbia - PaCO2 > 45 torr on maximum PIP and rate permitted for the group.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air leak</td>
</tr>
<tr>
<td></td>
<td>BPD at 30 days by Northway criteria.</td>
</tr>
<tr>
<td></td>
<td>Combined outcome of death and IVH</td>
</tr>
</tbody>
</table>

| Notes          | Years of study = 1978 - 79. Pre-surfactant. Age at recruitment not specified. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>C - Inadequate</td>
</tr>
</tbody>
</table>

### OCTAVE 1991

**Methods**
- Concealment of allocation: Yes - sealed opaque, serially numbered envelopes stored at co-ordinating centre.
- Blinding of intervention: No
- Completeness of follow up: Yes for short-term outcomes - 100% follow up for in-hospital outcomes with 97% of infants born less than 33 weeks accounted for in the long term outcome assessment at 18 months. Blinding of outcome measurement: not for primary outcomes. 98% of neurodevelopmental follow up completed by physicians blinded to ventilation strategy

<table>
<thead>
<tr>
<th>Participants</th>
<th>Newborns of any gestation ventilated for any reason (n=346). Infants with meconium aspiration excluded. Infants were enrolled before 72 hours of age.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Long IT (n=172) compared with short IT (n=174). Long IT= 1.0 seconds; starting rate=20bpm (range=20-40bpm) and I:E ratios not fixed. Short IT=0.33 seconds; rate used =60bpm and I:E ratio fixed at 1:2. Single ventilator (Sechrist IV 100B) used in both groups. Dopamine and tolazoline used at physician's discretion to treat hypotension or reduce right to left shunting. The use of muscle relaxants was permitted for recurrent air leaks and for poor gas exchange despite recruitment manoeuvres and optimisation of haemodynamics. Criteria for failed treatment and relaxation of allocated ventilator strategy were as follows; 1. Hypoxia - PaO2 &lt; 50mmHg despite FiO2 &gt;0.95 and MAP of 17cmH2O. 2. Recurrent pneumothoraces</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Death before discharge</td>
</tr>
<tr>
<td></td>
<td>Air leak</td>
</tr>
<tr>
<td></td>
<td>BPD defined as need for supplemental oxygen at 28 days</td>
</tr>
<tr>
<td></td>
<td>A subgroup of infants less than 33 weeks gestation had long term follow up at a median age of 18 months</td>
</tr>
</tbody>
</table>

| Notes                    | Years of study = 1983 - 86. Pre-surfactant. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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</thead>
</table>
# OCTAVE 1991 (Continued)

<table>
<thead>
<tr>
<th>Allocation concealment?</th>
<th>Yes</th>
<th>A - Adequate</th>
</tr>
</thead>
</table>

### Pohlandt 1992

#### Methods
Concealment of allocation: No - all ventilated infants provisionally randomised using one of three randomisation tables (stratified by gestational age). If infant subsequently excluded they were replaced by the next preterm infant in the same gestational age category.
Blinding of intervention: No
Completeness of follow up: Yes for primary outcomes - 100% follow up for in-hospital outcomes
Blinding of outcome measurement: Only for diagnosis of air leak and BPD

#### Participants
Preterm infants equal to or less than 32 weeks gestation and mechanically ventilated (n=181) were randomised if FiO2 >0.4 after 3 hours of birth (no upper age limit given). Infants later excluded if the FiO2 was < 0.4 to maintain PaO2 >50mmHg or if there were any violations of allocated ventilation protocol (exclusions post randomisation=44)

#### Interventions
Long IT (n=63) compared with short IT (n=74). Long IT=1.0 seconds; rates of 30 to 40bpm; I:E ratio 1:1 increased to 2:1 in case of hypoxaemia. IT reduced to 0.66 seconds during weaning. Short IT=0.33 seconds; rate=60bpm. I:E ratios kept constant at 1:2; weaned by reducing PIP, PEEP and inspired oxygen. Seven different ventilators were used in this study. No failure criteria described in the report.

#### Outcomes
Mortality
Extra-alveolar air leak
BPD at 28 days by Northway criteria

#### Notes
Years of study = 1983 - 85. Parental consent not sought as ventilator frequencies of 30-100 widely used in the participating units. Pre-surfactant.

### Risk of bias

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<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Allocation concealment</td>
<td>No</td>
<td>C - Inadequate</td>
</tr>
</tbody>
</table>

### Spahr 1980

#### Methods
Concealment of allocation: No - randomised by coin toss
Blinding of intervention: No
Completeness of follow up: Yes for short-term outcomes
Blinding of outcome measurement: No

#### Participants
All infants admitted in a 12 month period and ventilated for HMD (n=74). Five post randomisation exclusions (pre-existing air leaks=3, sepsis=1, use of paralysing agent=1)

#### Interventions
Long IT (n=36) compared with short IT (n=33). Long IT=2 seconds; rate=20bpm; I:E ratio 2:1. Short IT=1 seconds; rate=20bpm; I:E ratio 1:2. Target PaO2 45 - 60mmHg and pH 7.25 to 7.35. Single
ventilator (Babybird). No failure criteria described in the report.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mortality at 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air leak</td>
</tr>
<tr>
<td></td>
<td>BPD defined as need for supplemental oxygen at one month with typical radiographic findings</td>
</tr>
<tr>
<td></td>
<td>Pulmonary haemorrhage, IVH (all grades), PDA.</td>
</tr>
</tbody>
</table>

| Notes | Year of study = 1978. Pre-surfactant and pre antenatal steroids. |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>C - Inadequate</td>
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</tbody>
</table>

HMD = Hyaline Membrane Disease, RDS = Respiratory Distress Syndrome, IT = inspiratory time, IVH = intraventricular haemorrhage, HFPPV = High Frequency Positive Pressure Ventilation

**Characteristics of excluded studies** *(ordered by study ID)*

| Nilmeier 1995 | Randomised controlled trial of infants recruited at two weeks of age. Oxygenation and respiratory mechanics were compared after a week of intervention at two ITs (1.0 and 0.4 seconds). Published results however were incomplete (data from only one group) and descriptive in nature (not using our prespecified indices of AaDO2 and PF ratios). |
### DATA AND ANALYSES

Comparison 1. Long vs Short IT as defined by investigators (all trials)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality before discharge</td>
<td>5</td>
<td>694</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.26 [1.00, 1.59]</td>
</tr>
<tr>
<td>2 Air leak</td>
<td>5</td>
<td>685</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.56 [1.25, 1.94]</td>
</tr>
<tr>
<td>3 BPD (supplemental oxygen at 28 days)</td>
<td>4</td>
<td>654</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.91 [0.66, 1.24]</td>
</tr>
<tr>
<td>4 AaDO2 (mmHg) values after 6 hours of intervention</td>
<td>1</td>
<td>69</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-18.60 [-93.78, 56.58]</td>
</tr>
<tr>
<td>5 IVH (all grades)</td>
<td>2</td>
<td>171</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.11 [0.72, 1.71]</td>
</tr>
<tr>
<td>6 Patent ductus arteriosus (PDA)</td>
<td>2</td>
<td>206</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.91 [0.58, 1.43]</td>
</tr>
<tr>
<td>7 Cerebral palsy in survivors less than 33 weeks gestation at birth</td>
<td>1</td>
<td>177</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.9 [0.97, 8.65]</td>
</tr>
<tr>
<td>8 Visual impairment in survivors less than 33 weeks gestation at birth</td>
<td>1</td>
<td>177</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.09 [0.83, 5.26]</td>
</tr>
<tr>
<td>9 Sensorineural hearing loss in survivors less than 33 weeks gestation at birth</td>
<td>1</td>
<td>177</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.93 [0.60, 6.19]</td>
</tr>
</tbody>
</table>

Comparison 2. Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality before discharge</td>
<td>4</td>
<td>625</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.24 [0.96, 1.60]</td>
</tr>
<tr>
<td>2 Air leak</td>
<td>4</td>
<td>616</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.56 [1.24, 1.97]</td>
</tr>
<tr>
<td>3 BPD (supplemental oxygenation at 28 days)</td>
<td>3</td>
<td>585</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.92 [0.66, 1.28]</td>
</tr>
<tr>
<td>4 IVH (all grades)</td>
<td>1</td>
<td>102</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.08 [0.55, 2.14]</td>
</tr>
</tbody>
</table>
Comparison 3. Long vs Short IT in HMD (subgroup analysis by diagnosis)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality before hospital discharge</td>
<td>2</td>
<td>306</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.54 [1.06, 2.23]</td>
</tr>
<tr>
<td>2 Air leak</td>
<td>2</td>
<td>303</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.73 [1.17, 2.57]</td>
</tr>
<tr>
<td>3 BPD (supplemental oxygen at 28 days)</td>
<td>2</td>
<td>253</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.88 [0.60, 1.30]</td>
</tr>
</tbody>
</table>

Comparison 4. Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality before discharge</td>
<td>5</td>
<td>694</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.26 [1.00, 1.59]</td>
</tr>
<tr>
<td>1.1 Muscle relax allowed</td>
<td>3</td>
<td>585</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.26 [0.97, 1.62]</td>
</tr>
<tr>
<td>1.2 No muscle relaxation</td>
<td>2</td>
<td>109</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.26 [0.73, 2.18]</td>
</tr>
<tr>
<td>2 Air leak</td>
<td>5</td>
<td>685</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.56 [1.25, 1.94]</td>
</tr>
<tr>
<td>2.1 Muscle relax allowed</td>
<td>3</td>
<td>576</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.54 [1.22, 1.94]</td>
</tr>
<tr>
<td>2.2 No muscle relaxation</td>
<td>2</td>
<td>109</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.69 [0.82, 3.47]</td>
</tr>
<tr>
<td>3 BPD (supplemental oxygen at 28 days)</td>
<td>4</td>
<td>654</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.91 [0.66, 1.24]</td>
</tr>
<tr>
<td>3.1 Muscle relax allowed</td>
<td>3</td>
<td>585</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.92 [0.66, 1.28]</td>
</tr>
<tr>
<td>3.2 No muscle relaxation</td>
<td>1</td>
<td>69</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.73 [0.21, 2.50]</td>
</tr>
<tr>
<td>4 IVH (all grades)</td>
<td>2</td>
<td>171</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.11 [0.72, 1.71]</td>
</tr>
<tr>
<td>4.1 Muscle relax allowed</td>
<td>1</td>
<td>102</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.08 [0.55, 2.14]</td>
</tr>
<tr>
<td>4.2 No muscle relaxation</td>
<td>1</td>
<td>69</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.13 [0.65, 1.97]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 1 Mortality before discharge.

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 1 Long vs Short IT as defined by investigators (all trials)

**Outcome:** 1 Mortality before discharge

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Greenough 1989</td>
<td>0/20</td>
<td>1/20</td>
<td>1.7% [0.01, 77.72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heicher 1981</td>
<td>17/51</td>
<td>14/51</td>
<td>15.7% [0.67, 2.19]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>50/172</td>
<td>41/174</td>
<td>45.8% [0.86, 1.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>25/63</td>
<td>22/74</td>
<td>22.7% [0.84, 2.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>18/36</td>
<td>12/33</td>
<td>14.1% [0.79, 2.40]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total** (95% CI) 342 352 100.0% 1.26 [1.00, 1.59]

Total events: 110 (Long IT), 90 (Short IT)

Heterogeneity: $\chi^2 = 0.87$, df = 4 ($P = 0.93$); $I^2 = 0.0$

Test for overall effect: $Z = 1.95$ ($P = 0.052$)

---

### Analysis 1.2. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 2 Air leak.

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 1 Long vs Short IT as defined by investigators (all trials)

**Outcome:** 2 Air leak

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Greenough 1989</td>
<td>2/20</td>
<td>1/20</td>
<td>0.6% [0.26, 98.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heicher 1981</td>
<td>18/51</td>
<td>7/51</td>
<td>8.6% [1.18, 5.62]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>44/167</td>
<td>32/170</td>
<td>38.9% [0.94, 2.09]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>46/63</td>
<td>37/74</td>
<td>41.7% [1.11, 1.92]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>13/36</td>
<td>8/33</td>
<td>10.2% [0.71, 3.13]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total** (95% CI) 337 348 100.0% 1.56 [1.25, 1.94]

Total events: 123 (Long IT), 84 (Short IT)

Heterogeneity: $\chi^2 = 2.67$, df = 4 ($P = 0.62$); $I^2 = 0.0$

Test for overall effect: $Z = 3.95$ ($P = 0.000077$)
## Analysis 1.3. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 3 BPD (supplemental oxygen at 28 days).

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 1 Long vs Short IT as defined by investigators (all trials)

**Outcome:** 3 BPD (supplemental oxygen at 28 days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Heicher 1981</td>
<td>4/51</td>
<td>5/51</td>
<td>0.80 [0.23, 2.81]</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>38/172</td>
<td>42/174</td>
<td>0.92 [0.62, 1.34]</td>
<td>65.3%</td>
<td></td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>11/63</td>
<td>13/74</td>
<td>0.99 [0.48, 2.06]</td>
<td>18.7%</td>
<td></td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>4/36</td>
<td>5/33</td>
<td>0.73 [0.21, 2.50]</td>
<td>8.2%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 57 (Long IT), 65 (Short IT)

Heterogeneity: $\chi^2 = 0.22$, df = 3 ($P = 0.97$); $I^2 = 0.0$

Test for overall effect: Z = 0.61 ($P = 0.54$)

## Analysis 1.4. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 4 AaDO2 (mmHg) values after 6 hours of intervention.

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 1 Long vs Short IT as defined by investigators (all trials)

**Outcome:** 4 AaDO2 (mmHg) values after 6 hours of intervention

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>36 282.3 (156)</td>
<td>33 300.9 (162)</td>
<td>-18.60 [-93.78, 56.58]</td>
<td>100.0%</td>
<td>-18.60 [-93.78, 56.58]</td>
</tr>
</tbody>
</table>

Total events: 57 (Long IT), 65 (Short IT)

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 ($P = 0.63$)
**Analysis 1.5. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 5 IVH (all grades).**

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 1 Long vs Short IT as defined by investigators (all trials)

Outcome: 5 IVH (all grades)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heicher 1981</td>
<td>13/51</td>
<td>12/51</td>
<td>1.08 [0.55, 2.14]</td>
<td>46.9%</td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>16/36</td>
<td>13/33</td>
<td>1.13 [0.65, 1.97]</td>
<td>53.1%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>87</strong></td>
<td><strong>84</strong></td>
<td>1.11 [0.72, 1.71]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 29 (Long IT), 25 (Short IT)

Heterogeneity: $X^2 = 0.01$, df = 1 ($P = 0.93$); $I^2 = 0\%$

Test for overall effect: $Z = 0.46$ ($P = 0.65$)

---

**Analysis 1.6. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 6 Patent ductus arteriosus (PDA).**

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 1 Long vs Short IT as defined by investigators (all trials)

Outcome: 6 Patent ductus arteriosus (PDA)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pohlandt 1992</td>
<td>20/63</td>
<td>28/74</td>
<td>0.84 [0.53, 1.34]</td>
<td>92.5%</td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>4/36</td>
<td>2/33</td>
<td>1.83 [0.36, 9.36]</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>99</strong></td>
<td><strong>107</strong></td>
<td>0.91 [0.58, 1.43]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events: 24 (Long IT), 30 (Short IT)

Heterogeneity: $X^2 = 0.83$, df = 1 ($P = 0.36$); $I^2 = 0\%$

Test for overall effect: $Z = 0.40$ ($P = 0.69$)
## Analysis 1.7. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 7 Cerebral palsy in survivors less than 33 weeks gestation at birth.

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 1 Long vs Short IT as defined by investigators (all trials)

Outcome: 7 Cerebral palsy in survivors less than 33 weeks gestation at birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE 1991</td>
<td>12/90</td>
<td>4/87</td>
<td></td>
<td>100.0%</td>
<td>2.90 [0.97, 8.65]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>87</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.90 [0.97, 8.65]</strong></td>
</tr>
</tbody>
</table>

Total events: 12 (Long IT), 4 (Short IT)
Heterogeneity: not applicable
Test for overall effect: Z = 1.91 (P = 0.056)

Favours Long IT
Favours Short IT

## Analysis 1.8. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 8 Visual impairment in survivors less than 33 weeks gestation at birth.

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 1 Long vs Short IT as defined by investigators (all trials)

Outcome: 8 Visual impairment in survivors less than 33 weeks gestation at birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE 1991</td>
<td>13/90</td>
<td>6/87</td>
<td></td>
<td>100.0%</td>
<td>2.09 [0.83, 5.26]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>90</strong></td>
<td><strong>87</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>2.09 [0.83, 5.26]</strong></td>
</tr>
</tbody>
</table>

Total events: 13 (Long IT), 6 (Short IT)
Heterogeneity: not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

Favours Long IT
Favours Short IT
### Analysis 1.9. Comparison 1 Long vs Short IT as defined by investigators (all trials), Outcome 9 Sensorineural hearing loss in survivors less than 33 weeks gestation at birth.

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 1 Long vs Short IT as defined by investigators (all trials)

**Outcome:** 9 Sensorineural hearing loss in survivors less than 33 weeks gestation at birth

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE 1991</td>
<td>8/90</td>
<td>4/87</td>
<td>1.93 [ 0.60, 6.19 ]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Total events: 8 (Long IT), 4 (Short IT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity: not applicable</td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.11 (P = 0.27)</td>
</tr>
</tbody>
</table>

### Analysis 2.1. Comparison 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 1 Mortality before discharge.

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

**Outcome:** 1 Mortality before discharge

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenough 1989</td>
<td>0/20</td>
<td>1/20</td>
<td>0.33 [ 0.01, 7.72 ]</td>
<td>2.0%</td>
</tr>
<tr>
<td>Heischer 1981</td>
<td>17/51</td>
<td>14/51</td>
<td>1.21 [ 0.67, 2.19 ]</td>
<td>18.3%</td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>50/172</td>
<td>41/174</td>
<td>1.23 [ 0.86, 1.76 ]</td>
<td>53.3%</td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>25/63</td>
<td>22/74</td>
<td>1.33 [ 0.84, 2.12 ]</td>
<td>26.5%</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Total events: 92 (Long IT), 78 (Short IT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterogeneity: Chi^2 = 0.77, df = 3 (P = 0.86); I^2 =0.0%</td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.66 (P = 0.098)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>0.02</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours Long IT</td>
<td>Favours Short IT</td>
<td>Favours Long IT</td>
<td>Favours Short IT</td>
<td></td>
</tr>
</tbody>
</table>
## Analysis 2.2. Comparison 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 2 Air leak.

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

Outcome: 2 Air leak

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenough 1989</td>
<td>2/20</td>
<td>0/20</td>
<td></td>
<td>0.7 %</td>
<td>5.00 [ 0.26, 98.00 ]</td>
</tr>
<tr>
<td>Heicher 1981</td>
<td>18/51</td>
<td>7/51</td>
<td></td>
<td>9.6 %</td>
<td>2.57 [ 1.18, 5.62 ]</td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>44/167</td>
<td>32/170</td>
<td></td>
<td>43.3 %</td>
<td>1.40 [ 0.94, 2.09 ]</td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>46/63</td>
<td>37/74</td>
<td></td>
<td>46.5 %</td>
<td>1.46 [ 1.11, 1.92 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>301</strong></td>
<td><strong>315</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>1.56 [ 1.24, 1.97 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 110 (Long IT), 76 (Short IT)

Heterogeneity: $\chi^2 = 2.68$, df = 3 ($P = 0.44$); $I^2 = 0.0$

Test for overall effect: $Z = 3.82$ ($P = 0.00013$)

<table>
<thead>
<tr>
<th>Risk</th>
<th>0.01</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours</td>
<td>Long IT</td>
<td>Short IT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Analysis 2.3. Comparison 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 3 BPD (supplemental oxygenation at 28 days).

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

Outcome: 3 BPD (supplemental oxygenation at 28 days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heicher 1981</td>
<td>4/51</td>
<td>5/51</td>
<td></td>
<td>8.5 %</td>
<td>0.80 [ 0.23, 2.81 ]</td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>38/172</td>
<td>42/174</td>
<td></td>
<td>71.1 %</td>
<td>0.92 [ 0.62, 1.34 ]</td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>11/63</td>
<td>13/74</td>
<td></td>
<td>20.4 %</td>
<td>0.99 [ 0.48, 2.06 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>286</strong></td>
<td><strong>299</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.92 [ 0.66, 1.28 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 53 (Long IT), 60 (Short IT)

Heterogeneity: $\chi^2 = 0.09$, df = 2 ($P = 0.96$); $I^2 = 0.0$

Test for overall effect: $Z = 0.49$ ($P = 0.63$)

<table>
<thead>
<tr>
<th>Risk</th>
<th>0.5</th>
<th>0.7</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favours</td>
<td>Long IT</td>
<td>Short IT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Analysis 2.4. Comparison 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds), Outcome 4 IVH (all grades).

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 2 Long (greater than 0.5 seconds) vs Short IT (less than or equal to 0.5 seconds)

**Outcome:** 4 IVH (all grades)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heicher 1981</td>
<td>13/51</td>
<td>12/51</td>
<td></td>
<td>100.0%</td>
<td>1.08 [0.55, 2.14]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>51</strong></td>
<td><strong>51</strong></td>
<td></td>
<td>100.0%</td>
<td>1.08 [0.55, 2.14]</td>
</tr>
</tbody>
</table>

Total events: 13 (Long IT), 12 (Short IT)

*Heterogeneity: not applicable*

*Test for overall effect: Z = 0.23 (P = 0.82)*

## Analysis 3.1. Comparison 3 Long vs Short IT in HMD (subgroup analysis by diagnosis), Outcome 1 Mortality before hospital discharge.

**Review:** Long versus short inspiratory times in neonates receiving mechanical ventilation

**Comparison:** 3 Long vs Short IT in HMD (subgroup analysis by diagnosis)

**Outcome:** 1 Mortality before hospital discharge

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE 1991</td>
<td>32/114</td>
<td>21/123</td>
<td></td>
<td>61.7%</td>
<td>1.64 [1.01, 2.68]</td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>18/36</td>
<td>12/33</td>
<td></td>
<td>38.3%</td>
<td>1.38 [0.79, 2.40]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>150</strong></td>
<td><strong>156</strong></td>
<td></td>
<td>100.0%</td>
<td>1.54 [1.06, 2.23]</td>
</tr>
</tbody>
</table>

Total events: 50 (Long IT), 33 (Short IT)

*Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 = 0.0%

*Test for overall effect: Z = 2.29 (P = 0.022)*
Analysis 3.2. Comparison 3 Long vs Short IT in HMD (subgroup analysis by diagnosis), Outcome 2 Air leak.

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 3 Long vs Short IT in HMD (subgroup analysis by diagnosis)

Outcome: 2 Air leak

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE 1991</td>
<td>37/112</td>
<td>22/122</td>
<td></td>
<td>71.6 %</td>
<td>1.83 [ 1.16, 2.91 ]</td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>13/36</td>
<td>8/33</td>
<td></td>
<td>28.4 %</td>
<td>1.49 [ 0.71, 3.13 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>148</td>
<td>155</td>
<td></td>
<td>100.0 %</td>
<td>1.73 [ 1.17, 2.57 ]</td>
</tr>
</tbody>
</table>

Total events: 50 (Long IT), 30 (Short IT)
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.76 (P = 0.0058)

Analysis 3.3. Comparison 3 Long vs Short IT in HMD (subgroup analysis by diagnosis), Outcome 3 BPD (supplemental oxygen at 28 days).

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 3 Long vs Short IT in HMD (subgroup analysis by diagnosis)

Outcome: 3 BPD (supplemental oxygen at 28 days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT n/N</th>
<th>Short IT n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTAVE 1991</td>
<td>27/82</td>
<td>37/102</td>
<td></td>
<td>86.3 %</td>
<td>0.91 [ 0.61, 1.36 ]</td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>4/36</td>
<td>5/33</td>
<td></td>
<td>13.7 %</td>
<td>0.73 [ 0.21, 2.50 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>118</td>
<td>135</td>
<td></td>
<td>100.0 %</td>
<td>0.88 [ 0.60, 1.30 ]</td>
</tr>
</tbody>
</table>

Total events: 31 (Long IT), 42 (Short IT)
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0.0%
Test for overall effect: Z = 0.63 (P = 0.53)
### Analysis 4.1. Comparison 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 1 Mortality before discharge.

**Review**: Long versus short inspiratory times in neonates receiving mechanical ventilation.

**Comparison**: 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

**Outcome**: 1 Mortality before discharge

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio (M-H,Fixed) 95% CI</th>
<th>Weight</th>
<th>Risk Ratio (M-H,Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Muscle relax allowed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heicher 1981</td>
<td>17/51</td>
<td>14/51</td>
<td>15.7% 1.21 [0.67, 2.19]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>50/172</td>
<td>41/174</td>
<td>45.8% 1.23 [0.86, 1.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>25/63</td>
<td>22/74</td>
<td>22.7% 1.33 [0.84, 2.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>286</td>
<td>299</td>
<td>84.2% 1.26 [0.97, 1.62]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 92 (Long IT), 77 (Short IT)

Heterogeneity: $\chi^2 = 0.09$, $df = 2$ ($P = 0.86$); $I^2 = 0.0$

Test for overall effect: $Z = 1.76$ ($P = 0.078$)

2 No muscle relaxation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio (M-H,Fixed) 95% CI</th>
<th>Weight</th>
<th>Risk Ratio (M-H,Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenough 1989</td>
<td>0/20</td>
<td>1/20</td>
<td>1.7% 0.33 [0.01, 7.72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>18/36</td>
<td>12/33</td>
<td>14.1% 1.38 [0.79, 2.40]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>56</td>
<td>53</td>
<td>15.8% 1.26 [0.73, 2.18]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 18 (Long IT), 13 (Short IT)

Heterogeneity: $\chi^2 = 0.78$, $df = 1$ ($P = 0.38$); $I^2 = 0.0$

Test for overall effect: $Z = 0.84$ ($P = 0.38$)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio (M-H,Fixed) 95% CI</th>
<th>Weight</th>
<th>Risk Ratio (M-H,Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>342</td>
<td>352</td>
<td>100.0% 1.26 [1.00, 1.59]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 110 (Long IT), 90 (Short IT)

Heterogeneity: $\chi^2 = 0.87$, $df = 4$ ($P = 0.93$); $I^2 = 0.0$

Test for overall effect: $Z = 1.95$ ($P = 0.052$)
Analysis 4.2. Comparison 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 2 Air leak.

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome: 2 Air leak

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Muscle relax allowed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heicher 1981</td>
<td>18/51</td>
<td>7/51</td>
<td>8.6 %</td>
<td>2.57 [1.18, 5.62]</td>
<td></td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>44/167</td>
<td>32/170</td>
<td>38.9 %</td>
<td>1.40 [0.94, 2.09]</td>
<td></td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>46/63</td>
<td>37/74</td>
<td>41.7 %</td>
<td>1.46 [1.11, 1.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>281</td>
<td>295</td>
<td><strong>89.2 %</strong></td>
<td><strong>1.54 [1.22, 1.94]</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 108 (Long IT), 76 (Short IT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.02, df = 2 (P = 0.37); I² = 1%</td>
<td>Test for overall effect: Z = 3.69 (P = 0.00023)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No muscle relaxation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenough 1989</td>
<td>2/20</td>
<td>0/20</td>
<td>0.6 %</td>
<td>5.00 [0.26, 98.00]</td>
<td></td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>13/36</td>
<td>8/33</td>
<td>10.2 %</td>
<td>1.49 [0.71, 3.13]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>56</td>
<td>53</td>
<td><strong>10.8 %</strong></td>
<td><strong>1.69 [0.82, 3.47]</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 15 (Long IT), 8 (Short IT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%</td>
<td>Test for overall effect: Z = 1.43 (P = 0.15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>337</td>
<td>348</td>
<td><strong>100.0 %</strong></td>
<td><strong>1.56 [1.25, 1.94]</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 123 (Long IT), 84 (Short IT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 2.67, df = 4 (P = 0.62); I² = 0%</td>
<td>Test for overall effect: Z = 3.95 (P = 0.000077)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long versus short inspiratory times in neonates receiving mechanical ventilation (Review)  
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Analysis 4.3. Comparison 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 3 BPD (supplemental oxygen at 28 days).

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation.

Comparison: 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation)

Outcome: 3 BPD (supplemental oxygen at 28 days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT</th>
<th>Short IT</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H Fixed 95% CI</td>
<td></td>
<td>M-H Fixed 95% CI</td>
</tr>
<tr>
<td>Muscle relax allowed</td>
<td>4/51</td>
<td>5/51</td>
<td>7.8%</td>
<td>0.80 [0.23, 2.81]</td>
<td></td>
</tr>
<tr>
<td>OCTAVE 1991</td>
<td>38/172</td>
<td>42/174</td>
<td>65.3%</td>
<td>0.92 [0.62, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Pohlandt 1992</td>
<td>11/63</td>
<td>13/74</td>
<td>18.7%</td>
<td>0.99 [0.48, 2.06]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>286</strong></td>
<td><strong>299</strong></td>
<td><strong>91.8%</strong></td>
<td><strong>0.92 [0.66, 1.28]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 53 (Long IT), 60 (Short IT)

Heterogeneity: Chi² = 0.09, df = 2 (P = 0.96); I² = 0.0%

Test for overall effect: Z = 0.49 (P = 0.63)

No muscle relaxation

Spahr 1980 | 4/36   | 5/33     | 8.2%       | 0.73 [0.21, 2.50] |

Subtotal (95% CI) | 36 | 33 | 8.2% | 0.73 [0.21, 2.50] |

Total events: 4 (Long IT), 5 (Short IT)

Heterogeneity: Not applicable

Test for overall effect: Z = 0.50 (P = 0.62)

Total (95% CI) | 322 | 332 | 100.0% | 0.91 [0.66, 1.24] |

Total events: 57 (Long IT), 65 (Short IT)

Heterogeneity: Chi² = 0.22, df = 3 (P = 0.97); I² = 0.0%

Test for overall effect: Z = 0.61 (P = 0.54)
## Analysis 4.4. Comparison 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation), Outcome 4 IVH (all grades).

Review: Long versus short inspiratory times in neonates receiving mechanical ventilation

Comparison: 4 Long vs Short IT (subgroup analysis by trials allowing use of muscle relaxation) Outcome: 4 IVH (all grades)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Long IT Risk Ratio</th>
<th>Short IT Risk Ratio</th>
<th>Risk Ratio Weight</th>
<th>Risk Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle relax allowed</td>
<td></td>
<td></td>
<td>46.9 % 1.08 [0.55, 2.14]</td>
<td></td>
</tr>
<tr>
<td>Heich 1981</td>
<td>13/51</td>
<td>12/51</td>
<td>46.9 % 1.08 [0.55, 2.14]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>51</td>
<td>51</td>
<td>46.9 % 1.08 [0.55, 2.14]</td>
<td></td>
</tr>
<tr>
<td>2 No muscle relaxation</td>
<td></td>
<td></td>
<td>53.1 % 1.13 [0.65, 1.97]</td>
<td></td>
</tr>
<tr>
<td>Spahr 1980</td>
<td>16/36</td>
<td>13/33</td>
<td>53.1 % 1.13 [0.65, 1.97]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>36</td>
<td>33</td>
<td>53.1 % 1.13 [0.65, 1.97]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>87</td>
<td>84</td>
<td>100.0 % 1.11 [0.72, 1.71]</td>
<td></td>
</tr>
</tbody>
</table>

WHAT'S NEW

Last assessed as up-to-date: 22 June 2003.

15 October 2008 Amended Converted to new review format.

HISTORY


Review first published: Issue 4, 2004
CONTRIBUTIONS OF AUTHORS

Dr Kamlin and Dr Davis performed the literature search, assessed the methodological quality of eligible trials and extracted data independently. Dr Kamlin wrote the review and Dr Davis reviewed the manuscript.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Royal Women’s Hospital, Melbourne, Australia.
- Murdoch Children’s Research Institute, Melbourne, Australia.

External sources

- National Health and Medical Research Council, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

*Inhalation; Hyaline Membrane Disease [*complications]; Infant, Newborn; Infant, Premature; Intermittent Positive-Pressure Ventilation [*methods]; Randomized Controlled Trials as Topic; Respiratory Insufficiency [etiology; *therapy]; Time Factors

MeSH check words

Humans
The adverse effects of prolonged endotracheal intubation on the preterm infant include bacterial colonisation, sepsis, subglottic injury, and bronchopulmonary dysplasia. Thus extubation of ventilated infants as early as possible is desirable. The decision to extubate is usually based on clinical assessment, blood gases, and ventilator settings. However, up to 40% of infants weighing <1000 g who are extubated on these criteria require reintubation, suggesting that the ability of clinicians to predict successful extubation is limited. Reintubation is destabilising, traumatic, and may prolong the duration of mechanical ventilation and intensive care. Accurate prediction of readiness for extubation of preterm infants may reduce morbidity.

Pulmonary function tests to assess readiness for extubation of adults and children have included measures of respiratory muscle strength, respiratory drive, ventilatory reserve, lung function, and gas exchange. In newborn infants, pulmonary function tests and invasive tests assessing muscle strength and during ET CPAP to V˙E ratio; (c) the spontaneous breathing test (SBT)—the infant passed this test if there was no hypoxia or bradycardia during ET CPAP. The clinical team were blinded to the results, and all infants were extubated. Extubation failure was defined as reintubation within 72 hours of extubation.

Results: Fifty infants were studied and extubated. Eleven (22%) were reintubated. The SBT was the most accurate of the three tests, with a sensitivity of 97% and specificity of 73% and a positive and negative predictive value for extubation success of 93% and 89% respectively.

Conclusion: The SBT used just before extubation of infants <1250 g may reduce the number of extubation failures. Further studies are required to establish whether the SBT can be used as the primary determinant of an infant’s readiness for extubation.

METHODS

Subjects/setting

The Royal Women's Hospital, Melbourne, is a tertiary perinatal centre with over 5000 deliveries per year. This study was conducted between June 2003 and October 2004. Infants with a birth weight of <1250 g, ventilated using the Dräger 8000 plus (software version 3; Dräger Inc, Lubeck, Germany) for at least 24 hours, and thought by the clinical team to be ready for extubation were eligible. Infants were weaned by either reducing delivered tidal volume to 3.5 ml/kg using assist-control or reducing ventilator rates to 20–30 breaths/min on synchronised intermittent mandatory ventilation. The inspiratory time was 0.3 second, the positive end expiratory pressure 5–6 cm H2O, and inspired oxygen concentration <40%. Extubation was considered if the infant had satisfactory blood gases and was breathing above the set ventilator rate. Sedation, when used, was stopped at least 12 hours before extubation. Methylxanthines were used before extubation or after extubation at the clinician’s discretion. Some infants were enrolled in a double blind trial of caffeine citrate versus placebo (the CAP trial). The endotracheal tube was suctioned within two hours of the study.

Manoeuvre

When the clinical team decided an infant was ready for extubation, the investigator switched the ventilator to ET CPAP at the same pressure as the positive end expiratory pressure setting. Airflow was measured using the sensor in the ventilator circuit just proximal to the ET tube. Airflow, integrated expired tidal volume (Vte), and respiratory rate were recorded at 200 Hz using Spectra software (Grove Medical, London, UK). Data were downloaded from the
Predicting extubation success in newborn infants

Despite a 15% increase in \( F_1 \) three minute SBT would be lower in infants requiring ventilation; (significant episode of apnoea requiring bag and mask stimulation in six hours, or more than one were specified a priori: (72 hours of extubation. The indications for reintubation were extubated to either nasal CPAP using Hudson prongs or were extubated, regardless of the results of the test. Infants were extubated to either nasal CPAP using Hudson prongs or nasal intermittent positive pressure ventilation (NIPPV) at the clinician’s discretion.

The primary study outcome was reintubation within 72 hours of extubation. The indications for reintubation were specified a priori: (a) more than six episodes of apnoea requiring stimulation in six hours, or more than one significant episode of apnoea requiring bag and mask ventilation; (b) respiratory acidity (\( PaCO_2 > 65 \text{ mm Hg} (>8.5 \text{ kPa}) \) and \( pH < 7.25 \)); (c) \( F_1O_2 > 0.60 \) to maintain \( SpO_2 \) in the target range (90–95%). The use of NIPPV was not considered a failure of extubation.

The research and human research ethics committees of the Royal Women’s Hospital, Melbourne approved the study, and informed written consent was obtained before testing.

Statistical analysis

Review of nursery data collected in 2002 revealed a 25% failure rate. We hypothesised that \( Vt \) measured during the three minute SBT would be lower in infants requiring reintubation. A sample size of 50 was planned to detect a difference of one standard deviation in mean \( Vt \) in the group failing extubation, assuming an overall mean (SD) \( Vt \) of 300 (50) ml/kg/min (power 80% and two tailed \( \alpha = 0.05 \)).

Continuous outcomes were compared by Student’s \( t \) test when normally distributed and by Mann-Whitney U test when skewed. Categorical data were assessed using the Fisher two tailed exact test. \( p < 0.05 \) was considered significant. The ability of respiratory variables to accurately discriminate between successful and failed extubation was assessed using receiver operating characteristic (ROC) curves. ROC curves are constructed by plotting the true positive rate on the y axis against the false positive rate on the x axis. Analysing the area under the curve determines the predictive value of a diagnostic test. A value <0.5 indicates no discriminatory value, and a value >0.8 suggests high predictive value.” Standard formulae were used to calculate sensitivity, specificity, and positive and negative predictive values and likelihood ratios. Statistical analyses were performed using SPSS version 11.5 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

During the study period, 251 babies with a birth weight <1250 g were admitted. Sixty five were ventilated from birth for at least 24 hours. Parental consent was obtained for 50 infants (31 male, 19 female). All had respiratory distress syndrome. Forty one infants were weaned using synchronised intermittent mandatory ventilation and nine infants on assist-control. Extubation was successful in 39 (78%). There were no significant differences in gestational age, ventilator settings, internal diameter of ET tube, and birth or study

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Basic and clinical data on the study infants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Successful extubation (n = 39)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>27.0 (1.7)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>957 (215)</td>
</tr>
<tr>
<td>Male/female</td>
<td>21/18*</td>
</tr>
<tr>
<td>Median age at study (days)</td>
<td>4 (1–45)</td>
</tr>
<tr>
<td>Median weight at study (g)</td>
<td>1043 (490–1270)</td>
</tr>
<tr>
<td>ET tube internal diameter (2.5/3.0 mm)</td>
<td>27/12</td>
</tr>
<tr>
<td>Weaning ventilator mode (SV/AC)</td>
<td>34/6</td>
</tr>
<tr>
<td>( F_1O_2 ) before ET CPAP [%]</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Mean airway pressure before ET CPAP (cm H(_2)O)</td>
<td>7.1 (1.1)</td>
</tr>
<tr>
<td>Ventilator rate before SBT (breaths/min)</td>
<td>29 (7)</td>
</tr>
<tr>
<td>Respiratory support after extubation (NCPAP/NIPPV)</td>
<td>28/11</td>
</tr>
</tbody>
</table>

Data are mean (SD) or numbers unless otherwise stated. No significant differences \( p < 0.05 \) were found between infants successfully extubated and those requiring reintubation. Male infants were more likely to be reintubated \( p = 0.03 \).

ET CPAP, endotracheal continuous positive airway pressure; NIPPV, nasal continuous positive airway pressure; SBT, spontaneous breathing test; SIMV, synchronised intermittent mandatory ventilation; AC, assist-control.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Variables predicting success or failure of extubation by ROC curve analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Area under the ROC curve</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.61</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.59</td>
</tr>
<tr>
<td>Postnatal age at study</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean airway pressure</td>
<td>0.56</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>0.57</td>
</tr>
<tr>
<td>( Vt ) during ET CPAP</td>
<td>0.60</td>
</tr>
<tr>
<td>( Vt ) ratios</td>
<td>0.74</td>
</tr>
</tbody>
</table>

\( ET \) CPAP, endotracheal continuous positive airway pressure; ROC, receiver operating characteristic.
weights between successfully and unsuccessfully extubated infants (table 1). Most (64%; 7/11) reintubations occurred in the first 24 hours (median 21 hours; range 1–71). Methylxanthines were used in 40 infants (23 before and 17 after extubation). Two infants never received methylxanthines and remained extubated. Eight infants were enrolled in the CAP study, and five were reintubated. Infants were extubated to either nasal CPAP (47) or NIPPV (three) as the primary mode of respiratory support. An additional 14 (28%) subsequently received NIPPV as rescue treatment for apnoea. Significant apnoea accounted for eight of the 11 reintubations.

The mean (SD) Ve during ET CPAP was greater in successfully extubated infants (314 (116) v 271 (113)), but the difference did not reach statistical significance. Figure 1 compares the Ve ratios for the infants who were successfully extubated with those reintubated. Although median Ve ratios were lower in infants who were reintubated (p = 0.015), there was considerable overlap between the groups.

Table 2 presents the area under the ROC curves and the 95% confidence intervals. The inflection points of the ROC curves were 220 ml/kg/min and 0.8 for Ve and Ve ratios respectively.

Accuracy of the SBT was greater (higher sensitivity, specificity, positive and negative predictive values) than the other two tests (table 3). Only three infants who passed the SBT were reintubated; one developed apnoea 71 hours after extubation, one was intubated for respiratory acidosis and an increasing oxygen requirement, and one developed stridor soon after extubation.

DISCUSSION

Our study was designed to determine the accuracy of three tests (Ve, Ve ratios, and the SBT) in preterm infants judged ready for extubation on clinical grounds. In our study population, the SBT performed better than both Ve and Ve ratios.

This pragmatic observational study investigated infants who were considered by clinicians to be ready for extubation. Our findings suggest that, if used to guide timing of extubation, the SBT, although not infallible, may result in fewer extubation failures and a greater proportion of successful extubations. False positive tests, such as those seen in two infants in this study (one with apnoea associated with subsequent sepsis and one with upper airway obstruction), are unlikely to be anticipated by any test at the time of extubation.

Infants who are immature and recovering from respiratory distress syndrome are at greatest risk of complications of prolonged mechanical ventilation. However, it is not easy, even for experienced clinicians, to determine when these infants have sufficient respiratory drive to tolerate extubation. It is not surprising that reported rates of reintubation vary from 15% to 40%, 6 8 10–12 16 17 20–21 This variability is largely due to differences in study population. Only four studies investigated extubation of preterm infants.6 10 12 17 We limited our study to infants <1250 g because they represent the majority of intubated infants and are at highest risk of extubation failure. Accurate tests of readiness for extubation would be a valuable addition to the clinical armamentarium. Studies examining respiratory muscle strength are invasive and need expert application and interpretation. This and measurements of lung volumes after extubation limits their clinical utility.11 16 21 Measurements of dynamic compliance, Vte, Ve, and lung volumes have not provided clear threshold values for reliable discrimination between extubation success and failure.1 2 13 14 19

The optimal duration of a trial of spontaneous breathing before extubation to determine an infant’s independent breathing ability is uncertain. An adult study compared 30 and 120 minutes and found no differences in safety or rates of extubation success.22 Vento et al21 measured mean Ve of infants <1000 g during a two hour period on ET CPAP and concluded that the test “could be useful” in identifying an infant’s readiness for extubation. However, ET CPAP adds to the resistance of the respiratory system21 leading to increased work of breathing, potentially jeopardising successful extubation. There is evidence that extubation after several hours of ET CPAP is less successful than extubation from low rate ventilation.23 Published studies evaluating Ve ratios used 10 minutes,21 whereas Veness-Meehan and coworkers’ measured Vte during one minute of ET CPAP. Before conducting this study, we observed that most infants who failed a trial of ET CPAP did so in the first 90 seconds. Our results suggest that three minutes is long enough to identify most infants who would fail extubation without risking fatigue. The advantages and potential benefits of the SBT are that it is easy to apply using standard monitoring devices in the neonatal intensive care unit and simple to interpret.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>LR+</th>
<th>LR–</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBT</td>
<td>93</td>
<td>89</td>
<td>97</td>
<td>73</td>
<td>3.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Ve (ET CPAP) &gt; 220 ml/kg/min</td>
<td>87</td>
<td>50</td>
<td>85</td>
<td>45</td>
<td>1.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Ve ratio &gt; 0.8</td>
<td>87</td>
<td>55</td>
<td>87</td>
<td>54</td>
<td>1.9</td>
<td>0.24</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; Sens, sensitivity; Spec, specificity; LR+, positive likelihood ratio; LR–, negative likelihood ratio; SBT, spontaneous breathing test; Ve, minute ventilation; ET CPAP, endotracheal continuous positive airway pressure.
In summary, we have shown that a simple three minute SBT has a high negative predictive value when used in a unit with access to both NCPAP and NIPPV to optimise management after extubation. Whether this test can be applied earlier in the course of weaning to reduce the duration of mechanical ventilation remains to be investigated.

ACKNOWLEDGEMENTS
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Competing interests: none declared

REFERENCES
A trial of spontaneous breathing to determine the readiness for extubation in very low birth weight infants: a prospective evaluation

C O F Kamlin,¹ P G Davis,¹,² B Argus,¹ B Mills,¹ C J Morley¹,²,³

ABSTRACT
Extrusion failure in premature infants is common. A spontaneous breathing trial (SBT) was prospectively evaluated to determine timing of extubation. Compared with historical controls, infants were extubated at significantly higher ventilator rates and airway pressures using the SBT. No differences in rates of bronchopulmonary dysplasia or duration of ventilation were seen.

Endotracheal (ET) intubation and mechanical ventilation remains the standard of care for managing respiratory failure in very low birth weight (VLBW) infants. The adverse effects of prolonged endotracheal intubation include bacterial colonisation, sepsis, subglottic injury and bronchopulmonary dysplasia (BPD). The decision to extubate is usually based on clinical assessment. This is subjective and up to 40% of extubated infants require reintubation of their ET tube. Reintubation is destabilising, traumatic and may prolong the duration of mechanical ventilation. Objective criteria to identify the earliest opportunity to successfully extubate VLBW infants are lacking.

We have previously described and evaluated respiratory drive in VLBW infants using a 3-minute spontaneous breathing trial (SBT) during ET continuous positive airway pressure (CPAP) before extubation. The test when applied once a clinical decision was made to extubate was highly sensitive and appeared to identify infants for whom extubation was most likely to fail (a high negative predictive value). The SBT was then incorporated into clinical practice at our hospital. The aim of our current study was to audit the effect of this change in policy on timing and success of extubation of VLBW infants.

METHODS
The study was conducted between 1 June 2005 and 30 June 2006 at The Royal Women’s Hospital, Melbourne and approved by the human research and ethics committees as an audit of practice. All ventilated infants with a birth weight <1250 g were eligible for inclusion. Infants with lethal or chromosomal malformations or who died before extubation were excluded.

Using the Dräger Babylog 8000plus (Lubeck, Germany), an SBT was performed when ventilated infants fulfilled entry criteria (set ventilator rate ≤45 bpm, volume guarantee (VG) ≤4.5 ml/kg or peak inspiratory pressures ≤25 cm H2O, inspired fractional oxygen ≤40%). This was repeated daily, typically on ward rounds until either extubation criteria were met (“successful SBT”), unplanned extubation occurred or when the attending clinician made a decision to extubate (whichever was the sooner). Infants were ventilated and weaned using either assist control (AC) or synchronised intermittent mandatory ventilation (SIMV) ± VG modes. The ET CPAP pressure used was equivalent to the positive end expiratory pressure used in conventional ventilation (5–6 cm H2O). A failed SBT was recorded if the infant had bradycardia (<100/min) for >15 seconds and/or the SpO2 fell below 85% despite a 15% increase in fractional inspired oxygen (FiO2) during the period of ET CPAP. At this point the SBT was discontinued and ventilation restarted. Infants who passed the SBT were extubated unless the attending clinicians disagreed. Non-compliance of the clinician with the results of the SBT was recorded.

The primary study outcome was reintubation within 72 hours of extubation. The indications for reintubation were specified a priori: (a) more than six episodes of apnoea requiring stimulation in 6 hours, or more than one significant episode of apnoea requiring bag and mask ventilation; (b) respiratory acidosis (PaCO2 >65 mm Hg (>8.5 kPa) and pH <7.25); (c) FiO2 >0.60 to maintain SpO2 in the target range (90 – 94%). BPD was defined as supplemental O2 or CPAP requirement at 36 weeks’ corrected gestational age. Data were compared with a cohort of VLBW infants admitted to the same institution in 2002, before the SBT was part of clinical practice.

Power calculation and statistical analysis
During a 2-year period (2003–4), the rate of reintubation was 24%. Given the skewed nature of the duration of ventilation, the mean (SD) log transformed duration of ventilation for VLBW infants was 2.0 (0.7), corresponding to a geometric mean of 100 hours (10%). We hypothesised a reduction of 50% in the duration of assisted ventilation compared with historical controls using the SBT to drive extubation (geometric mean of 50 hours, log transformed = 1.7). Eighty-seven patients in each group were required to achieve 80% power and an α error of 0.05. Statistical analyses were performed using SPSS, version 11.5 (Cary, NJ, USA).

RESULTS
One hundred and eighty infants were studied (90 SBT and 90 controls). Table 1 demonstrates that the baseline variables were well matched between the two groups. However, fewer infants in the SBT cohort were intubated in the delivery room. During
the latter period (SBT), VG ventilation was more commonly used compared with the control population (94% vs 26%) and there was a shift of weaning ventilation modes at the time of extubation from SIMV (93% in controls) to AC (81% in SBT cohort).

The mean (SD) number of SBTs applied to infants was 3 (2). Clinicians’ compliance with the SBT was excellent (97%). Six (7%) infants self-extubated after a failed SBT, three of whom were reintubated. The sensitivity of the SBT to predict successful extubation was 83%. The overall duration of mechanical ventilation was not significantly different (table 2). However, infants were extubated at significantly higher ventilator rates and mean airway pressure (Paw) when the SBT was applied. Duration of CPAP was significantly higher in the SBT cohort, although there was no difference in the duration of all forms of ventilatory support or the incidence of BPD.

**DISCUSSION**

We showed previously that the SBT applied to infants judged by their clinician as being ready for extubation was accurate in predicting success or failure. This audit of a change in clinical practice was performed in order to evaluate the safety and effectiveness of the SBT to drive extubation of VLBW infants. Although using historical controls limits the number of conclusions that can be drawn from the study, there were two potentially harmful outcomes that we wished to exclude. First, the period of endotracheal intubation could be prolonged if clinicians waited for infants to pass the SBT when they might otherwise have decided to extubate earlier. Alternatively, by encouraging extubation sooner than the clinician might have decided, more infants might have required reintubation.

We have shown that invasive mechanical ventilatory support in VLBW infants can be safely discontinued using the SBT at significantly higher Paw and set ventilator rates with similar reintubations compared with clinical decision-making. A clinical trial, randomising infants to have extubation guided by SBT versus clinical decision-making alone is therefore feasible. From our data, the median duration of ventilation for VLBW infants is <3 days and a very large sample size would be needed to demonstrate a significant reduction in duration of mechanical ventilation.

Limitations of our study design are highlighted by the differences seen in the two tables. While the patient demographics and indicators of illness severity are similar, the data demonstrate changes in the ventilator management of VLBW infants within one institution. Significantly fewer infants are being intubated in the delivery room and ventilator breathing modes have changed, with greater use of AC with VG. Extubating infants from a higher Paw in the SBT group may be due changes in ventilator mode between the two time periods. The proportion of supported breaths during AC would be greater than infants received on SIMV. Our data suggest it is safe to wean and extubate from AC with a mean Paw of 7.2 cm H2O.

Our findings are consistent with reports in paediatric patients, where standardised protocols for weaning compared with clinical judgment confer no benefit on duration of ventilation and rates of extubation success.

In conclusion a 3-minute SBT to determine readiness to extubate VLBW infants is safe and as effective as clinical decision-making alone. Whether this mode of weaning can reduce duration of all respiratory support, BPD and length of stay needs further evaluation in a prospective randomised controlled study.

**REFERENCES**


**Table 1** Demographic data, comorbidities of the spontaneous breathing trial (SBT) cohort and of the historical controls

<table>
<thead>
<tr>
<th>Data</th>
<th>SBT (n = 90)</th>
<th>Control (n = 90)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight* (g)</td>
<td>861 (229)</td>
<td>914 (189)</td>
<td>0.09</td>
</tr>
<tr>
<td>Gestational age* (weeks)</td>
<td>27 (2)</td>
<td>27 (2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Multiple births (%)</td>
<td>34 (38)</td>
<td>38 (42)</td>
<td>0.12</td>
</tr>
<tr>
<td>Antenatal steroids (%)</td>
<td>72 (60)</td>
<td>70 (76)</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>39/51</td>
<td>43/47</td>
<td>0.55</td>
</tr>
<tr>
<td>Ventilated from birth (%)</td>
<td>54 (60)</td>
<td>77 (86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from birth to intubation (hours)</td>
<td>0 (0–558)</td>
<td>0 (0–261)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

| Surfactant (%)              | 81 (90)     | 84 (93)         | 0.42   |
| PDA treated (%)             | 37 (41)     | 33 (37)         | 0.54   |
| Air leak (%)                | 7 (8)       | 10 (11)         | 0.44   |
| HFOV (%)                    | 16 (18)     | 13 (14)         | 0.54   |
| Postnatal steroids (%)      | 7 (8)       | 6 (7)           | 0.77   |

**Table 2** Pre-extubation ventilation parameters and outcomes following extubation in both cohorts (spontaneous breathing trial (SBT) and historical controls)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SBT (n = 90)</th>
<th>Control (n = 90)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of first period of ET ventilation (days)</td>
<td>2.6 (0.2–48.8)</td>
<td>2.7 (0.1–47.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>Ventilator rate at extubation (breaths/min)*</td>
<td>42 (6)</td>
<td>27 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP at extubation (cm H2O)*</td>
<td>7.2 (1.4)</td>
<td>6.5 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FiO2 at extubation*</td>
<td>0.23 (0.05)</td>
<td>0.23 (0.03)</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of extubation successes (%)</td>
<td>70 (78)</td>
<td>65 (72)</td>
<td>0.49</td>
</tr>
<tr>
<td>Days of nasal CPAP</td>
<td>24.0 (0.9–103.8)</td>
<td>15.3 (0.0–75.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Total duration of all forms of assisted ventilation (days)</td>
<td>31.2 (1.1–141.0)</td>
<td>23.8 (0.3–125.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of cases of BPD (%)</td>
<td>32 (36)</td>
<td>32 (36)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Notes:**

- Data are either mean (SD) or median (range) and analysed with independent t tests or median (range) and analysed using Mann–Whitney tests.
- BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; ET, endotracheal; FiO2, fractional inspired oxygen; MAP, mean arterial pressure.
Author/s:  
Kamlin, Camille Omar Farouk

Title:  
Respiratory support of newborn infants in the delivery room and neonatal intensive care

Date:  
2010

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Respiratory support of newborn infants in the delivery room and neonatal intensive care

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