Monitoring respiratory function during neonatal resuscitation

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(Doctor medicinae universae)

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

Ritchie Centre for Bay Health Research, Monash Institute of Medical Research

Monash University

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I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 6 original papers published in peer reviewed journals, 3 original papers currently in press in peer reviewed journals, 1 original papers accepted in peer reviewed journals and 2 unpublished publications, which currently under review. The core theme of the thesis is **Monitoring Respiratory Functions during Neonatal Resuscitation.** The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within The Ritchie Centre, Monash Institute of Medical Research under the supervision of Prof. Stuart Hopper and the Department of Newborn Research, The Royal Women's Hospital under supervision of Prof. Peter Davis and Prof. Colin Morley.

[The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.]

In the case of 12 Thesis chapters my contribution to the work involved the following:

[If this is a laboratory-based discipline, a paragraph outlining the assistance given during the experiments, the nature of the experiments and an attribution to the contributors could follow.]

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
II	Reducing lung injury during neonatal resuscitation of preterm infants	Published J Pediatr. 2008 Dec;153(6):741-5.	Literature search and review of literature, writing the manuscript
III	Respiratory function monitoring during simulation-based mannequin teaching	In Press Applied Technologies in pulmonary medicine ISBN: 978-3-8055-9584-1	Literature search and review of literature, writing the manuscript
IV	Respiratory monitoring of neonatal resuscitation	Published Arch Dis Child Fetal Neonatal Ed. 2009 Sep 22.	Literature search and review of literature, writing the manuscript
V	Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room	Published Arch Dis Child Fetal Neonatal Ed Published Online First: 14 June 2010	Idea, protocol design, ethics application, data collection, data analysis, writing the manuscript
VI	Assessment of chest rise during positive pressure ventilation in the delivery room	In press Resuscitation	Idea, protocol design, ethics application, data collection, data analysis, writing the manuscript
VII	Airway Obstruction and gas leak during mask ventilation of preterm infants in the delivery room	In Press Arch Dis Child Fetal Neonatal Ed	Idea, protocol design, ethics application, data collection, data analysis, writing the manuscript
VIII	Comparison of Self-inflating bag and T-Piece during positive pressure	Submitted The Journal of Pediatrics	Data collection, data analysis, writing the manuscript

	ventilation in the delivery room		
IX	Choice of flow meter determines pressures delivered on a T-piece neonatal resuscitator.	Published Arch Dis Child Fetal Neonatal Ed Published Online First: 10 June 2010	Data collection, data analysis, writing the manuscript
X	Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation	Published Cochrane Review Protocol, Cochrane Database of Systemic Reviews 2010, Issue 3	Idea, Literature search and review of literature, writing the manuscript
XI	Respiratory Function Monitor for Tidal Volume Targeting during Positive Pressure Ventilations in the Delivery room – a randomised trial	Submitted American Journal of Respiratory and Critical Care Medicine	Idea, protocol design, ethics application, data collection, data analysis, writing the manuscript
XII	Assessment of gas flow waves for endotracheal tube placement in an ovine model of neonatal resuscitation	Published Resuscitation.2010 Jun;81(6):737-41. Epub 2010 Mar 23	Idea, protocol design, ethics application, data collection, data analysis, writing the manuscript
XIII	Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation	Accepted Resuscitation	

[* For example, 'published'/ 'in press'/ 'accepted'/ 'returned for revision']

I have / have not (circle that which applies) renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed:

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Publications and Presentations arising from this Thesis

Publications:

1. ***Schmölzer GM***, Kamlin COF, Dawson JA, Morley CJ, Davis PG; Tidal volume delivery during surfactant administration in the delivery room (submitted for peer review to Archives of Disease in Childhood Fetal & Neonatal Edition)

2. ***Schmölzer GM***, Roehr CC, Use of Respiratory Function Monitors during simulated neonatal resuscitation (submitted to klinische Pädiatrie)

3. ***Schmölzer GM***, Morley CJ, Wong C, Dawson JA, Kamlin COF, Donath SM, Hooper SB, Davis PG; Respiratory Function Monitor for Tidal Volume Targeting during Positive Pressure Ventilations in the Delivery room – a randomised trial (submitted for peer review to American Journal of Respiratory and Critical Care Medicine)

4. Yam CH, Dawson JA, ***Schmölzer GM***, Morley CJ, Davis PG, The change in heart rate during neonatal resuscitation - an observational study (re-submitted after peer review to Archives of Disease in Childhood Fetal & Neonatal Edition)

5. Dawson JA, Kamlin COF, **Schmölzer GM**, te Pas AB, O'Donnell CPF, Donath SM, Davis PG, Morley CJ, T-Piece versus self-inflating bag for ventilation of extremely preterm infants at birth, effect on oxygenation in the first six minutes: A randomized controlled trial (re-submitted after peer review to The Journal of Pediatrics)

6. ***Schmölzer GM***, Poulton DA, Dawson JA, Kamlin COF, Morley CJ, Davis PG; Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation (accepted to Resuscitation)

7. Poulton DA, ***Schmölzer GM***, Morley CJ, Davis PG, Assessment of chest rise during positive pressure ventilation in the delivery room (in press Resuscitation)

8. ***Schmölzer GM***, Dawson JA, Kamlin COF, O'Donnell CPF, Morley CJ, Davis PG, Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room (in press Archives of Disease in Childhood Fetal & Neonatal Edition)

9. ***Schmölzer GM***, Morley CJ, Davis PG, Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation; Cochrane Review Protocol, Cochrane Database of Systemic Reviews 2010, Issue 3

10. ***Schmölzer GM***, Kamlin COF, O'Donnell CPF, Dawson JA, Morley CJ, Davis PG; Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room; Archives of Disease in Childhood Fetal & Neonatal Edition Published Online First: 14 June 2010

11. ***Schmölzer GM***, Bhatia R, Morley CJ, Davis PG; Choice of flow meter determines pressures delivered on a T-piece neonatal resuscitator; Archives of Disease in Childhood Fetal & Neonatal Edition Published Online First: 10 June 2010

12. ***Schmölzer GM***, Hooper SB, Crossley KJ, Allison BJ, Morley CJ, Davis PG; Assessment of gas flow waves for endotracheal tube placement in an ovine model of neonatal resuscitation; Resuscitation. 2010 Jun;81(6):737-41. Epub 2010 Mar 23

13. Morley CJ, ***Schmölzer GM,*** Davis PG**:** Potential hazards of the Neopuff: using appropriate gas flow; Archives of Disease in Childhood Fetal & Neonatal Edition 2009 Nov;94(6):F467-8;

14. ***Schmölzer GM***, Kamlin OF, Dawson JA, Davis PG, Morley CJ: Respiratory monitoring of neonatal resuscitation; Archives of Disease in Childhood Fetal & Neonatal Edition 2009 Sep 22.

15. ***Schmölzer GM***, Te Pas AB, Davis PG, Morley CJ; Reducing lung injury during neonatal resuscitation of preterm infants; The Journal of Pediatrics 2008 Dec;153(6):741-5.

Book review:

GM Schmölzer; Small for gestational age (Pediatric and Adolescent Medicine Vol. 13); Journal of Paediatrics and Child Health, published online, April 27 2010

Books chapters:

1. ***Schmölzer, GM***, Morley, CJ: Equipment and Technology for Continuous Positive Airway Pressure during Neonatal Resuscitation; Yearbook *Non-invasive Mechanical Ventilation-Equipment and Theory*; 2010. pp. 8

2. ***Schmölzer, GM***, Morley, CJ: Respiratory Function Monitoring during simulation-based mannequin teaching; Yearbook *Respiratory Care and Applied Technologies*; 2010. pp. 8

3. ***Schmölzer, GM***, Kamlin, COF: Resuscitation of the Newly born infant; *Handbook of Anaesthesiology*; Melbourne, Australia: The Royal Women's Hospital; 2008. pp. 6

Awards, Achievements and Nominations

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2008   The Royal Women's Hospital Postgraduate Research Degree Scholarship, Melbourne, Australia

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Invited speaker - Respiratory function monitoring in the DR: practical observations and outlook, Virchow Klinikum, Berlin, Germany	**27/09/2010**
Invited speaker - Invasive and Non-Invasive respiratory support in the delivery room, Managing the lung of the extremely low gestational age neonate (ELGAN) in the delivery room,; Barcelona, Spain	**18/09/2010**
Invited speaker - Respiratory function monitoring in the DR: practical observations and outlook, Managing the lung of the extremely low gestational age neonate (ELGAN) in the delivery room, Barcelona, Spain	**18/09/2010**
Invited speaker - The use of the Florian and Ventcheck Respiratory Function monitors during Neonatal Transports, , Newborn Emergency Transport Service Victoria, Melbourne, Australia	**17/06/2010**
Invited speaker - Update in Neonatal Resuscitation, Children's Hospital, University of Ottawa; Ottawa, Canada	**11/05/2010**
Invited speaker - Monitoring of respiratory function after birth, use of a Respiratory Function Monitor, 2nd Neonatal Resuscitation Research Workshop; Vancouver, Canada	**05/05/2010**

51th Annual Meeting European Society of Paediatric Research, Copenhagen, Denmark　　　　**23-26/10/2010**
Poster presentation
Schmölzer GM, Dawson JA, Kamlin COF, Hooper S, Morley CJ, Davis PG, A Respiratory Function Monitor during Positive Pressure Ventilation - A Randomized Trial

K Schilleman, **GM Schmölzer**, COF Kamlin, AB te Pas, CJ Morley, PG Davis, Different gas flow rates and effects on tidal volume and mask leak during positive pressure ventilation (PPV)

Pediatric Academic Societies, Vancouver, Canada　　　　**01-04/05/2010**
Platform presentation
Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CPF, Morley CJ, Davis PG, Prevalence of airway obstruction and mask leak during face mask ventilation of preterm infants in the delivery room

Bhatia R, **Schmölzer GM**, Davis PG, Tingay DG, Electrical Impedance Tomography (EIT) an rapidly detect small Pneumothoraces

Poster presentation
Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CPF, te Pas AB, Morley CJ, Davis PG, Randomised Control Trial (RCT) of Neopuff vs. Laerdal-Bag for Resuscitation of Newborn Infants: Respiratory Function Outcomes

Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CPF, Morley CJ, Davis PG Prevalence of airway obstruction and mask leak during face mask ventilation of preterm infants in the delivery room

2010 Perinatal Society of Australia and New Zealand 14th Annual Congress, Wellington, New Zealand　　　　**28-31/03/2010**
Platform presentation
Schmölzer GM, Dawson JA, Kamlin, COF O'Donnell CPF, te Pas AB, Morley CJ, Davis PG, Randomised Control Trial (RCT) of Neopuff vs. Laerdal-Bag for Resuscitation of Newborn Infants: Respiratory Function Outcomes

Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CPF, Morley CJ, Davis PG, Prevalence of airway obstruction and mask leak during face mask ventilation of preterm infants in the delivery room

Schmölzer GM, Dawson JA, Kamlin COF, O'Donnell CPF, te Pas AB, Morley CJ, Davis PG, Ventilation and spontaneous breathing after intubation of preterm infants in the delivery room

Yam C, Dawson JA, **Schmölzer GM**, Morley CJ, Davis, PG, The Change in Heart Rate during Neonatal Resuscitation- an observational study

Poster presentation
Schmölzer GM, Bhatia R, Davis PG, Tingay DG, A Comparison of Different Bedside Techniques of determining endotracheal tube malposition

Chua CT, **Schmölzer GM,** Morley CJ, DavisPG, Historical Perspective of various airway manoeuvres in airway management during positive pressure ventilation in newborn infants

Schmölzer GM, Dawson JA, Kamlin COF, Hooper S, Morley CJ, Davis PG, A Respiratory Function Monitor during Positive Pressure Ventilation - A Randomized Trial

Bhatia R, **Schmölzer GM**, Davis PG, Tingay DG, Electrical Impedance Tomography (EIT) an rapidly detect small Pneumothoraces

2009

Invited speaker - Respiratory monitoring during neonatal resuscitation; Annual Program Grant Meeting, Melbourne, Australia   **03/12/2009**

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Cool Topics in Neonatology, Melbourne, Australia   **09-10/11/2009**
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Schmölzer GM, Kamlin COF, Dawson JA, Davis PG, Morley CJ, Operator performance during Positive Pressure Ventilation in the Delivery Room

50th Annual Meeting European Society of Paediatric Research, Hamburg, Germany   **09-12/10/2009**
Platform presentation
Dawson JA, Kamlin COF, te Pas AB, **Schmoelzer GM**, Donath SM, O'Donnell CPF, Davis PG, Morley CJ, Neopuff Compared with Laerdal Self-Inflating Bag for the First Five Minutes of Resuscitation in Infants < 29 Weeks Gestation at Birth: A Randomised Controlled Trial

Poster presentation
Schmölzer GM, Kamlin COF, Dawson JA, Davis PG, Morley CJ, Resuscitators performance during neonatal mask ventilation in the delivery room

Schmölzer GM, Crossley KJ, Allison BJ, Hooper SB, Davis PG, Morley CJ, Pedi-Cap® vs. Respiratory Function Monitor to identify endotracheal or oesophageal intubation in a lamb model of neonatal resuscitation

47th Annual Meeting of the Austrian Society of Paediatrics and Youth Health, Graz, Austria   **01-03/10/2009**
Platform presentation
Schmölzer GM, Kamlin COF, Dawson JA, Davis PG, Morley CJ, Operator performance during Positive Pressure Ventilation in the Delivery Room

Poster presentation
Schmölzer GM, Crossley KJ, Allison BJ, Hooper SB, Davis PG, Morley CJ, Pedi-Cap® vs. Respiratory Function Monitor to identify endotracheal or oesophageal intubation in a lamb model of neonatal resuscitation

Schmölzer GM, Hacking D, Savoia H, Fox L, Cheong JLY, Neonatal bilirubin encephalopathy secondary to Anti-C[w]-Antibodies: A case for routine screening in newborn?

Keynote speaker - Respiratory monitoring during neonatal resuscitation; Graz, Austria   **24/09/2009**

17th Annual International Neonatal Conference, Middlesbrough, United Kingdom　　　　**04-06/06/2009**
Platform presentation
Schmölzer GM, Kamlin COF, Dawson JA, Davis PG, Morley CJ, Operator performance during Positive Pressure Ventilation in the Delivery Room

2009 Pediatric Academic Societies, Baltimore, Maryland　　　　**02-05/05/2009**
Platform presentation
Schmölzer GM, Kamlin COF, Dawson JA, Davis PG, Morley CJ, Operator performance during Positive Pressure Ventilation in the Delivery Room

"Late Breaker" - Dawson JA, Kamlin COF, te Pas AB, **Schmoelzer GM**, Donath SM, O'Donnell CPF, Davis PG, Morley CJ, Neopuff Compared with Laerdal Self-Inflating Bag for the First Five Minutes of Resuscitation in Infants < 29 Weeks Gestation at Birth: A Randomised Controlled Trial

Poster presentation
Schmölzer GM, Crossley KJ, Allison BJ, Hooper SB, Davis PG, Morley CJ, Pedi-Cap® vs. Respiratory Function Monitor to identify endotracheal or oesophageal intubation in a lamb model of neonatal resuscitation

Perinatal Society of Australia and New Zealand 13th Annual Congress, Darwin, Australia　　**19-22/04/2009**
Platform presentation
Schmölzer GM, Kamlin COF, Dawson JA, Davis PG, Morley CJ, Operator performance during Positive Pressure Ventilation in the Delivery Room

Schmölzer GM, Crossley KJ, Allison BJ, Hooper SB, Davis PG, Morley CJ, Pedi-Cap® vs. Respiratory Function Monitor to identify endotracheal or oesophageal intubation in a lamb model of neonatal resuscitation

Poster presentation
Schmölzer GM, Wheeler KI, Davis PG, Morley CJ, A Bibliographic Tool for Apple Macintosh Computers

Schmölzer GM, Hacking D, Savoia H, Fox L, Cheong JLY, Neonatal bilirubin encephalopathy secondary to Anti-C^w-Antibodies: A case for routine screening in newborn?

2008

Invited speaker - Uses of a respiratory function monitor; Annual Program Grant Meeting;, Melbourne, Australia　　**16/12/2008**

Invited speaker - Do we over or under inflate the lungs? "Start measuring tidal volume in the delivery room!" Colin Morley Festschrift Symposium, Melbourne, Australia　　**17/11/2008**

Pediatric Academic Societies, Honolulu Hawaii　　**3-6/05/2008**
Poster presentation
Schmölzer GM, tePas AB, Dawson JA, Kamlin COF, Davis PG, Morley CJ, Use of a respiratory function monitor during stabilisation of neonates in the delivery room (DR)

2008 Perinatal Society of Australia and New Zealand 12th Annual Congress, Gold Coast, Australia　　**20-23/04/2008**
Poster presentation
Schmölzer GM, tePas AB, Dawson JA, Kamlin COF, Davis PG, Morley CJ, Use of a respiratory function monitor during stabilisation of neonates in the delivery room

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List of Abbreviations

NICU	– Neonatal intensive care unit
PPV	– Positive pressure ventilation
FRC	– Functional residual capacity
DR	– Delivery room
TLC	– Total lung capacity
PIP	– Peak inspiratory pressure (cm H_2O)
PEEP	– Positive end expiratory pressure (cm H_2O)
CPAP	– Continuous positive airway pressure (cm H_2O)
ILCOR	– International Liaison Committee on Resuscitation
ETT	– Endotracheal tube
RFM	– Respiratory function monitor
RR	– Respiratory rate
MV	– Minute ventilation
MVe	– Expired minute ventilation
V_T	– Tidal volume
V_{Te}	– Expired tidal volume
V_{Ti}	– Inspired tidal volume
i-time	– Inflation time
e-time	– Expiration time
MAP	– Mean airway pressure (cm H_2O)
HR	– Heart rate
SpO_2	– Percentage of oxygen saturation in blood (%)
SaO_2	– Saturation of oxygen in arterial blood flow (mm Hg)
FiO_2	– Fraction of inspired oxygen
$paCO_2$	– Arterial carbon dioxide pressure (mm Hg)
Hz	– Hertz
BPM	– Beats per minute
LCD	– Liquid crystal display
IVH	– Intraventricular haemorrhage
BPD	– Bronchopulmonary dysplasia
RDS	– Respiratory distress syndrome
C_{rs}	– Lung compliance
L/kPa	– Litres per kilopascal
mL/cm H_2O	– Millilitres per centimetre of water
V	– Volume
P	– Pressure

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Chapter I

Introduction

Chapter I

General Introduction

Introduction

Approximately 6% of newborn infants require respiratory assistance immediately after birth (Singhal et al., 2001). Preterm infants are particularly susceptible to respiratory failure immediately after birth because their lungs have had insufficient time *in utero* to develop the gas exchange structures required to sustain the respiratory needs of the infant. Ventilatory support in the delivery room (DR) is usually provided in the form of positive pressure ventilation (PPV), but very little objective information is available to assess the effectiveness of the PPV. Traditionally, adequacy of ventilation in the delivery room (DR) is based on an assessment of an increase in the infant's heart rate, counted every 30 seconds. However, if the heart rate does not increase, chest wall movements are observed to gauge the effectiveness of ventilatory support (ILCOR Part 7: Neonatal resuscitation, 2005). This contrasts with practise in the neonatal intensive care unit (NICU) where the effectiveness of ventilation is guided by the continuous display of airway pressures, gas flow, tidal volume, (V_T) endotracheal tube leak, oxygen saturation and heart rate (South and Morley, 1986; Bhutani, 2002; Keszler, 2005; Klimek et al., 2006).

To achieve adequate gas exchange following delivery, lung liquid has to be cleared from the airways to allow the entry of gas and the establishment of a functional residual capacity (FRC) as quickly as possible. Recent imaging studies have demonstrated that this is achieved by the hydrostatic pressure gradient generated during inspiration which facilitates the movement of water across the distal respiratory epithelium into the surrounding tissue compartment. As the liquid within the airways is gradually absorbed and replaced by air, the resistance to lung expansion decreases by ~100 fold (Hooper et al., 2007; Hooper et al., 2009; Siew et al., 2009). As a result, the pressures required to promote airflow into the lung

decreases as the lung aerates and if these pressures are not quickly adjusted, the risk of hyper-expansion is very high (Te Pas et al., 2008). Therefore, relying on a fixed inflating pressure and subjective assessment of chest rise (Stenson et al., 2006) may result in harm by either under- or over-ventilation (Schmölzer et al., 2010). PPV during neonatal resuscitation is conventionally pressure limited. However, the purpose of the pressure is to deliver an appropriate tidal volume. Lung compliance and therefore the peak inspiratory pressure (PIP) corresponding to an appropriate tidal volume varies greatly in the minutes after birth. There are even greater differences *between* infants as the mechanical properties of the lungs depend on the immaturity of the lung. In addition, many infants make their own variable contributions to ventilation, adding to the inconsistency of volumes delivered by a set PIP. At present no objective indicators are routinely used to assess the tidal volumes administered during neonatal resuscitation. The tidal volume delivered is not measured and therefore airway pressure cannot be adjusted to optimise the tidal volume and reduce volutrauma or underventilation (Clark et al., 2000; Menakaya et al., 2004; Stenson et al., 2006; Schmölzer et al., 2008).

Although there are many methods available for assessing the effectiveness of respiratory support applied to very preterm infants in the NICU, these methods are not commonly applied in the DR. In the NICU, the methods available include arterial blood gas measurements, continuous heart rate (HR) and oxygen saturation (SpO$_2$) display as well as a variety of respiratory parameters including, spontaneous breathing, respiratory rate, tidal volumes airway pressure, resistance and compliance. Pulse oximetry (PO), which provides continues display of oxygen saturation and heart rate is increasingly used in the delivery room to titrate inspired oxygen concentration. PO provides only indirect information about ventilation. A Respiratory Function Monitor measures and continuously displays respiratory parameters, from the first breath and can help the resuscitator adjust the assisted ventilation to meet the infants' requirements.

When infants fail to breathe adequately immediately after birth, it is important to apply PPV in an appropriate, gentle, way to create and maintain a FRC, facilitate gas exchange and minimize lung injury. However, the application of adequate PPV in the

delivery room can be difficult because the assessment of whether the ventilation is effective is subjective and simply relies on an impression of adequate chest wall rise and the heart rate measured every 30 seconds (ILCOR Part 7: Neonatal resuscitation, 2005). Applying the same technologies in the DR as those used in the NICU could improve the effectiveness of ventilation in preterm infants immediately after birth.

The studies presented in this thesis focus on the physiology of the fetal to neonatal transition after birth and were performed with the aim of identifying physiological indicators that provide feedback on the effectiveness of the neonatal transition.

Part I - **Respiratory function monitoring during neonatal resuscitation**

In **Chapter II,** the literature about reducing lung injury during neonatal resuscitation of preterm infants is reviewed. I discuss what is known about the causes of neonatal lung injury, based on animal and human research and a possible approach to minimize lung injury during respiratory support immediately after birth.

In **Chapters III and IV,** the literature and our observations in the delivery room are reviewed. I describe video observations and recordings of respiratory signals from mannequin studies and delivery room resuscitations. These chapters discuss the potential benefits of a respiratory function monitor during simulation-based neonatal resuscitation teaching programs and resuscitations as well as potential pitfalls and limitations of this device.

Part II - *Assessment of effectiveness of respiratory support provided for preterm infants*

The aims of the observational studies presented in **Chapters V and VI** are to investigate the assessment of delivered tidal volumes, face mask leak and chest wall movements in the delivery room. In **Chapter V** I compared the resuscitators' self-assessment of the delivered tidal volume and face mask leak with measured values during PPV of preterm infants in the delivery room. In **Chapter VI** I compare the

assessment of chest wall rise made from both the infants' head and infants' side with measured tidal volume values during PPV in the DR.

Part III - Monitoring respiratory function in the delivery room

In **Chapter VII** I discuss the prevalence of serious airway obstruction and large face mask leaks during mask ventilation of very preterm infants in the first two minutes of PPV. I demonstrate that a respiratory function monitor can help to identify both causes of failure of PPV by careful observation of gas flow, tidal volume and pressure waves. In **Chapter VIII** I compare the performance of a self-inflating bag and a T-piece during positive pressure ventilation. These are secondary outcomes of a randomised control trial comparing both devices during PPV in the DR. In **Chapter IX** I present results from an observational study evaluating pressure delivery with different flow meters. In **Chapter X** the literature on respiratory function monitoring to reduce mortality and morbidity in preterm infants is presented in a Cochrane review. However, a thorough review of the literature found no studies addressing this question. A randomised control trial addressing this issue is presented in **Chapter XI.** I compared PPV where a respiratory function monitor was either masked or visible for the clinical team during resuscitation. In **Chapter XII** a randomised control trial comparing the usefulness of a flow sensor and a colorimetric CO_2 detector – the PediCap® for correct endotracheal tube placement in an animal model of neonatal resuscitation is discussed and in **Chapter XIII** observations using both devices for correct tube placement in the delivery room are presented.

In **Chapter XIV** the main findings of the thesis are discussed and perspectives and proposals for future research are presented.

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Chapter II

Reducing lung injury during neonatal resuscitation of preterm infants

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter II "Reducing lung injury during neonatal resuscitation"

Declaration by candidate

In the case of Chapter II the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Literature search and review of literature, writing the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Te Pas AB	Revising the manuscript	
Davis PG	Revising the manuscript	
Morley CJ	Revising the manuscript	

Candidate's Signature	███████████	Date	20/7/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Date
Signature 1	
Signature 2 ██████████	19/7/·0
Signature 3 ██████████	18.7.10

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PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter II "Reducing lung injury during neonatal resuscitation"

Declaration by candidate

In the case of Chapter II the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Literature search and review of literature, writing the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Te Pas AB	Revising the manuscript	
Davis PG	Revising the manuscript	
Morley CJ	Revising the manuscript	

Candidate's Signature		Date	

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
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(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

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Signature 1	███████████████		6/7/2010
Signature 2			
Signature 3			

2.2 INTRODUCTION

Approximately 6% of all newborn infants require respiratory support at birth. International guidelines recommend adequate positive pressure ventilation (PPV) if infants fail to initiate spontaneous breathing. The object of PPV is to deliver an adequate tidal volume to facilitate gas exchange. PPV is conventionally pressure limited and the purpose of the pressure is to deliver an appropriate tidal volume, which is rarely measured and therefore airway pressure is not adjusted to optimise the tidal volume. Lung compliance and therefore the PIP corresponding to an appropriate tidal volume vary greatly in the minutes after birth. There are even greater differences between infants as the mechanical properties of the lungs depend on the immaturity of the lung. In addition, when many infants will make their own variable contributions to ventilation adding to the inconsistency of volumes delivered by a set airway pressure. PPV may cause lung injury by various mechanisms, including high airway pressure (barotrauma), large tidal volumes and overdistension (volutrauma), repeated alveolar collapse and re-expansion (atelectrauma), infection and inflammation (biotrauma). These injuries cause proteinaceous fluid and blood to leak into the airways, alveoli, and the lung interstitium. These inhibit surfactant function, interfere with lung mechanics, and contribute to lung injury. In this chapter I describe what is known about the causes of neonatal lung injury, based on animal and human research. In addition, I suggest ways in which the current practice might be changed to help minimise lung injury during neonatal resuscitation.

2.3 Reducing lung injury during neonatal resuscitation of preterm infants

The following chapter has been published in The Journal of Pediatrics thus it is presented in PDF as per Monash University guidelines for thesis by publication.

Reducing Lung Injury during Neonatal Resuscitation of Preterm Infants

Georg M. Schmölzer, MD, Arjan B. te Pas, MD, Peter G. Davis, MD, and Colin J. Morley, MD

Neonatologists are familiar with the concept of ventilator-induced lung injury (VILI)[1,2] and are increasingly careful in the neonatal intensive care unit (NICU) to apply positive-pressure ventilation (PPV) strategies that are gentle to the lungs.[3] Although PPV also is commonly used in the delivery room (DR), clinicians appear less aware that the same gentle approach should be applied to reduce lung injury during the first few minutes of life.

To achieve adequate gas exchange after delivery, lung fluid is cleared and replaced with air, and functional residual capacity (FRC) is established. Mechanical ventilation requires an appropriate minute volume to achieve adequate gas exchange. Clinical signs are used to evaluate the response to ventilation during neonatal resuscitation. The tidal volume (V_T) delivered is rarely measured; thus, airway pressure is not adjusted to optimize V_T and reduce volutrauma or underventilation.[4-6] The use of end-expiratory pressure, considered essential to avoid lung injury in the NICU, is still not uniformly applied in the DR.

PPV may cause lung injury through various mechanisms, including high airway pressure (barotrauma), high V_T and overdistention (volutrauma), repeated alveolar collapse and reexpansion (atelectrauma), and infection and inflammation (biotrauma).[1] These injuries cause leakage of proteinaceous fluid and blood into the airways, alveoli, and lung interstitium, inhibiting surfactant function, interfering with lung mechanics, and contributing to lung injury.[1]

In this review, we describe what is known about the causes of neonatal lung injury, based on animal and human research. Although human data are scanty, and randomized control trials are needed, we suggest ways in which current practice might be changed to help minimize lung injury during neonatal resuscitation.

VOLUTRAUMA

High V_T that causes overdistention of the lung plays a key role in VILI. Animal studies have demonstrated that lung injury can occur during resuscitation with just a few large manual inflations.[7,8] In their classic experiments with mature animals, Dreyfuss et al[9] and Hernandez et al[10] showed that lung injury was caused mainly by high V_T ventilation, not by high pressure. Many lesions occurred within 2 minutes of starting ventilation; however, when the V_T was controlled so as to avoid lung overdistention, little or no injury occurred.[10]

At birth, the lungs of very preterm infants are uniquely susceptible to injury because they are structurally immature, surfactant-deficient, fluid-filled, and not supported by a stiff chest wall. In addition, the difference in volume between FRC and total lung capacity (TLC) is considerably less than in term infants.[11] Vilstrup et al[12] reported that term infants have a TLC of 43 to 52 mL/kg. In contrast, by 10 hours of age, preterm infants with respiratory distress syndrome have an FRC of approximately 11 mL/kg and a TLC of only 19 ml/kg.[13] These values suggest that a $V_T > 8$ mL/kg can distend the lung above TLC and cause damage.[4,14] This suggestion is supported by a study of V_T measurements in spontaneously breathing infants born at ≤ 32 weeks' gestation during continuous positive airway pressure (CPAP), with a mean V_T of 4.4 mL/kg (range, 2.6 to 7.2 mL/kg).[15]

These studies suggest that to reduce acute lung injury during resuscitation, clinicians should be aware of the V_T used during PPV and deliver < 8 mL/kg, particularly in very preterm infants. V_T targeted in the NICU (4 to 5 mL/kg) may represent a good starting point.[16]

CPAP	Continuous positive airway pressure	PIP	Peak inspiratory pressure
DR	Delivery room	PPV	Positive-pressure ventilation
FiO_2	Fraction of inspired oxygen	SpO_2	Saturation of peripheral oxygen
FRC	Functional residual capacity	TLC	Total lung capacity
NICU	Neonatal intensive care unit	VILI	Ventilator-induced lung injury
PEEP	Positive end-expiratory pressure	V_T	Tidal volume

ATELECTRAUMA

Atelectrauma involves alveolar damage as a result of transient and repeated collapse and reopening of alveoli and respiratory bronchioles during the respiratory cycle. Lung injury occurs when the lung is repeatedly reinflated from atelectasis, subjecting the alveoli to high shear forces.[2] Cytokines are released,[11] and leukocytes accumulate and are activated in the lungs,[2] causing damage characterized by epithelial disruption, hyaline membrane formation, airway cell loss, increased alveolar capillary permeability, surfactant dysfunction, decreased lung compliance, and poor gas exchange.[3]

PPV with inadequate positive end-expiratory pressure (PEEP) leads to a low residual volume and atelectasis. Using PPV without PEEP may lead to failure to establish FRC, inadequate oxygenation, and increasing atelectrauma.[17] In surfactant-treated preterm lambs, PPV without PEEP was associated with reduced compliance and oxygenation compared with ventilation with PEEP of 4 to 7 cm H_2O.[18] In addition, preterm lambs ventilated with PEEP of 8 cm H_2O had a significantly lower oxygen requirement by 10 minutes of age compared with lambs ventilated with no PEEP.[19] In fact, improved oxygenation has been found to occur more rapidly with PEEP than with administration of exogenous surfactant.[20]

HIGH INSPIRED OXYGEN INJURES THE LUNGS

Randomized controlled trials have shown that resuscitating asphyxiated newborn infants with air reduces mortality compared with resuscitation with 100% oxygen.[21] A high fraction of inspired oxygen (FiO_2) is toxic to lung tissue in animal and human experimental models; both term and preterm subjects may develop lung injury when treated with a high FiO_2 for prolonged periods.[3] Very preterm infants are particularly susceptible to free-radical damage, because antioxidant mechanisms are not fully developed until the third trimester.[22] Prolonged exposure to hyperoxia has been associated with leukocyte activation and sequestration in the neonatal rat lung.[23] A high FiO_2 may contribute to arrested alveolar development in very preterm infants who develop bronchopulmonary dysplasia.

Gladstone et al[24] analyzed lung lavage fluid in neonates who received ventilation for respiratory distress syndrome and a correlation between the change in protein-bound carbonyl level during the first 24 hours and oxygen requirement. FiO_2 >0.4 was associated with a significant increase in protein-bound carbonyl, which is a marker for oxidative injury. Munkeby et al[25] ventilated asphyxiated term piglets for 30 minutes with 21% or 100% oxygen and found that even this brief period of 100% oxygen produced a significant increase in inflammatory markers.

These findings suggest that in the first minutes after birth, avoiding the use of high oxygen concentrations may reduce acute lung injury, particularly in very preterm infants. Oxygen, like any drug, should be monitored and titrated to the patient's individual requirements.

PROPHYLACTIC VERSUS RESCUE SURFACTANT STRATEGY

Systematic reviews of randomized control trials have demonstrated that prophylactic surfactant therapy reduces mortality, air leaks, and initial inspired oxygen requirements[26-30] for infants < 30 weeks' gestation or with birth weight < 1250 g.[31] But these trials were conducted in an era when most very preterm infants were electively intubated and antenatal steroid treatment or early CPAP was rare, and thus it is possible that these data do not apply to the present era. Ammari et al[32] recently evaluated their hospital's experience with early nasal CPAP and found that after 25 weeks, most infants could be treated with nasal CPAP without surfactant. The COIN trial[33] demonstrated that 50% of the infants born at 25 to 28 week's gestation could be successfully treated with nasal CPAP without surfactant.

RESPIRATORY SUPPORT AT BIRTH: IMPLEMENTING AVAILABLE KNOWLEDGE

In a preterm infant, knowledge about the causes and prevention of lung injury must be applied from birth, instead of waiting until the infant is in the NICU.

MEASURING AND TARGETING V_T

A lung-protective strategy should be implemented immediately after birth. The volume difference between FRC and TLC is small in very preterm infants;[2,12] therefore, relying on a fixed inflation pressure and subjective assessment of chest rise[4] may result in harm due to either underventilation or overventilation. PPV during neonatal resuscitation is conventionally pressure-limited; however, the purpose of the pressure is to deliver an appropriate V_T. Lung compliance, and thus the peak inspiratory pressure (PIP) corresponding to an appropriate V_T, vary greatly in the minutes after birth. The differences are even greater *between* infants, because the lungs' mechanical properties depend on their maturity. In addition, an infant will make his or her own variable contributions to ventilation, adding to the inconsistency of volumes delivered by a set PIP.

Immediately after birth, delivering an appropriate V_T using ventilation with a set pressure is impossible, because lung compliance varies from infant to infant and also throughout the course of lung aeration.[6] Therefore, measuring and adjusting the V_T delivered during PPV is imperative in the minutes after birth, especially in very preterm infants. All modern neonatal ventilators continuously measure and display V_T, endotracheal tube leak, PIP, PEEP, inspiratory and expiratory times, and minute volume, and neonatologists are learning their value.

The use of a respiratory function monitor during initial stabilization in the DR has not yet been well evaluated.[6,15,34-37] Tracy et al[34] reported that during initial stabilization and transportation from the DR to the nursery, infants were often overventilated and had a mean V_T > 7 mL/kg. Dammann et al[38] found that by 20 minutes after birth, 20%

of infants had a partial pressure of CO_2 in arterial blood < 25 mm Hg—a known risk factor for brain injury. McCallion et al[39] suggested that volume-targeted ventilation can optimize ventilation in the NICU. Using a respiratory function monitor in the DR during PPV to ensure delivery of an appropriate V_T shows promise. The PIP is adjusted appropriately as lung compliance changes and the infant starts to breathe.

FACE MASK LEAKS

Ventilation with a face mask is the primary technique used to support infants who are breathing inadequately immediately after birth. The often large and variable gas leak between the mask and face is a major problem with this technique, however.[35,36,40] Face mask leaks are frequent even for experienced operators and can significantly affect the delivered V_T.[40] The V_T changes as the leak changes, even when the same inflating pressure is used. In practice, this means that for the same inflating pressure, the V_T may be low, appropriate, or excessive, depending on the leak. In studies using a mannequin, Wood et al[41] showed that face mask leak can be decreased from 55% to 15% when the resuscitator is able to see the V_T and leak displayed on a respiratory function monitor. Our experience during difficult resuscitations is that seeing the V_T and mask leak enables the resuscitator to adjust the mask hold and inflating pressure to optimize the V_T.

PEEP AND CPAP

PEEP is used in the NICU during mechanical ventilation to help maintain end-expiratory lung volume, and CPAP is used to support lung volume and improve gas exchange in nonintubated neonates with respiratory failure. Neither of these treatments is mandated in neonatal resuscitation guidelines, however. The very preterm infant has difficulty maintaining FRC and upper airway patency for many reasons.[42] CPAP or PEEP can reduce the risk of atelectrauma and improve respiratory function in various ways: (1) CPAP reduces upper airway obstruction by decreasing upper airway resistance and increasing the pharyngeal cross-sectional area;[43] (2) both CPAP and PEEP increase FRC;[44,45] (3) CPAP and PEEP reduce inspiratory resistance[44,46] by dilating the airways and allow a larger V_T for a given pressure with reduced work of breathing;[47] (4) CPAP and PEEP increase the compliance and V_T of stiff lungs with a low FRC by stabilizing the chest wall;[47] (5) CPAP and PEEP increase the mean airway pressure and improve ventilation–perfusion mismatch;[48] (6) PEEP conserves surfactant on the alveolar surface;[49,50] and (7) as CPAP and PEEP increase lung volume, oxygenation also improves.[19,20]

Studies using animal models of resuscitation support the use of PEEP in the DR.[51-53] Polglase et al[54] reported that PEEP of 4 to 8 cm H_2O maintained arterial oxygenation and decreased pulmonary vascular blood flow with no adverse effects to the cardiovascular system. Probyn et al[19] ventilated preterm lambs at PEEP levels of 0, 4, 8, and 12 cm H_2O and found that all lambs ventilated with a PEEP above 0 exhibited improved oxygenation, but increasing the PEEP to 12 cm H_2O resulted in pneumothoraces. PEEP levels up to 8 cm H_2O should be considered for resuscitation of preterm infants. Randomized controlled trials of different levels of PEEP during resuscitation of human infants at birth are needed.[55] CPAP or PEEP should be applied at the initiation of respiratory support to facilitate the early development of an effective FRC, reduce atelectrauma, and improve oxygenation during the transition of preterm infants.

THE BEST DEVICE FOR RESPIRATORY SUPPORT DURING RESUSCITATION

Currently, there is little evidence to guide clinicians' choice of ventilation device; however, any device chosen must provide PEEP or CPAP to facilitate the development of FRC immediately after birth, improve oxygenation, and reduce atelectrauma. T-piece devices allow operators to adjust both PEEP and CPAP.[56-58] A flow-inflating resuscitation bag can provide PEEP, but the pressure delivered is highly variable and operator-dependent,[59] making it very difficult to provide a consistent end-expiratory pressure. A self-inflating bag (still the most commonly used device for neonatal resuscitation) does not provide PEEP or CPAP. Inconsistent PEEP is provided with the addition of a PEEP valve, and CPAP cannot be delivered.[58,60,61]

PULSE OXIMETRY

Because observations of newborn infants' color are inaccurate and imprecise,[62] using color to determine the appropriate FiO_2 during resuscitation seems illogical. Oximetry readings of heart rate and oxygen saturation can be obtained from the newborn's right hand or wrist within 90 seconds of birth.[63] After birth, an increasing heart rate is the key sign of the infant's successful transition to the extrauterine environment. Pulse oximetry can display the heart rate continuously during resuscitation, thereby allowing the team to continue resuscitation efforts without stopping to determine the heart rate.

Transcutaneous oxygen saturation is approximately 60% in utero and can drop to 30% during labor and delivery.[64] A normal term infant has a saturation of peripheral oxygen (SpO_2) value of around 60% immediately after birth, which rises to > 90% over the next 10 minutes At 5 minutes, some normal infants have an SpO_2 as low as 70%.[65,66] When considering using oxygen for resuscitation, it is important to keep in mind that a relatively low SpO_2 in the first few minutes after birth is not in itself an indication for oxygen therapy. Inspired oxygen concentration should be titrated against the infant's SpO_2, bearing in mind the normal changes occurring during the first minutes of life.[65]

DISCUSSION

The information presented herein is from applicable animal studies and extrapolations from clinical studies in

neonatal intensive care. Unfortunately, human data are scanty, and clinical trials are needed. Undertaking a good, detailed randomized study involving the emergency situation of neonatal resuscitation is very difficult, however. Waiting for clinical studies to evaluate the techniques described herein will delay improvement in the care of high-risk infants immediately after birth.

When preterm infants fail to breathe adequately immediately after birth, it is important to apply PPV in an appropriate, gentle way to create an FRC, facilitate gas exchange, and minimize lung injury. To minimize volutrauma, the PIP should be adjusted to ensure delivery of a V_T of approximately 5 mL/kg. Using a respiratory function monitor can help achieve a target V_T. To minimize atelectrauma, help establish an FRC, and improve oxygenation, CPAP or PEEP should be used immediately on initiation of any respiratory support. A T-piece resuscitation device can accurately deliver either form of end-expiratory pressure. Techniques for monitoring and adjusting respiratory support that are currently routinely used in the NICU should be used in the DR as well. Better DR care of preterm infants offers considerable potential for improving important short- and long-term outcomes.

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Chapter III

Respiratory Function Monitoring during simulation-based mannequin teaching

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter III "Respiratory function monitoring during simulation-based mannequin teaching"

Declaration by candidate

In the case of Chapter III the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Literature search and review of literature, writing and revising the manuscript	90%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Morley CJ	Revising the manuscript	

Candidate's Signature	███████████	Date 20/7/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia	

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	███████████	Date 18.7.10

3.2 INTRODUCTION

Approximately 5% of neonates require active resuscitation at birth. There is general agreement that the key to successful neonatal resuscitation is adequate positive pressure ventilation (PPV), provided by manual inflation devices and a face mask. However, the provision of adequate PPV relies on appropriate mask hold and seal, and the delivery of defined pressures[8] and tidal volumes. An international consensus statement and regional and national guidelines provide advice regarding techniques and equipment used for neonatal resuscitation. According to these guidelines, the need for ventilation and the evaluation of its effectiveness should be done by clinical assessment of an increase in an infants' heart rate at regular 30 second intervals. Adequacy of effective ventilation should be judged by assessment of chest wall rise in order to gauge ventilatory support. However, recent studies have shown that assessment of face mask seal, tidal volume delivery and chest wall rise is limited and subjective. In addition, various studies have shown that patient assessment in the delivery room based merely on clinical impression is inaccurate. Recently, experts suggested applying technologies used in the intensive care units to the delivery room to more objectively monitor resuscitation efforts.

The clinical skills of manual PPV provision are being taught at neonatal life support courses. These courses are universally offered and in many regions a compulsory element of neonatal training. They emphasise the importance of "bag and mask" ventilation, however, the evaluation of how well the trainee applies the mask and ventilates the manikin again remains subjective. This could be overcome by the routine use of objective monitoring devices, like a respiratory function monitor.

In this chapter I will describe how a RFM can been used during neonatal training purposes to i) help identifying correct mask hold and optimize mask positioning techniques to reduce

gas leak between the mask and face; ii) continuously measure and display the peak inflation pressure and positive end expiratory pressure, iii) enable the operator to adjust the pressure to deliver an appropriate tidal volume; iv) provide an objective assessment of the trainee's performance.

3.3 Respiratory Function Monitoring during simulation-based mannequin teaching

The following chapter has been provisionally accepted in Applied Technologies in Pulmonary Medicine but is not yet published, thus it is presented in manuscript form as per Monash University guidelines for thesis by publication.

Respiratory Function Monitoring during simulation-based mannequin teaching

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Key words:

- Positive Pressure Ventilation
- Respiratory Function Monitor
- Neonatal Resuscitation
- Tidal volume
- Face mask leak
- Simulation-based mannequin training

Abbreviations:

MV_e - Expiratory Minute Ventilation

PEEP   - Positive End Expiratory Pressure

PIP   - Peak Inflation Pressure

PPV   - Positive Pressure Ventilation

RFM   - Respiratory Function Monitor

RR   - Respiratory Rate

t_E - Expiratory Time

t_I - Inflation Time

V_T - Tidal Volume

V_{Te} - Expiratory Tidal Volume

V_{Ti} - Inspiratory Tidal Volume

Introduction

Adequate ventilation remains the cornerstone of respiratory support during neonatal transition[1]. International agreed consensus statements on neonatal resuscitation recommend that breathing should be assisted by giving PPV with a manual inflation device[2]. However, PPV can be difficult because the assessment of face mask seal, tidal volume and effective ventilation is subjective relying on clinical impression of adequate chest rise and an increase in heart rate[2].

Neonatal life support courses are a mandatory part of neonatal training in many countries. Although they emphasise the importance of "bag and mask" ventilation, the evaluation of how well the trainee apply the mask and ventilate the mannequin is subjective.

Face mask leak is both a common and unrecognised problem during PPV which can lead to failure of ventilation. Recently, a RFM was used to evaluate "bag and mask" ventilation during simulation-based mannequin teaching[3-7]. Participants had large and unrecognised leaks between the face and the mask[5]. When the participants used a respiratory function monitor they were able to adjust the mask position and face mask leak was halved[6].

During resuscitation the spontaneous tidal volume or the tidal volume being delivered during PPV is unknown. Various studies suggest a V_T within a range of 4 to 8 ml/kg. Insufficient V_T can lead to inadequate gas exchange, where as excessive V_T can lead to volutrauma[8-12]. PPV is always pressure limited however the purpose of applying a peak pressure is to inflate the lung with a appropriate tidal volume. However, the tidal volume delivered is not fixed but dependent on the size, compliance, and resistance

of the lungs, and the applied pressure. During resuscitation as the lung aerates the tidal volume delivered will change as the infants starts breathing. Recent studies have been shown, that operators are unable to deliver accurate and appropriate tidal volumes during simulation-based PPV or during neonatal resuscitation[13;14]. When the participants could see a displayed of the tidal volume they were able to achieve the desired volume more accurately[13].

Respiratory Function Monitor

Any RFM which measures and displays airway pressure, gas flow and V_T can be used during simulation-based mannequin training. The flow sensor is placed between the face mask and the ventilation device[3]. By integrating the flow signal the inspiratory and expiratory tidal volume passing through the sensor is automatically calculated. An airway pressure line is connected to measure and display the PIP and PEEP.

A RFM continuously displays airway pressure, gas flow and V_T waves. In addition, it measures and displays numerical values for PIP, PEEP, V_{Ti}, V_{Te}, RR, expiratory minute ventilation, inspiration and expiration time (t_I, t_E) (Figure 1). The percentage of leak between mask and face is calculated and displayed with the following equation: $[(V_{Ti} - V_{Te}) \div V_{Ti}] \times 100$ (Figure 2)[3].

All figures were obtained during PPV of a Laerdal neonatal mannequin (Laerdal Medical AS; Stavanger; Norway), which was made internally leak free. PPV was performed using a round silicone face mask (Laerdal Medical AS; Stavanger;

Norway) and a Neopuff Infant T-Piece Resuscitator (Fisher & Paykel Healthcare; Auckland; New Zealand), a continuous flow, pressure limited, T-piece device with a built in manometer and a PEEP valve.

Mask hold and positioning techniques

During simulation-based mannequin training a RFM can be use to teach the best technique of positioning, holding and ventilating with a face mask (Figure 1). This can be easily demonstrated using a resuscitation mannequin that is internally leak free and a flow sensor placed between the face mask and the ventilation device[3;4;6]. Any leak will be displayed as the difference between V_{Ti} and V_{Te} or the difference in area of the flow curve above and below zero (Figure 2)[3].

During PPV the trainee receives constant visual feedback because the RFM displays the amount of leak and the trainee can adjust the position of the face mask to minimise leak (Figure 3)[6].

Assessment of PIP and PEEP

The purpose of applying any inflating pressure during PPV is to inflate the lungs with an appropriate tidal volume to create a functional residual capacity and thereby facilitate gas exchange. With a self- or flow inflating bag the pressure delivered is unknown unless it is measured and displayed using a manometer[15-18]. The applied pressure is usually shown on a dial during PPV with a T-piece device. Although this is useful, as pressure rises and falls rapidly, it can be difficult to see the PIP and PEEP[18]. During simulation-based mannequin training with a RFM the trainee can easily assess the whole pressure wave and the numerical values of PIP and PEEP (Figure 1).

Adjusting PIP to achieve appropriate tidal volumes

Once a trainee is able to obtain leak free face mask ventilation, he then can concentrate on assessing the delivered tidal volume by adjusting the inflating pressure. With a self- or flow inflating bag they will learn how hard they need to squeeze and with a T-piece device adjust the PIP they should set to deliver an appropriate tidal volume (Figure 4). Although mannequins are different from infants, the principles can be learned and then applied during real resuscitation.

Assessment of the trainee's performance

Assessment of a trainee's performance remains a substantial part of any neonatal resuscitation training courses. However, the assessment of adequate "bag and mask" ventilation remains subjectively. The "instructor" judges' mask position, ventilation rate, and chest rise to assess the adequacy of the trainees' performance of positive pressure ventilation. I have recently shown that during neonatal resuscitation operators were unable to judge their delivered V_{Te} or face mask leak by looking a chest rise[19]. I showed that the majority of operators underestimated their delivered V_{Te} and face mask leak. A RFM can assist the "instructor" to objectively assess the provider's performance during "bag and mask" ventilation.

Conclusion

In this chapter I have summarized the current available literature on how a respiratory function monitor can aid during simulation-based mannequin training. A RFM can assist during mask ventilation: i) it can help identifying correct mask hold and positioning techniques to reduce leak of gas between the mask and face; ii)

continuously measure and display the peak inflation pressure and positive end expiratory pressure, iii) enable the operator to adjust the pressure to deliver an appropriate tidal volume; iv) provide an objective assessment of the trainee's performance.

Figure legend

Figure 1: PPV with a face mask and no leak

PPV with a set PEEP and PIP of 5 and 20 cmH_2O. Gas flow curves of inflation and expiration are returning to the baseline. This indicates sufficient inspiration and expiration time. The areas underneath both inflation and expiration gas flow curves are similar reflecting an equal amount of gas entering and leaving the lung. The tidal volume curve displays V_{Ti} and V_{Te}, showing an equal volume of gas entering and leaving the lung. In addition, no leak is present. V_{Ti} has reached a plateau indicating no further gas continues to enter the lung as inflation is continued.

Figure 2: Airway leak during PPV

The area underneath the inflation gas flow curve is larger than that under the expiratory gas flow curves. The tidal volume curve displays a larger V_{Ti} compared to V_{Te} and leak is shown as a straight line in the tidal volume curve.

Figure 3: Correction of face mask position

During PPV the airway pressure curve fails to achieve the set PIP of 30 cm H_2O. A returning inspiratory gas flow curve to baseline indicates gas flow towards the face mask. In contrast, there is much less expiratory gas flow indicating a leak around the face mask. The V_T curve reflects the gas flow curve and displays a leak of around 80%. There is almost no gas entering or leaving the lung. A significant reduction in the face mask leak is achieved after correction of face mask position. Adequate gas flow is entering and leaving the lung and the set PIP is delivered.

Figure 4: Adjusting PIP to achieve appropriate tidal volumes

Initially, the inflation and expiratory gas flow curves are small; the measured V_{Te} is approximately 2 mL/kg. An increase in V_{Te} to 6 mL/kg is achieved with an increase in PIP to 42 cm H_2O. The consequence of a further PIP increase to 50 cm H_2O is an increase in V_{Te} to 12 mL/kg, which is excessive. Decreasing the PIP to 30 cm H_2O resulting in a delivered V_{Te} of 7 ml/kg.

Figure 1
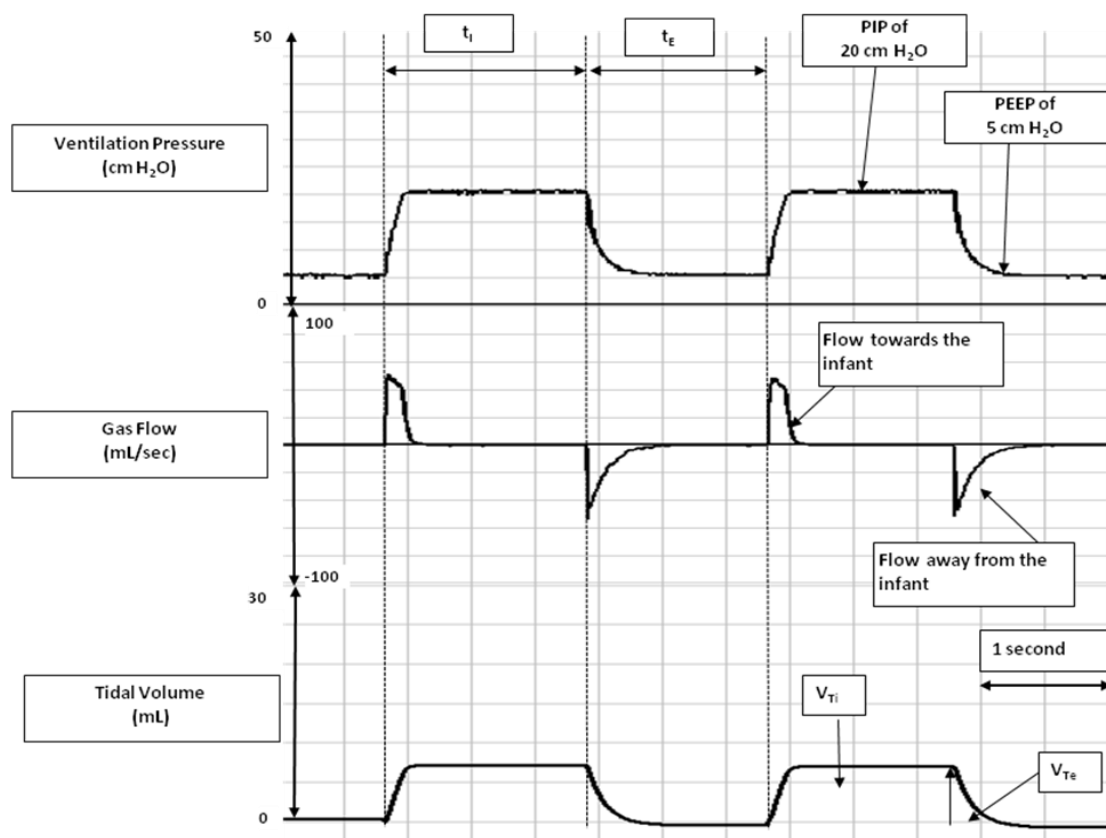
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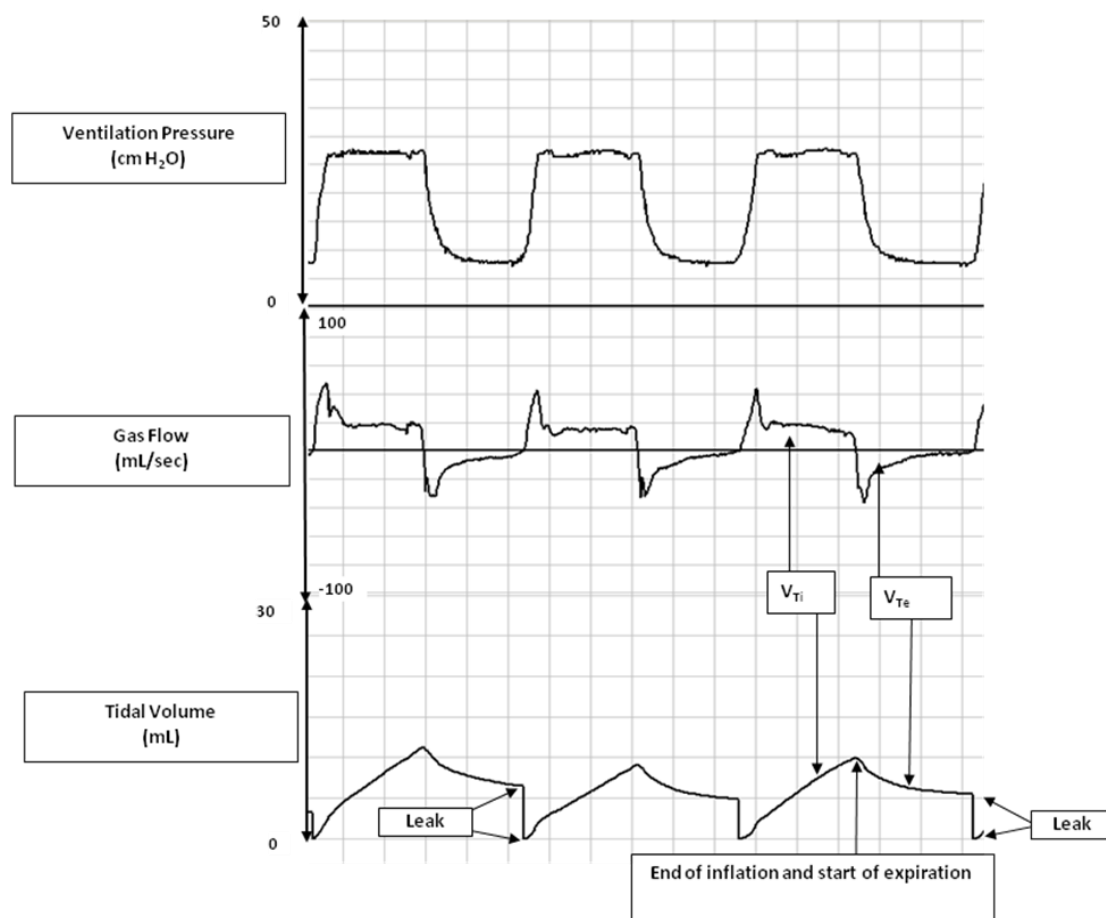
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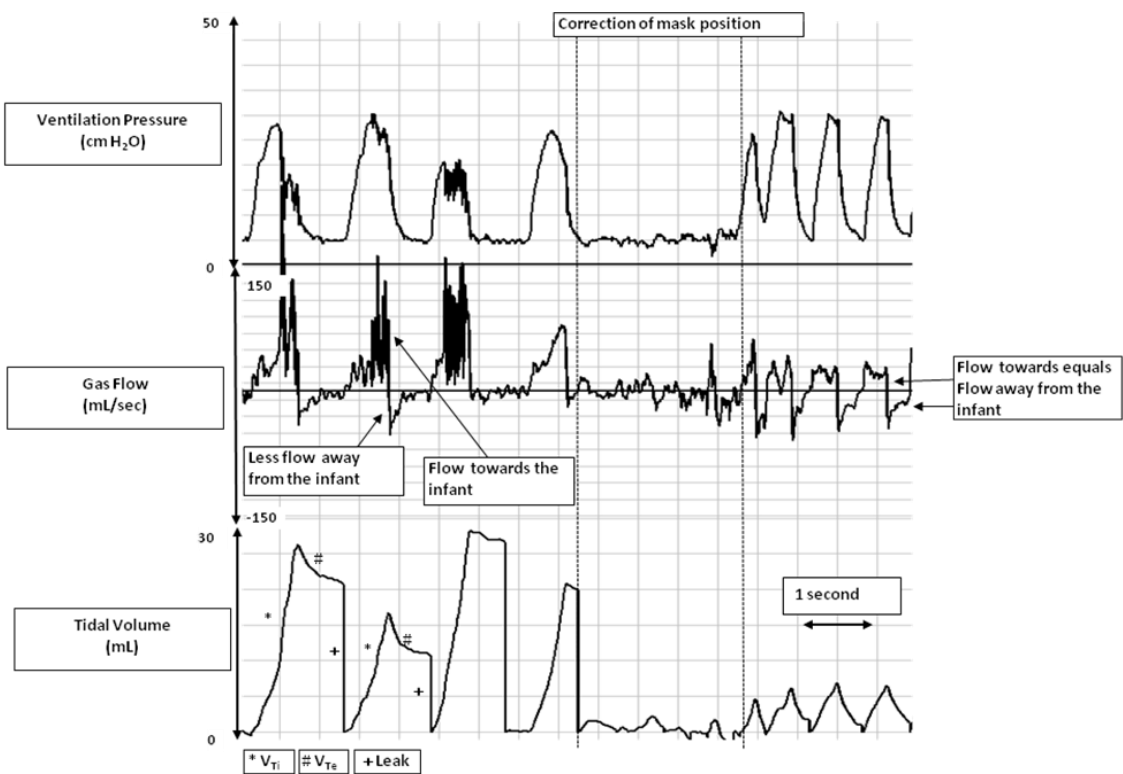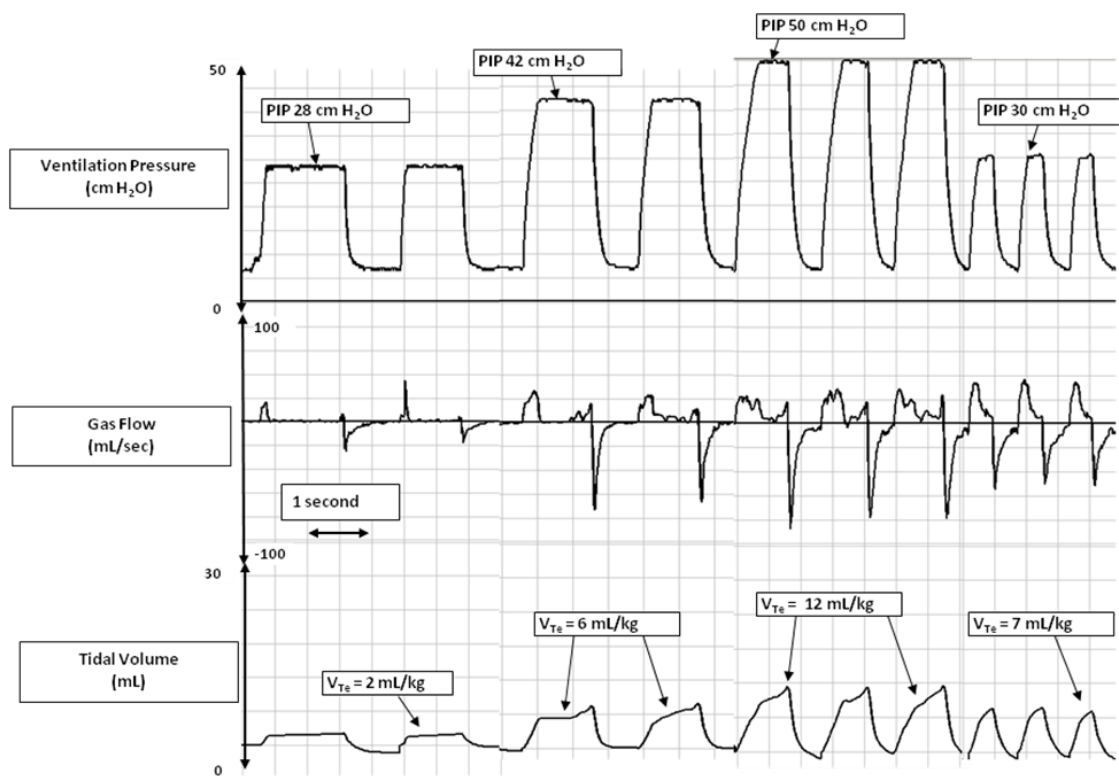
Figure 4

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Chapter IV

Respiratory monitoring of neonatal resuscitation

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter IV "Respiratory monitoring during neonatal resuscitation"

Declaration by candidate

In the case of Chapter IV the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Data collection, data analysis, writing and revising the manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Kamlin COF	Involved in data collection, revising the manuscript	
Dawson JA	Involved in data collection, revising the manuscript	
te Pas AB	Involved in data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature	███████████	Date	20/7/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	███████████████████	20/7/10
Signature 2	███████████████████	20/07/2010
Signature 3	███████	
Signature 4	███████████	18.7.10
Signature 5	█████████████	20.7.10

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter IV "Respiratory monitoring during neonatal resuscitation"

Declaration by candidate

In the case of Chapter IV the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Data collection, data analysis, writing and revising the manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Kamlin COF	Involved in data collection, revising the manuscript	
Dawson JA	Involved in data collection, revising the manuscript	
te Pas AB	Involved in data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature		Date

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
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[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Date
Signature 1	
Signature 2	
Signature 3	6/7 2010
Signature 4	
Signature 5	

4.2 INTRODUCTION

Approximately 6% of newborn infants require respiratory assistance at birth. An internationally agreed consensus statement and various guidelines provide advice about equipment and techniques for neonatal resuscitation. They all agree that the key to successful neonatal resuscitation is adequate positive pressure ventilation (PPV). The adequacy of tidal volume delivery during PPV in the delivery room is assessed by observing chest wall movements and a prompt increased in heart rate. In comparison, ventilation on the neonatal intensive care unit is guided by continuous measurements of airway pressure, gas flow and tidal volume.

In this Chapter I illustrate how a respiratory function monitor can be used to improve simulation based mannequin training and respiratory support during neonatal resuscitation.

In this Chapter I discuss the uses of a respiratory function monitor (RFM) during training and resuscitations along with potential pitfalls and limitations made by observations of respiratory signals during delivery room resuscitations. A RFM can objectively assess the mask ventilation compared to clinical assessment by providing real-time quantitative information including tidal volume and mask leak.

4.3 Respiratory monitoring of neonatal resuscitation

The following chapter has been published in Archives of Disease in Childhood Fetal &

Neonatal Edition thus it is presented in PDF as per Monash University guidelines for thesis

by publication.

Respiratory monitoring of neonatal resuscitation

Georg M Schmölzer, Omar C O F Kamlin, Jennifer A Dawson, et al.

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Respiratory monitoring of neonatal resuscitation

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ABSTRACT
Video observations and recordings of respiratory signals from mannequin studies and delivery room (DR) resuscitations are described. This article discusses the uses of a respiratory function monitor (RFM) during training and resuscitations along with potential pitfalls and limitations. It adds objectivity to the clinical assessment. A respiratory function monitor provides real-time quantitative information including tidal volume and leak. It may be used to teach correct mask hold and positioning techniques during simulation-based mannequin. Examples demonstrating its potential usefulness during resuscitations are provided. However, further studies are needed to investigate whether it can help improve short-term and long-term outcomes.

BACKGROUND
Approximately 3% to 6% of newborn infants require respiratory assistance at birth.[1] An internationally agreed consensus statement[2] and various guidelines[3–5] provide advice about equipment and techniques for neonatal resuscitation. They all agree that the key to successful neonatal resuscitation is adequate positive pressure ventilation (PPV).[2–5]

Traditionally, adequacy of ventilation during PPV in the delivery room (DR) is assessed by adequate chest rise and increased heart rate.[2] This contrasts with evidence that optimal ventilation in the neonatal intensive care unit should be guided by a continuous display of airway pressure, gas flow, tidal volume (V_T) and gas leak at the endotracheal tube (ETT)[6–8]

The aim of this clinical practice review is to illustrate how monitoring respiratory signals can improve manikin-based training and respiratory support during neonatal resuscitation.

Over 6 years, at the Royal Women's Hospital, Melbourne, Australia, a respiratory function monitor (RFM) was used for training and during neonatal resuscitation in the DR for audit, research and clinical management. The studies were approved by the Hospital Research and Ethics Committees and parental consent to use the recordings was obtained.

RFM
We use a Florian Neonatal RFM (Acutronic Medical Systems AG, Zug, Switzerland). It uses a small, low dead space (approximately 1 ml) hotwire anemometer with an accuracy of ±8% (manufacturer's data), which is placed between a ventilation device and a facemask or ETT.[9–12] The inspiratory and expiratory tidal volumes (V_{Ti}, V_{Te}) are automatically calculated by integrating the flow signal. A monitoring line measures and displays the airway pressures.

The monitor can be set to continuously display pressure, flow and tidal volume waves. It also measures and displays numerical values for peak airway pressure (PIP), positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP), V_{Te}, respiratory rate (RR), expiratory minute ventilation (MV_e) and the leak between mask and face or around an ETT as a percentage (($(V_{Ti} - V_{Te})/V_{Ti}) \times 100$ (see figures 1 and 2). Leak is graphically presented as the difference in area under the flow curves above (inflation) and below (deflation) zero flow.[12]

Measurements were recorded from the Florian monitor at 200 Hz and displayed using Spectra software (Grove Medical, London, UK). The figures were obtained during PPV of either a leak free manikin or resuscitation of an infant in the DR. The ventilation device used was either a Neopuff Infant Resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand), which is a continuous flow, pressure limited, T-piece device with a built in manometer and a PEEP valve, or a Laerdal infant resuscitator (Laerdal, Stavanger, Sweden), which is a 240 ml silicone self-inflating bag. Default Neopuff settings were a gas flow of 8 litres/min, PIP and PEEP of 30 and 5 cm H_2O. For the Laerdal the gas flow was 8 litres/min and no PEEP valve was used.

OPTIMISING FACE MASK HOLD AND POSITION
A RFM can be used to find the best technique of mask application and mask position when using a face mask. This can be demonstrated using a resuscitation manikin that has been made internally leak free (see figure 1).[10 12] In manikin-based training as well as during real resuscitations, the monitor displays the leak around the face mask as graphical and numerical output. The operators can then adjust the face mask hold and position to minimise leak (see figure 3).[9] During PPV training[9–13] operators averaged 60% leak around the face mask.[11] When they used a RFM they were able to adjust the mask position and reduce the leak to about 10%.[9] Using a RFM improves the effectiveness of PPV via a face mask by providing immediate feedback to the operator.[9–12] In addition, it enables an instructor or examiner to assess the operator's performance by observing their face mask leak in real time.

In our experience a large face mask leak is a common, usually unrecognised, problem during resuscitation, which can lead to inadequate ventilation (see figure 2). Mask leak varies during each resuscitation due to the baby's movements,

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Figure 1 Leak at face mask in an extremely low birthweight (ELBW) infant. Positive pressure ventilation with a face mask in a 28-week infant. The inspiratory flow curve returns to baseline indicating gas flow towards the face mask. In contrast, there is no expiratory flow curve indicating a leak around the face mask. The tidal volume curve reflects the gas flow curve and displays 80% to 100% leak with almost no gas entering and leaving the lung. In addition, the pressure curve fails to achieve the set peak airway pressure (PIP) of 30 cm H_2O. After correction of face mask position there is a significant reduction in face mask leak to 15%, adequate gas flow entering and leaving the lung and the set PIP is reached.
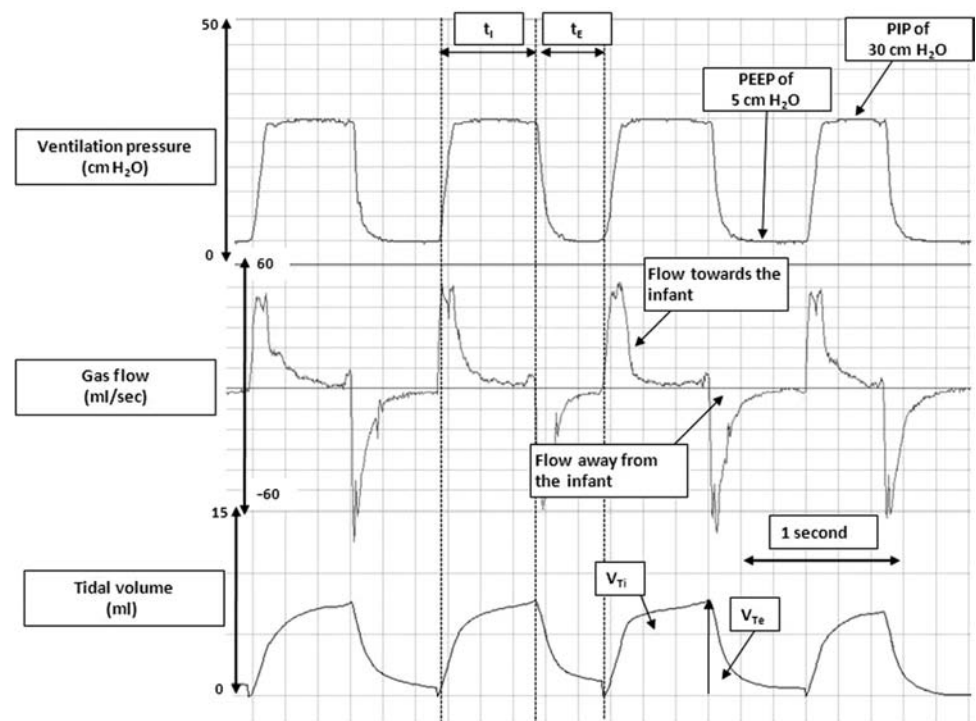
Figure 2 Airway leak in extremely low birthweight (ELBW) infants. Variable leak during positive pressure ventilation with a face mask in a 27-week infant. The area underneath the inflation flow curve is greater than that under the expiratory flow curves. This is reflected in the tidal volume (V_T) curve, which displays a larger inspiratory V_T (V_{Ti}) compared to expiratory V_T (V_{Te}). Leak is displayed as a straight line in the tidal volume curve.
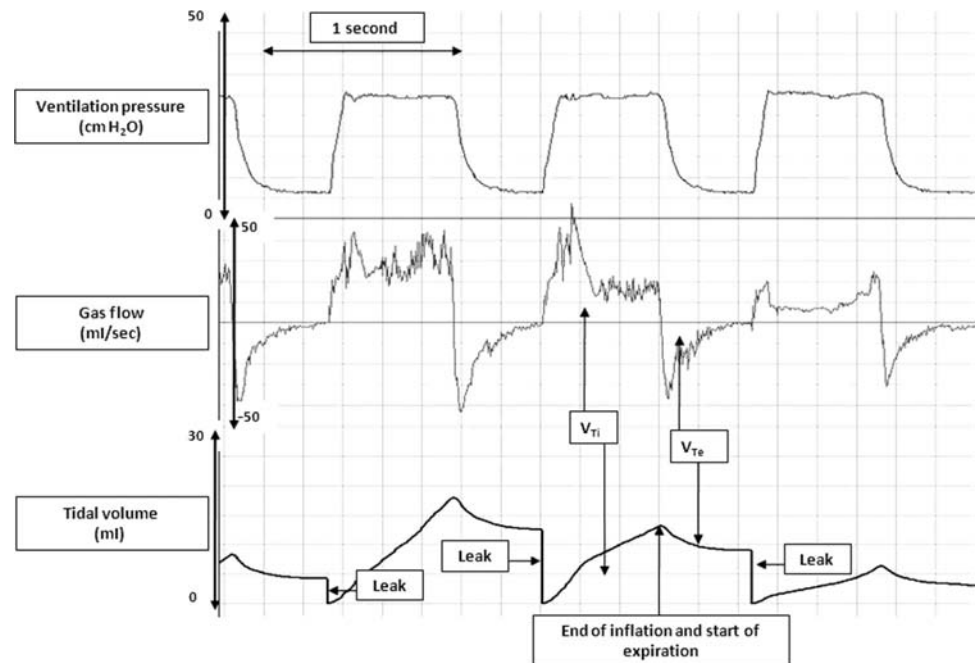
movements of the operator's hand or procedures such as fitting a hat. Variable mask leak leads to the delivery of variable tidal volumes. When the leak is large, the tidal volume may be insufficient to achieve adequate gas exchange. Conversely, if the leak is small the tidal volumes may be excessive and cause over ventilation and lung damage. Observation of a continuous display of leak and V_T will help the operator to quickly recognise any mask leak and then adjust mask position to maintain stable tidal volumes throughout the resuscitation.

Failure to achieve a set PIP or PEEP with a T-piece resuscitation device may be due to a large face mask leak. The operator can alter the mask position to minimise the leak (see figure 3).

However, if a high gas flow is used (eg, 8 litres/min) PIP and PEEP may be delivered at close to the set value even with a substantial face mask leak and low delivered tidal volume (see figure 2).[9–12 14 15] Thus, achieving the pressures set on a pressure dial may falsely reassure the operator that satisfactory ventilation is being delivered.[14 16]

ENDOTRACHEAL INTUBATION
The same principles apply during ETT intubation. After the first inflation a RFM will show correct ETT placement by displaying gas flow in and out of the trachea (see figure 4A).[17] If the ETT is not in the trachea, the flow wave shows gas going down the ETT but not returning (see figure 4B).

Figure 3 Positive pressure ventilation with a face mask on a manikin: no leak. The inflation and expiratory flow curves return to the baseline, indicating sufficient t_I and t_E. The similar areas underneath the inflation and expiration flow curves mean an equal amount of gas entered and left the airways. The tidal volume curve shows the inspiratory and expiratory tidal volumes (V_{Ti} and the V_{Te}). It shows an equal volume of gas entering and leaving the lung and no leak. V_{Ti} has almost formed a plateau indicating that very little gas continues to enter the lung as inflation is continued.
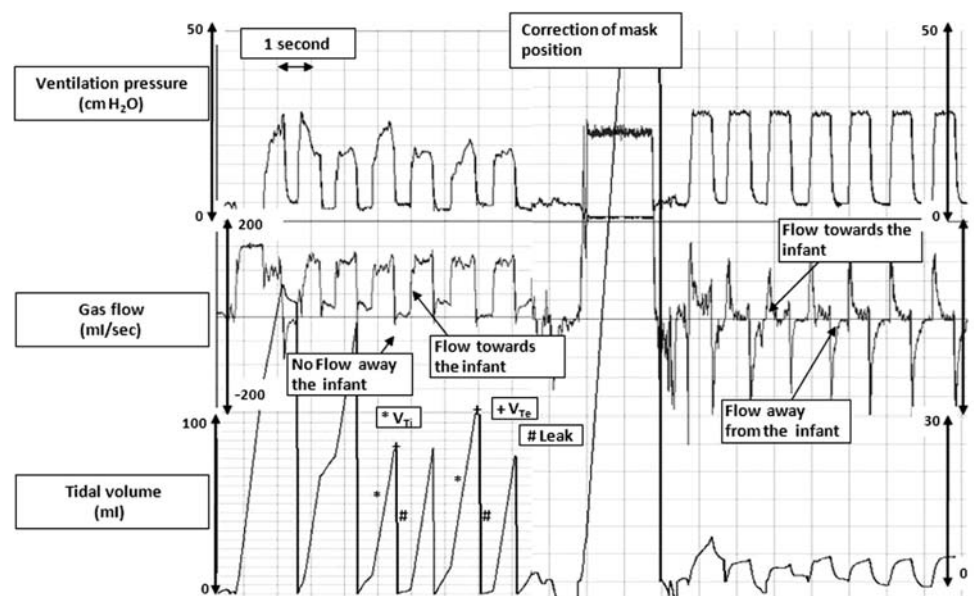
Figure 4 A. Correct endotracheal tube (ETT) placement in a 26-week infant. The inflation and expiratory flow curves return to baseline, indicating correct placement of an ETT. The areas underneath the inflation and expiration flow curves are very similar and show that an equal volume of gas entered and left the airways. The tidal volume (V_T) curve shows an equal volume of gas entering and leaving the lung and no leak. The pressure curve displays vary peak airway pressure and no positive end expiratory pressure during positive pressure ventilation. B. Oesophageal tube placement in a piglet. The inspiratory flow curve returns to baseline indicating gas flow towards the ETT. In contrast, there is no expiratory flow curve indicating ETT placement in the oesophagus. The V_T curve reflects the gas flow curve and displays 100% leak with no gas entering and leaving the lung.
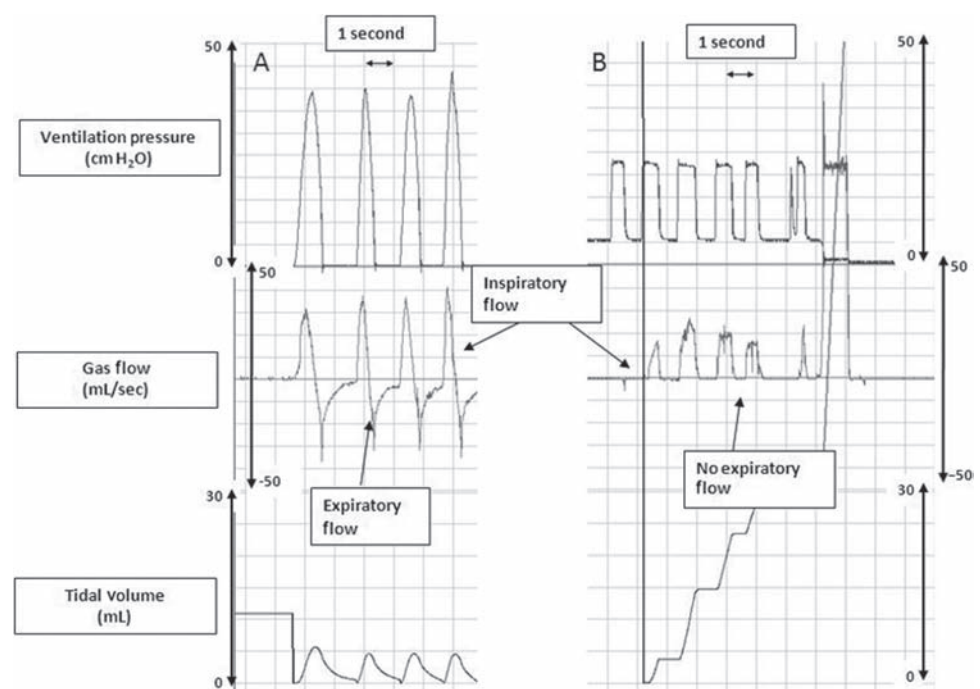
This is important because oesophageal intubation is quite common.[17–19] Without a RFM, or CO_2 detector, it may take several minutes to recognise that an inadequate response to ventilation is due to a misplaced ETT.[20] Although a CO_2 detector is now frequently used for assessing ETT placement,[2–5 21 22] it can take up to six inflations before a colour change indicating the presence of CO_2 occurs, whereas the flow signal from a RFM can be used from the first inflation.[2 23–25] If no colour change is seen with a CO_2 detector, it may be that although the ETT is correctly placed, the tidal volume is too low. This is not clear with a CO_2 detector but can be immediately seen with a RFM and the PIP increased until an appropriate tidal volume is achieved.

An ETT can easily become dislodged, this can be seen immediately as there is little or no expiratory flow and volume (see figure 5).

ETT SIZE

One reason for an unsatisfactory or failed resuscitation might be that insufficient gas enters the lung due to a large leak around the ETT.[12 26] A RFM displays the leak around the ETT. With an appropriate sized ETT any leak will be small (see figure 6B). Clinicians may use small diameter ETTs in the belief that these are easier to insert. Unfortunately, this can cause a large leak of the inflating volume around the ETT (see figure 6A) and may result in ineffective ventilation. The use of a RFM enables the operator to assess the degree of leak as soon as inflations are applied and decide whether the ETT size is appropriate or needs to be changed.

EVALUATING TIDAL VOLUMES

The purpose of applying PIP during PPV is to inflate the lungs with an appropriate V_T and thereby facilitate gas exchange.

Figure 5 Leak followed by dislodgement of endotracheal tube (ETT) in 27-week infant. The inspiratory flow curve returns to baseline indicating gas flow towards the ETT. In contrast, there is almost no expiratory flow curve indicating a large leak around the ETT, which is reflected in the tidal volume (V_T) curve displaying 100% leak. Suddenly, the ETT becomes dislodged. There is still some gas flow towards the ETT, but no expiratory gas flow. In addition, the V_T curve is not longer displayed. An attached PediCap failed to change colour. The ETT was removed and the infant was reintubated.
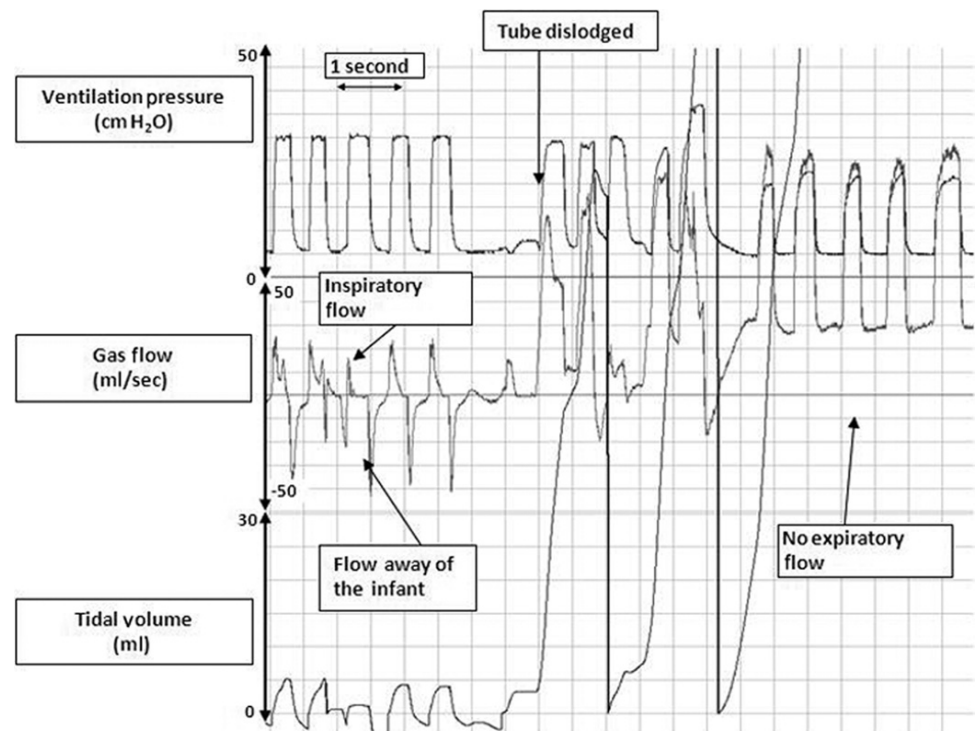
Figure 6 A. Leak at endotracheal tube (ETT) and correction after reintubation. Positive pressure ventilation after correct placement of a too small ETT resulting in a large leak and ineffective ventilation. The inspiratory and expiratory flow curve returns to baseline indicating gas flow towards and away the infants lungs. The areas underneath the expiration flow curves are smaller compared to the inflation flow curve indicating a leak around the ETT, which is reflected in the tidal volume (V_T) curve displaying 80% leak around the ETT. B. After reintubation with a larger ETT, the areas underneath the inflation and expiration flow curves are very similar meaning an equal amount of gas entered and left the airways. The V_T curve shows an equal volume of gas entering and leaving the lung and no leak.
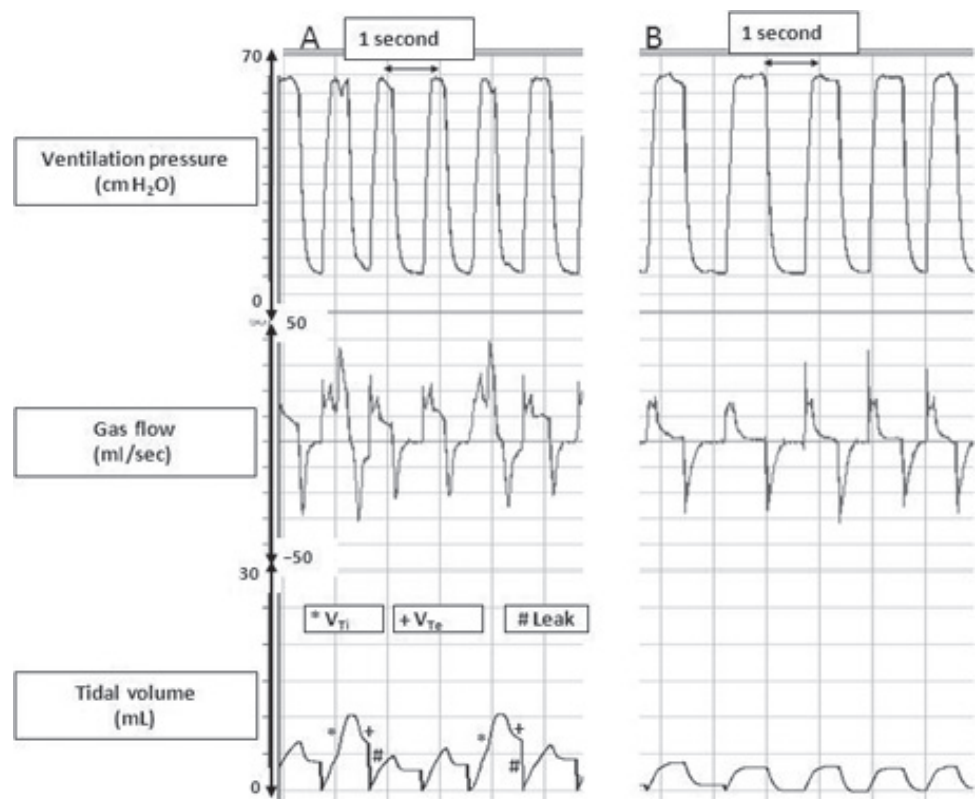
When a fixed pressure is used, the delivered V_T will be dependent on the size of the infant, any spontaneous breaths and whether they are synchronised with each inflation, compliance of the lungs and chest wall, airways resistance and mask leak.[27–30] This means that the use of a single set PIP is unlikely to be appropriate during the ventilation of any one infant at all times.

The appropriate V_T to be delivered during various phases of resuscitation is unknown. Studies of spontaneously breathing infants, animal studies and our own observations suggest the V_T during resuscitation should be within the range 4–8 ml/kg. Excessive V_T can over inflate the lungs and lead to volutrauma, whereas insufficient V_T can lead to inadequate gas exchange.[31–36] A RFM enables the resuscitator to see a graphical and numerical output of the V_{Te} and adjust the PIP to ensure an appropriate V_T is delivered (see figure 7B). Resuscitators may not be able to judge the tidal volume by observing chest wall rise. Figure 7A was a recording made of a resuscitation where the operator was blinded to the display of the RFM.[51] During
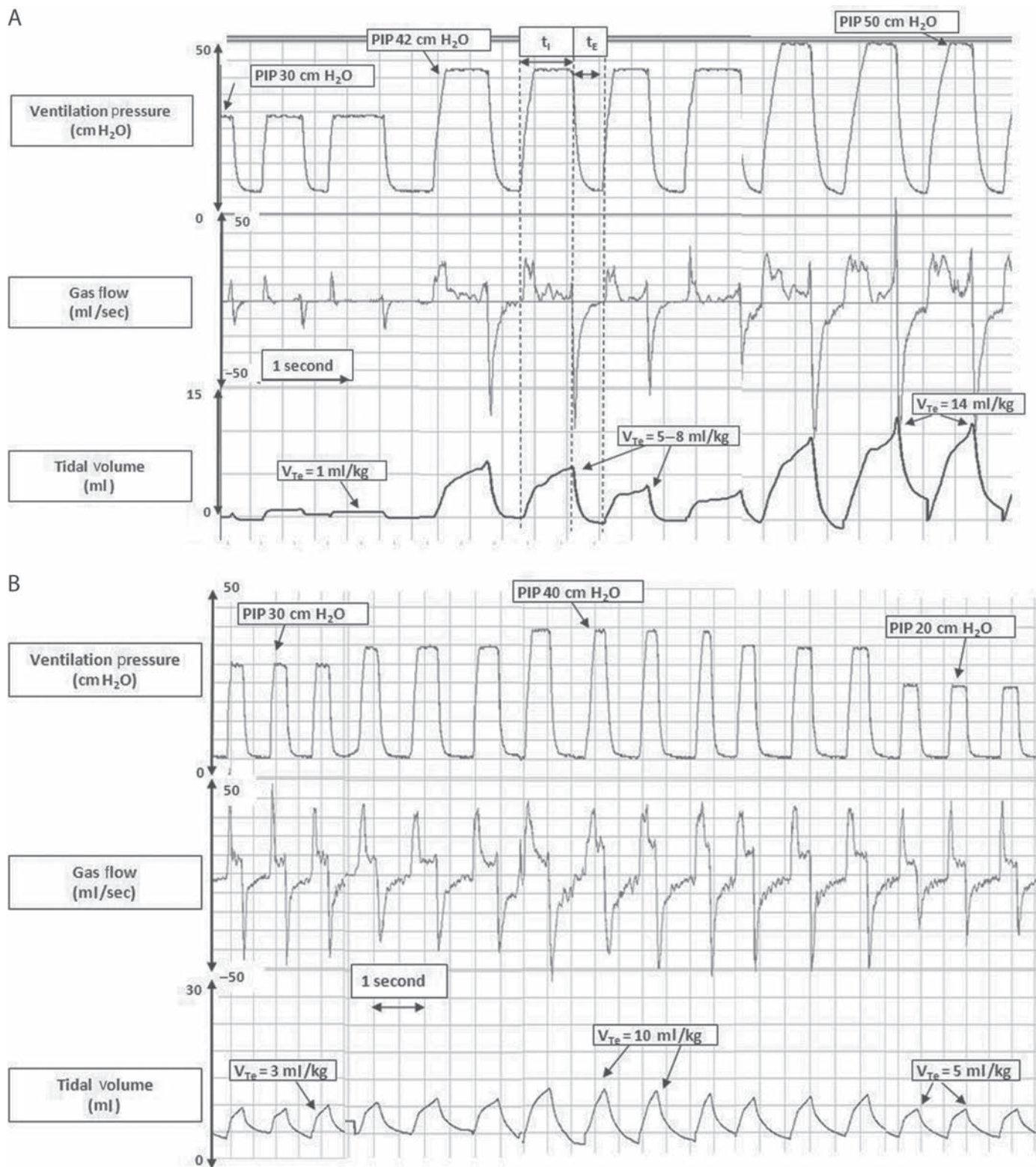
Figure 7 A. Expiratory tidal volume (V_{Te}) variations during positive pressure ventilation (PPV) in 25-week infant. Initially, the inflation and expiratory flow curves are small, and the measured V_{Te} is approximately 1 ml/kg. An increase in peak airway pressure (PIP) to 42 cm H_2O showed an increase in V_{Te} to 5–8 ml/kg. A further increase to a PIP of 50 cm H_2O PIP resulted in an increase of V_{Te} to 14 ml/kg. B. V_{Te} variations during PPV in 27-week infant. Initially, the V_{Te} was 3 ml/kg. After an increase in PIP the delivered V_{Te} increased to 10 ml/kg. A continued reduction of PIP to 20 cm H_2O showed a decrease in the delivered V_{Te} to about 5 ml/kg.

PPV the PIP was increased to improve chest movements but this resulted in excessive tidal volumes.

If there is little or no V_T displayed on the RFM during an inflation, then either the PIP is too low to expand poorly compliant lungs or the airway is obstructed (see figure 8). Initially, the clinical response to a very low V_T should be to increase the PIP until an appropriate V_T is displayed on the RFM. High inflating pressures will not injure the lungs if the V_T delivered is

Figure 8 Complete airway occlusion during facemask positive pressure ventilation (PPV) in an extremely low birthweight (ELBW) infant. The peak airway pressure and positive end expiratory pressure are maintained during PPV, but the inflation and expiratory flow curves display almost no flow movements. This is reflected in the tidal volume (V_T) curve, which displays no tidal volume.
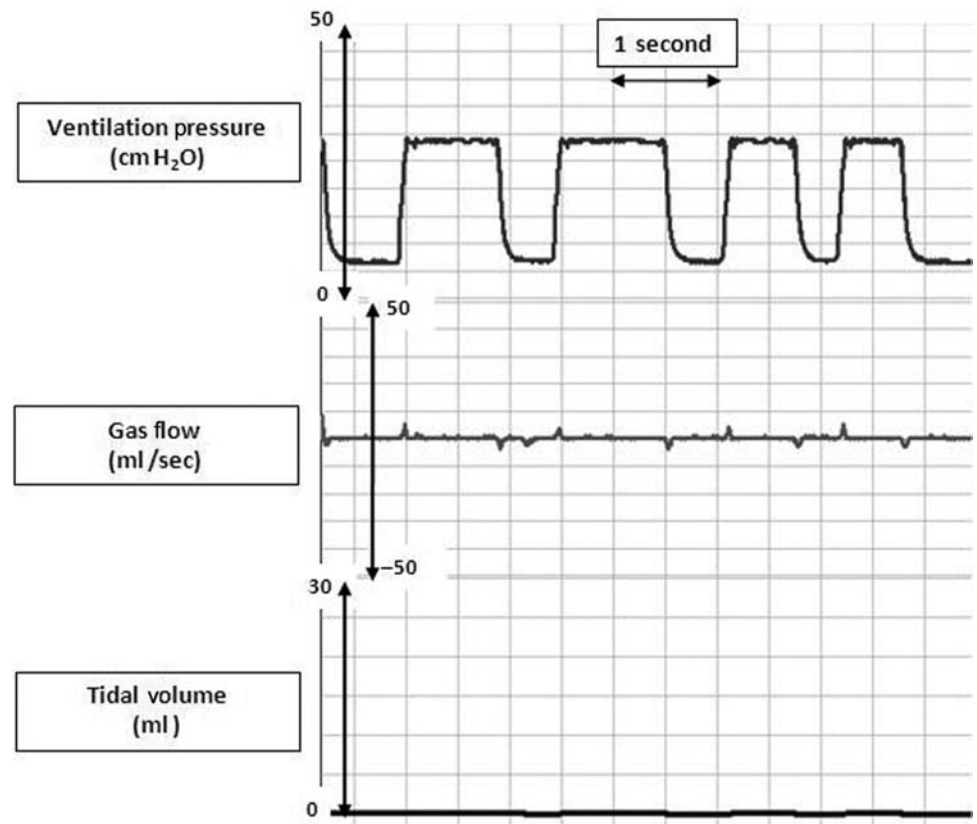
Figure 9 Insufficient inflation and expiration time in an extremely low birthweight (ELBW) infant. The inflation and expiratory flow curves do not return to baseline before changing direction, indicating insufficient inflation and expiration time. The inflation flow is continuing this means gas is still entering the lung. If expiratory flow is continuing this means gas is still leaving the lung. If the next inflation starts before expiratory flow has stopped gas trapping will occur.

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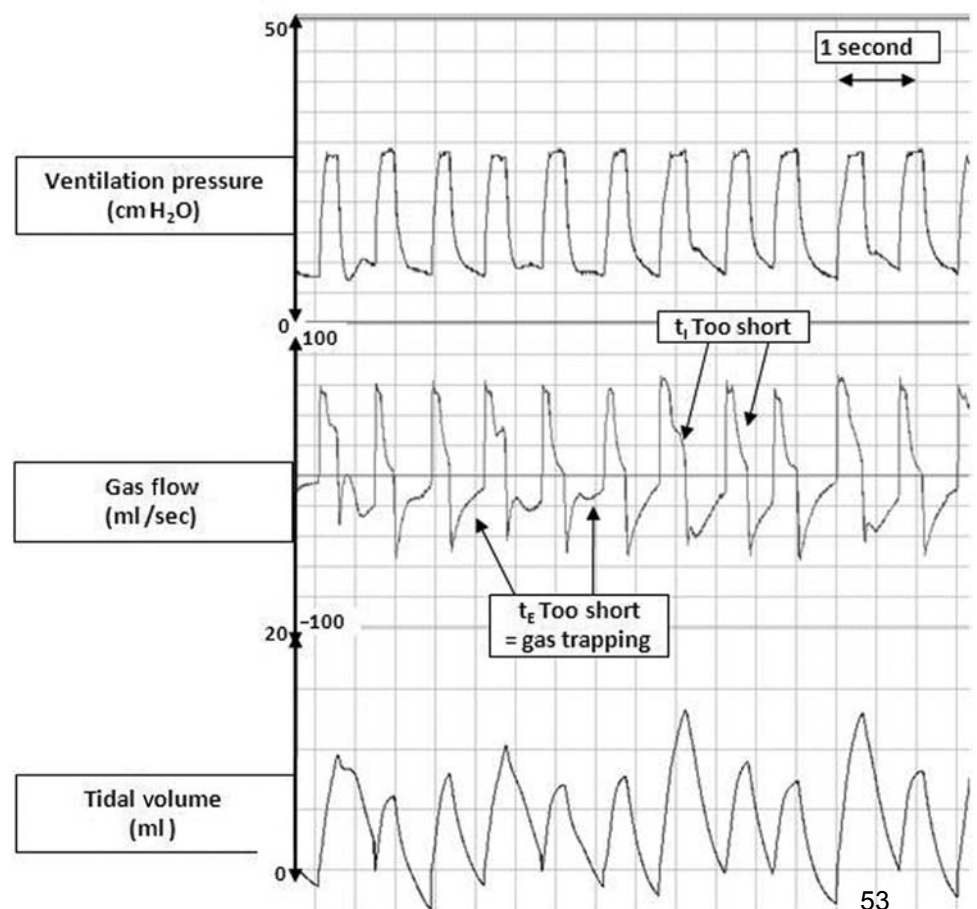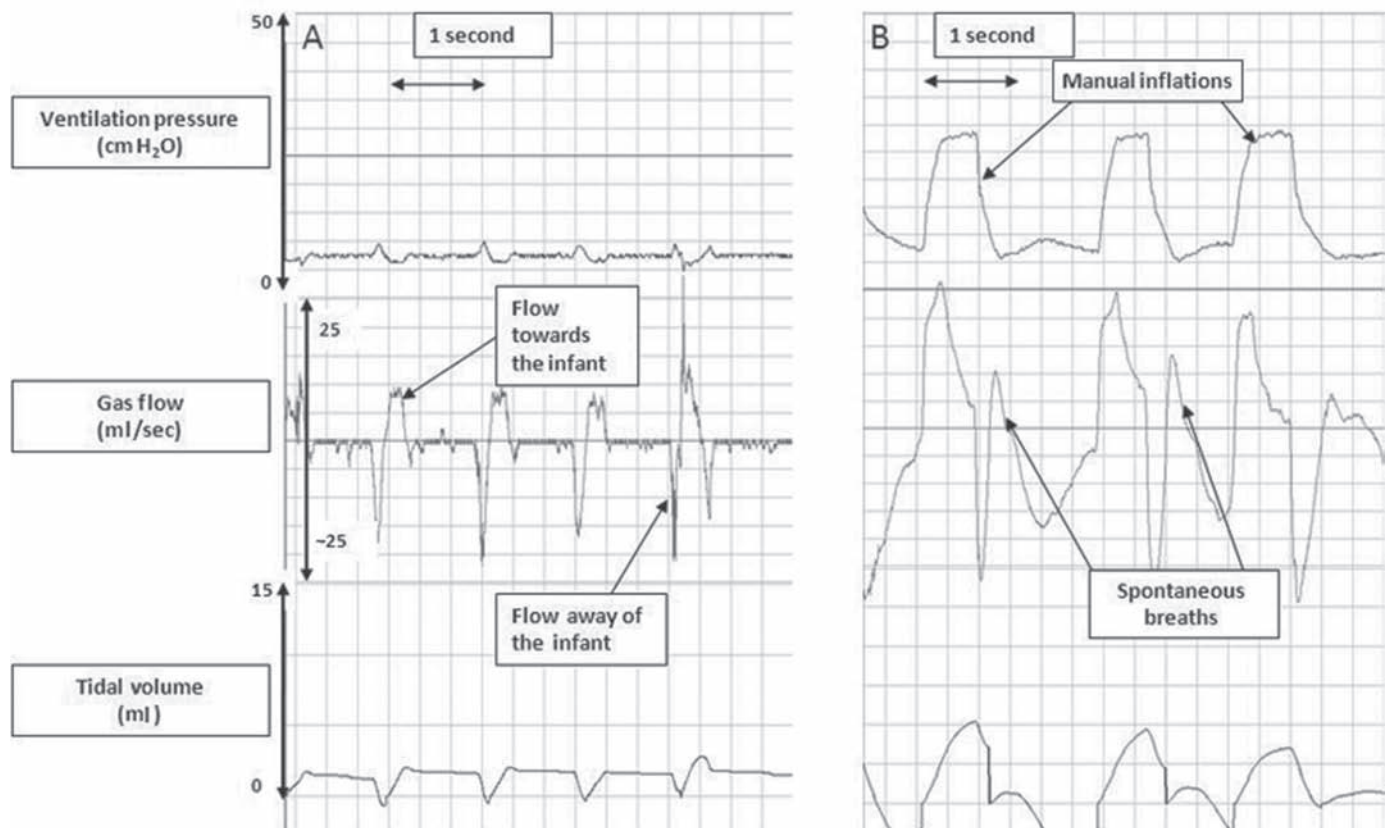
Figure 10 A. A spontaneously breathing infant. Expiratory breath hold in a spontaneous breathing infant with continuous positive airway pressure (CPAP) support of 5 cm H_2O. After inspiration, the infant holds his breath for about a second before expiration occurs. The gas flow pattern is reflected in the tidal volume (V_T) curve. The pressure curve shows the CPAP of 5 cm H_2O with small pressure drops during inspiration. B. Asynchrony between an infant's breaths and manual inflations in a preterm infant. The manual inflations are immediately followed by spontaneous breaths from the infant, which are displayed as a second inspiratory and expiratory gas flow curve. The operator is unable to synchronise his manual inflations with the infant's spontaneous breathing. The positive pressure ventilation and spontaneous breaths are out of synchrony and the infant is fighting against these inflations.

monitored and maintained in the appropriate range.[37] [38] It is not uncommon for an apnoeic infant, or one with hypoplastic lungs, to require a high PIP initially to aerate the lungs. Once the lungs have aerated the PIP may need to be reduced rapidly (see figure 7B). The appropriate PIP will vary between infants and in the same infant over time and can be gauged by using a RFM to display the tidal volumes.[28] [29] [39]

AIRWAY OBSTRUCTION

If there is little or no increase in a very low V_T in response to increased PIP then the resuscitator should consider obstruction to the airway.[40] Obstruction can be due to poor mask technique and can occur in two places. In our experience, the commonest cause is the resuscitator applying mask to the face too tightly and obstructing the nose and mouth. This can be identified and corrected by releasing the mask a little and observing the gas flow and V_T signals. Second, the neck may be hyperflexed and the airway becomes obstructed. This can be diagnosed by observing the flow and V_T signals as the head is repositioned. Rarely, obstruction may be due to a congenital abnormality of the airways (see figure 8).

VENTILATION RATE

Many clinicians are unaware of their ventilation rate during PPV because it is not measured and displayed (see figure 9).

High ventilation rates can lead to inappropriately short inflation time (t_I) and expiration time (t_E) with the risk of either inadequate V_T delivery at a given PIP or air trapping. A high rate and satisfactory tidal volume will rapidly cause over ventilation and hypocarbia. A RFM enables the resuscitator to see their ventilation rate and adjust as necessary.

INFLATION TIME

The flow and V_T waves can be used to assess t_I and t_E during PPV. The t_I should be long enough to allow an appropriate V_T to be delivered (see figure 1). Sharply spiked V_T waves indicate gas is still rapidly entering the lungs when the inflation is stopped and therefore the t_I is too short for that PIP (see figure 9). If the operator delivers an inconsistent t_I, the V_T will vary. This may lead to either under ventilation (reduced V_T) or too large a tidal volume and volutrauma.

If the t_I is too long there will be no increase in V_T towards the end of inflation. Using a RFM enables the resuscitator to see what is happening to the V_T and adjust the inflation time.[41] [42]

EXPIRATORY TIME

The expiratory flow wave should return to zero before the next inflation starts (see figure 1). If the t_E is too short and the next inflation starts before expiratory flow has stopped, gas trapping will occur (see figure 9).

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Review

OBSERVING SPONTANEOUS BREATHING

At some point during resuscitation most infants will start breathing.[42][43] A RFM attached to a face mask or ETT shows an infant's spontaneous V_T, breathing patterns and interaction with any manual inflations (see figure 10A).[42][43] To assess an infant's own breathing patterns the mask is applied to the face with a good seal, inflations are stopped and the flow and V_T signal observed. Within a few seconds the infant's spontaneous respiratory rate and V_T will be displayed. If the infant is breathing regularly and generating adequate tidal volumes, assisted ventilation may be stopped and the infant managed either with no assistance or mask CPAP. During PPV a RFM shows whether infants are breathing synchronously or asynchronously with manual inflations. Infants often have their own respiratory rate and inspiratory and expiratory patterns regardless of any inflations.[42] A RFM often shows an infant breathing out of phase with the inflations (see figure 10B), which can lead to inefficient PPV. A trial of mask CPAP, as described earlier, may be appropriate.

POSSIBLE PROBLEMS FROM USING A RESPIRATION FUNCTION MONITOR

Inexperience and lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals. Therefore anyone using a RFM must be trained to interpret pressure, flow and tidal volume signals. In addition, the attention of an inexperienced user may be diverted from the baby to the monitor screen. With this device, the displayed V_{Te} must be converted to ml/kg (eg, a displayed V_{Te} of 5 ml/kg for a 500 g infant will be V_{Te} of 10 ml/kg). For people unfamiliar with the device they may find that placement of a flow sensor between the mask and resuscitation device makes holding the device a little awkward.

LIMITATION OF A RESPIRATION FUNCTION MONITOR

With this device, the numerical value for leak is averaged over 1 min and so cannot be used for individual inflations. A RFM only displays the waves and data to aid the resuscitator and does not provide interpretation of the signals or a diagnosis. For example, a signal showing absent V_T may be due to malposition of the face mask, obstruction of the airways or a congenital abnormality.

CONCLUSIONS AND FUTURE DIRECTIONS

We have presented observations and recordings from manikin studies and DR resuscitations that show how a RFM can aid training and resuscitations by adding objectivity to the assessment. A RFM can be used during manikin-based training to teach correct mask hold and positioning techniques. We have shown examples demonstrating its usefulness during resuscitations. However, more studies are needed to investigate whether during resuscitations information displayed by a RFM can: (1) improve mask hold and positioning techniques to diminish leak and obstruction; (2) reduce the need for endotracheal intubation; (3) reduce the incidence of hypocarbia and hypercarbia on admission to the NICU; (4) reduce the incidence of acute lung injury including air leaks; (5) reduce the incidence of bronchopulmonary dysplasia; and (6) reduce the incidence of death and neurodevelopmental disability.

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Chapter V

Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter V "Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room"

Declaration by candidate

In the case of Chapter V the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, ethics application, data collection, data analysis, writing and revising the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Kamlin COF	Help with data collection, revising the manuscript	
O'Donnell CPF	Revising the manuscript	
Dawson JA	Help with data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature	██████████	Date 20/7/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
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Signature 3	████████████	20/7/10
Signature 4	████████████	18.7.10
Signature 5	███████████	20.7.10

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter V "Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room"

Declaration by candidate

In the case of Chapter V the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, ethics application, data collection, data analysis, writing and revising the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Kamlin COF	Help with data collection, revising the manuscript	
O'Donnell CPF	Revising the manuscript	
Dawson JA	Help with data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature		Date	

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

60

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Signature 1	
Signature 2	07.07-2010
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5.2 INTRODUCTION

Approximately 5% of all newborn infants require some form of resuscitation at birth. An internationally agreed consensus statement and various guidelines advise how newborn infants should be resuscitated and suggest equipment to use. They all agree that the key to successful neonatal resuscitation is adequate positive pressure ventilation (PPV).

The object of PPV is to deliver an adequate tidal volume to achieve gas exchange. However, PPV is conventionally pressure limited and the delivered tidal volume is rarely measured and therefore airway pressure is not adjusted to optimise the delivered tidal volume.

The assessment of adequate tidal volume delivery during PPV is based on an increase in heart rate, assessed every 30 seconds. However, if heart rate does not increase chest wall movements should be assessed to gauge ventilation. In this chapter I will compare the clinical assessment of chest wall movements with the measured tidal volume during PPV in the delivery room.

5.3 Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room

The following chapter has been published in Archives of Disease in Childhood Fetal & Neonatal Edition thus it is presented in PDF as per Monash University guidelines for thesis by publication.

Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room

Georg M Schmölzer, Omar C O F Kamlin, Colm P F O'Donnell, et al.

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Original article

Assessment of tidal volume and gas leak during mask ventilation of preterm infants in the delivery room

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Accepted 8 February 2010

ABSTRACT

Aim The aim was to compare resuscitators' estimates of tidal volume (V_T) and face mask leak with measured values during positive pressure ventilation (PPV) of newborn infants in the delivery room.

Patients and methods The authors measured inflating pressures and V_T delivered using a respiratory function monitor, and calculated face mask leak. After 60 s of PPV, resuscitators were asked to estimate V_T and face mask leak. These estimates were compared with measurements taken during the previous 30 s.

Results The authors studied 20 infants who received a mean (SD) of 21 (6) inflations during the 30 s. The median (IQR) expired tidal volume (V_{Te}) delivered was 8.7 ml/kg (5.3–11.3). V_{Te} varied widely during each resuscitation and between resuscitators. Five resuscitators could not estimate V_{Te}, one overestimated and 14 underestimated their median delivered V_{Te}. The median (IQR) face mask leak was 29% (16–63%). Leak also varied widely during each resuscitation and between resuscitators. One resuscitator could not estimate mask leak, four overestimated leak and 15 underestimated leak.

Conclusion During face mask ventilation in the delivery room, V_T and face mask leak were large and variable. The resuscitators were unable to accurately assess their face mask leak or delivered V_T.

What is already known on this topic

► Assessment of mask ventilation relies on a clinical impression of 'adequate chest rise' and increased heart rate.
► In manikin studies resuscitators had large and unrecognised leaks around the face mask during positive pressure ventilation.
► Lung injury can occur if tidal volumes are greater than 8 ml/kg.

What this study adds

► Assessment of face mask leak and delivered VT is inaccurate.
► Face mask leak varies between resuscitators and between inflations, while delivered VTs also vary considerably and bear little relationship to peak inflation pressure.
► A respiratory function monitor might help improve face mask leak detection and optimise VT delivery.

INTRODUCTION

Approximately 3–6% of all newborn infants receive some form of respiratory support at birth.[1] Positive pressure ventilation (PPV) is commonly used in the delivery room and is a cornerstone of respiratory support after birth.[2,3] An international consensus statement recommends that infants with inadequate breathing or bradycardia be given PPV via a face mask with a self-inflating bag, flow-inflating bag or T-piece device.[4,5] The purpose of PPV is to establish a functional residual capacity and deliver an appropriate tidal volume (V_T) to achieve effective gas exchange.[6] Adequacy of ventilation is then judged by assessing the heart rate.[4,5] However, if the heart rate does not increase, chest wall movements should be assessed to gauge adequacy of ventilation.[4,5] The resuscitator judges the delivered V_T by observing chest wall movements during PPV.[4,5] The V_Ts are not routinely measured.

A human observational study reported a mean V_T of 6.5 ml/kg in spontaneous breathing preterm infants in the first minutes of life.[7] When assisted ventilation is required, a peak inflating pressure (PIP) is chosen with the assumption that this will deliver an appropriate V_T.[4,5] However, lung compliance and

therefore the PIP required to deliver an appropriate V_T vary in the minutes after birth.[8,9] It is likely that there are even greater differences between infants as the mechanical properties of the lung vary with gestational age and disease states.[6] In addition, many infants breathe during PPV adding to the inconsistency of V_T delivered with a set PIP.[10,11] Therefore, relying on a fixed PIP and subjective assessment of chest wall movement may result in either under- or over-ventilation.[10,12] Animal studies have shown that PPV with V_T >8 ml/kg or inflations with large V_Ts can damage the lungs.[13–16]

Face mask seal is an important determinant of successful PPV. Manikin studies have shown that resuscitators were unaware of large and variable leaks between the face and mask during PPV.[17–19] Large leaks may lead to inadequate V_Ts during PPV in the delivery room and may result in ineffective ventilation.

We hypothesised that resuscitators are unable to accurately assess the delivered V_T and face mask leak during PPV. The aims of this study were as follows: (1) to measure V_T and face mask leak

during PPV in the delivery room and (2) to compare these measurements with resuscitators' estimates of these parameters.

PATIENTS AND METHODS

We conducted this observational study at The Royal Women's Hospital, Melbourne, Australia, a tertiary perinatal centre where approximately 6000 infants are delivered and more than 100 infants <1000 g birth weight are admitted to the neonatal intensive care unit annually. Infants were enrolled from February 2008 to November 2008. This study was approved by The Royal Women's Hospital Research and Ethics Committees and written parental consent was obtained.

Infants of <32 weeks' gestation were eligible for this study if the clinicians judged they had inadequate breathing immediately after birth and so provided face mask PPV. Infants with a congenital abnormality or whose parents did not consent were excluded. When the research team were available they attended deliveries to make recordings. The research team did not participate in the clinical care of the infant.

Face masks

All infants received PPV via a round silicone size 00 face mask (Laerdal, Stavanger, Norway).

Ventilation devices

Infants received mask PPV with either a T-piece device (Neopuff Infant Resuscitator; Fisher & Paykel Healthcare, Auckland, New Zealand) or a self-inflating bag (Laerdal). Both devices are commonly used in our hospital. The T-piece is a continuous flow, pressure-limited device with a built-in manometer and a positive end expiratory pressure (PEEP) valve. The default settings used were a gas flow of 8 l/min, PIP of 30 cm H_2O and PEEP of 5 cm H_2O. The 240 ml silicone self-inflating bag was used with an 8 l/min gas flow and without a manometer or a PEEP valve.

Respiratory function monitor

A Florian respiratory function monitor (RFM) (Acutronic Medical Systems, Zug, Switzerland) was used to measure inflating pressures and gas flow. The monitor measured pressure directly from the circuit and measured gas flow with a hot wire anemometer flow sensor. The flow sensor was placed between the ventilation device and the face mask. The monitor automatically calculates the V_T passing through the sensor by integrating the flow signal.

Data acquisition and analysis

The gas flow, V_Ts and airway pressure data measured with the RFM were recorded at 200 Hz using a laptop computer with Spectra software (Grove Medical, London, UK), a program specifically designed for recording physiological data. In the delivery room, neither the RFM nor the computer screen were visible to the resuscitators and the monitor's alarm was disabled.

We examined every inflation given to each infant and calculated the leak from the mask by expressing the volume of gas that did not return through the flow sensor during expiration as a percentage of the volume that passed through the flow sensor during inflation[19]:

$$\text{Leak (\%)} = \frac{\text{Inspiratory tidal volume} - \text{expiratory tidal volume}}{\text{Inspiratory tidal volume}} \times 100$$

Resuscitators' assessment of VT and leak

If PPV was performed for at least 60 s the resuscitator was asked four questions while they continued PPV:

1. Do you think you have a leak around the face mask?
2. If yes, estimate the percentage of your leak.
3. How well do you think the chest is moving? ('appropriately', 'too low', 'too much', 'not at all', 'not sure').
4. Estimate the V_T you are delivering in ml/kg.

All answers could include: 'don't know', 'cannot do it' or 'not sure'.

Questions were asked when the resuscitator was comfortable with the progress of the resuscitation. Resuscitators were given the opportunity to decline to participate in the study but all were willing to contribute. All resuscitators had received neonatal resuscitation training prior to participation in this study and were familiar with both ventilation devices

Statistical analysis

The waveforms of pressure, flow and V_T were analysed and the V_T and mask leak for each inflation were measured for the 30 s prior to the questioning. The face mask leak was retrospectively corrected for body temperature, pressure and water vapour saturation.[20] The mean/median values obtained were compared to the estimates of the resuscitator. Results are presented as mean (SD) for normally distributed continuous variables and median (IQR) for variables with a skewed distribution. Data were analysed using STATA v 10 (STATA, College Station, Texas, USA).

RESULTS

A total of 163 eligible infants were born between February and November 2008. A delay in registering recording equipment after relocation of the hospital meant that 69 infants were not studied. The research team was not notified of the impending delivery of 35 infants. A further 34 did not receive PPV. We therefore recorded 25 infants who received PPV in the delivery room. The recording was of poor quality in five cases. The characteristics of the remaining 20 infants are presented in table 1. Fifteen infants were ventilated with a T-piece and five with a self-inflating bag.

A total of 419 inflations were analysed, with a mean (SD) of 21 (6) inflations per infant during 30 s. PPV was started at a median (IQR) of 91 (44–122) s after birth. The need for PPV was determined by the resuscitator. The median (range) level of neonatal resuscitation experience was 31 (4–144) months. After answering the questions the resuscitator was told the current expired tidal volume (V_{Te}) and face mask leak.

PIP and PEEP

Mean (SD) PIP was 26.3 (8.8) cm H_2O. The mean (SD) PEEPs with the Neopuff and Laerdal self-inflating bag were 4.0 (2.9) cm H_2O and 0.6 (0.3) cm H_2O, respectively.

Table 1 Infant characteristics (N=20)

Gestational age (weeks)*	27 (1)
Birth weight (g)*	841 (276)
Male	6 (30%)
Antenatal steroids	17 (85%)
Caesarean section	14 (70%)
Apgar score at 1 min†	5 (2–6)
Apgar score at 5 min†	6 (5–7)

Values are numbers (percentage) unless indicated: *mean (SD), †median (IQR).
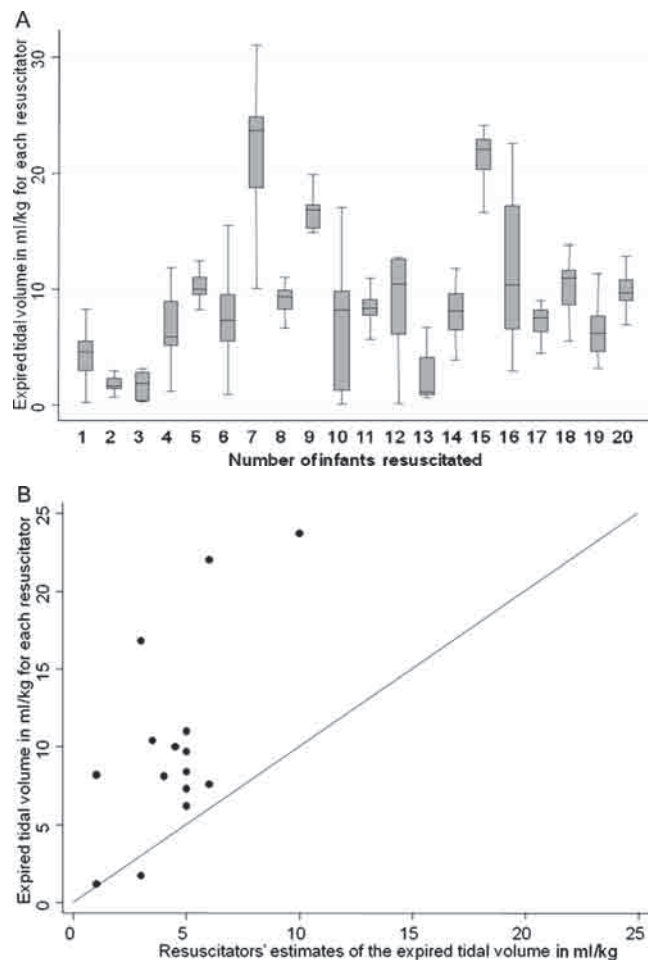
Figure 1 (A) Expired tidal volume (V_{Te}) in ml/kg for each infant. Box plots show median (solid bar), IQR (margins of the box) and 95% CI. (B) Comparison of the median V_{Te} in ml/kg with the resuscitators' estimates.

Figure 2 (A) Face mask leak as a percentage of the inspired tidal volume for each infant. Box plots show median (solid bar), IQR (margins of the box) and 95% CI. (B) Comparison of the median face mask leak with the resuscitators' estimates.

Expiratory VT

The median (IQR) expiratory V_T (V_{Te}) was 8.7 (5.3–11.3) ml/kg. The V_T varied widely between inflations and resuscitators (figure 1A). Five resuscitators could not estimate the V_T, one overestimated and the remaining 14 underestimated the median V_T they delivered (figure 1B).

Face mask leak

The median (IQR) face mask leak, as a percentage of the inspired V_T, was 29% (16–63%) (figure 2A). The face mask leak varied widely between inflations and resuscitators. One resuscitator could not estimate the leak, one correctly estimated the leak and four overestimated the leak, while the remaining 14 underestimated it (figure 2B).

Correlation between peak pressure and expired VT

There was only a weak relationship between each PIP and V_T. For example at a PIP of approximately 30 cm H_2O, the V_{Te} ranged from 0 to 30 ml/kg (figure 3).

Judgement of chest wall movements

Comparison between resuscitators' judgement of chest rise and delivered V_{Te} showed a median (IQR) delivered V_{Te} for 'appropriate' chest rise of 9.6 (7.1–12.9) ml/kg, 'too low' of

Figure 3 Comparison of delivered expired tidal volume in ml/kg and peak inflation pressure in cm H_2O.

2.4 (1.5–7.6) ml/kg, 'not at all' of 8.3 (1.3–9.9) ml/kg and 'not sure' of 8.6 (7.6–10.5) ml/kg. Resuscitators who judged chest rise as 'too low' more accurately assessed the chest rise (figure 4).

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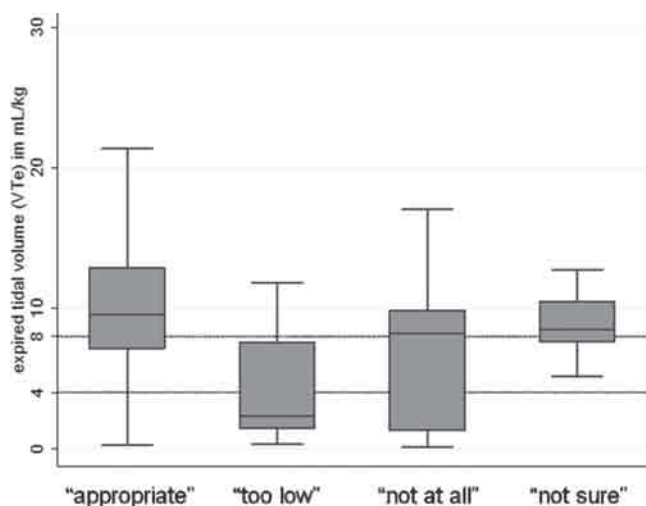
Figure 4 Comparison of expired tidal volume with the operator estimates of chest rise. The horizontal lines show the range of V_{Te} which would provide reasonable ventilation. The y axis represents V_{Te} in ml/kg and the x axis operator estimates of chest rise. The box plots show median values (solid bar), IQR (margins of box) and 95% CI.

DISCUSSION

Resuscitation of an infant born at <32 weeks' gestation is an emotional and stressful event, even for experienced neonatologists. Decisions have to be made quickly and resuscitators have to be skilled in clinical assessment and resuscitation. However, observational studies have shown the clinical assessment of colour and heart rate is unrealiable.[21 22] The accuracy of clinical assessment of adequacy of ventilation (ie, chest rise) is unknown.

To our knowledge this is the first study which compares clinical assessments with measurements of pressure, V_T and face mask leak in newly born infants during PPV in the delivery room. We found resuscitators delivered highly variable V_Ts with both ventilation devices, from almost 0 to 31 ml/kg. In our study the median delivered V_{Te} was 8.7 ml/kg. V_Ts of this order or above might be excessive and cause lung damage.[13–16] The assessment of chest rise by the resuscitator was an unreliable estimate of V_{Te}.

We found airway pressure was a poor proxy for the delivered V_{Te}. Often the desired PIP was not achieved because of large leaks. This has also has been shown in manikin studies.[19] Clinicians should not assume that effective ventilation is occurring when the desired pressures are achieved.[23–26] Measurement of V_{Te} during PPV may be more useful than relying on an inflating pressure or clinical judgment to ensure that over- or under-ventilation is not occurring.[18]

Face mask leak is both a common and an unrecognised problem during PPV which can lead to failure of ventilation.[17 24 26] We found that face mask leak varied widely from almost 0 to 100%. In addition, resuscitators were unable to accurately self-assess their leak. These findings are consistent with those of manikin studies during PPV.[17 24] In manikin studies, a RFM allowed resuscitators to adjust the face mask position during PPV and reduce leak by more than half.[18]

We speculate that face mask leak during PPV might be beneficial and if there was no leak the V_{Te} might have been even higher. The problem, as we have shown, is that the V_T varies and is unknown. A display showing PIP and V_T allows the resuscitator to alter face mask position to diminish face mask leak and also adjust the PIP to optimise V_T delivery.

This study has several limitations. Although the number of enrolled infants was small, we found a wide variation in V_{Te} and leak during PPV. One could argue that a median of 31 months' resuscitation experience caused this wide variation. However, in manikin studies operators had wide variations in V_{Te} delivery and face mask leak regardless of training.[17 25]

CONCLUSION

During mask ventilation in the delivery room, leak and V_T are very variable and correlated weakly with the PIP. On average the V_Ts were high at 8.7 ml/kg and in a range that might injure the lungs.

The measured face mask leak and delivered V_T correlated poorly with the estimated values of each operator. Resuscitators were unable to accurately assess their face mask leak or V_T.

Using a respiratory monitor in the delivery room to continuously measure and display face mask leak and V_T might improve the effectiveness of neonatal resuscitation.
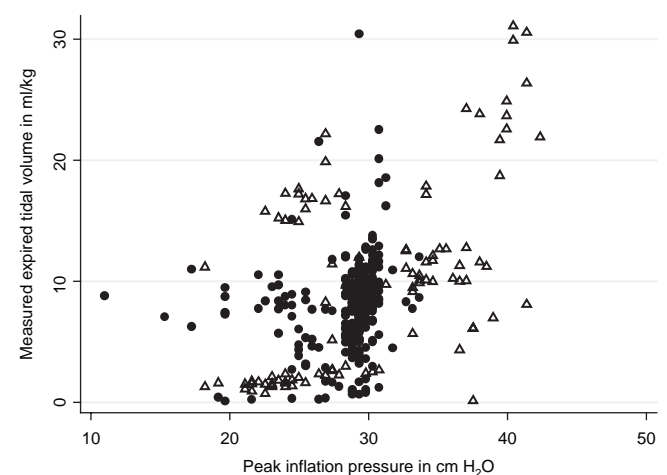
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Chapter VI

Assessment of chest rise during positive pressure ventilation in the delivery room

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter VI "Assessment of chest rise during positive pressure ventilation in the delivery room"

Declaration by candidate

In the case of Chapter VI the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, ethics application, data collection, data analysis, writing and revising the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Poulton DA	Data collection, data analysis, writing the 1st draft of the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature		Date
	███████████	20/1/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Date
Signature 1	
Signature 2	18.7.10
Signature 3	20.7.10

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter VI "Assessment of chest rise during positive pressure ventilation in the delivery room"

Declaration by candidate

In the case of Chapter VI the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, ethics application, data collection, data analysis, writing and revising the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Poulton DA	Data collection, data analysis, writing the 1st draft of the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature		Date

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
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Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	████████	
		21 / 7 /10
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Signature 3		

6.2 INTRODUCTION

Approximately 5% of all newborn infants require respiratory assistance at birth. The International Liaison Committee on Resuscitation recommends positive pressure ventilation (PPV) if infants fail to initiate spontaneous breathing. The purpose of PPV is to establish and maintain a functional residual capacity, deliver an appropriate tidal volume and facilitate gas exchange. Adequacy of gas exchange is judged by an increase in heart rate. However, if the heart rate does not increase, chest wall movements should be assessed. The current neonatal resuscitation guidelines do not describe how chest wall movement during PPV should be assessed. In *Chapter V*, I compared the clinical assessment of resuscitators standing at the infant's head with tidal volume measurements. I demonstrated that resuscitators standing at the infant's head were unable to accurately assess chest wall movements during PPV. However, someone could argue that assessing chest rise during PPV whilst standing at the infant's head might be difficult mainly because the ventilation device partly obstructs the resuscitators view or the resuscitator is focused on mask ventilation. In this Chapter, I used a questionnaire to compare the assessment of tidal volume delivery form junior medical staff positioned at the infants head with the assessment form senior medical staff at the infants' side. This might provide a more accurate assessment of tidal volume during mask PPV.

6.3 Assessment of chest rise during positive pressure ventilation in the delivery room

The following chapter has been accepted in Resuscitation but is not yet published; the proof for publication is presented in PDF as per Monash University guidelines for thesis by publication.

Assessment of chest rise during mask ventilation of preterm infants in the delivery room

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Conflict of interest: None;

No reprints requested

Keywords: Positive Pressure Ventilation, Delivery room, Respiratory Function Monitor, Preterm infants, Neonatal Resuscitation, Chest wall movements

Abstract

Background

Current neonatal resuscitation guidelines recommend using visual assessment of chest wall movements to guide the choice of inflating pressure during positive pressure ventilation (PPV) in the delivery room. The accuracy of this assessment has not been tested. We compared the assessment of chest rise made by observers standing at the infants' head and at the infants' side with measurements of tidal volume.

Methods

Airway pressures and expiratory tidal volume (V_{Te}) were measured during neonatal resuscitation using a respiratory function monitor. After 60 seconds of PPV, resuscitators standing at the infants' head (head view) and at the side of the infant (side view) were asked to assess chest rise and estimate V_{Te}. These estimates were compared with V_{Te} measurements taken during the previous 30 seconds.

Result

We studied 20 infants who received a mean (SD) of 23 (4) inflations during the 30 sec. Some observer felt unable to assess chest rise both from the head view (6/20) and from the side view (3/20). Observers from both head and side tended to underestimate tidal volume by 3.5 mL and 3.3 mL respectively. Agreement between clinical assessment and measured V_{Te} was generally poor.

Conclusion

During mask ventilation, resuscitators were unable to accurately assess chest wall movement visually from either head or side view.

Abbreviations

PPV   - Positive pressure ventilation

V_T - Tidal volume

NICU   - Neonatal intensive care unit

PEEP   - Positive end expiratory pressure

V_{Te} - Expiratory tidal volume

Introduction

If preterm infants fail to initiate spontaneous breathing immediately after birth positive pressure ventilation (PPV) should be given(1). The purpose of PPV is to establish and maintain a functional residual capacity, deliver an appropriate tidal volume (V_T) and facilitate gas exchange(2;3). Adequacy of gas exchange is judged by an increase in heart rate(1;4). However, if the heart rate does not increase, chest wall movements should be assessed(1).

The current neonatal resuscitation guidelines do not describe how chest wall movement during PPV should be assessed(1). We recently reported that resuscitators standing at the infant's head were unable to accurately assess chest wall movements during PPV(5).

Assessing chest wall movement during PPV whilst standing at the infant's head might be difficult. The ventilation device partly obstructs the resuscitators view and the resuscitator is focused on ventilation. Assessment by an observer standing on the side of the infant and not providing assisted ventilation may overcome these difficulties.

We hypothesised that a resuscitator positioned at the side of the infant would assess chest wall movements more accurately compared to resuscitator positioned at the infants head. The aim of this study was to compare observers' clinical estimates of tidal volume with the tidal volume measured using a flow sensor during PPV of newborns in the delivery room.

Patients and Methods

This study was carried out at The Royal Women's Hospital, Melbourne, a tertiary perinatal centre admitting more than 100 infants with a birth weight of <1000g to the neonatal nursery annually. Infants were enrolled between September 2009 and February 2010 when a member of the research team was available to attend the delivery. The study was approved by the Royal Women's Hospital Research and Ethics Committees. Written consent was obtained before birth if the mother was not in established labor and if time permitted. Where this was not possible, retrospective consent was obtained

as per Australian National Health and Medical Research Council (NHMRC) guidelines for studies in emergency medicine(6). Consent to use data obtained was sought from the parents of these infants as soon as possible after birth.

Infants <32 weeks gestation who received face mask PPV immediately after birth were eligible for inclusion. Infants with congenital abnormalities and infants whose parents did not consent were excluded from the study. The research team were not involved in the clinical care of the infants.

Ventilation device and face mask

PPV was given via a round silicone face mask of appropriate size (Laerdal, Stavanger, Norway). A T-piece device was used (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand). This is a continuous flow, pressure-limited device with a built-in manometer and a positive end-expiratory pressure (PEEP) valve. The default settings at our institution are gas flow of 8L/min, peak inflation pressure of 30 cm H_2O and PEEP of 5 cm H_2O.

Respiratory Function Monitor (RFM)

A hot-wire anemometer flow sensor (Florian Respiratory Function Monitor, Acutronic Medical Systems AG, Zug, Switzerland) was placed between the ventilation device and the face mask to measure gas flow, tidal volume and airway pressure. The inspiratory and expiratory tidal volumes (V_{Te}) passing through the sensor were automatically calculated by integrating the flow signal.

Data Acquisition and Analysis

Pressure, gas flow and tidal volume from the respiratory function monitor were recorded at 200 Hz using a desktop computer with Spectra physiological recording software (Grove Medical, London, UK). In the delivery room, the monitor's alarm was disabled and the resuscitators were prevented from seeing either the respiratory function monitor or the computer screen.

Observers' assessment of chest wall movements

All team members received training in neonatal resuscitation prior to participation in this study. After at least 60 seconds of PPV, two members of the resuscitation team were asked to answer questions about their estimates of delivered tidal volume and chest wall movements. A junior medical staff member performed PPV (head view) while a senior medical staff member observed chest movements from one side of the infant (side view). The team member observing from the side wrote down their estimates prior to the resuscitator at the head stating their estimates. The resuscitation team were then told the measured V_{Te} by the research team.

The questions asked were:
* How well do you think the chest is moving?

   "Appropriately", "too low", "too much", "not at all", "not sure"
* Estimate the tidal volume in mL/kg you are delivering?

All answers could include "cannot do it", "don't know". The questions were asked only if both resuscitators felt comfortable with the progress of the resuscitation. Resuscitators had the opportunity to decline to participate or withdraw from the study at any time.

Statistical Analysis

A recording of each inflation was carefully examined, and the V_T, airway pressure and gas flow of each inflation were measured. Measurements obtained in the 30 seconds prior to the questions were compared with the two observers' estimates. Results are presented as mean (SD) for normally distributed continuous variables and median (IQR) for variables with skewed distribution. The level of agreement between the measured V_T and the observers' estimates from head view and side view were assessed using Bland-Altman plots(7). Data were analysed using STATA version 10 (Stata Corp, College Station, Texas, US). A convenience sample of 20 infants was chosen.

Results

One hundred and five infants < 32 weeks gestation were born between September 2009 and January 2010. The research team was not notified of impending delivery of 66 infants a further 19 did not receive PPV in the delivery room. We recorded 20 infants who received PPV. Infant demographics are presented in Table 1. None of the infants received chest compressions or adrenaline.

A total of 433 inflations were analysed; a mean (SD) of 23 (4) inflations per infant during the 30 seconds baseline. PPV was commenced at a median (IQR) of 47 (38-70) seconds after birth. Resuscitators who were assessing chest rise from the head view had a median (range) level of experience of 20 (1 - 120) months compared to 60 (12 - 470) months for those who assessed from the side. Apart from one observer who participated in this study twice, the remaining 38 observations were all performed by different medical staff.

A mean (SD) peak inflating pressure of 29.2 (4.5) cm H_2O and positive end expiratory pressure of 4.9 (1.1) cm H_2O were delivered. Overall, the median (IQR) mask leak was 48 % (27-76) and the median (IQR) V_{Te} was 6.4 (3.1-9.5) mL/kg (Figure 1).

Assessment of expiratory tidal volume

Table 2 shows the median (IQR) V_{Te} and the estimates of the resuscitators standing at the head and the side of the infant. Six resuscitators were unable to estimate the delivered V_{Te} at the head of the infant while performing PPV, compared to three observers at the side of the infant (p=0.26). The estimates of the delivered V_{Te} at the head view and side view were compared with the delivered V_{Te} in Bland-Altman plot (Figure 2 & 3). Using assessments at the head of the infant, the mean difference (V_{Te} – head view estimates) was 3.5 mL (confidence interval -0.07 to 7.0) and the 95% limit of agreement was -8.8 to 15.8 mL (Figure 2).

Using assessments at the side of the infant, the mean difference (V_{Te} – side view estimates) was 3.3 mL (confidence interval -0.07 to 6.5) and the 95% limit of agreement was -9.2 to 15.7 mL (Figure 3).

Chest rise assessment standing at the head of the infant

Resuscitators who assessed chest rise as "not at all" delivered a median (IQR) V_{Te} of 3.5 (2.3-6.8) mL/kg. The assessment "not sure" corresponded to a V_{Te} of 3.7 (3.0 to 5.6) mL/kg. Those who thought it was "appropriate" delivered a V_{Te} of 3.0 (1.2 - 8.2) mL/kg. Those who thought it was "too much" delivered a V_{Te} of 5.4 (4 - 13.3) mL/kg. Those who thought it was "too low" delivered a V_{Te} of 8.4 (7.0-10.5) mL/kg.

Chest rise assessment standing at the side of the infant

Chest rise assessed as "not at all" was associated with a median (IQR) V_{Te} 4.4 (3.0-7.0) mL/kg. The assessment "not sure" corresponded to a V_{Te} of 3.7 (3.0 to 5.6) mL/kg. A chest rise of "appropriate" was associated with a V_{Te} of 5.2 (2.9-8.9) mL/kg. A chest rise of "too much" was associated with a V_{Te} of 5.8 (2.4-8.6) mL/kg, for "too low" it was 7.8 (3.6-10.3) mL/kg. No observer answered the question with "cannot do it".

Discussion

Neonatal resuscitation can be stressful, which may contribute to the imprecision and inaccuracy of assessment of colour and heart rate in the delivery room(8;9). We recently reported that junior doctors standing at the infants' head were unable to simultaneously assess chest wall movements while performing mask ventilation(5). Some could argue that the resuscitator's limited experience of neonatal resuscitation might have contributed to this result. In our delivery room junior medical staff routinely performs PPV supervised by senior medical staff. We aimed to compare the assessment of chest rise seen from the head and the side of the infant. The accuracy of clinical assessment of chest wall movement was poor and did not appear to be influenced by either the observers' position or the level of experience. However, more resuscitators were unable to assess chest wall movements while performing PPV than those observing from the side. This might be reflected in the lower level of experience for resuscitators who assessed chest rise at the infants' head compared to those assessing chest rise from the side of the infant.

Our current study confirms our previous observations that despite a constant set PIP level there is a considerable variability of delivered tidal volume(5;10). These observations suggest that relying on a fixed inflating pressure and subjective assessment of chest rise may result in either under- or over-ventilation. The purpose of the inflating pressure is to deliver an adequate V_T. Lung compliance and therefore the pressures required to deliver an appropriate V_T varies greatly in the minutes after birth. There are even greater differences *between* infants depending on the immaturity of the lung and their own spontaneous breathing efforts(2;3;11;12). These observations suggest that it is necessary to measure the delivered tidal volumes and adjust inflating pressures during PPV immediately after birth, especially in very preterm infants.

Conclusion

Resuscitators were unable to accurately assess chest wall movements from either head or side view. Using a respiratory function monitor in the delivery room to continuously measure and display the delivered tidal volume might improve the effectiveness of neonatal resuscitation.

Table 1: Infant demographics:

	N = 20
Gestational age (weeks)*	27 (2)
Birth weight (g)*	955 (310)
Female	12 (60%)
Antenatal steroids	15 (75%)
Caesarean section	11 (55%)
Apgar score at 1 min$^{#}$	4 (3-6)
Apgar score at 5 min$^{#}$	7 (7-8)

Values are numbers (percentage) unless indicated *mean (standard deviation), $^{#}$median (interquartile range)

Table 2: Assessment of estimated and measured expired tidal volume

Infant (n=20)	Median V_{Te} (mL/kg)	25th & 75th Centile of V_{Te} (mL/kg)	Side view V_T estimates (mL/kg)	Head view V_T estimates (mL/kg)
1	3.4	2.5 - 4.7	can't do	6
2	8.0	7.6 - 8.5	can't do	can't do
3	10.8	8.7 -12.0	1	9
4	6.0	4.5 -7.3	1	can't do
5	2.6	2.1 -2.6	3	can't do
6	0.5	0.2 -0.7	8	can't do
7	3.7	2.9 -3.4	3	can't do
8	9.5	5.8 -12.0	4.5	3
9	4.6	3.8 -5.6	can't do	can't do
10	7.5	6.5 -8.7	5	3
11	4.1	3.4 -5.1	6	10
12	11.7	9.9 -13.1	3	3.5
13	21.0	19.7 -21.9	6	3.5
14	1.2	0.9 -1.4	5	5
15	8.6	8.1 - 9.0	3	5
16	7.3	4.7 -9.8	10	2
17	13.8	11.5 -15.4	3	10
18	13.5	7.45 -16.6	4	3
19	5.8	3.2 -8.6	10	7
20	5.5	3.0 -7.1	2	5

Figure Legend

Figure 1: Expired tidal volume (V_{Te}) for each infant. The horizontal lines show the range of V_{Te} which would provide reasonable ventilation. The Box plots show median (solid bar), interquartile range (margins of the box) and 95% confidence interval. The horizontal lines show the range of V_{Te} (4 and 8 mL/kg) which would provide reasonable ventilation.

Figure 2: Bland-Altman plot showing the level of agreement between measured V_{Te} and the estimates of the resuscitators at the head of the infant.

Figure 3: Bland-Altman plot showing the level of agreement between measured V_{Te} and the estimates of the resuscitators at the side of the infant.

Figure 1
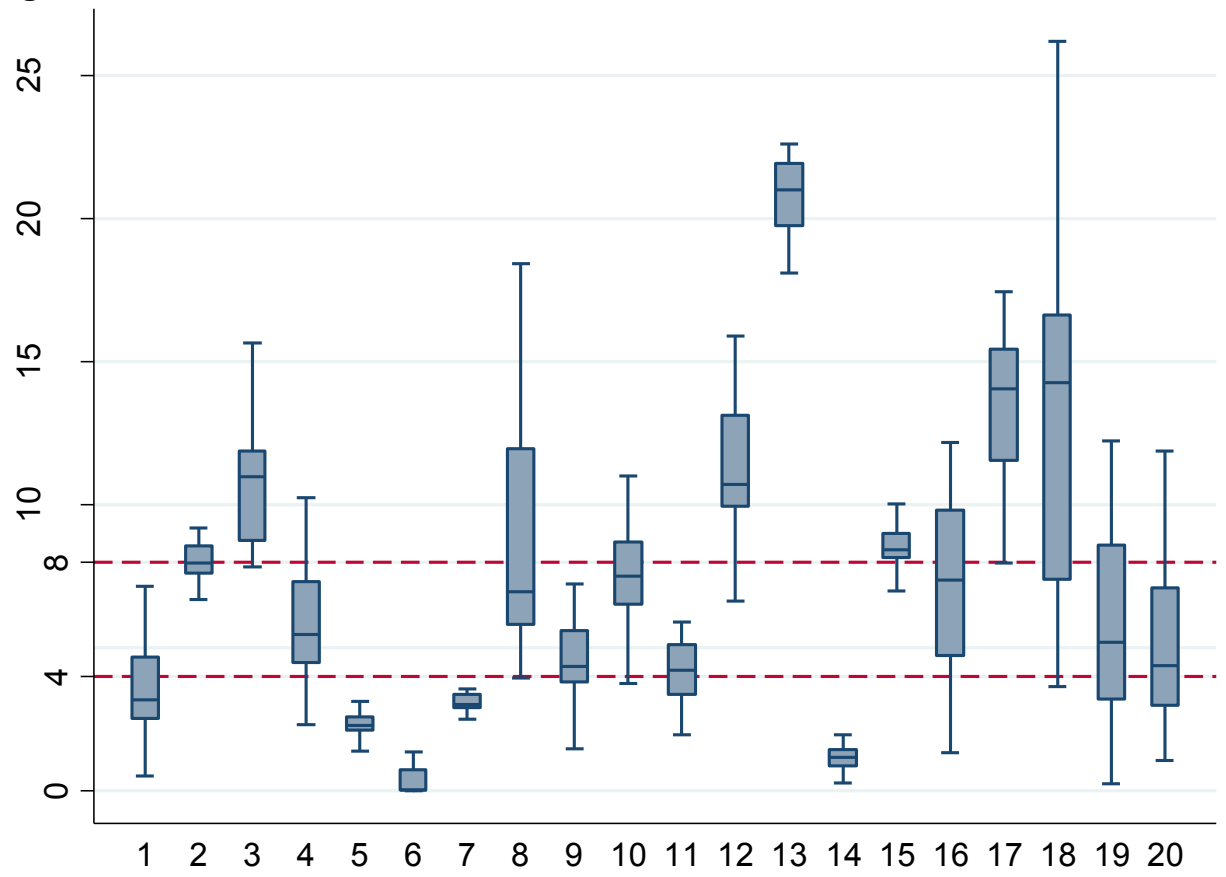
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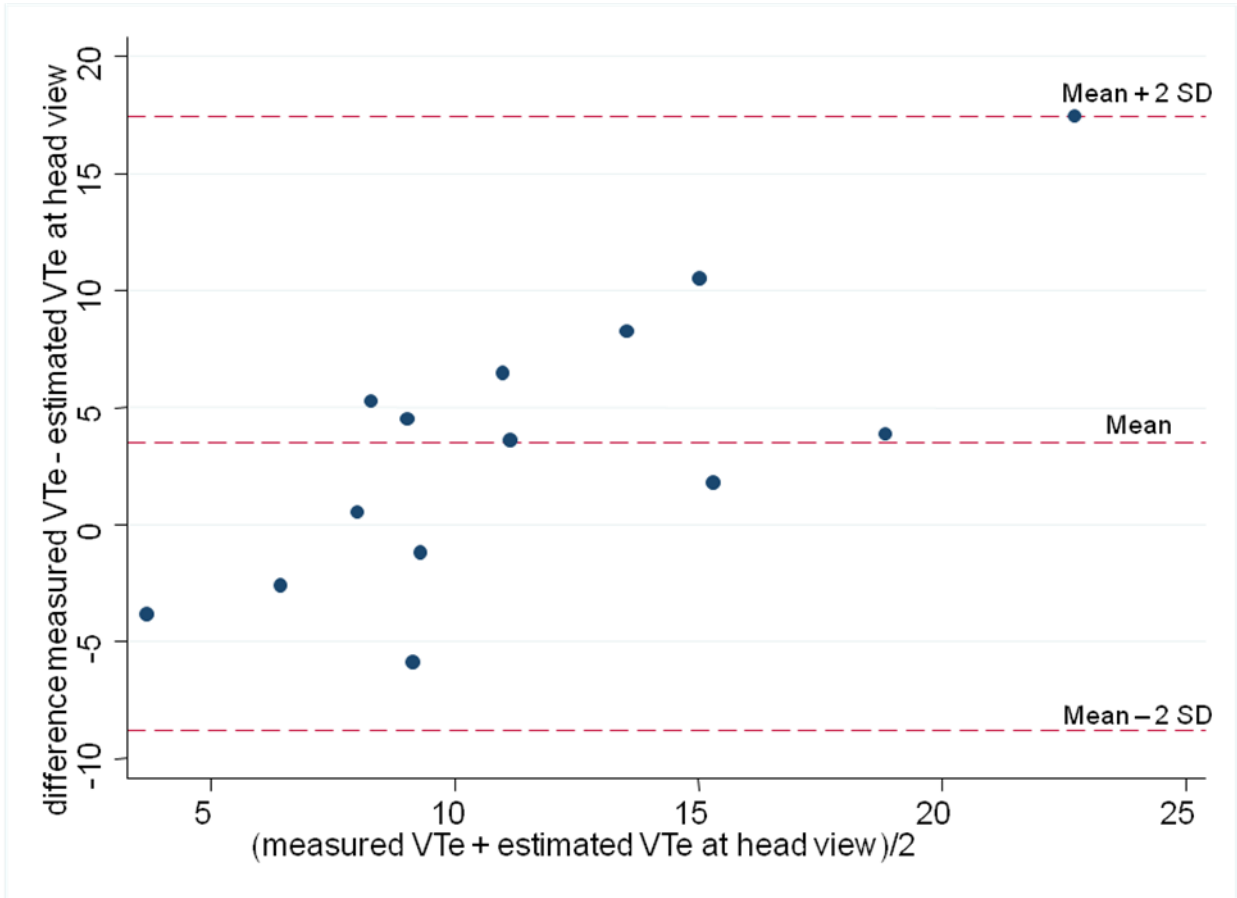
Figure 3
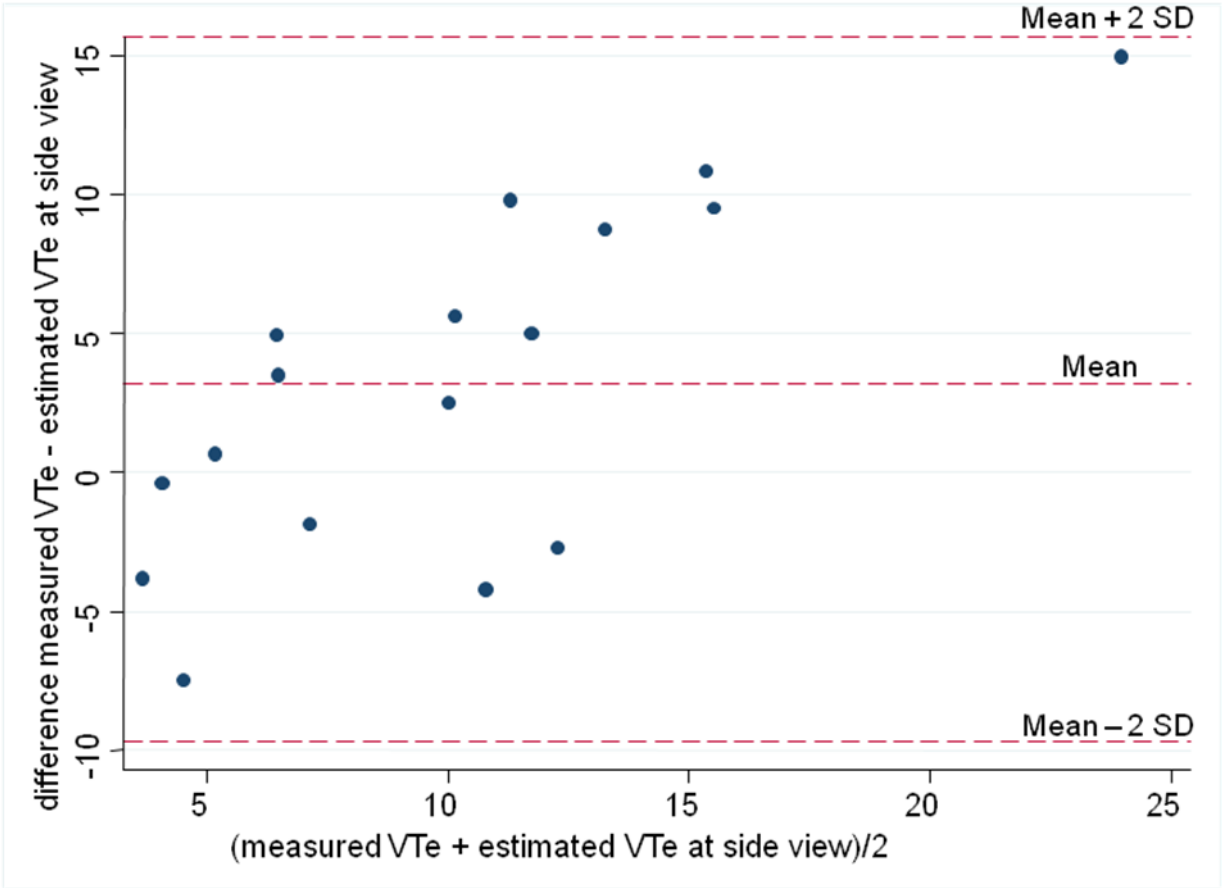
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Chapter VII

Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter VII "Airway Obstruction and gas leak during mask ventilation of preterm infants in the delivery room"

Declaration by candidate

In the case of Chapter VII the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, data collection, data analysis, writing the manuscript	60%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dawson JA	Involved in data collection and revising the manuscript	
Kamlin COF	Involved in data collection and revising the manuscript	
O'Donnell CPF	Involved in data collection and revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature	███████████████	Date	20/7/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	███████████	20/7/10
Signature 2	███████████	20/07/2010
Signature 3		
Signature 4	███████████	18.7.10
Signature 5	███████████	20.7

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PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter VII "Airway Obstruction and gas leak during mask ventilation of preterm infants in the delivery room"

Declaration by candidate

In the case of Chapter VII the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, data collection, data analysis, writing the manuscript	60%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dawson JA	Involved in data collection and revising the manuscript	
Kamlin COF	Involved in data collection and revising the manuscript	
O'Donnell CPF	Involved in data collection and revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature		Date	

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Date
Signature 1	
Signature 2	
Signature 3	07-07 - 2012
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Signature 5	

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7.2 INTRODUCTION

When infants fail to initiate spontaneous breathing immediately after birth, international resuscitation guidelines recommend mask positive pressure ventilation (PPV) to create a functional residual capacity, facilitate gas exchange and initiate spontaneous breathing. However, the delivery of adequate mask PPV in the delivery room depends on appropriate face mask techniques. Several factors including poor face mask technique, spontaneous movements of the baby, movements by or distraction of the resuscitator, and procedures such as changing the wraps or fitting a hat can reduce the effectiveness of PPV and cause mask leak or airway obstruction.

Several mannequin studies have shown that face mask leak is common and variable during PPV. In *Chapter V*, I measured mask leak during mask PPV and compared it to the clinical assessment of each resuscitator. The median (range) mask leak was 29% (0% - 100%). In addition, most resuscitators were unaware of the extent of their mask leak.

Airway obstruction is a further cause of inadequate PPV. Finer et al. recently reported airway obstruction during PPV using a colorimetric carbon dioxide detector. They identified airway obstruction in 75% of infants receiving mask PPV in the delivery room. Even though a colorimetric carbon dioxide detector can be used to assess effective ventilation however, differentiation between an inadequate tidal volume or airway obstruction is difficult. In *Chapter IV*, I described the use a Respiratory Function Monitor to assess airway obstruction by observing gas flow and tidal volume waves. In this Chapter I

analysed video recordings to determine the frequency of mask leak and airway obstruction and identify the contribution of ineffective mask techniques to failure of neonatal resuscitation.

7.3 Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room

The following chapter has been provisionally accepted in Archives of Disease in Childhood Fetal & Neonatal Edition but is not yet published, thus it is presented in manuscript form as per Monash University guidelines for thesis by publication.

Airway obstruction and gas leak during mask ventilation of preterm infants in the delivery room

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Conflict of interest: None
Keywords: Positive Pressure Ventilation, Delivery room, Respiratory Function Monitor, Preterm infants, Neonatal Resuscitation, Obstruction, Face mask leak

No reprints requested

Abbreviations:

PPV   - Positive Pressure Ventilation

DR   - Delivery Room

CO_2 - Carbon dioxide

RFM   - Respiratory Function Monitor

NICU   - Neonatal intensive care unit

PEEP   - Positive End Expiratory Pressure

PIP   - Peak Inflation Pressure

SpO_2 - Oxygen Saturation

HR   - Heart Rate

V_{Te} - Expired Tidal Volume

Abstract

Introduction

Preterm infants with inadequate breathing receive positive pressure ventilation (PPV) by mask with variable success. We examined recordings of PPV given to preterm infants in the delivery room for prevalence of mask leak and airway obstruction.

Methods and Patients

We reviewed recordings of infants < 32 weeks gestation born between February 2006 and March 2009. PPV was delivered with a T-piece or self-inflating bag and a round silicone face mask. Airway pressures and gas flow were recorded with a respiratory function monitor. Videos recorded from a web camera were used to review the resuscitation. The first two minutes of PPV were analysed for each infant. Obstruction was arbitrarily defined as a 75% reduction in delivered expired tidal volume (V_{Te}) and significant face mask leak as $\geq$ 75%.

Results

We analysed recordings of 56 preterm infants. Obstruction occurred in 14 (26%) recordings and leak in 27 (51%). Both obstruction and mask leak were seen in eight (14%) recordings and neither was seen in 15 (27%). Obstruction occurred at a median (IQR) of 48 (24 - 60) seconds after start of PPV. A median (range) of 22 (3 - 83) consecutive obstructed inflations were delivered. Face mask leak occurred from the first inflation in 19/27 (70%) and in the remaining 8 at a median (IQR) of 30 (24 - 46) seconds after start of PPV. A median (range) of 10 (3-117) consecutive inflations with a leak $\geq$ 75% were delivered.

Conclusion

Airway obstruction and face mask leak are common during the first two minutes of PPV. A respiratory function monitor enables detection of important airway obstruction and mask leak.

Introduction

When preterm infants fail to breathe adequately immediately after birth, it is important to apply positive pressure ventilation (PPV) to create a functional residual capacity, facilitate gas exchange and initiate spontaneous breathing[1;2]. However, the delivery of adequate PPV in the delivery room (DR) is dependent on good face mask technique. Guidelines suggest that the effectiveness of PPV should be gauged by the presence of increasing heart rate and adequate chest rise[3]. Several factors can reduce the effectiveness of PPV. These include poor face mask technique resulting in leak or airway obstruction, spontaneous movements of the baby, movements by or distraction of the resuscitator, and procedures such as changing the wraps or fitting a hat [4-7].

Mannequin studies have shown that face mask leak varies widely during PPV[6-9]. An observational study in the DR reported similar results[10] where resuscitators had a median (range) mask leak of 29% (0% - 100%). Most resuscitators were unaware of the extent of their mask leak[10]. Another cause of inadequate PPV is airway obstruction. Finer et al. recently reported airway obstruction during PPV using a colorimetric carbon dioxide (CO_2) detector. They found airway obstruction in 75% of infants receiving PPV in the DR[4]. A CO_2 detector is a very useful device to assess effective ventilation however, it cannot differentiate between an inadequate tidal volume or airway obstruction[11]. In comparison, a Respiratory Function Monitor (RFM) displays flow and tidal volume signals allowing the characteristic pattern associated with mask leak and airway obstruction to be identified[12]. The contribution of ineffective technique to failure of neonatal resuscitation is unknown. We reviewed

recordings of neonatal resuscitation in order to determine the frequency of face mask leak and obstruction.

Patients and Methods

This study was carried out between February 2006 and March 2009 at The Royal Women's Hospital, Melbourne, a tertiary perinatal centre admitting more than 100 infants with a birth weight of <1000g to the neonatal nursery annually. During this period, if the research team was available, they attended deliveries in addition to the resuscitation team (usually a nurse, paediatric resident, fellow and consultant). The research team was not involved in the clinical care of the infants. The study was approved by The Royal Women's Hospital Research and Ethics Committees and parental consent to use the recordings was obtained.

Infants who clinicians judged to have inadequate breathing were given PPV with either a T-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) or a 240 ml self-inflating bag and attached gas reservoir (Laerdal, Stavanger, Norway). The Neopuff is a continuous flow, pressure-limited device with a manometer and a positive end-expiratory pressure (PEEP) valve. The default settings were a gas flow of 8 L/min, peak inflation pressure (PIP) of 30 cm H_2O and PEEP of 5 cm H_2O. The self-inflating bag was used with 8 L/min gas flow and without a manometer or a PEEP-valve.

Infants reviewed between February 2007 and February 2009 were included in a randomised control trial comparing PEEP with no PEEP during PPV in the first five minutes after birth. These infants were randomized to receive PPV with either a Neopuff or a Laerdal bag.

Staff members attending deliveries were trained to use both devices. A size 00 round silicone face mask (Laerdal, Stavanger, Norway) was used with both devices. Resuscitation was started with air for all infants. Clinicians could change to 100% oxygen if they felt the infant was not responding to initial resuscitation.

A Florian Respiratory Function Monitor (Acutronic Medical Systems AG, Zug, Switzerland) was used to measure airway pressures and gas flow. Airway pressure was directly measured from the circuit. A hot-wire anemometer flow sensor placed between the ventilation device and the face mask measured gas flow. The RFM automatically calculated the tidal volume passing through the sensor by integrating the flow signal. The gas flow, tidal volumes and airway pressure were recorded at 200Hz using a dedicated computer with Spectra software (Grove Medical, London, UK), a program specifically designed for recording neonatal physiological data. In the delivery room, neither the RFM nor the computer screen were visible to the resuscitators and the monitor's alarm was disabled. However, mask leak and airway obstruction was communicated to the clinical team. A webcam recorded the resuscitation at 5 frames per second. A Masimo Radical pulse oximeter (Masimo Corporation, Irvine CA, USA) probe set at maximum sensitivity and two second averaging was placed around the infant's right wrist to measure oxygen saturation (SpO_2) and heart rate (HR)[13;14]. A decrease of $\geq$ 15% for SpO_2 or $\geq$ 15 bpm for HR was considered to be clinically important.

Two researchers (JAD and GMS) reviewed RFM and video recordings to identify infants who received PPV in the DR. Each RFM recording was analysed for two minutes from the first inflation. The videos were used to identify when the mask was

repositioned.

Airway obstruction

Clinically significant airway obstruction was arbitrarily defined as either a 75% reduction in expired tidal volume (V_{Te}) compared to the baseline of 10 inflations prior to the obstructed inflation (see Figure 1) or a 75% increase of V_{Te} after correction for obstruction. Obstruction was characterized by a similar reduction in both inspired and expired tidal volumes.

Face mask leak

The leak from the mask was calculated by expressing the volume of gas that did not return through the flow sensor at the end of inflation as a percentage of the volume that passed through the flow sensor during inflation (Leak (%) = [(inspired tidal volume – V_{Te}) ÷ inspired tidal volume] x 100) (see Figure 2)[6]. We considered a mask leak of $\geq$ 75% as clinically important.

Statistical analysis

A breath by breath analysis of pressure, flow, and tidal volume was performed and the tidal volume and mask leak for each inflation were measured. The face mask leak was corrected for body temperature, pressure and water vapour saturation using a standardised equation[15]. Results are presented as mean (SD) for normally distributed continuous variables and median (IQR or range) for variables with a skewed distribution. Data were analysed using STATA version 10 (Stata Corp, College Station, Texas, US).

Results

Of the 106 resuscitations recorded, 56 (53%) infants received PPV while 50 (47%) infants received CPAP only. Twenty-five (45%) were ventilated with a T-piece-device and 31 (55%) with a self-inflating bag. Infant demographics are shown in Table 1. A total of 4048 inflations were analysed, with a median (IQR) of 76 (53-98) per infant. PPV started at a median (range) of 82 (33-125) seconds after birth.

Inflations showing airway obstruction and mask leak were identified in 14/56 (25%) and 27/56 (48%) of the recordings respectively. In 8/56 resuscitations both obstruction and mask leak occurred and in 15/56 neither occurred. None of the infants received cardiac compressions or adrenaline.

Airway obstruction

In 14 (25%) infants (6 with a T-piece and 8 with a self-inflating bag) airway obstruction was identified. The median (IQR) time of obstruction was 48 (24-60) seconds after start of PPV. In two infants airway obstruction occurred from the first inflation. A median (range) of 22 (3-83) consecutive obstructed inflations were identified. The median (IQR) delivered V_{Te} during airway obstruction was 0.6 (0.2-1.2) ml/kg compared to 7.2 (4.9-8.9) mL/kg during unobstructed PPV. To improve ventilation the resuscitator either repositioned face mask (n=8), changed mask hold (n=3), repositioned the head (n=2) or was replaced by another resuscitator (n=1). Airway obstruction re-occurred after initial correction in three cases, where changing mask hold (n=1), replaced by another resuscitator (n=1) or increased airway pressure (n=1) was used. In seven cases (50%) the inspired oxygen was increased

from 21% to 100% during obstruction. Six of these seven infants were intubated because of poor response to ventilation.

During five resuscitations, obstruction occurred before SpO_2 or HR was recorded. In one recording only three obstructed inflations were delivered and no changes in SpO_2 and HR were observed. In three recordings SpO_2 decreased by $\geq$ 15 % and in six recordings HR decreased by $\geq$ 15 beats per minute during obstruction.

Face mask leak

A T-piece was used in 13 and the self-inflating bag in 14 infants where a mask leak >75% was identified. This occurred in 19 (70%) infants as soon as PPV was started. In the remaining 8 (30%) infants mask leak occurred later, at a median (range) time of 30 (13-69) seconds after start of PPV. A median (range) of 10 (3-117) consecutive inflations with a large mask leak were delivered. The median (IQR) expiratory tidal volume during large face mask leaks was 5.6 (2.4-11.5) mL/kg. Different measures were taken to improve ventilation: Repositioned face mask (n=23), changed mask hold (n=7), repositioned the head (n=2) or replacment by another resuscitator (n=1). In some cases several measures were taken. In no case was the inflating pressure increased. Three infants were intubated. In six cases mask leak reoccurred after initial correction and in three of them face mask leak reoccurred after the second correction. In three cases the inspired oxygen was increased from 21% to 100% during PPV.

During six resuscitations mask leak occurred before SpO_2 or HR was recorded. In 15 infants no changes in SpO_2 or HR were observed. In one infant mask leak was followed by obstruction and therefore SpO_2 and HR were not analysed (see Figure

3). In five either SpO_2 decreased by $\geq$ 15 % or HR decreased by $\geq$ 15 bpm during mask leak.

Discussion

We recently reported that a RFM can be used to guide clinicians during PPV in the DR[12]. Several factors prevent effective ventilation, including obstruction (pressing the mask onto the infant's face too tightly, flexing or overextending the neck) or leak due to holding the mask incorrectly[4;6;8;11;16].

In this study we have shown that both significant airway obstruction and face mask leaks occur during the first two minutes in about half of the very preterm infants who received PPV in the DR. Although we observed both obstruction and leak in 8 (15%) recordings, in general, large mask leak was observed in twice as many recordings as airway obstruction. In about a third neither obstruction nor face mask leak occurred. Mask leak was more likely to occur at the start of PPV, while airway obstruction more often occurred later on. A recent mannequin study by Schilleman et al. showed that operators had frequent airway obstruction once they had adjusted mask hold to correct for leak[16]. However, we did not find this in our observations.

Assessment of the infant may distract the resuscitators focus from mask position and mask holding techniques during the initial phase of PPV. We observed that procedures such as fitting a hat or putting the infant in a plastic bag contributed to large face mask leak. Once PPV was established, leak was less likely to be observed. In the current study a round silicone face mask size 00 (Laerdal, Stavanger, Norway) was used. These results might vary with different face masks. The rate of intubation was four times higher in infants having airway obstruction

(43%) compared to mask leak (11%). This suggests that airway obstruction is more likely to cause major clinical deterioration.

Conventional resuscitation training teaches that airway obstruction may be due to manual compression of the soft tissues of the neck and thus the trachea, or hyperextension or flexion of the head[17]. However, after examining many recordings we think most obstruction is due to the face mask being held on the face so tightly that it obstructs the mouth and nose. We believe this was the case because the obstruction was resolved by reapplying the face mask rather than altering the head position. However, we cannot be sure that neck obstruction is not occurring in some infants.

Both, mannequin and observational studies in the delivery room have shown that mask leak is common[6;8;10;16]. However, none have reported a close relationship between percentage mask leak and delivered tidal volume. Arbitrarily defining mask leak of >75% clinical significant is a limitation of this study. We chose this because we hypothesised that such a high leak might lead to failure in tidal volume delivery and an increase in adverse events. However, we noted that in spite of large mask leak adequate tidal volumes continued to be delivered. Only a minority of infants with a large leak experienced a clinical deterioration.

Possible role of a respiratory function monitor in the delivery room

Reports suggest a RFM may be useful in the delivery room to measure and carefully adjust respiratory support[10;18-22]. In particular a RFM may help avoid volutrauma and overventilation by enabling clinicians to achieve a desired target tidal volume[18]. In

addition, we have shown that it can be used to detect inadequate ventilation by observing tidal volume waves[12].

Limitations

There are some limitations of this technology. Inexperience and lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals. Therefore anyone using a RFM must be trained to interpret pressure, flow and tidal volume signals. In addition, the attention of an inexperienced user may be diverted from the infant to the monitor[12].

Conclusion

During DR mask ventilation in very preterm infants significant airway obstruction or a large mask leak frequently occurred during the first two minutes of PPV. A respiratory function monitor can help identify both causes of failure of PPV by displaying gas flow, and tidal volume and pressure waves.

What's Known on This Subject
- Mask leak is common during ventilation in the delivery room
- Assessment of airway obstruction during mask ventilation with a CO_2 detector has been described
- Respiratory function monitors are routinely used in intensive care units to monitor and target tidal volume

What This Study Adds
- Mask leak and airway obstruction are common during mask ventilation
- A respiratory function monitor can be used to recognise and correct these problems

Table 1: Infant Demographics

Infant Demographics (n=56)	
Gestational age (weeks)*	26 (24 – 30)
Birth weight (g)#	839 (223)
1-min Apgar score†	5 (3,6)
5-min Apgar score †	7 (6,8)
Male‡	24 (45%)

Data are mean (range)*, mean (SD)#, median (interquartile range)† and n (%)‡

Figure legend

Figure 1: Airway obstruction during mask PPV in a very preterm infant with a self inflating bag

Initially, PPV delivered V_{Te} of 5 mL/kg. Suddenly, both inflation and expiratory flow waves are much smaller. This is reflected in the V_T curve, which displays a 90% reduction of V_{Te}. With correction of face mask position the tidal volume is restored. Throughout PPV the PIP is achieved.

Figure 2: Large leak at the mask in a very preterm infant ventilated with a self inflating bag

After inflation 4, for about 4 seconds the inspiratory flow curve suddenly shows just gas flow towards the face mask and no expiratory flow. This demonstrates a very large leak around the face mask. The tidal volume curve shows a large flow of gas out of the face mask but little gas returning indicating about 80-100% leak. In addition, the pressure curve fails to achieve the target PIP of about 30 cmH$_2$O. After correction of face mask position there is a reduction in face mask leak to 15%, adequate gas flow entering and leaving the lung and the set PIP is reached.

Figure 1
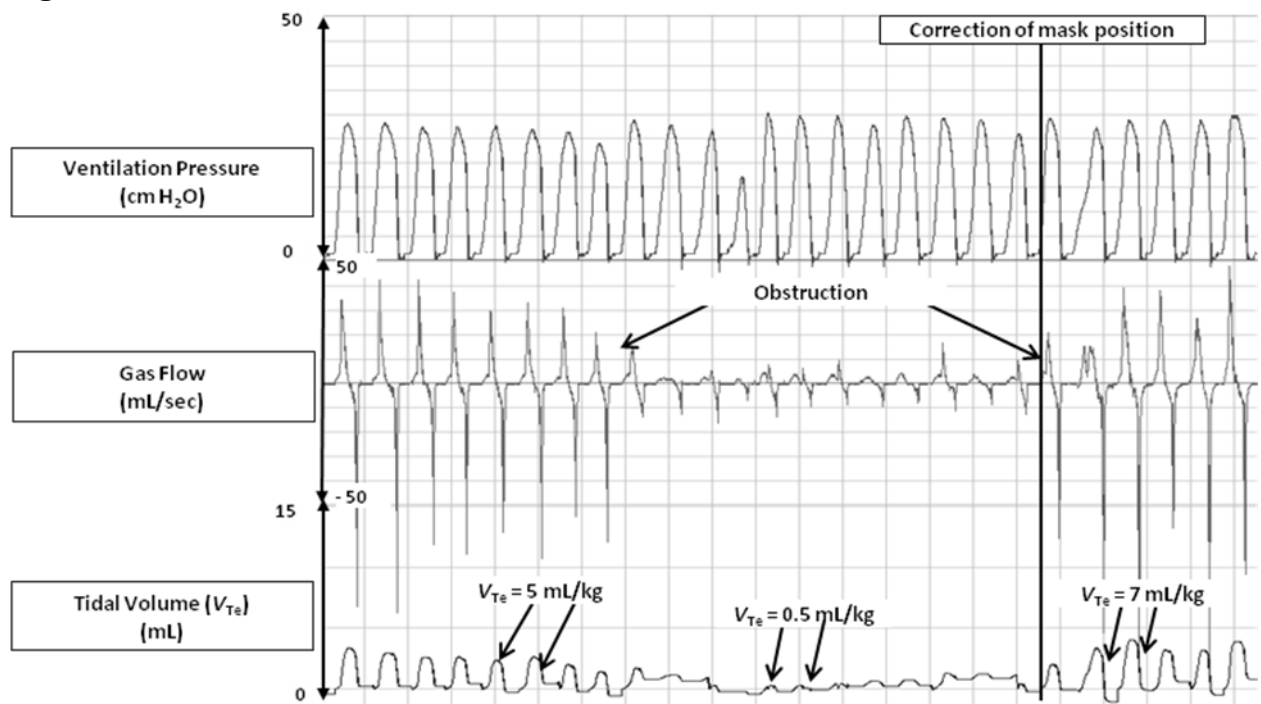
Figure 2
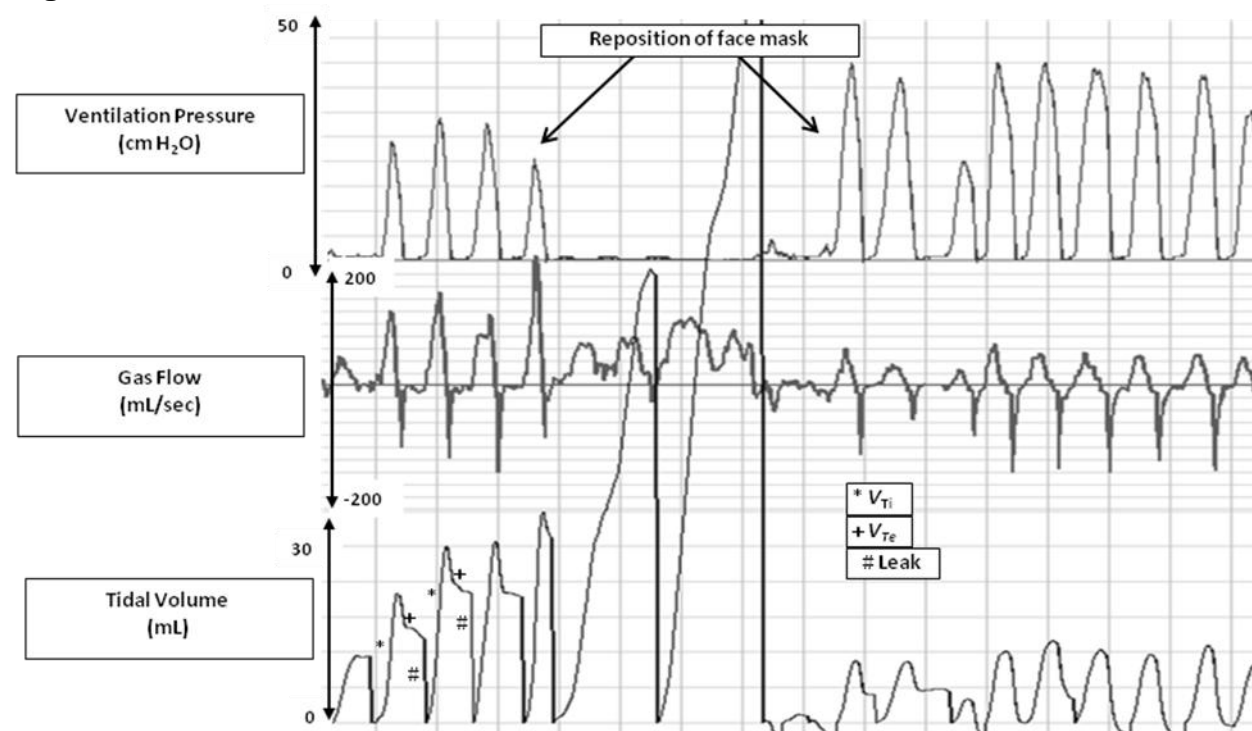
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Chapter VIII

Comparison of T-piece and self-inflating bag ventilation of preterm infants after birth

Comparison of T-piece and self-inflating bag ventilation of preterm infants after birth

In this chapter I would like to present respiratory function data from a randomized control trial comparing two ventilation devices during positive pressure ventilation in the delivery room.

Introduction

Positive pressure ventilation (PPV) is commonly used in the delivery room (DR) and remains a cornerstone of respiratory support during neonatal transition. The aim of PPV is to establish a functional residual capacity (FRC) and deliver an appropriate tidal volume (V_T) to facilitate effective gas exchange (Te Pas et al., 2008a). PPV should be given via using a face mask connected to either a self-inflating bag, flow-inflating bag or T-piece device (ILCOR Part 7: Neonatal resuscitation, 2005).

Currently there is little evidence to guide clinicians' choice of ventilation device. However, to facilitate the development of a FRC immediately after birth, improve oxygenation, and reduce atelectrauma, the device must provide positive end expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). A T-piece device enables resuscitators to deliver and adjust both PEEP and CPAP very accurately (O'Donnell et al., 2004; Finer et al., 2004; Bennett et al., 2005). A self-inflating bag (O'Donnell et al., 2004; Leone et al., 2006; Iriondo et al., 2009), does not provide PEEP

or CPAP (Bennett et al., 2005). Inconsistent PEEP is provided with the addition of a PEEP valve and CPAP cannot be delivered (Bennett et al., 2005).

This article reports the secondary outcomes from a randomised controlled trial enrolling very preterm infants, in which we compared a T-piece device which provided PEEP and a self inflating-bag (SIB) without PEEP, during PPV in the DR and found no significant differences in heart rate or oxygen saturation at five minutes (Dawson et al., 2009). I report a secondary analysis of respiratory function undertaken in some infants.

Methods

Infants were born at The Royal Women's Hospital (RWH), Melbourne, Australia, a tertiary perinatal centre where ~ 6000 infants are delivered and > 100 infants < 1000 g birth weight are admitted to the NICU annually. The research team attended deliveries in addition to the resuscitation team (usually a nurse, paediatric resident, fellow and consultant) and were not involved in the clinical care of the infants.

For all the infants, a pulse oximetry sensor (LNOP Neo-L, Masimo Corporation, Irvine CA, USA) was applied to the right wrist immediately after birth and connected to the pulse oximeter. Infants received PPV with a round silicone face mask size 00 (Laerdal, Stavanger, Norway) with either a T-piece (Neopuff Infant Resuscitator Fisher & Paykel Healthcare, Auckland, New Zealand) or a *Laerdal* 240 mL self inflating bag (Laerdal Silicone Resuscitator Preterm, Laerdal, Stavanger, Norway).

The Neopuff is a continuous flow, pressure-limited T-piece device with a built-in manometer and a PEEP valve. The default settings used were a gas flow of 8 L/min,

peak inflating pressure (PIP) of 30 cm H_2O and PEEP of 5 cm H_2O. The 240 mL silicone self-inflating bag was used with 8 L/min gas flow without a manometer or a PEEP-valve. Staff attending deliveries were trained to use both devices.

Respiratory parameters were measured with a Florian Respiratory Function Monitor (RFM) (Acutronic Medical Systems, Zug, Switzerland) for airway pressures and gas flow. Airway pressure was measured from the circuit and a hot-wire anemometer flow sensor placed between the ventilation device and face mask to measured gas flow. The RFM automatically calculates the tidal volume by integrating the flow signal. Airway pressure, gas flow and tidal volume were recorded at 200Hz using a dedicated computer with Spectra software (Grove Medical, London, UK), a program designed to record neonatal physiological data. In the DR, the RFM and computer screen were not visible to the resuscitation team and the monitor's alarm was disabled. A webcam recorded the resuscitation at 5 frames per second.

Patients

Infants were included in the evaluation of the trial's secondary outcome, if the RFM and the webcam data were available. When there was insufficient time to set the recording equipment or there were no additional personal available to help with the recording these infants were excluded from this analysis.

Consent

Parental consent was obtained before delivery, if possible or retrospectively as per Australian National Health and Medical Research Council (NHMRC) guidelines for studies in emergency medicine as soon as possible after birth. The studies were

approved by the RWH Research and Ethics Committees and registered with Australian and New Zealand Clinical Trials Registry no ACTRN12607000062426.

Data analysis

A breath-by-breath analysis was performed manually to identify inflations (Figure 1A), spontaneous breaths (Figure 1B) and spontaneous breaths coinciding with an inflation (Figure 1C) during PPV as described by te Pas et al (Te Pas et al., 2008c). During manual inflations the airway pressure waveform coincided with the inspiratory gas flow curve. The start of the expiratory gas flow curves follows when the airway pressure curve returns to baseline. A spontaneous breath was defined as having inspiratory and expiratory flow without a concurrent inflation pressure wave form. A spontaneous breath coinciding with a manual inflation was characterized by a combination of a juxtaposed spontaneous breath occurring during a manual inflation. Two inspiratory flow wave curves are resulting in one tidal volume wave (Te Pas et al., 2008c). The expired tidal volume (V_{Te}) for each inflation and breath in the first five minutes after birth during PPV was measured (Te Pas et al., 2008c). The waveforms of pressure, gas flow for each inflation were analyzed to measure PIP, PEEP, tidal volume, inflation time (T_i), ventilation rate, minute ventilation (MV) and calculate mask leak. We calculated the leak from the mask by expressing the volume of gas that did not return through the flow sensor during expiration as a percentage of the volume that passed through the flow sensor during inflation (Leak (%) = [(inspiratory tidal volume – expiratory tidal volume) ÷ inspiratory tidal volume] x 100) (O'Donnell et al., 2005b). Face mask leak was corrected for body temperature, pressure and water vapour saturation using a standardized equation (Turner et al., 1989). In a subset of infants who were intubated, details of waveforms of pressure, gas flow and V_T for the first five minutes of PPV after intubation

were examined. Results are presented as mean (SD) for normally distributed continuous variables and median (IQR) for variables with a skewed distribution. Data were analysed using STATA version 10 (Stata Corp, College Station, Texas, US).
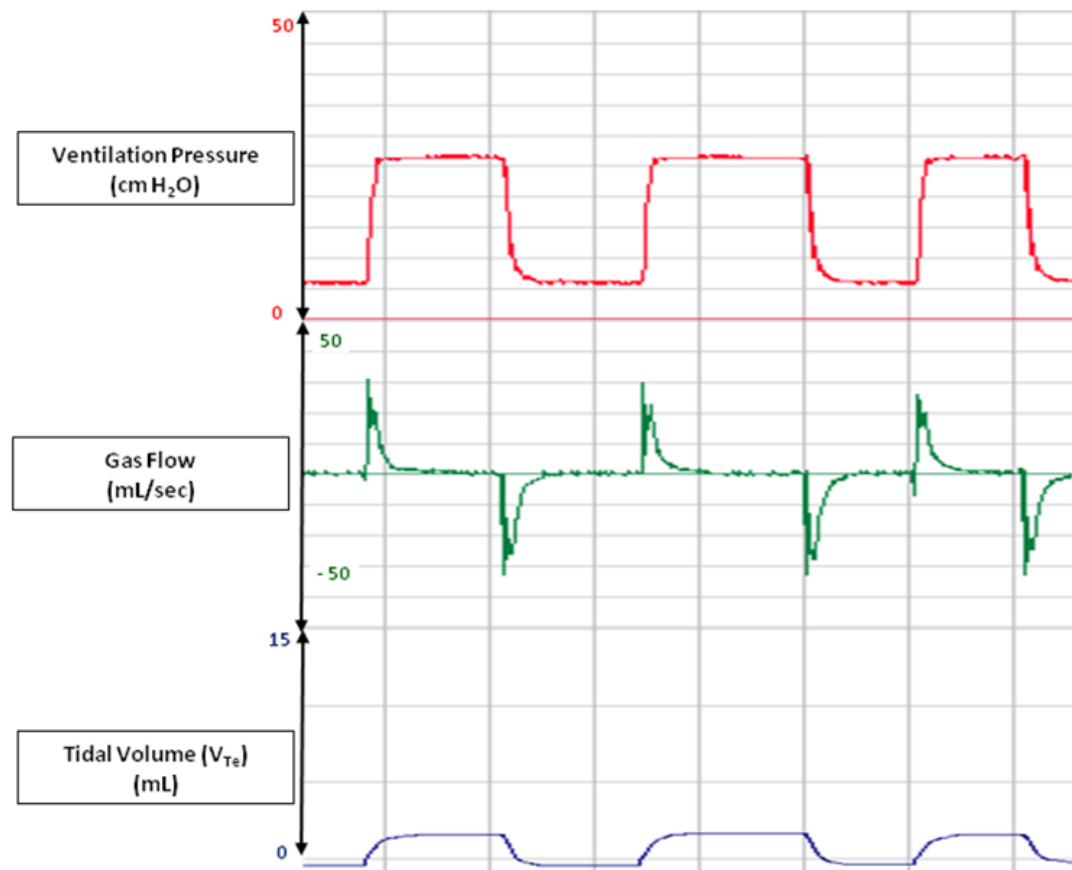
Figure 1A: Manual inflations during positive pressure ventilation with a face mask and a T-piece. The airway pressure rises concurrently with the inspiratory gas flow curve. The start of the expiratory gas flow curves coincides with a return of the airway pressure waveform to the baseline
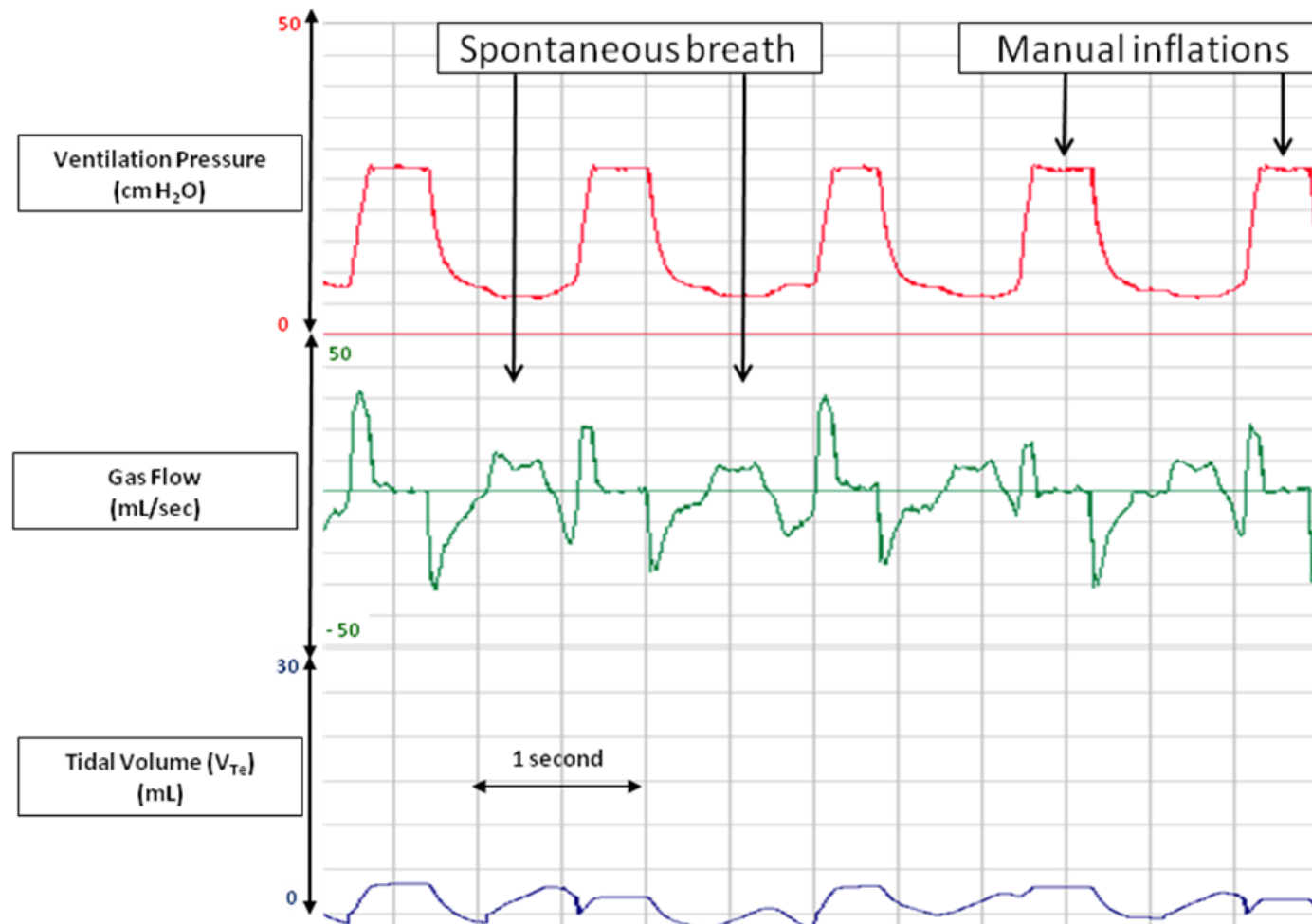
Figure 1B: Preterm infants taking a spontaneous breath after intubation during positive pressure ventilation with a self-inflating bag. The spontaneous breath was characterized by an inspiratory and expiratory flow in between manual inflations
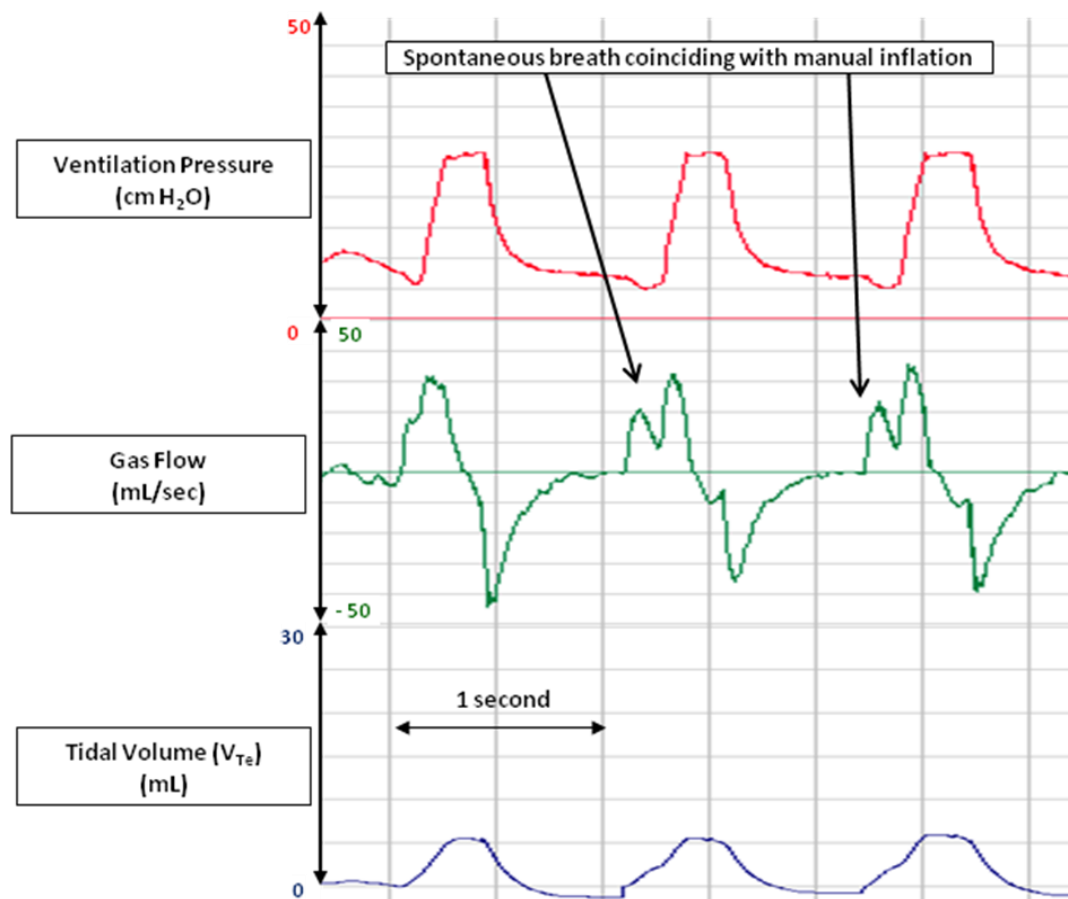
Figure 1C: During positive pressure ventilation the infant is taking a spontaneous breath which is coincides with a manual inflation. This characterized by a combination of a synchronized or juxtaposed spontaneous breath occurring during a manual inflation. Two inspiratory flow wave curves are resulting in one tidal volume wave

Results

Respiratory parameters during PPV were recorded in 47 infants. The mean (SD) gestational age and birth weight was 26 (1) weeks and 822 (230) grams. 21 (45%) were male infants, 26 (55%) received antenatal steroids and 36 (76%) were born by caesarean section. The median (IQR) 1 and 5 minute Apgar score was 4 (3-6) and 7 (6-8). Twenty (43%) of these infants required intubation in the DR and four received surfactant in the DR. The remaining infants were transported on nasal CPAP to the neonatal unit. No infants required chest compressions or received adrenaline in the DR.

Nineteen (41%) infants were ventilated with a T-piece and 28 (59%) with a SIB. A total of 6679 (84%) inflations, 156 (2%) spontaneous breaths, and 1099 (14%) spontaneous breaths coinciding with inflation were delivered during PPV in the first five minutes. Infants ventilated with a T-piece received a median (IQR) of 80 (51-139) inflations each and 139 (68-200) with a SIB. There was a significant difference between the manual inflations in the first five minutes between both devices 2107 (31%) with a T-Piece and 4572 (69%) with the SIB (p< 0.0001). However, there was no significant difference between spontaneous breaths (p=0.32) or spontaneous breaths coinciding with inflations (p=0.21) between the devices. The infants ventilated with a T-piece had 95 (4%) spontaneous breaths and 483 (18%) inflations coinciding with spontaneous breaths. The infants ventilated with a SIB had 61 (1%) spontaneous breaths and 616 (12%) spontaneous breaths coinciding with inflation. Overall, PPV was started at a median (IQR) of 81 (47-97) sec after birth, at the discretion of the clinical team.

Peak inflation pressure and PEEP

There was no significant difference between the mean (SD) PIP delivered with the T-piece or the SIB at 30 (1.9) and 31.5 (5.6) cm H_2O (p=0.0578), respectively. There was more variation in PIP when using the SIB (Figure 2A & 2B). The mean (SD) PEEP was significantly different at 5.6 (1) cm H_2O with the T-piece and 0.5 (0.5) cm H_2O with the SIB (p<0.0001).
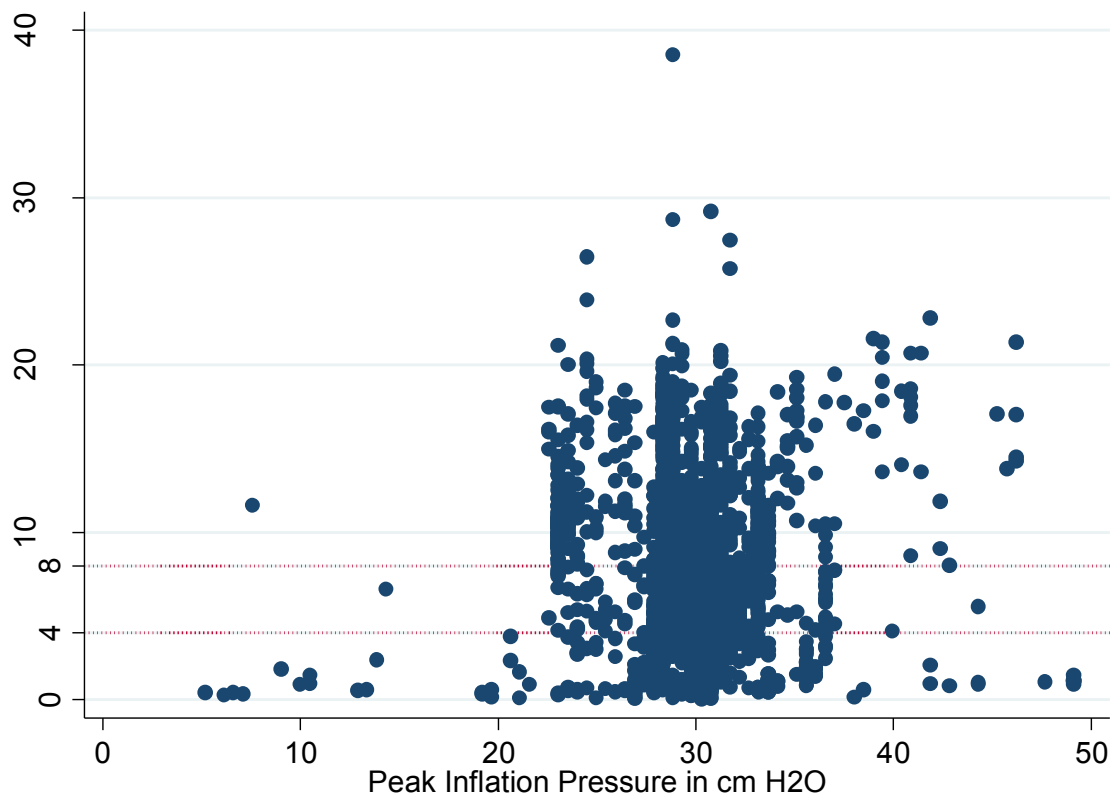
Figure 2A: Comparison of delivered expired tidal volume in mL/kg and peak inflation pressure in cm H_2O during mask positive pressure ventilation with the T-Piece. The two read lines at 4 and 8 mL/kg represent an expired tidal volume range that is considered appropriate during neonatal ventilation.
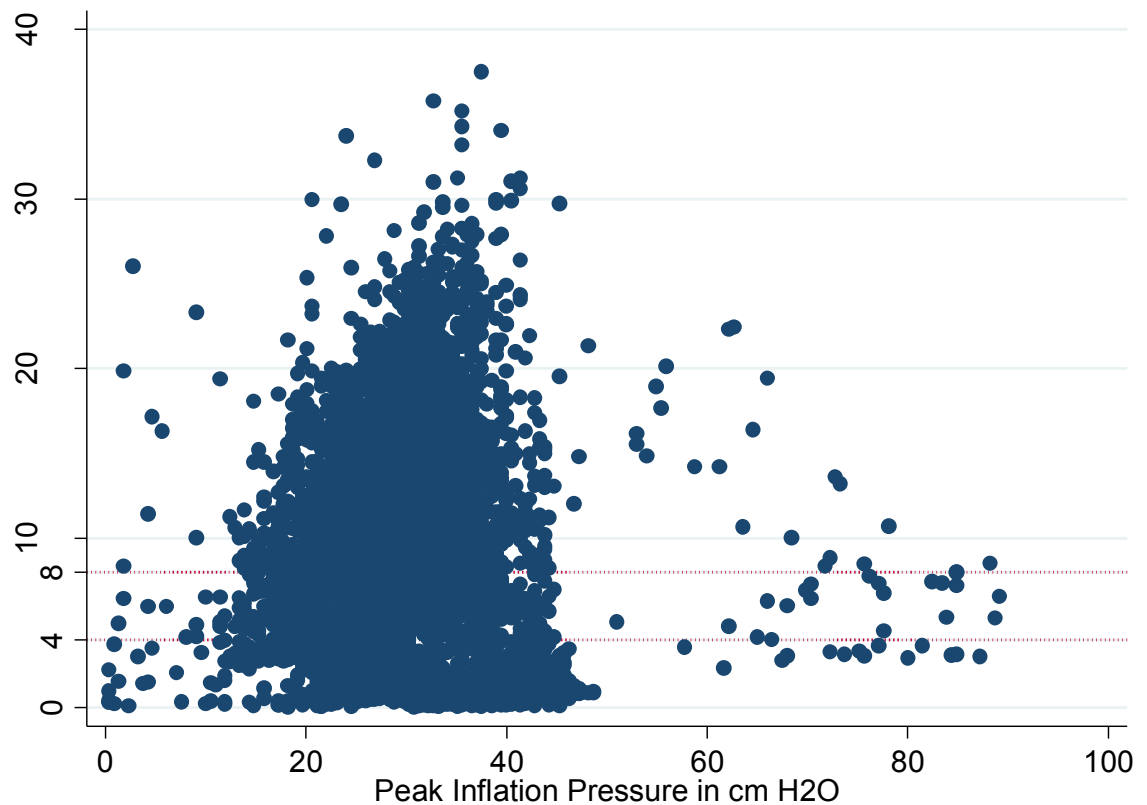
Figure 2B: Comparison of delivered expired tidal volume in mL/kg and peak inflation pressure in cm H_2O during mask positive pressure ventilation with a self-inflating bag. The two read lines at 4 and 8 mL/kg represent an expired tidal volume range that is considered appropriate during neonatal ventilation.

Expiratory tidal volume (V_{Te})

There was no significant difference between median (IQR) V_{Te} during manual inflations between the devices; 6.6 (5.5-9.9) mL/kg with the T-piece versus 9.2 (4.9-11.5) mL/kg with the SIB (p=0.34). The median (IQR) V_{Te} for spontaneous breaths coinciding with manual inflations was 5.7 (2.6-9.5) mL/kg with the T-Piece and 8.1 (2.8-11.7) mL/kg with the SIB (p=0.24). During spontaneous breaths V_{Te} was 1.4 (0.8-4.3) mL/kg in T-piece group and 2.0 (0.4-5.0) mL/kg in the SIB group (p=0.60).

Face mask leak

There was no significant difference in the mean (SD) mask leak. Mask leak with the T-piece was 42% (18%) versus 35% (17%) in the SIB (p=0.23).

Correlation between peak pressure and expired tidal volume

There was only a weak relationship between each PIP and V_{Te} for both devices. At a PIP of ~30 cm H_2O, for the T-piece the V_{Te} range was 0 to 20 mL/kg and for the SIB the range was 0 to 26 mL/kg (Figure 2A & 2B).

Resuscitators used lower ventilation rates, longer inflation times and smaller minute ventilation with the T-Piece (see Table 1).

Table 1: Respiratory parameters

	T-Piece (n=19) n=2107	SIB (n=27) n=4572	p-value $p < 0.0001$*
Ventilation rate (/min)	47 (7)	63 (20)	0.0037*
Inflation time (s)	0.63 (0.11)	0.44 (0.13)	<0.0001*
Minute ventilation (mL/kg/min)[#]	348 (179-582)	501 (228-863)	0.039*
PIP (cm H_2O)[#]	29.8 (28.3-31.2)	31.7 (24.9-36.0)	0.0578
PEEP (cm H_2O)[#]	5.6 (4.6-6.6)	0.3 (0.3-0.6)	<0.0001*
V_{Te} (mL/kg)[#]	6.6 (5.5-9.9)	9.2 (4.9-11.5)	0.34
Mask Leak (%)[#]	36% (15-68)	26% (13-46)	0.23

Values are mean (standard deviation) unless indicated [#] median (interquartile range)

Endotracheal intubation

Twenty infants were intubated in the DR (10 T-piece and 10 SIB). Overall 4705 breaths, inflations and spontaneous breaths coinciding with a manual inflation were analysed in intubated infants, 2537 with a T-piece versus 2168 with a SIB (p=0.019). Spontaneous breathing after intubation occurred in 16 (80%) infants with a median (IQR) of 43 (34-56) spontaneous breaths. There was no significant difference between manual inflations spontaneous breaths or spontaneous breaths coinciding with inflation between both devices (see Table 2). After intubation, resuscitator delivered a median (IQR) V_{Te} during inflations of 6.7 (5.3 to 8.8) mL/kg, spontaneous breaths 3.2 (1.1 to 5.0) mL/kg, and spontaneous breaths coinciding with inflation 9.4 (6.7 to 13.4) mL/kg. In comparison, with the SIB, the median (IQR) V_{Te} for inflations was 9.2 (3.3 to 15.0) mL/kg, during spontaneous breaths 3.4 (1.3 to 7.6) mL/kg and spontaneous breaths coinciding with inflation was 11 (4.7 to 15.8) mL/kg.

Table 2: Number (%) of inflations, spontaneous breaths and spontaneous breaths coinciding with inflation between both devices

	T-piece n=2537 inflations	SIB n=2168 inflations	p-value
Inflations	1328 (52%)	1140 (53%)	0.639
Spontaneous breaths	769 (30%)	708 (33%)	0.213
Spontaneous breaths coincide with inflation	440 (18%)	320 (14%)	0.0598

Values are numbers (percentage)

Discussion

There is little evidence to guide clinicians' choice of ventilation device during PPV in the DR (ILCOR Part 7: Neonatal resuscitation, 2005). Resuscitation guidelines suggest using either a flow inflating-bag, a self inflating-bag or a T-piece device if PPV is applied (2005; Biarent et al., 2005; Morley, 2007a). However, these recommendations have been extrapolated from animal and mannequin studies. This is the first study reporting respiratory parameters of two ventilation devices in preterm infants receiving PPV in the DR. We have shown that during PPV resuscitators used significant higher ventilation rates, longer inflation times and delivered higher minute ventilation with an SIB. However, there were no significant differences in the delivered V_{Te}, PIPs and mask leak between the devices.

A manometer is recommended to monitor PIP during PPV to avoid high pressure delivery and provide more consistent inflations (Morley, 2007b). In the T-Piece group resuscitators were able to use a manometer during PPV to guide PIP delivery. In comparison, in the SIB group resuscitators delivered PPV without a manometer. The delivered pressures were similar but more variable (O'Donnell et al., 2005a; Kattwinkel et al., 2009a). However, during manual inflations the delivered PIP was a very weak proxy for the tidal volume delivery which ranged from 1 to 40 mL/kg. In addition, the delivered V_{Te} was often too high or too low and likely to result in over- or under-ventilation and lung damage (Bjorklund et al., 1997; Hillman et al., 2007; Schmölzer et al., 2008; Kattwinkel et al., 2009a). This supports the idea that one single set PIP is not appropriate for all infants (Schmölzer et al., 2008). Further, compliance and resistance of

the lung will change during resuscitation (Hooper et al., 2007; Schmölzer et al., 2008; Te Pas et al., 2008a; Hooper et al., 2009), face mask leak will affect the delivered V_T (Schmölzer et al., 2010a; Schmölzer et al., 2010b; Schmölzer et al., 2010c) and many babies will breathe during PPV contributing to the V_T (Te Pas et al., 2008b; Te Pas et al., 2008c; Te Pas et al., 2009). Therefore it would be more appropriate to measure tidal volume and adjust the PIP to provide a reasonable V_T during PPV instead of targeting a single PIP (Te Pas et al., 2008d; Kattwinkel et al., 2009a; Kattwinkel et al., 2009b). In addition, the delivered V_T was similar during mask PPV and PPV after endotracheal intubation. Furthermore, we have shown that the combination of a spontaneous breath with a manual inflation results in a potentially damagingly high tidal volume.

We found significantly higher ventilation rates, shorter inflations times, higher tidal volumes and a higher MV when a SIB was used. High ventilation rates rapidly lead to overventilation, hypocarbia and cerebral vasoconstriction (Tracy et al., 2004). In addition, the higher ventilation rate in the SIB group might have created "Auto PEEP" or air trapping. The maximum delivered PEEP in the SIB group was 0.6 cm H_2O and therefore any effect of PEEP was very unlikely (Probyn et al., 2004). Although, we observed air trapping in both groups we can only speculate of a possible effect during the first minutes of PPV. Longer inflation times were delivered with the T-Piece, which was most likely due to the observation of the pressure dial during PPV. Although the appropriate MV during neonatal resuscitation of very preterm infants has not been established

yet, the values obtained with the SIB are likely to result in overventilation (Bhutani, 2002; Tracy et al., 2004).

A limitation of our study is the low number in both groups. Respiratory functions could only be measured in a small sample of the randomized infants due to limited availability of personal and equipment. In addition, we did not measure arterial carbon dioxide levels after admission to evaluate if the higher minute ventilation did cause lower CO_2 levels ad admission.

Conclusions

The tidal volume for both devices varied widely during PPV of extremely preterm infants and may have been too high with the SIB. Resuscitators used lower ventilation rates, longer inflation times and delivered smaller minute ventilation with a T-Piece. There were no differences with respect to tidal volume, mask leak or peak inflation pressure. Monitoring of delivered tidal volume during respiratory support after birth might reduce the large variance and provide safer, more effective ventilation.

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Chapter IX

Choice of flow meter determines pressures delivered on a T-piece neonatal resuscitator

Choice of flow meter determines pressures delivered on a T-piece neonatal resuscitator

Introduction

In this chapter I will present the findings form an observational study evaluating pressure delivery with different flow meters.

The Neopuff Infant Resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) is commonly used to provide respiratory support for newborn infants in the delivery room. Hawkes *et al.* (Hawkes et al., 2009) recently highlighted a potentially dangerous feature of this device. Using a commercially available flow meter set at maximum flow, they found that they could deliver peak inflating pressure (PIP) greater than 100 cm H_2O even when the PIP was set at 30 cm H_2O.

We tested a series of different flow meters to determine the pressures delivered at different flow rates.

Methods

The gas flow of five commercially available flow meters (see Figure 1) was analysed using the Timeter RT-200 Flow Analyser (Timeter Instruments Inc., Missouri, USA)

as the gold standard. The scale of each flow meter ranged from 0 to 15 L/min. They were:

- Flow meter 1 (Amvex Corporation, Ontario, Canada, manufacturer number: FM-15IO-AH)

- Flow meter 2 (Ezi-Flow™, Comweld Group Pty. Ltd., Victoria, Australia, manufacturer number: 301307-07-1098)

- Flow meter 3 (Comweld Group Pty. Ltd., Victoria, Australia, manufacturer number: 515817-10-795);

- Flow meter 4 (Anaequip Medical, South Australia, Australia, manufacturer number: 8MFA1001);

- Flow meter 5 (Mediquip Pty. Ltd., Queensland, Australia)

Each flow meter was tested when connected to a wall oxygen outlet. The experiments were repeated with a low flow air/oxygen blender (Cardinal Health Inc., Ohio, USA) in the circuit.

Flowmeter 1 (Amvex Corporation, Ontario, Canada)	Flowmeter 2 (Comweld Group Pty. Ltd., Victoria, Australia)	Flowmeter 3 (Comweld Group Pty. Ltd., Victoria, Australia)	Flowmeter 4 (Anaequip Medical, South Australia, Australia)	Flowmeter 5 (Mediquip Pty. Ltd., Queensland, Australia)

Figure 1

Images of all studied flow meters

We observed the effect of different flow meters on PIP, positive end expiratory pressure (PEEP) and maximum delivered pressure (P_{max}) with increasing gas flow. Positive pressure ventilation was given to a leak free test lung using a Neopuff Infant Resuscitator. PIP and PEEP were measured between the T-piece and test lung using a Florian Respiratory Function Monitor (RFM) (Acutronic Medical Systems, Zug, Switzerland) and recorded at 1000 Hz using Spectra (Grove Medical, London, UK), a program designed for recording physiological data.

Experiment 1: Each flow meter was tested at a gas flow rate of 5 L/min with the Neopuff set to PIP 20 cm H_2O, PEEP 5 cm H_2O and P_{max} 30 cm H_2O. Subsequently, the flow was increased to 10, 15 L/min and maximum gas flow. The gas flow rate of

each flow meter at each set flow rate was recorded and pressures measured. The experiment was repeated with a low flow air/oxygen blender placed in the circuit.

Experiment 2: The series of experiment were repeated with the PIP and P_{max} both set to 30 cm H_2O and using a starting gas flow 10 L/min.

Results

The gas flow measured by the Timeter RT-200 Flow Analyser for each flow meter set at 5, 10, and 15 L/min and maximum gas flow with either wall outlet oxygen or 100% oxygen via a blender are shown in Table 1.

Flow meters: No. 1 Amex; No. 2 Comweld; and No. 3 Comweld

The measured oxygen flows at all set flow rates were similar with either the low flow air/oxygen blender or the wall outlet (see Table 1). Even when the flow was set at maximum, the delivered flow did not rise above 18 L/min. PIP and PEEP did not exceed P_{max} in experiment 1. However, when the P_{max} was set at 30 cm H_2O and the flow set at maximum the delivered flow was up to 18 L/min and the measured PIP slightly exceeded that set (see Figure 2A).
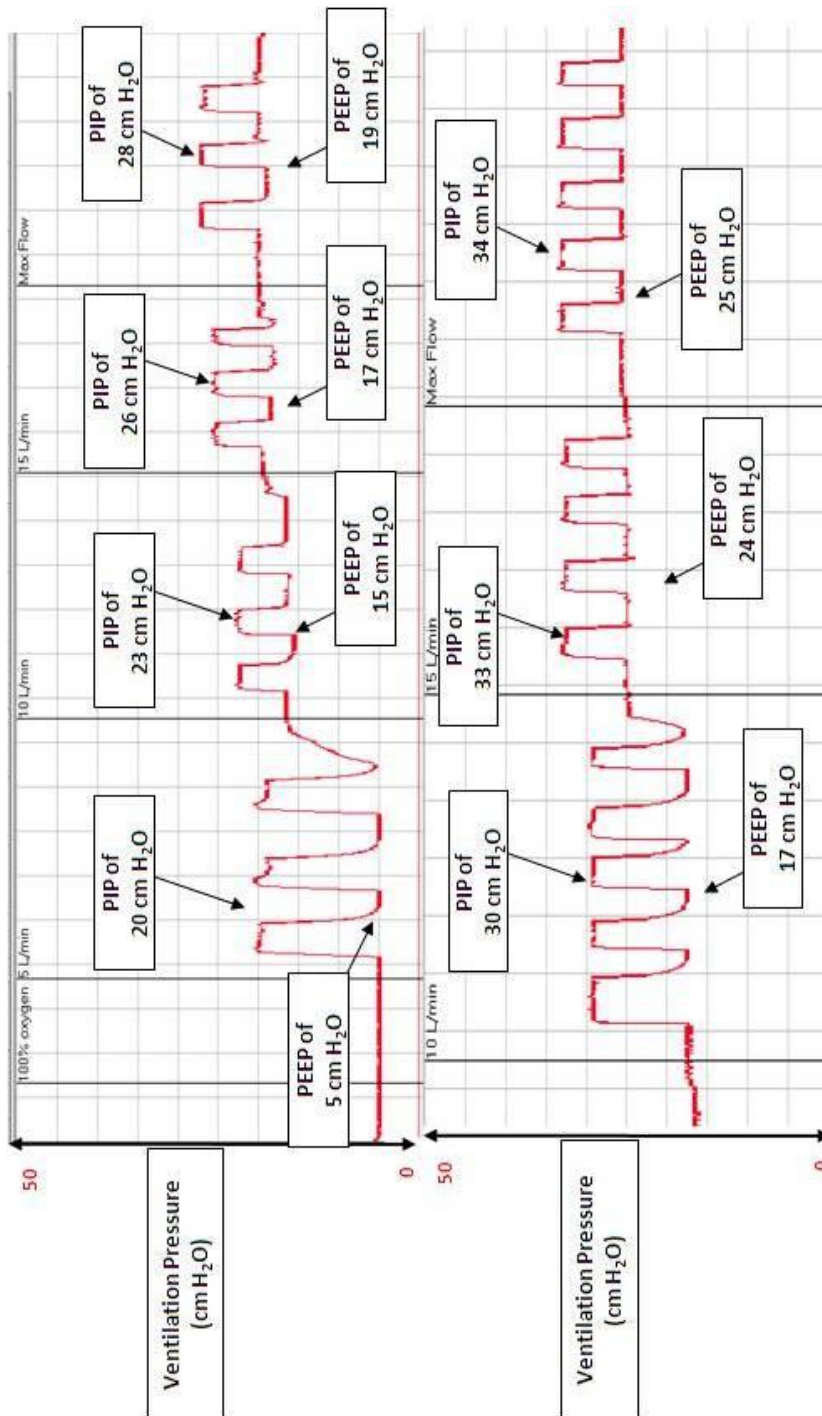
Figure 2A

Positive pressure ventilation (PPV) with a Neopuff infant resuscitator, increasing gas flow rates of 5, 10, 15 L/min and maximum gas flow. PPV with default settings of P_{max} 30 cm H_2O, PIP 20 cm H_2O, PEEP 5 cm H_2O (above); PPV with default settings of P_{max} 30 cm H_2O, PIP 30 cm H_2O, PEEP 5 cm H_2O (below).

Flow meters: No. 4 Anaequip; and No. 5 Mediquip

The delivered oxygen flow at 5, 10 and 15 L/min, were close to the set flow and similar with both the low flow air/oxygen blender and the wall outlet (see Table 1). However, when connected to the wall outlet they delivered a maximum flow of 84.9 and 86.1 L/min respectively. When a low flow air/oxygen blender was placed in the circuit it limited gas flow to 36 L/min for both flow meters.

At oxygen flow rates of 5, 10 and 15 L/min the PIP and PEEP did not exceed the set P_{max}. However, when connected to the wall outlet with oxygen and the flow at maximum, both PIP and PEEP were far above the set P_{max} at 80 cm H_2O and 66 cm H_2O respectively (see Figure 2B). The maximum PIP and PEEP with the low flow air/oxygen blender was 39 cm H_2O and 31 cm H_2O in experiment 1 and 41 cm H_2O and 34 cm H_2O in experiment 2.
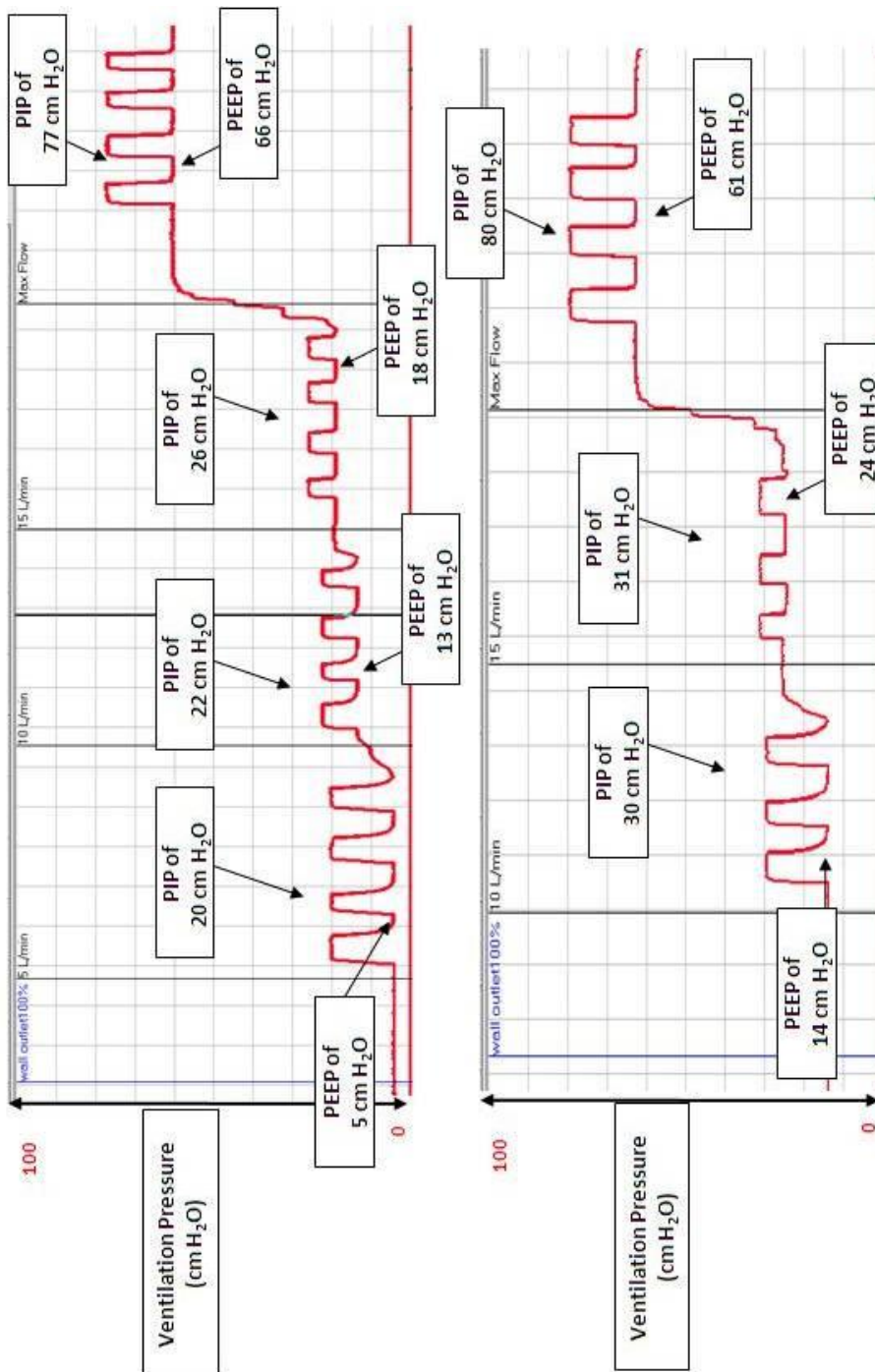
Figure 2B

Positive pressure ventilation (PPV) with a Neopuff infant resuscitator, increasing gas flow rates of 5, 10, 15 L/min and maximum gas flow. PPV with default settings of P_{max} 30 cm H_2O, PIP 20 cm H_2O, PEEP 5 cm H_2O (above); PPV with default settings of P_{max} 30 cm H_2O, PIP 30 cm H_2O, PEEP 5 cm H_2O (below).

Set Flow	Flowmeter 1 (Amvex Corporation, Ontario, Canada) (Manufacturer number: FM-15IO-AH)		Flowmeter 2 (Comweld Group Pty. Ltd., Victoria, Australia) (Manufacturer number: 301307-07-1098)		Flowmeter 3 (Comweld Group Pty. Ltd., Victoria, Australia) (Manufacturer number: 515817-10-795)		Flowmeter 4 (Anaequip Medical, South Australia, Australia) (Manufacturer number: 8MFA1001)		Flowmeter 5 (Mediquip Pty. Ltd., Queensland, Australia) (Manufacturer number: CIG515800)	
	wall outlet 100% O2	Blender 100% O2	wall outlet 100% O2	Blender 100% O2	wall outlet 100% O2	Blender 100% O2	wall outlet 100% O2	Blender 100% O2	wall outlet 100% O2	Blender 100% O2
Flow 5 L/min	4.8	4.7	6	6	4.8	4.8	4.8	4.8	4.2	4.3
Flow 10 L/min	10.5	10.1	11.4	11	10	10	9	9	9.8	9.5
Flow 15 L/min	15.3	15	15.3	13.9	14.9	14.6	12.3	13.1	14.8	14.3
max Flow	17.8	16.8	15.6	14.8	18	17.1	84.9	32.9	86.1	36

Table 1

Gas flow measured with the Timeter RT-200 flow analyser using each flow meter at 5, 10, and 15 L/min and maximum gas flow with 100% oxygen either from an oxygen wall outlet or a low flow air/oxygen blender

Discussion

When using a Neopuff, failure to deliver the set airway pressures may be due to large face mask leak (O'Donnell et al., 2005;Wood et al., 2008;Schmölzer et al., 2009b). Resuscitators commonly try to improve the airway pressure by increasing gas flow instead of correcting face mask position. This study and the paper of *Hawkes et al. (Hawkes et al., 2009).*, showed high flows through a Neopuff can cause excessive PIP and PEEP.

A study by Hawkes *et al. (Hawkes et al., 2009).*, using a Neopuff, demonstrated the P_{max} valve can be overridden when the gas flow is very high. When the measured gas flow was 85 L/min the delivered PIP and PEEP exceeded 100 and 70 cm H_2O. Our study found the performance of different flow meters varies. Some of that flow meters have a safety feature incorporated whereby the maximum delivered flow is restricted. Using two of the commercially available flow meters we were able to reproduce *Hawkes et al. (Hawkes et al., 2009).* results (see Figure 2B). However three other flow meters did not deliver excessive PIPs even when the flow was maximal (see Figure 2A). A low flow air/oxygen blender placed in the circuit provided some safeguard against excessive flow and pressure. In addition, we observed an increase in PEEP in all flow meters with increasing gas flow rates (see Figure 2A & 2B). In particular the increase from 5 L/min to 10 L/min showed the greatest increase in PEEP. This might be associated with a lower tidal volume delivery during positive pressure ventilation and may reduce its effectiveness.

The important messages from these studies for clinicians using the Neopuff Infant Resuscitator are: Some flow meters that are marked to deliver a flow from 0 to 15 L/min can deliver very high gas flows, when turned to maximum, which will overwhelm the pressure control valves in the Neopuff. The Neopuff should always be used according to the manufacturer's instructions which state that the recommended operating gas flow range is 5 to 15 L/min and, "Do not attempt to use a gas flow higher than 15 L/min" (Morley et al., 2009).

We suggest that operators set the gas flow to 8 L/min, set the desired PEEP and PIP and then do not alter the flow. If the PEEP and PIP are not delivered this is probably due to a large leak between the mask and face and should be remedied by altering mask position and not by increasing the flow (Morley et al., 2009;Schmölzer et al., 2009a).

The important message from these studies for designers of flow meters is also simple: Flow meters should not be able to deliver gas flow above 15 L/min. Existing flow meters which are able to deliver higher gas flows should be equipped with a flow restrictor to limit the gas flow to 15 L/min (Ryan et al., 2009).

Conclusion

In this chapter I have presented that Flow meters differ in the maximum flow they can deliver. When set to maximal flow, some deliver far more than the expected flow and consequently excessive PIP and PEEP. The presence of a low flow air/oxygen blender reduces the risk of excessive flow delivery.

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Chapter X

Respiratory Function Monitor to reduce Mortality and Morbidity in preterm infants

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter X "Respiratory Function Monitor to reduce Mortality and Morbidity in preterm infants"

Declaration by candidate

In the case of Chapter X the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, Literature search and review of literature, writing the manuscript	80%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Morley CJ	Revising the manuscript	
Davis PG	Literature search and review of literature, revising the manuscript	

Candidate's Signature	███████████████████	Date 20/7/10

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

	Date
Signature 1 ████████	18.7.10
Signature 2 ████████	20.7.10

10.2 INTRODUCTION

The purpose of applying a peak inflation pressure (PIP) during positive pressure ventilation (PPV) is to inflate the lungs with an appropriate tidal volume and thereby facilitate gas exchange. The appropriate tidal volume (V_T) to be delivered during various phases of resuscitation is unknown. Tidal volumes that are too high can damage the lungs by over inflation and tidal volumes that are too small will result in inadequate gas exchange.

In *Chapter* V and *Chapter VI,* I have shown that during PPV highly variable tidal volumes are delivered. In addition, human and animal observational studies suggest V_T during resuscitation should be within a range of 4 to 8 mL/kg and that large tidal volumes can damage the lungs by over inflation. Lung compliance and therefore the pressures required to deliver an appropriate tidal volume, varies greatly immediately after birth. There are even greater differences *between* infants depending on the immaturity of the lung and their own variable contributions, which are adding to the inconsistency of volumes delivered by a set PIP. Experts have suggested that the techniques used in the neonatal intensive care unit to monitor heart rate, oxygen saturation and tidal volume should be applied during neonatal resuscitation. Instituting such practice may help to improve survival rate and reduce neurodevelopmental morbidity of term and preterm infants. In this Chapter I aimed to summarise the evidence from randomised controlled trials related to the use of a Respiratory Function Monitor during neonatal resuscitation to highlight gaps in the evidence base and assist in the identification of best practice.

10.3 Respiratory Function Monitor to reduce Mortality and Morbidity in preterm infants

The following chapter has been published as a Cochrane Review thus it is presented in PDF as per Monash University guidelines for thesis by publication.

Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation (Review)

Schmölzer GM, Morley CJ, Davis PG

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[Intervention Review]

Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation

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A B S T R A C T

Background

A respiratory function monitor is routinely used in neonatal intensive care units to continuously measure and display airway pressures, tidal volume and leak during ventilation. During positive pressure ventilation in the delivery room, clinical signs are used to monitor the effectiveness of ventilation. The additional use of a respiratory function monitor during positive pressure ventilation in the delivery room might help to improve the effectiveness of ventilation.

Objectives

To determine whether the use of a respiratory function monitor in addition to clinical assessment compared to clinical assessment alone in newborn infants resuscitated with positive pressure ventilation reduces mortality and morbidity.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 3, 2010), MEDLINE (January 1996 to March 2010), EMBASE (January 1980 to March 2010) and CINAHL (January 1982 to March 2010). Clinical trials registers and the abstracts of the Society for Pediatric Research and the European Society for Pediatric Research were searched from 2004 to 2009. No language restrictions were applied.

Selection criteria

We planned to include randomised and quasi-randomised controlled trials and cluster trials that compared the use of a respiratory function monitor in addition to clinical assessment, compared to clinical assessment alone, in newborn infants resuscitated with positive pressure ventilation.

Data collection and analysis

Two review authors independently evaluated the search results against the selection criteria. Data extraction and risk of bias assessment were not performed because there were no studies that met our inclusion criteria.

Main results

No studies were found meeting the criteria for inclusion in this review

Authors' conclusions

There is insufficient evidence to determine the efficacy and safety of a respiratory function monitor in addition to clinical assessment during positive pressure ventilation at neonatal resuscitation. Randomised clinical trials comparing positive pressure ventilation with and without a respiratory function monitor in addition to clinical assessment at neonatal resuscitation are warranted.

PLAIN LANGUAGE SUMMARY

Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation

When resuscitating a newborn baby, the team attending to the baby uses clinical judgement to determine how much assisted breathing is required during resuscitation. However, this approach is frequently inadequate. A respiratory function monitor measures the amount of air going into the babies lung. The clinical team can use this information to deliver better care to a newborn baby when assisted breathing alone is required. We were unable to identify any studies that compared the clinical judgement of assisted breathing with clinical judgement of assisted breathing plus the additional use of a respiratory function monitor to reduce mortality and morbidity in newborn infants receiving resuscitation.

BACKGROUND

Description of the condition

Approximately three to six percent of all newborn infants require respiratory assistance at birth (Singhal 2001). An internationally agreed consensus statement provides advice regarding techniques and equipment for neonatal resuscitation (International Liaison Committee on Resusc. 2005). Positive pressure ventilation (PPV) is commonly used in the delivery room (Singhal 2001) and is a cornerstone of neonatal resuscitation (Bennett 2005; O'Donnell 2004). The object of the first few inflations is to establish a functional residual capacity (FRC) and deliver an appropriate tidal volume (V_T) to achieve effective gas exchange (te Pas 2008b).

Clinical signs including visible chest wall movements and increases in heart rate are used to monitor the effectiveness of ventilation techniques during neonatal resuscitation (International Liaison Committee on Resusc. 2005). This contrasts with neonatal intensive care units where ventilation is guided by respiratory function monitors that are built into all modern ventilators (Bhutani 2002; Keszler 2005; Klimek 2006; South 1986).

The delivered V_T is usually not measured during neonatal resuscitation. Excessive V_T can damage the lungs by overinflation (volutrauma) and insufficient V_T will result in inadequate gas exchange (Bhutani 2002; Bjorklund 1996; Bjorklund 1997; Dreyfuss 1993; Dreyfuss 1998; Hillman 2007; Jobe 1998; Polglase 2008; Tremblay 2006; Vilstrup 1996; Wada 1997). Animal studies have shown that lung injury can occur during resuscitation with just a few large manual inflations (Bjorklund 1997). Dreyfuss (Dreyfuss 1985) demonstrated in a rat model that high tidal volumes rather than high pressures were responsible for lung injury. When the V_T was controlled to prevent overdistention of the lungs, there was little or no injury. These animal and human observational data suggest that the V_T during resuscitation should be within the range 4 to 8 mL/kg (Bjorklund 1997; Hillman 2007; Polglase 2008; Vilstrup 1996; Wada 1997). The delivered V_T and, therefore, the optimum peak inflation pressure (PIP) will vary both between infants and in the same infant over time as the lung aerates, the infant starts to breathe and compliance and resistance change (Hooper 2007; te Pas 2008b).

Susceptibility to volutrauma as a result of excessive tidal volume delivery may be increased in more immature infants. Some observational studies of pulmonary function monitoring have been conducted in the delivery room (Menakaya 2004; te Pas 2008a; te Pas 2009; Tracy 2004). In an observational study, Menakaya 2004 compared a standard anaesthetic rebreathing circuit with volume guarantee ventilation using a Draeger ventilator during neonatal resuscitation. In both groups infants were overventilated and had mean tidal volumes of more than 9 mL/kg.

Research by te Pas and coworkers described different breathing patterns in preterm infants (te Pas 2008a) and the interactions between spontaneous breaths, manual ventilation and tidal volumes during stabilisation of infants with congenital diaphragmatic hernia (te Pas 2009).

Ventilation may be inadequate because of a leak between the mask and the face. This occurs frequently, even for experienced operators, and may be highly variable (O'Donnell 2005; Schmölzer 2010; Wood 2008b; Wood 2008c). In studies using a mannequin, Wood and coworkers (Wood 2008a) showed that mask leak could

be halved if the resuscitator was able to see the V_T and leak displayed by a respiratory function monitor.

Clinical assessment

During PPV the clinician should look at an increase in heart rate and observe chest wall movements to gauge effectiveness of ventilation. Rapid improvement of heart rate remains the primary clinical indicator of effective PPV. However, if heart rate does not increase, chest wall movements should be assessed to gauge adequacy of ventilation. If a manometer is used during PPV, clinicians can gauge the applied pressures. If the heart rate is not rising and the chest is not moving, the clinician may seek to improve mask position or increase the applied pressure (International Liaison Committee on Resusc. 2005). Clinicians require training in these procedures. This is usually provided by recognized training programs such as the *Neonatal Resuscitation Program* (USA) or the *Newborn Life Support Course* (United Kingdom).

Ventilation devices

The effectiveness of a respiratory function monitor (RFM) might vary depending on the type of ventilation device used.

Self-inflating bag

A self-inflating bag will re-expand following compression due to its own elastic recoil; a compressed gas source is not required to function, though one is usually attached to enhance oxygen delivery. The greatest advantage is the simplicity of use, particularly for the inexperienced operator. However, the same operator could be falsely reassured that a sufficient V_T is being delivered when in reality, due to a large leak, it is not.

Flow-inflating bag

A flow-inflating (anaesthesia) bag requires a compressed gas source to inflate the bag during use. Large leaks at the facemask or too low flow will result in complete collapse of the bag and inability to deliver any tidal volume. While this makes operation technically more difficult, the operator's attention is immediately drawn to large leaks. These devices can apply very high pressures and should only be used with a manometer and a blow off valve in the circuit (Bennett 2005; O'Donnell 2004).

T-piece mechanical device

A T-piece has a gas flow into the attached facemask, nasal prong or endotracheal tube through an "inlet" arm. Inflation is achieved by interrupting the escape of gas through the "outlet" hole with a finger. A safety blow-off valve is usually attached.

Skills and accreditation in the use of the listed devices is provided by recognized training programs such as the *Neonatal Resuscitation Program* (USA) or the *Newborn Life Support Course* (United Kingdom).

Interfaces

The effectiveness of a RFM might vary depending on the type of ventilation interface used. PPV might be performed using either a face mask, nasal prong or an endotracheal tube.

Face mask

A face mask attached to a ventilation device can be used to deliver PPV. A face mask will cover the mouth and nose of an infant which maybe is an advantage; however, achieving a good face mask seal is difficult (Schmölzer 2010a).

Nasal prong

Either a single prong or two prongs inserted a short distance into the nostrils and attached to a ventilation device can be used to deliver PPV.

Endotracheal tube

An internationally agreed consensus statement advises that PPV can be initiated using manual ventilation devices via a face mask (International Liaison Committee on Resusc. 2005); however, endotracheal intubation may be indicated to continue PPV.

Description of the intervention

A RFM measures and displays airway pressure, gas flow and tidal volume. A flow sensor is placed between the face mask or endotracheal tube and the ventilation device. The inspiratory and expiratory tidal volumes (V_{Ti}, V_{Te}) passing through the sensor are automatically calculated by integrating the flow signal. In addition, the percentage of leak between mask and face or around an endotracheal tube (ETT) is calculated and displayed with the following equation: $[(V_{Ti} - V_{Te})\ V_{Ti}] \times 100$. An airway pressure monitoring line is connected to measure and display Peak Inflation Pressure (PIP) and Positive End Expiratory Pressure (PEEP) (Schmölzer 2010a).

It is unclear whether similar benefits will be observed and outcomes following resuscitation improved if a RFM is used in the delivery room in conjunction with the standard techniques of clinical assessment.

We planned to include studies evaluating all commercially available RFMs (e.g. Florian Neonatal Respiratory Function Monitor, Acutronic Medical Systems AG, Zug, Switzerland; Respironics NICO and NICO2 Philips, Amsterdam, Netherlands; $CO_2 SMO$ $^{+\circledR}$, Novametrix Inc., Wallingford, CT, USA). Any studies evaluating similar devices were also to be included in the review. All of these devices are applicable to patients of different size (e.g. neonates, children, adults).

- A Florian Neonatal Respiratory Monitor (Acutronic Medical Systems AG, Zug, Switzerland) continuously displays pressure, flow and tidal volume waves. It also measures and displays numerical values for PIP, PEEP, V_{Ti}, V_{Te}, respiratory rate (RR), expiratory minute ventilation (MV_e) and displays the percentage of the leak between mask and face or around an ETT.

- A Respironics NICO2 Monitor (Philips, Amsterdam, Netherlands) continuously measures and displays numerical

values for V_{Te}, RR, alveolar minute volume (MV_{alv}), PIP and PEEP.

• The pneumotachograph $CO_2SMO^{+®}$, (Novametrix Inc., Wellingford, CT, USA) continuously measures and displays numerical values for V_T, RR, PIP and PEEP.

The displayed information as well as the design of the screen are the major differences between all available RFMs. These differences might have an effectiveness on the feedback to the resuscitator during PPV. Inexperience and lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals. Therefore, anyone using a RFM must be trained to interpret pressure, flow and tidal volume signals (Schmölzer 2010a). Likewise, resuscitation using clinical signs (with or without the RFM) should be performed by an operator trained in the techniques.

How the intervention might work

A RFM may be applied during PPV in the delivery room. The resuscitator receives real-time measures of delivered tidal volume, applied airway pressure and gas leak. During PPV the resuscitator is able to see a RFM that displays waveforms and numerical values of V_T, PIP, gas flow, RR or percentage of mask leak. Using this information in addition to clinical assessment, the clinician can alter face mask position to reduce face mask leak as well as observe the delivered tidal volume to adjust the delivered PIP (Schmölzer 2010a).

Failure of ventilation may be due to a big leak either around the face mask or ETT. A RFM displays any leak; hence, the resuscitator can alter the face mask position and optimise face mask hold or change to a larger diameter ETT if the leak is big and no effective ventilation occurs (Schmölzer 2010a).

During PPV the compliance and, therefore, the delivered tidal volume varies. In order to maintain a constant tidal volume the applied pressure has to be adjusted. A RFM displays the delivered tidal volume, so that the resuscitator then can alter the delivered pressure by either squeezing a flow- or self-inflating bag harder or alter the pressure dial on a T-piece resuscitator.

Why it is important to do this review

In spite of improvements in neonatal resuscitation, some infants die and some survive with cognitive impairments. Experts have suggested that the techniques used in the neonatal intensive care unit to monitor heart rate, oxygen saturation and tidal volume should be applied during neonatal resuscitation (Kattwinkel 2009; Schmölzer 2010a; Vento 2008a; Vento 2008b). Instituting such practice may help to improve survival rate and reduce neurodevelopmental morbidity of term and preterm infants (Vento 2008a; Vento 2008b). This review aims to summarise the evidence from randomised controlled trials related to the use of a RFM during

neonatal resuscitation. The results from this review will highlight gaps in the evidence base and assist in the identification of best practice.

OBJECTIVES

To determine the effect of using a respiratory function monitor in addition to clinical assessment, compared to clinical assessment alone, on mortality and morbidity in newborn infants resuscitated with positive pressure ventilation.

Further subgroup analysis was planned to determine whether the safety and efficacy vary according to:

• Gestational age: Term (37 weeks' gestation and above) vs. preterm between 29 and 36 weeks vs. preterm < 29 weeks infants

• Interface for delivering positive pressure ventilation: Mask vs. single nasal prong vs. endotracheal tube

• Ventilation device for delivering positive pressure ventilation: Self-inflating bag vs. flow-inflating bag vs. T-piece device

• Type of Respiartory Function Monitor: Subgroup analysis based on the model of the RFM

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials available as abstracts or peer-reviewed manuscripts were to be included. Cluster trials were to be individually examined and, if possible, included in the same meta-analysis.

Types of participants

Term and preterm infants resuscitated using a RFM in addition to clinical assessment compared to clinical assessment alone.

Types of interventions

Positive pressure ventilation with a RFM visible versus positive pressure ventilation where the operator is blinded to the display of the RFM. Inexperience and lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals. Therefore, anyone using a RFM must be trained to interpret pressure, flow

and tidal volume signals. Likewise, resuscitation using clinical signs (with or without the RFM) should be performed by an operator trained in the techniques. For the purposes of this review, only studies where clinical staff were trained in both resuscitation and the use of a RFM were considered eligible for inclusion.

Types of outcome measures

Primary outcomes

- Neonatal death < 28 days.
- Death before discharge.

Secondary outcomes

- Percentage leak during positive pressure ventilation with any interface (e.g. face mask, nasal prong).
- Tidal volume (in mL/kg) during positive pressure ventilation with any interface (face mask, nasal prong, endotracheal tube).
  - Apgar score at one and five minutes.
  - Heart rate (beats per minute) at five minutes.
  - Oxygen saturation (%) at one and five minutes.
  - Endotracheal intubation in the delivery room.
- Endotracheal intubation in the neonatal intensive care unit during hospitalisation.
- Air leaks (pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema) reported either individually or as a composite outcome.
- Duration of supplemental oxygen requirement (number of days).
- Duration of respiratory support, i.e. nasal continuous airway pressure and ventilation via an endotracheal tube considered separately and in total (number of days).
- Chronic lung disease: Need for supplemental oxygen at 28 days of life; need for supplemental oxygen at 36 weeks postmenstrual age for infants born at or before 32 weeks gestation.
- Cranial ultrasound abnormalities: Any intraventricular haemorrhage (IVH) grade 3 or 4 according to Papile classification (Papile 1978) and cystic periventricular leukomalacia.
  - Seizures including clinical and electroencephalographic.
  - Hypoxic ischaemic encephalopathy (Grade I-III; Sarnat 1976).

Search methods for identification of studies

We used the standard methods of the Cochrane Neonatal Review Group guidelines.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*, Issue 3, 2010), MEDLINE via PubMed (January 1996 to March 2010), EMBASE (January 1980 to March 2010) and CINAHL (January 1982 to March 2010) using the search terms Infant, Newborn, Resuscitation, Positive Pressure Respiration, Respiratory Function Tests and Monitoring, physiologic. All languages were included. The full search strategies used are detailed in Appendix 1.

Searching other resources

Published abstracts: The abstracts of the Society for Pediatric Research from 2004 to 2009 were searched electronically through the PAS web site (abstractsonline). Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp). The results of the search of trials registries are detailed in Appendix 2.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group guidelines.

Selection of studies

We planned for each review author to independently select studies for inclusion, based on the criteria set out above, by screening the titles and abstracts obtained through the searches. We planned to obtain the full text articles in cases where studies appeared to be eligible for inclusion. Disagreements were to be resolved by discussion. All randomised and quasi-randomised controlled studies as well as cluster trials fulfilling the described in the previous section were included.

Data extraction and management

We planned for each review author to independently assess methodology and extract data followed by comparison of results and discussion to resolve any differences found at each stage. Assessment of methodology regarding blinding of randomisation, intervention and outcome measurements as well as completeness of follow-up was planned.

Assessment of risk of bias in included studies

We planned to independently review the methodological quality of each trial including assessment of a) masking of allocation; b) masking of intervention; c) completeness of follow-up; and d) masking of outcome assessment. This information was to be included in the 'Characteristics of included studies' table.

In addition, we planned to complete the Risk of Bias table addressing the following methodological issues:

1. Sequence generation: Was the allocation sequence adequately generated?

For each included study, we planned to describe the method used to generate the allocation sequence as: adequate (any truly random process, e.g. random number table; computer random number generator); inadequate (any nonrandom process, e.g. odd or even date of birth; hospital or clinic record number); or unclear.

2. Allocation concealment: Was allocation adequately concealed?

For each included study, we planned to describe the method used to conceal the allocation sequence as: adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or unclear.

3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

For each included study, we planned to describe the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We planned to assess the methods as: adequate, inadequate or unclear for participants; adequate, inadequate or unclear for study personnel; and adequate, inadequate or unclear for outcome assessors and specific outcomes assessed.

4. Incomplete outcome data: Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis. We planned to address whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We planned to assess methods as: adequate ($\leq$ 20% missing data); inadequate (> 20% missing data) or unclear.

5. Selective outcome reporting: Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we planned to assess the possibility of selective outcome reporting bias as: adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported); inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or unclear.

6. Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we planned to note any important concerns regarding other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or

whether the trial was stopped early due to some data-dependent process). We planned to assess whether each study was free of other problems that could put it at risk of bias as: yes; no; or unclear.

Measures of treatment effect

We planned to evaluate the treatment effect using a fixed-effect model as follows:

- categorical data using relative risk (RR), relative risk reduction, risk difference (RD) and number needed to treat (NNT);
- continuous data using mean and standard deviation and weight mean difference;
- the 95% confidence interval (CI) for each measure of effect;
- for cluster trials, analysis at the level of the individual while accounting for the clustering.

Assessment of heterogeneity

We planned to apply tests for between study heterogeneity including the I^2 test to assess the statistical heterogeneity. If heterogeneity was identified, we planned to perform further analyses to identify the cause.

Data synthesis

If multiple studies were identified, we planned to perform meta-analysis using Review Manager 5 (RevMan) software. For estimates of typical relative risk and risk difference, we planned to use the Mantel-Haenszel method. For measured quantities, we planned to use the inverse variance method. We planned to conduct all meta-analyses using the fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to perform the following subgroup analyses:

- gestational age < 29 weeks, 29 to 36 weeks, 37 weeks and above;
- ventilation device used (self-inflating bag, flow-inflating bag, T-piece, mechanical ventilator);
- patient interface used (face mask, endotracheal tube, nasopharyngeal tube);
- specific respiratory function monitors.

Sensitivity analysis

We planned to perform sensitivity analyses to evaluate the effect of trial quality. We planned to define high quality trials as those having adequate randomisation and allocation concealment, blinded measurement of outcomes and < 10% losses to follow up in intention-to-treat analysis.

RESULTS

Description of studies

See: Characteristics of ongoing studies.
The initial search identified 34 abstracts. Of these, we identified one as potentially relevant. However, on closer inspection, it did not meet the inclusion criteria for this review.

Results of the search

No studies were found meeting the criteria for inclusion in this review. One ongoing trial was found comparing a RFM either visible or covered during PPV in preterm infants < 32 weeks gestation.

Included studies

No studies were found meeting the criteria for inclusion in this review.

Excluded studies

One ongoing trial was found comparing a RFM either visible or covered during PPV in preterm infants < 32 weeks gestation. Each infant requiring PPV at birth will have a flow sensor placed between the ventilation device and the face mask. The clinical team will have either a RFM visible or masked to assist with the clinical judgement. The primary outcomes of this trial are a reduction in face mask leak and reduction in tidal volume delivery.
See: Characteristics of ongoing studies.

Risk of bias in included studies

No studies met the criteria for inclusion in this review.

Effects of interventions

No studies met the criteria for inclusion in this review.

DISCUSSION

We found no randomised or quasi-randomised controlled trials addressing the use of a respiratory function monitor in addition to clinical assessment compared to clinical assessment alone during neonatal resuscitation, thus, this systematic review does not establish whether its use reduces mortality and morbidity, or results in harm. We conclude that the additional use of a respiratory function monitor in this context is based only on evidence derived from mannequin studies (O'Donnell 2005; Wood 2008a; Wood

2008c) and observational studies (Schmölzer 2010a; Schmölzer 2010). Future studies should enrol both term and preterm infants who require positive pressure ventilation at birth. Important outcomes would include those specified in our criteria for considering studies for this review.

Summary of main results

No studies met the criteria for inclusion in this review.

Overall completeness and applicability of evidence

There is insufficient evidence to determine the efficacy and safety of a respiratory function monitor in addition to clinical assessment during positive pressure ventilation at neonatal resuscitation.

Quality of the evidence

There is insufficient evidence to determine the efficacy and safety of a respiratory function monitor in addition to clinical assessment during positive pressure ventilation at neonatal resuscitation.

Potential biases in the review process

No studies met the criteria for inclusion in this review.

Agreements and disagreements with other studies or reviews

No studies met the criteria for inclusion in this review.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine the efficacy and safety of a respiratory function monitor in addition to clinical assessment during positive pressure ventilation at neonatal resuscitation.

Implications for research

Randomised clinical trials comparing positive pressure ventilation with and without a respiratory function monitor in addition to clinical assessment at neonatal resuscitation are warranted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of ongoing studies *[ordered by study ID]*

Schmölzer 2010

Trial name or title	In extremely low birth weight (ELBW) infants who require positive pressure ventilation at birth, does the use of a respiratory function monitor reduce face mask leak and improve the target tidal volume in the first ten minutes of life?
Methods	A randomised controlled trial of a respiratory function monitor during positive pressure ventilation during resuscitation of infants. A flow sensor will be placed between the mask and the Neopuff T-piece-device. This flow sensor measures the airflow and calculates the tidal volume. Each infant requiring positive pressure ventilation at birth will be recorded with the flow sensor in place. The duration of this recording will last during the initial stabilisation in the delivery room.
Participants	Preterm infants ≤ 32 weeks gestation
Interventions	Intervention: In the intervention group the respiratory function monitor is visible, so that the resuscitator can see the display of the respiratory function monitor to alter their technique and adjust the delivered tidal volume. Control: In the comparator group the respiratory function monitor is masked, so that the resuscitator cannot see the display or hear any alarms of the respiratory function monitor.
Outcomes	• Reduction of face mask leak during positive pressure ventilation • Difference in the delivered tidal volume • Changes in heart rate in the first ten minutes of life • Changes in oxygen saturation in the first ten minutes of life • Rate of intubation in the delivery room • Total days of ventilation support during hospital stay • Total days of respiratory (ventilation, continuous positive airways pressure (CPAP), oxygen) support during hospital stay • Oxygen treatment at 36 weeks gestational age
Starting date	11/11/2008
Contact information	Dr. Georg Schmölzer Department of Newborn Research The Royal Women's Hospital 20 Flemington Road, Parkville, 3052, Victoria, Australia Email: ▮▮▮▮▮▮▮▮▮▮▮▮▮▮ Tel: +61 (0)3 8345 - 3775 Fax: +61 (0)3 8345 - 3789
Notes	Update: Recruitment completed

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategies

Search strategy for MEDLINE/PubMed

Limits activated: Humans, Clinical Trial, Randomized Controlled Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinical Trial, All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Publication Date from 1996/01/01 to 2010/06/20

#1 MeSH descriptor Infant explode all trees (Result: 23,584)

#2 MeSH descriptor Newborn explode all trees (Result: 11,117)

#3 MeSH descriptor Resuscitation explode all trees (Result: 1,101)

#4 (#1 OR #2) AND #3 (Result: 702)

#5 MeSH descriptor Positive Pressure Respiration explode all trees (Result: 401)

#6 MeSH descriptor Respiratory Function Tests explode all trees (Result: 3,651)

#7 MeSH descriptor Monitoring, physiologic all trees (Result: 1,947)

#8 #5 AND (#6 OR #7) (Result: 188)

#9 (#4 AND #8) (Result: 34 ; Number needed to read the full article 1)

Search strategy for EMBASE

Limits activated: ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([newborn]/lim OR [infant]/lim OR [preschool]/lim OR [child]/lim) AND [humans]/lim AND [1980-2010]/py

#1'infant'/exp OR infant (Result: 13,597)

#2'newborn'/exp OR newborn (Result: 9,121)

#3'resuscitation'/exp OR resuscitation (Result: 176)

#4 (#1 OR #2) AND #3 (Result: 129)

#5 positive AND ('pressure'/exp OR pressure) AND ('respiration'/exp OR respiration) (Result: 278)

#6 respiratory AND function AND tests (Result: 1,22)

#7 monitoring, AND physiologic (Result: 33)

#8 #5 AND (#6 OR #7) (Result: 15)

#9 #4 AND #8 (Result: 0)

Search strategy for CINAHL

Limits activated: Human, 01/1982 - 05/2010, Infant, Newborn: birth - 1month

S1 (MH "Infant") (Result: 52,185)

S2 (MH "Newborn") (Result: 52,185)

S3 (MH "Resuscitation") (Results 1,029)

S4 (S1 or S2) AND S3 (Result: 1,031)

S5 (MH "Positive Pressure Respiration") (Result: 2)

S6 (MH "Respiratory Function Tests") (Result: 100)

S7 (MH "Monitoring, physiologic") (Result: 198)

S8 S5 and (S6 OR S7) (Result: 0)

S9 S4 and S8 (Result: 0)

Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Infant explode all trees (Result: 9,243)

#2 MeSH descriptor Newborn explode all trees (Result: 9,240)

#3 MeSH descriptor Resuscitation explode all trees (Result: 2,505)

#4 #1 AND #3 (Result: 471)

Respiratory function monitoring to reduce mortality and morbidity in newborn infants receiving resuscitation (Review)   **11**

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#5 MeSH descriptor Positive Pressure Respiration explode all trees (Result: 1,371)
#6 MeSH descriptor Respiratory Function Tests explode all trees (Result: 16,698)
#7 MeSH descriptor physiologic Monitoring explode all trees (Result: 6,569)
#8 #6 AND (#7 OR #8) (Result: 730)
#9 (#4 AND #8) (Result: 17) (Number needed to read the full article 1)

Appendix 2. Trials registries

Search strategy for International Clinical Trial Registry Platform (http://who.int/ictrp)
#1 Infant OR Newborn AND Resuscitation AND Positive Pressure Respiration - Result: 4
#2 Infant OR Newborn AND Resuscitation AND Respiratory Function Tests - Result: 0
#3 Infant OR Newborn AND Resuscitation AND physiologic Monitoring - Result: 0
Search strategy for http://clinicaltrials.gov/
#1 Infant OR Newborn AND Resuscitation AND Positive Pressure Respiration - Result: 3 and 1 terminated
#2 Infant OR Newborn AND Resuscitation AND Respiratory Function Tests - Result:
#3 Infant OR Newborn AND Resuscitation AND physiologic Monitoring - Result: 0
Search strategy for http://controlled-trials.com
#1 Infant OR Newborn AND Resuscitation AND Positive Pressure Respiration - Result: 0
#2 Infant OR Newborn AND Resuscitation AND Respiratory Function Tests - Result: 0
#3 Infant OR Newborn AND Resuscitation AND physiologic Monitoring - Result: 0

H I S T O R Y

Protocol first published: Issue 3, 2010

Review first published: Issue 9, 2010

C O N T R I B U T I O N S   O F   A U T H O R S

Dr. Georg Schmölzer and Prof. Peter Davis performed the literature search. Dr. Georg Schmölzer wrote the manuscript, which was reviewed by Prof. Peter Davis and Prof. Colin Morley.

D E C L A R A T I O N S   O F   I N T E R E S T

Dr. Georg Schmölzer is an investigator for the ongoing study cited in this review (Schmölzer 2010).

S O U R C E S   O F   S U P P O R T

Internal sources

- The Royal Women's Hospital, Australia.
- University of Melbourne, Australia.
- Monash University, Australia.

External sources

- Murdoch Childrens Research Institute, Australia.
- National Health and Medical Research Council, Australia.
- Medical University Graz, Austria.

Chapter XI

Respiratory Function Monitor for tidal volume targeting during Positive Pressure Ventilation in preterm infants in the Delivery Room – a randomised trial

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter XI "Respiratory Function Monitor for Tidal Volume Targeting during Positive Pressure Ventilations in the Delivery room – a randomised trial"

Declaration by candidate

In the case of Chapter XI the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, ethics application, data collection, data analysis, writing and revising the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Hooper SA	Revising the manuscript	
COF Kamlin	Help with data collection, revising the manuscript	
Dawson JA	Help with data collection, revising the manuscript	
Donath S	Statistics advice	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature	███████████████	Date 28/10/15

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	███████████	3/ 1φ/10
Signature 2	███████████	01/10/10
Signature 3	███████████	01/10/10
Signature 4	███████████	29/10/10
Signature 5	██████	16/10/10
Signature 6	███████████	29/10/10

11.2 INTRODUCTION

The purpose of applying a peak inflation pressure (PIP) during positive pressure ventilation (PPV) is to inflate the lungs with an appropriate tidal volume and thereby facilitate gas exchange. The appropriate tidal volume (V_T) to be delivered during various phases of resuscitation is unknown. Tidal volumes that are too high can damage the lungs by over inflation and V_Ts that are too small will result in inadequate gas exchange. In *Chapter* V and *Chapter VI,* I have shown that during PPV highly variable tidal volumes are delivered. Human and animal observational studies suggest V_T during resuscitation should be within a range of 4 to 8 mL/kg and that large tidal volumes can damage the lungs by over inflation. Lung compliance and therefore the pressures required to deliver an appropriate tidal volume, varies greatly immediately after birth. There are even greater differences *between* infants depending on the immaturity of the lung and their own variable contributions, which are adding to the inconsistency of volumes delivered by a set PIP. These observations suggest that it is necessary to measure and adjust the delivered tidal volumes during PPV immediately after birth, especially in very preterm infants.

In *Chapter X* I presented a literature review on the use of a Respiratory Function Monitor (RFM) to reduce morbidity and mortality in preterm infants. Unfortunately, no study addressing the issue was identified.

In this Chapter I present the results of a randomised control trial in preterm infants <32 weeks gestation, which were randomly allocated to receive PPV with either the screen of a "Florian respiratory function monitor" visible to assist the resuscitator during PPV ("RFM visible") or the screen of the "Florian respiratory function monitor" was covered during PPV ("RFM masked"). I hypothesised that continuously display of expired tidal volume and mask leak will lead to more adequate tidal volume delivery.

11.3 Respiratory Function Monitor for tidal volume targeting during Positive Pressure Ventilation in preterm infants in the Delivery Room – a randomised trial
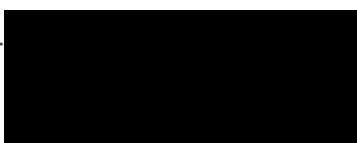
The following chapter has been submitted to American Journal of Respiratory and Critical Care Medicine for peer review; thus it is presented in manuscript form as per Monash University guidelines for thesis by publication.

Respiratory Function Monitor for Tidal Volume Targeting during Positive Pressure

Ventilations in the Delivery Room: A Randomized Controlled Trial

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No reprints requested

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Conflict of interest: none

Abbreviations

DR	- Delivery room
PPV	- Positive pressure ventilation
V_T	- Tidal volume
PIP	- Peak inflating pressure
V_{Te}	- Expiratory tidal volume
RFM	- Respiratory function monitor
RWH	- The Royal Women's Hospital
T_i	- Inflation time
MV	- Minute ventilation
CPAP	- Continuous positive airway pressure

Abstract

Objective: Investigate whether using a Respiratory Function Monitor (RFM) to guide ventilation (PPV) of preterm infants immediately after birth improves targeting of tidal volumes (V_{Te}) and reduces facemask leak.

Methods: Infants receiving PPV immediately after birth were randomized to have a RFM displaying pressure, flow and tidal volume waves visible or masked.

Result: Twenty-seven infants received PPV with a RFM visible and 31 with it masked. The median (IQR) V_{Te} for all inflations was lower in the "RFM visible group" 5.9 (3.2-9.2) mL/kg compared to 7.9 (5.0-11.0) mL/kg (p=0.0001). In the "RFM visible" group 27% of inflations were <4 mL/kg, 32% 4-8 mL/kg and 41% >8mL/kg. In the "RFM masked" group, 18% of inflations were <4mL/kg, 28% 4-8 mL/kg and 54% >8mL/kg. The mean (SD) mask leak for all inflations in the RFM visible and masked groups were 41% (27) and 43% (28) (p=0.012). There were no significant differences between the groups in the use of continuous positive airway pressure, endotracheal intubation or surfactant treatment.

Conclusion: The tidal volume was significantly lower when resuscitators could see a respiratory function monitor during ventilation in the delivery room. There were no differences in mask leak or other respiratory parameters.

Background

Approximately 6% of infants receive respiratory assistance immediately after birth[1]. International guidelines advocate positive pressure ventilation (PPV) via a face mask if preterm infants do not breathe immediately after birth[2]. The purpose of PPV is to create a functional residual capacity, deliver an adequate tidal volume (V_T) to facilitate gas exchange and initiate spontaneous breathing while minimizing lung injury[3;4]. A peak inflating pressure (PIP) is chosen with the assumption this will deliver an adequate tidal volume[2;5] although this is rarely measured[6]. A low V_T may lead to inadequate ventilation, whereas excessive V_T causes volutrauma. Animal studies have shown that PPV with $V_T > 8$ mL/kg can damage the lungs[7-10]. A human observational study reported a mean V_T of 6.5 mL/kg in spontaneously breathing preterm infants in the first 90 seconds after birth[11]. These studies suggest that ventilating with a V_T of 4 to 8 mL/kg after birth might be appropriate.

Several factors can reduce the effectiveness of PPV including baby's movements, movements of the operator's hand, or procedures such as fitting a hat[12-14]. A large face mask leak is a common, usually unrecognized, problem during resuscitation. An observational study in the DR reported that resuscitators had a median mask leak of 29% with a range between 0% and 100% and most resuscitators were unaware of the extent of their mask leak[6]. When the leak is large, the tidal volume may be insufficient to achieve adequate gas exchange. However, if the tidal volumes are excessive, hypocarbia and volutrauma may result[17].

Kattwinkel et al., recently showed that resuscitators respond faster to compliance changes if the tidal volume rather than pressure is displayed. We have demonstrated

that a respiratory function monitor (RFM) may have a role in guiding PPV in the DR[6;17]. Continuous display of flow, V_T, pressure waves and mask leak during PPV can assist the clinical team quickly recognise any mask leak, inadequate V_T or obstruction[15;18]. They can then adjust the mask hold and position or the airway pressure to deliver safe and effective tidal volumes throughout the resuscitation[15;17]. It also enables them to see the babies' spontaneous breathing pattern[19;20], tidal volume and asynchrony with inflations[21].

Targeting tidal volumes in order to minimise lung damage and avoid hyper- and hypocarbia is accepted therapy in many neonatal intensive care units. Clinicians are increasingly realizing the importance of optimizing the respiratory management of preterm infants from the first minutes of life.[ref Finer, Vento] Therefore, we sought to examine whether seeing a RFM would improve the way resuscitators targetted tidal volumes in the delivery room. We hypothesised that if a resuscitator could see a continuously display of mask leak and delivered V_T during PPV it would lead lead to: i) a reduction in mask leak, and ii) more adequate tidal volume delivery.

Methods

Patients and setting

All infants were born at The Royal Women's Hospital (RWH), Melbourne, Australia, a tertiary perinatal centre where ~ 6000 infants are delivered and > 100 infants < 1000g birth weight are admitted to the NICU annually. The trial was conducted between November 2008 and January 2010. Infants who were <32 weeks gestational age and the clinicians judged to have inadequate breathing in the first minutes after birth were eligible for the trial. Infants were excluded if their gestational

age was uncertain or they had a congenital abnormality that might adversely affect their breathing. The resuscitation team usually comprised a neonatal nurse, pediatric resident, neonatal fellow and neonatal consultant. The resuscitation team functioned independently and was not involved in the clinical care of the infants. The trial was approved by the RWH Research and Ethics Committees and was registered with Australian and New Zealand Clinical Trials Registry ACTRN12608000357358.

Randomization

Infants were randomly allocated to either have the screen of a RFM visible (RFM visible) or covered (RFM masked). Allocation was block randomized with variable sized blocks (4 to 8). A sequentially numbered, sealed, opaque envelope containing the allocation was opened by a researcher just before the birth of an eligible infant. Twins and triplets were randomized as individuals.

Consent

Consent was obtained before birth if the mother was not in established labor and if time permitted. Where this was not possible, retrospective consent was obtained as per Australian National Health and Medical Research Council (NHMRC) guidelines for studies in emergency medicine[22]. Consent was sought from the parents of these infants, to use data obtained, as soon as appropriate after the birth.

Ventilation device and face mask

Infants received mask PPV with a size 00 round silicone face mask (Laerdal, Stavanger, Norway) connected to a T-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand), a continuous flow, pressure-

limited device with a manometer and a positive end expiratory pressure (PEEP) valve. The default settings were a gas flow of 8 L/min, PIP of 30 cm H_2O and PEEP of 5 cm H_2O. Staff members attending deliveries were trained to use the device.

Respiratory Function Monitor

A hot-wire anemometer flow sensor (Florian Respiratory Function Monitor, Acutronic Medical Systems AG, Zug, Switzerland) was placed between the ventilation device and the face mask to measure and display gas flow, tidal volume and airway pressure. The inspiratory and expiratory tidal volumes (V_{Te}) passing through the sensor were automatically calculated by integrating the flow signal. Staff members attending deliveries were trained to interpreted tidal volume and flow waves. During the trial period junior doctor received repeatedly one-on-one mannequin training in how to interpreted flow and tidal volume waves. In addition, prior to each delivery a brief revision of interpretation of displayed waves was provided.

Resuscitation

Resuscitation was started with air for all infants. All resuscitative measures (e.g. use of oxygen, intubation, cardiac massage or drugs) were at the discretion of the clinical team, following the Australian guidelines for neonatal resuscitation[23].

Sample size and power estimates

The primary outcome measure was face mask leak during PPV. Previous observational data showed a mean (SD) mask leak of 45% (20). We hypothesized that the mask leak would be less in the RFM visible group. A sample size of 56 (28 in

each group) was sufficient to detect a (15%) reduction in mask leak i.e. 45% vs. 30%, with 80% power and a 2-tailed alpha–error of 0.05.

Data collection and analysis

Demographic and clinical characteristics of study infants were recorded. A breath-by-breath analysis was performed manually from the recording throughout the period of PPV. PIP, PEEP, V_T, inflation time (T_i), ventilation rate and minute ventilation (MV) were measured. We calculated the leak from the mask by expressing the volume of gas that did not return through the flow sensor during expiration as a percentage of the volume that passed through the flow sensor during inflation (Leak (%) = [(inspiratory tidal volume – expiratory tidal volume) ÷ inspiratory tidal volume] x 100[14]. Face mask leak was corrected for body temperature, pressure and water vapour saturation using a standardized equation[24]. The data are presented as mean and standard deviation (SD) for normally distributed continuous variables and medians and interquartile range (IQR) when the distribution was skewed. All infants were analyzed according to their group at randomization i.e. analysis was by intention-to-treat. The clinical characteristics and outcome parameters were compared using Student's *t-test* for parametric and Mann-Whitney *U* test for nonparametric comparisons for continuous variables, and χ^2 for categorical variables. Logistic regression were performed after adjustment for the number of inflations delivered to each infant. *P* values are 2-sided and *P* <0.05 was considered statistically significant. Statistical analyses were performed with Stata (Intercooled 10, Statacorp Texas, USA).

Results

Two hundred and sixty two potentially eligible infants were born at RWH during the study period (Figure 1). One hundred and sixty two were not enrolled (29 were born when the research team was unavailable, 25 were born before the resuscitation team arrived; the research coordinator was not contacted for 104 and there was no randomization envelope for four infants). One hundred infants were randomized; 54 to the RFM visible group and 46 to the RFM masked group. Twenty seven infants did not receive PPV, 14 (26%) in the RFM visible group and 13 (28%) in the RFM masked group and were excluded from further analysis. Consent was not obtained for one infant in the "RFM visible" group and two infants in the "RFM masked" group. In 11 infants the recording was unsatisfactory. One infant in the "RFM visible group" was excluded because of protocol violation. Therefore twenty seven infants randomized to "RFM visible group" and 32 infants to "RFM masked group" received PPV and had respiratory function data available for analysis. The median (IQR) level of experience of the primary resuscitator was similar in both groups; 12 (5-36) months in the RFM visible group and 10 (6-14) months in the RFM masked group.

Eighteen infants (66%) in the RFM visible group were male and 11 (35%) in the RFM masked group. The other demographic characteristics are shown in Table 1. The demographic characteristics of babies enrolled in the study were similar to those not included (data not shown).

Primary outcome measures

A total of 3288 inflations in the RFM visible group and 2795 inflations in the RFM masked group were delivered (p=0.61). A median (IQR) of 115 (81-156) inflations per

infant were analysed in RFM visible group and 63 (41-115) in RFM masked group (p=0.11).

Mask leak

The mean (SD) mask leak for all inflations in the RFM visible and the RFM masked groups were 41% (27) and 43% (28) (p=0.012), respectively. After adjustment for the number of inflations delivered to each infant there was no difference in the mean mask leak between the groups RFM visible versus RFM masked 43% (16) versus 48% (20) (p=0.34), respectively. In addition, we found no difference in the mean (SD) number of repositioning of the face mask during PPV in both groups RFM visible 2 (1) versus RFM masked 3 (1) (p=0.5), respectively. There were no significant differences in any other respiratory parameter (Table 2).

Tidal volumes

The median (IQR) V_{Te} for all inflations was lower in the RFM visible group at 5.9 (3.2-9.2) mL/kg compared to 7.9 (5.0-11.0) mL/kg (p=0.0001) (Figure 2). After adjustment for the number of inflations delivered to each infant the median V_{Te} with RFM visible was significantly lower compared with RFM masked; 6.6 (4.5-8.0) versus 7.5 (6.0-10.5) mL/kg p=0.044), respectively. In the RFM visible group, 27% of inflations were < 4 mL/kg, 32% 4-8 mL/kg and 41% > 8 mL/kg. In the "RFM masked" group 18% of inflations were < 4mL/kg, 28% 4-8 mL/kg and 54% > 8 mL/kg (Figure 3). After adjustment for the number of inflations delivered to each infant, the odds ratio for delivering a V_{Te} > 8 mL/kg was 0.50 (95% CI 0.23-1.05) when the RFM was masked.

Secondary outcome measures

Resuscitation treatments

The median (IQR) time PPV was started after birth was RFM visible, 52 (38-70) sec and RFM masked, 62 (47-107) sec (p=0.07). There was no significant difference between the groups in the use of continuous positive airway pressure (CPAP), oxygen treatment, endotracheal intubation or administration of surfactant in the DR (Table 3). No infant received cardiac compressions or adrenaline in the DR.

Thirty seven infants (64%) left the DR treated with CPAP [RFM visible 19/27 (70%) vs. RFM masked 18/31 (58%) (p=0.96)]. Following admission to the NICU there was no significant difference in the rate of intubation in these 37 infants in the next 24 hrs (Table 4). There was no significant difference in the need for supplemental oxygen at 28 days. At 36 weeks corrected gestational age there was no significant difference between the groups in the proportion receiving respiratory support or supplemental oxygen. There were no significant differences in mortality or other secondary outcomes (Table 4).

Discussion

Ventilation in the DR is provided in the form of PPV, but very little objective information is available to the clinician to assess its effectiveness[6]. This contrasts with practise in neonatal intensive care units where ventilation is guided by the continuous display of airway pressures, gas flow, tidal volume and endotracheal tube leak[25-28]. Others have noted the critical importance of the first "golden hour" and the potential usefulness of extending monitoring techniques used in NICU to the delivery room.[refs – Finer, Vento?]

This is the first study comparing a display of pressure, tidal volume and mask leak with clinical assessment alone in newly born infants in the DR. We recently reported the delivered V_T varies widely during PPV[6]. In the current study the V_T was significantly lower when a RFM was visible. Kattwinkel et al.[29] showed similar results in a mannequin study. They showed that operators were able to adjust ventilation faster in response to compliance changes when V_T was continuously displayed. However, in his study 40% of inflations were in the target range[29]. Our study showed only 32% and 28% of all inflations within the range of 4-8 mL/kg for the RFM visible and RFM masked groups respectively[4]. However, more inflations were delivered with a V_{Te} >8mL/kg in the RFM masked group. Previous studies suggest these tidal volumes are likely to cause lung damage[7-10].

Future studies of using a display of respiratory parameters should be powered to detect differences in important clinical outcomes such as bronchopulmonary dysplasia and days on assisted ventilation.

We have shown that relying on subjective assessment resuscitators were unable to accurately assess their mask leak during PPV[6]. A mannequin study by Wood et al. showed that mask leak can be halved during PPV when resuscitators use a RFM[13]. We did not find similar reductions in the delivery room. A weakness of this study is that we do not know whether the resuscitators looked at the monitor or used the information displayed. We found no difference in the number of times the mask position was changed between the groups which suggests the resuscitators may not have responded to information displayed on the screen. The resuscitator had to

observe the gas flow and V_T waves to identify mask leak and then alter mask position. This might have been difficult for some operators, particularly those with limited experience. Having a team leader to observe and interpret the waves and then advise the resuscitator might have been more effective approach.

We observed that junior medical staff, in particular, used clinical assessment of chest rise during PPV despite the availability of a RFM. This suggests that the RFM was not used as much we hoped. The focus of resuscitation training is on assessment of chest rise to assess adequacy of ventilation. During neonatal resuscitation resuscitators may not fully utilize the information available from the RFM, relying more on their basic resuscitation training and experience. Increasing training with an RFM and an experienced clinician interpreting the data on the monitor during PPV is likely to improve the use of a RFM.

Conclusion

In this pilot study we found that the use of a RFM in the delivery room is feasible and not associated with any obvious harmful effects. There was some evidence that its use could reduce potentially harmful over-ventilation. These findings suggest that this technology is worthy of further testing, using improved training, larger numbers of patients and clinically important outcomes.

Table 1: Infants characteristics

	RFM visible n=27 infants	RFM masked n=31 infants
Gestation (weeks)*	28 (1)	27 (2)
Birth weight (g) *	1024 (334)	990 (323)
Male	18 (66%)	11 (35%)
Caesarean Section	19 (70%)	23 (74%)
Full course of antenatal steroids	21 (77%)	19 (61%)
Apgar 1 #	5 (4-6)	5 (4-6)
Apgar 5 #	8 (7-8)	8 (7-8)

Values are numbers (percentage) unless indicated, *mean (standard deviation), # median (interquartile range)

Table 2: Respiratory functions measurement in both groups

	RFM visible n=27 infants	RFM masked n=31 infants	
Number of inflations	**115 (81-156)**	**63 (41-115)**	**p-value**
V_{Te} mL/kg#	6.5 (4.5-8.3)	7.8 (5.3-10.8)	0.043*
Inflation time (sec)*	0.61 (0.16)	0.67 (0.26)	0.26
Ventilation rate (/min)*	54 (12)	51 (11)	0.25
PEEP (cm H_2O)*	5.3 (1.4)	4.9 (1.4)	0.35
PIP (cm H_2O)*	29.5 (3.5)	28.9 (3)	0.50
Face mask leak (%)	43 (16)	48 (21)	0.33
Minute Ventilation# mL/kg/min	361 (224-482)	395 (305-490)	0.30

Values are numbers (percentage) unless indicated *mean (standard deviation), # median (interquartile range)

Table 3: Delivery Room interventions

	RFM visible n=27 infants	RFM masked n=31 infants	p-value
Time PPV started (min from birth)[#]	52 (38-70)	62 (47-107)	0.07
Duration of PPV (seconds)[#]	191 (94-240)	107 (63-218)	0.81
CPAP	19 (70%)	18 (58%)	0.96
Endotracheal intubation	8 (30%)	13 (42%)	0.33
Surfactant administration	4 (15%)	5 (16%)	0.89
Oxygen administration	17 (63%)	24 (77%)	0.12
Time oxygen started (min from birth)[#]	282 (180-300)	300 202-306)	0.91

Values are numbers (percentage) unless indicated, [#] median (interquartile range)

Table 4: Secondary outcomes

	RFM visible group n=27 infants	RFM masked group n=31 infants	p-value
Intubation in the first 24 hours after birth in infants leaving the DR on CPAP	5/19 (26%)	6/18 (33%)	0.93
Intubation at any time in the first 24 hrs	13 (48%)	19 (61%)	0.32
Surfactant administration at any time in the first 24 hrs	13 (48%)	18 (58%)	0.45
Air leaks in the first 48 hours	1 (4%)	2 (6%)	0.64
Oxygen treatment at 28 days	8 (30%)	9 (29%)	0.79
Respiratory support at 28 days	8 (30%)	10 (32%)	0.64
Oxygen treatment at 36 weeks PMA	5 (18%)	7 (22%)	0.70
Respiratory support at 36 weeks PMA	2 (7%)	4 (13%)	0.57
Oxygen, CPAP or mechanical ventilation at 36 weeks PMA	6 (22%)	7 (22%)	0.88
Combined death or IVH grade 4	4 (15%)	5 (16%)	0.89
Death before discharge from RWH	4 (15%)	4 (13%)	0.83

Figure legend

Figure 1: Study flow chart

Figure 2: Expired tidal volume (V_{Te}) in mL/kg (y-axis) for both groups (x-axis). Box plots show median (solid bar), interquartile range (margins of the box) and 95% confidence interval. The horizontal lines show the range of V_{Te} which would provide reasonable ventilation.

Figure 3: Face mask leak as a percentage of the inspired tidal volume (y-axis) for both groups (x-axis). Box plots show median (solid bar), interquartile range (margins of the box) and 95% confidence interval.

Figure 1
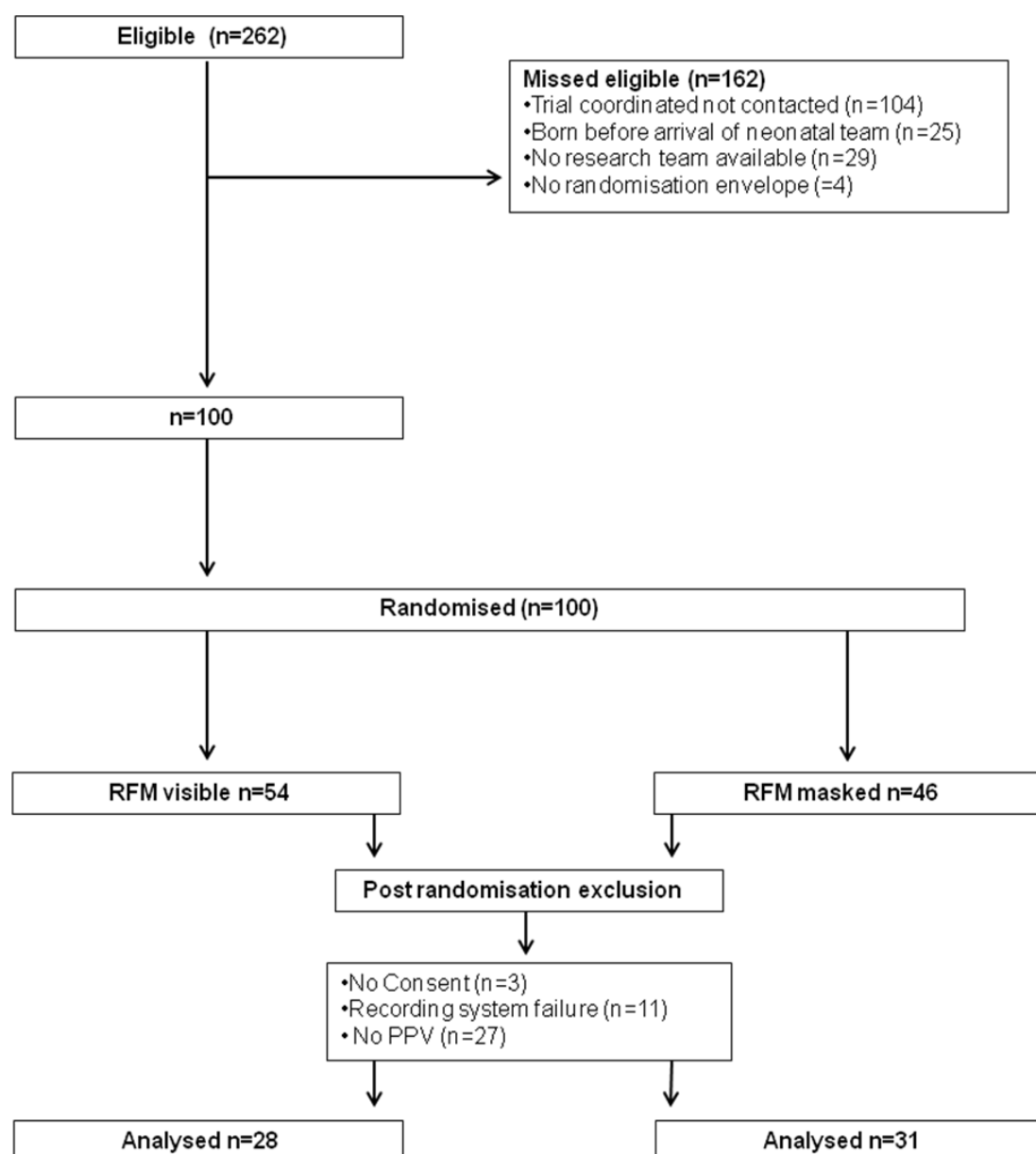
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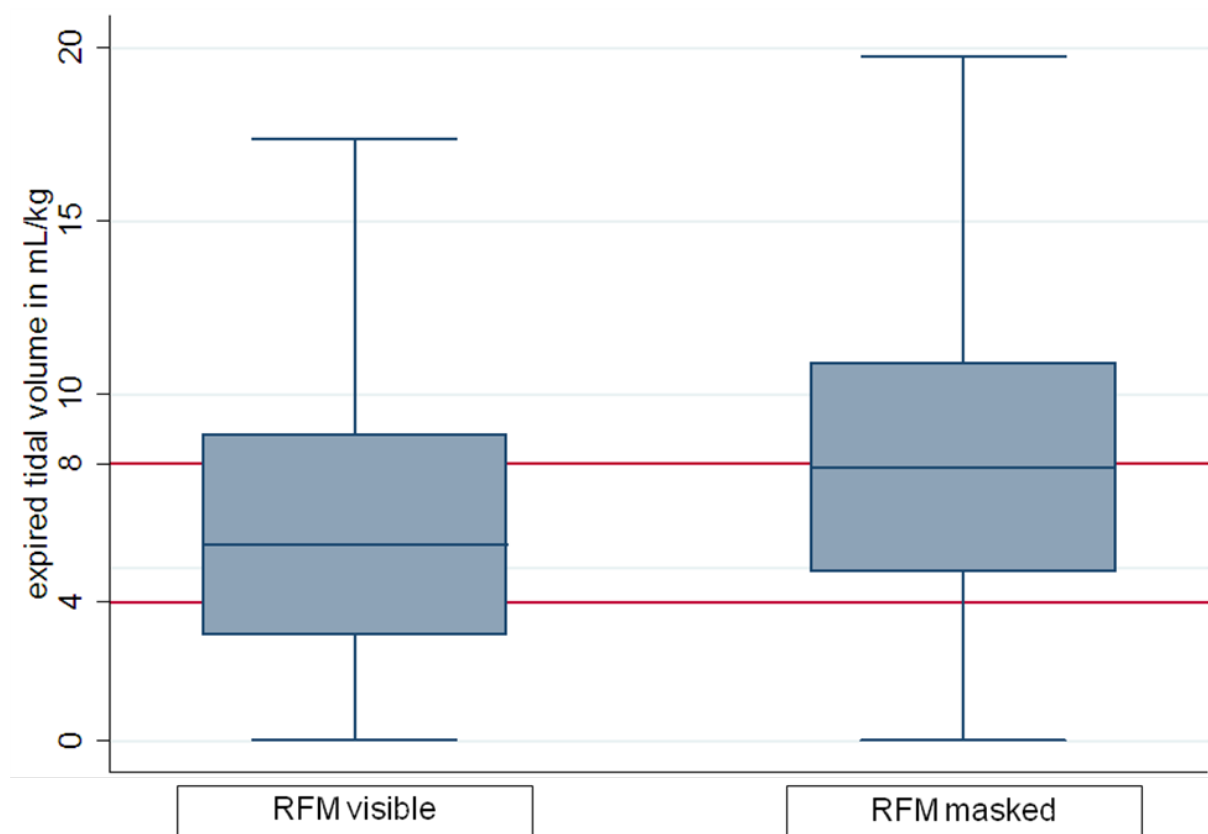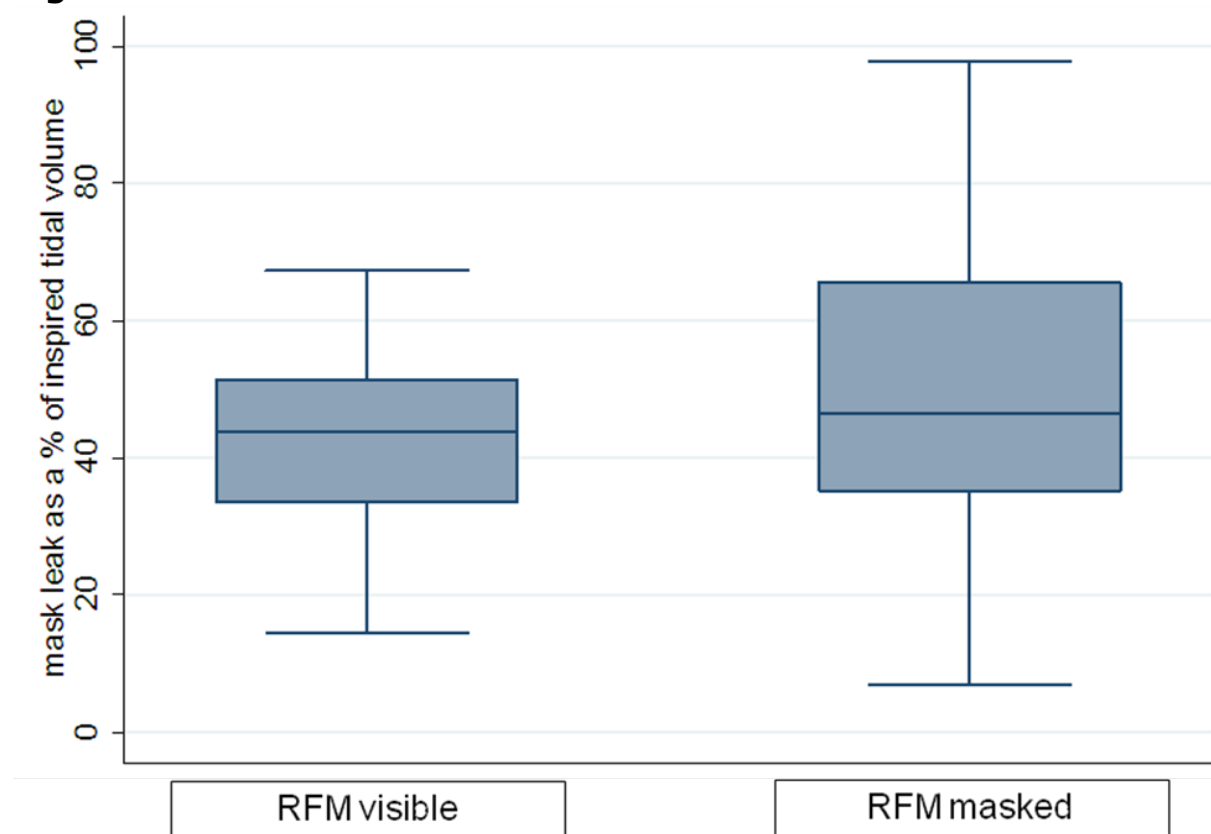
Figure 3

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Chapter XII

Assessment of gas flow waves for endotracheal tube placement in an ovine model of neonatal resuscitation

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter XII "Assessment of gas flow waves for endotracheal tube placement in an ovine model of neonatal resuscitation"

Declaration by candidate

In the case of Chapter XII the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, ethics application, data collection, data analysis, writing the manuscript	60%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Hooper SB	Help during the experiments, help with data collection, revising the manuscript	
Crossley KJ	Help during the experiments, help with data collection, revising the manuscript	
Allison BJ	Help with ethics application, help during the experiments, help with data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature	████████████	Date $20/7/10$

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)   **The Ritchie Centre, Monash Institute for Medical Research, Monash University, Melbourne, Australia**

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	████████████	Date 3/11/10
Signature 2	████████████	21/7/10
Signature 3	████████████	21/7/10
Signature 4	████████████	18.7.10
Signature 5	████████████	20.7.10

12.2 INTRODUCTION

Endotracheal intubation in the delivery room remains a common procedure, it is technically difficult, the success rate of correct endotracheal tube (ETT) placement for junior medical staff is less than 50% and accidental oesophageal intubation is common. An international consensus statements and regional guidelines on neonatal resuscitation advise that correct tube placement should be confirmed by observation of clinical signs and detection of exhaled carbon dioxide. Some of the clinical indicators include a prompt increase in heart rate, adequate chest rise, confirmation of tube position by direct laryngoscopy and observation of ETT passage through the vocal cords. However, these indicators are subjective and can be misleading even in experienced hands. Furthermore, recognition of an ETT placed in the oesophagus, using clinical indicators alone, can take several minutes.

There are several different adjunct (e.g.: flow sensor or colorimetric devices) to objectively assess correct tube placement. As carbon dioxide is exhaled at a much higher concentrations much higher than inhaled it can be detected with semi-quantitative colorimetric devices (e.g. Pedi-Cap$^®$), or devices who display numeric or graphic values. Several studies have shown that CO_2 detection in expired gas is a very useful method to confirm tube placement. Even though these devices are frequently used in the delivery room to assess tube placement, it can display false negative results particularly when cardiac output is low, or the inflation pressure is too low to ventilate the lungs. In comparison, a gas flow sensor continuously measures and displays the gas flow in and out of the ETT and is increasingly used in neonatal intensive care units to guide ventilation. Observing flow waves can be used to determining correct tube placement. In *Chapter IV*, I have described that a flow sensor can be used to identify correct tube placement.

However, no study has compared a flow sensor with a semi-quantitative colorimetric device. In this Chapter I compared a flow sensor and a with a Pedi-Cap® in animal model of neonatal resuscitation to evaluate the accuracy of a flow sensor and to compare the speed of both devices to recognise tube position.

12.3 Assessment of gas flow waves for endotracheal tube placement in an ovine model of neonatal resuscitation

The following chapter has been published in Resuscitation thus it is presented in PDF as per Monash University guidelines for thesis by publication.
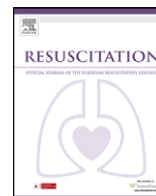
Experimental paper

Assessment of gas flow waves for endotracheal tube placement in an ovine model of neonatal resuscitation[☆]

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ABSTRACT

Aim: Clinical assessment and end-tidal CO_2 ($ETCO_2$) detectors are routinely used to verify correct endotracheal tube (ETT) placement. However, $ETCO_2$ detectors may mislead clinicians by failing to correctly identify placement of an ETT under a variety of circumstances. A flow sensor measures and displays gas flow in and out of an ETT. We compared endotracheal flow sensor recordings with a colorimetric CO_2-detector (Pedi-Cap®) to detect endotracheal intubation in a preterm sheep model of neonatal resuscitation.

Methods: Six preterm lambs were intubated and ventilated immediately after delivery. At 5 min the oesophagus was also intubated with a similar tube. The endotracheal tube and oesophageal tubes were attached to a Pedi-Cap® and flow sensor in random order. Two observers, blinded to the positions of the tubes, used a $ETCO_2$ detector and the flow sensor recording to determine whether the tube was in the trachea or oesophagus. The experiment was repeated 10 times for each animal. In the last three animals (30 recordings) the number of inflations required to correctly identify the tube placement was noted.

Results: The Pedi-Cap® and the flow sensor correctly identified tube placement in all studies. Thus, the sensitivity, specificity, and positive and negative predictive values of both devices were 100%. At least three, and up to 10, inflations were required to identify tube location with the Pedi-Cap® compared to one or two inflations with the flow sensor.

Conclusion: A flow sensor correctly identifies tube placement within the first two inflations. The Pedi-Cap® required more inflations to correctly identify tube placement.

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1. Introduction

During neonatal resuscitation, endotracheal intubation is recommended when positive pressure ventilation (PPV) via a face mask is ineffective or prolonged, when chest compressions are required or when drugs are administered, including surfactant.[1–3] Although, it remains a common procedure in the delivery room, the success rate of correct endotracheal tube (ETT) placement for junior medical staff is less than 50%, and accidental esophageal intubation is common.[4–8]

International consensus statements and guidelines on neonatal resuscitation advise that correct ETT placement should be confirmed by observation of clinical signs and detection of exhaled carbon dioxide (CO_2).[1–3] Clinical signs include prompt increase in heart rate, adequate chest wall movements, confirmation of position by direct laryngoscopy, observation of ETT passage through the vocal cords, presence of breath sounds in the axillae and absence in the epigastrium and condensation in the ETT during ventilation.[1] However, these indicators are subjective and can be misleading even in experienced hands.[9] Recognizing that the ETT is in the oesophagus, using clinical assessment alone, can take several minutes.[6,8,10,11] CO_2 is exhaled from the lungs at concentrations much higher than in air and can be detected with semi-quantitative colorimetric devices (e.g. Pedi-Cap®),[11,12] or measured with devices which give a numeric or graphic value.[8,10,13] Thus, CO_2-detection in expired gas is a very useful method to con-

firm ETT placement.[10] Although they are frequently used to confirm correct ETT placement,[14,15] CO_2-detectors (Pedi-Cap®) can display false negative results particularly when cardiac output is low,[16,17] or when the infant is in severe respiratory failure[18] and the inflation pressure is not high enough to ventilate the lungs.

A gas flow sensor continuously measures and displays gas flow and tidal volume (V_T) in and out of the ETT.[19] They are increasingly used in neonatal intensive care units to guide ventilation.[20–23] Observing flow sensor recordings to identify ETT placement has not been systematically assessed. The study had two aims: (i) to evaluate the accuracy of a flow sensor to determining tracheal versus oesophageal tube placement and (ii) to compare the speed of a flow sensor with that of a CO_2-detector (Pedi-Cap®) in determining correct tube position in a preterm sheep model of neonatal resuscitation.

2. Methods

All experimental procedures were approved by the Monash University Animal Ethics Committee. Preterm lambs ($n = 6$; ~126 days gestation, term 147 days) were delivered by caesarian section, anaesthetized, sedated, intubated (size 4.0 mm ETT) and ventilated with a Dräger 8000plus ventilator (Dräger Medical, Lübeck, Germany). All lambs were ventilated for 5 min with assist control and volume guarantee mode with a set expired V_T of 5 mL/kg and a ventilation rate of 60/min. At 5 min of age the oesophagus was also intubated with a size 4.0 ETT by an independent investigator. The Pedi-Cap® and flow sensor were connected in series. Blinded to the observers, the Pedi-Cap® and flow sensor were then randomly placed on either the ETT in the trachea or in the oesophagus. The Pedi-Cap® and flow sensor maintained their relative position (i.e. Pedi-Cap® closer to the ventilator and the flow sensor closer to the tube) on each occasion. Tube position – endotracheal (correct) or oesophageal (misplaced) – was assessed independently by one observer looking for color change in the Pedi-Cap® and by another observer examining the recordings measured with the flow sensor. This was done ten times (Pedi-Cap® and flow sensor placed on the tube in the trachea on five occasions and on the tube in the oesophagus on five occasions) in each lamb. In addition, in three lambs (30 recordings) the number of inflations required to establish position of the tube were determined for each device.

2.1. Pedi-Cap®

Pedi-Cap® (Nellcor Puritan Bennett, Pleasanton, CA) is a disposable noninvasive semi-quantitative colorimetric CO_2-detector. With each inflation and expiration a pH-sensitive chemical indicator undergoes color change, reflecting the change in CO_2 concentration in the gas passing through it.[12] In our study the Pedi-Cap® was placed between the ventilator and the ETT. It is purple in the absence of CO_2 but changes to yellow in the presence of even low concentrations of CO_2.[12,18] A persistent purple color indicates the ETT is not in the trachea,[8,10,11] or there is low cardiac output,[16,17] or under ventilated lungs.[18]

2.2. Flow sensor

A Dräger 8000plus Ventilator (Dräger Medical, Lübeck, Germany) was used to measure inflating pressures and gas flow. It consists of a small, low dead space (~1 mL) hot-wire anemometer flow sensor which is placed between the ventilation device and the ETT. Airway pressures were measured by the ventilator pressure transducer and gas flows by the flow sensor, which automatically calculated the V_T passing through the sensor by integrating the flow

signal. It can detect a tidal volume as low as 0.2 mL. Correct ETT placement was recognized when gas flow was detected in and out of the trachea (see Fig. 1A). If the ETT was not in the trachea, gas flow was only detected towards the ETT but no expiratory flow was seen (see Fig. 1B).

2.3. Data acquisition and analysis

The gas flow, V_T and airway pressure data were recorded at 1 kHz using a dedicated computerized data acquisition system (Powerlab, ADInstruments, Australia). During the experiment the ventilator's alarm was disabled and the flow wave display was visible to only one investigator (G.S.). The observer of the Pedi-Cap® (B.A.) was blinded to the flow wave display and vice versa.

3. Results

Six preterm lambs with a mean (SD) gestation age of 125 (1.4) days and birth weight of 3145 (510 g) were used in the study. None of the animals received antenatal steroids or surfactant.

3.1. Pedi-Cap®

The participant observing the Pedi-Cap® correctly identified tube placement in the trachea or oesophagus in all 60 studies (100%).

In 30 cases the number of inflations to identify tube position was also recorded. The median (IQR) number of inflations to correctly identify tube placement with a Pedi-Cap® was 4 (3–5). In three cases, up to 10 inflations were given before the Pedi-Cap® color indicator changed.

3.2. Flow sensor

The participant observing the flow sensor recordings was able to identify correct tube placement in all 60 cases (100%). The expired V_T through the ETT was approximately 10 mL.

In 30 cases the number of inflations to correctly identify tube position was also recorded. The median (IQR) number of inflations to identify correct tube placement with a flow sensor was 1 (1–2). The maximum number of inflations to determine tube placement was three inflations.

4. Discussion

Although endotracheal intubation in the delivery room remains a common procedure, it is technically difficult and oesophageal intubation is common.[4–8,24] In addition, several studies have shown that the delay in recognizing oesophageal intubation using clinical assessment may take several minutes.[6,8,10,11,24] It is not ethical to systematically study different monitors to detect malposition of the ETT in human infants; therefore we choose to compare the Pedi-Cap® and a flow sensor in an animal model.

The Pedi-Cap® is a sensitive CO_2-detector.[11] Garey et al.[12] recently reported the V_T threshold required to produce a color change in the Pedi-Cap® during PPV in a lung model was between 0.83 and 1.08 mL, which is well below the range of the target V_T of 4–8 mL/kg in preterm infants.[25] In the current study the Pedi-Cap® correctly identified all tracheal tube placements. Our animals were ventilated with pressures of 30 cm H_2O and the delivered V_T of approximately 3 mL/kg exceeded the reported V_T threshold by approximately 10-fold.[12]

The Pedi-Cap® manufacturer recommends interpretation of the color change after six inflations. Aziz et al.[11] showed that a color change was recognized after 4–12 inflations in preterm infants
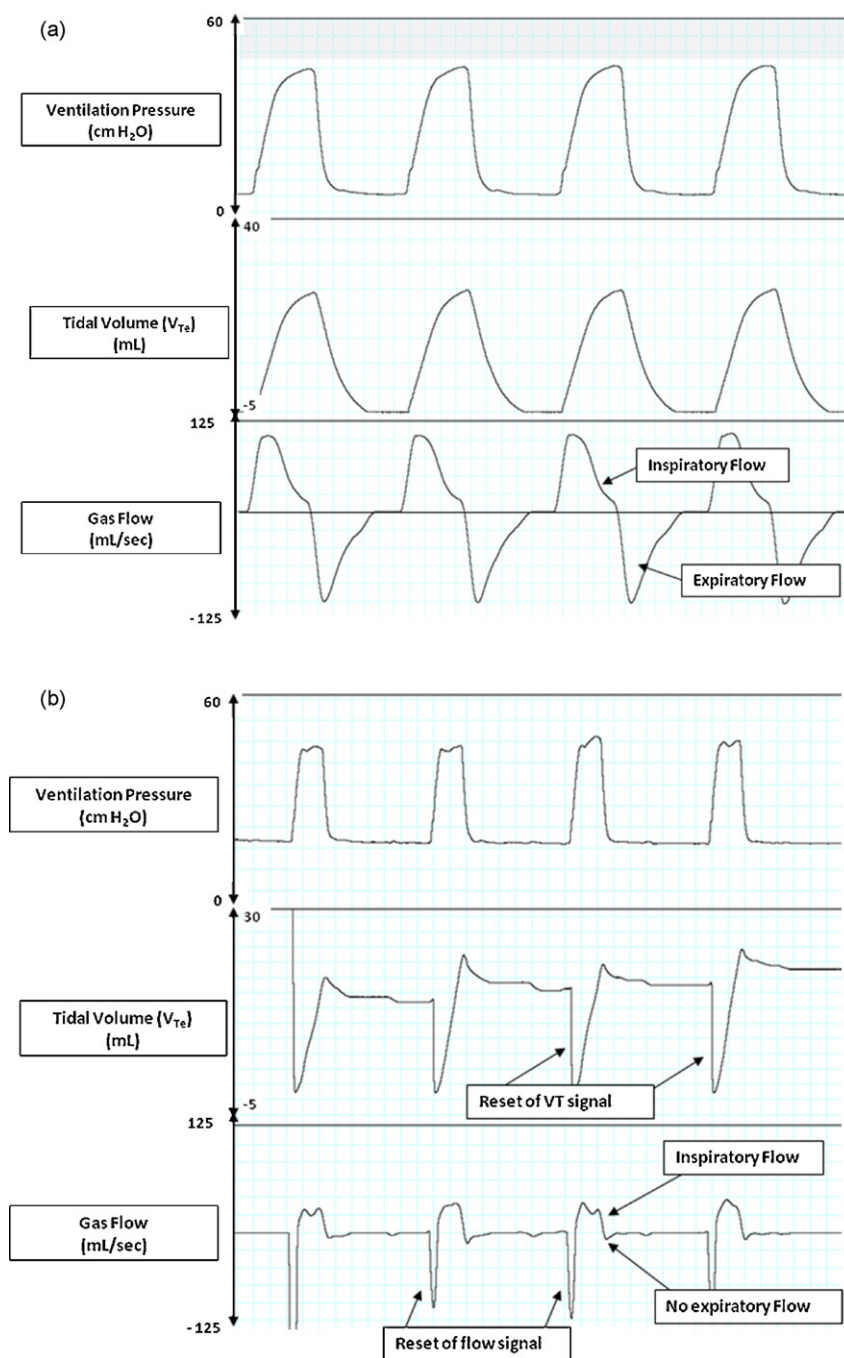
Fig. 1. (A) A flow recording showing correct ETT placement. Both inflation and expiratory flow curves return to baseline, indicating correct placement of the ETT. The areas underneath both inflation and expiration flow curves are similar showing that an equal volume of gas entered and left the airways and no leak. (B) A flow recording showing oesophageal tube placement. The inflation flow curve shows gas flow down the ETT. In contrast, there is no expiratory gas flow indicating ETT placement in the oesophagus. The V_T curve reflects the gas flow curve and displays 100% leak. The flow signal is reset before the next inflation starts, which is also shown in the V_T curve.

<1000 g, although various studies reported up to 17 s before the color changes was observed.[6,8,11] In the current study the Pedi-Cap® demonstrated correct tube placement within three inflations on most occasions.

On all but two occasions a flow sensor showed correct ETT placement by displaying gas flow in and out of the trachea during the first inflation (see Fig. 1A). If the ETT is not in the trachea, the flow wave shows gas going down the ETT but not returning (see Fig. 1B).[6,19] O'Donnell et al.[6] described the use of flow signals to confirm ETT placement in the delivery room in a case series of seven new-born infants. Compared to clinical assessment, the time required to assess ETT placement using the flow signal was halved. In the current study, the flow sensor identified 100% of ETT placement correctly and in most cases within the first or second inflation.

In the delivery room, failure of color change with the Pedi-Cap® may be due to incorrect ETT placement,[8,10,11] low cardiac output[16,17] or using an inflating pressure which is too low so that the V_T is below the threshold.[18] Color change during ventilation of the oropharynx has been reported.[26] In comparison, using gas flow in and out of the trachea can identify correct ETT placement, even in the presence of low cardiac output or low V_T. In addition, an ETT can become dislodged after it has been correctly placed (see Fig. 2).
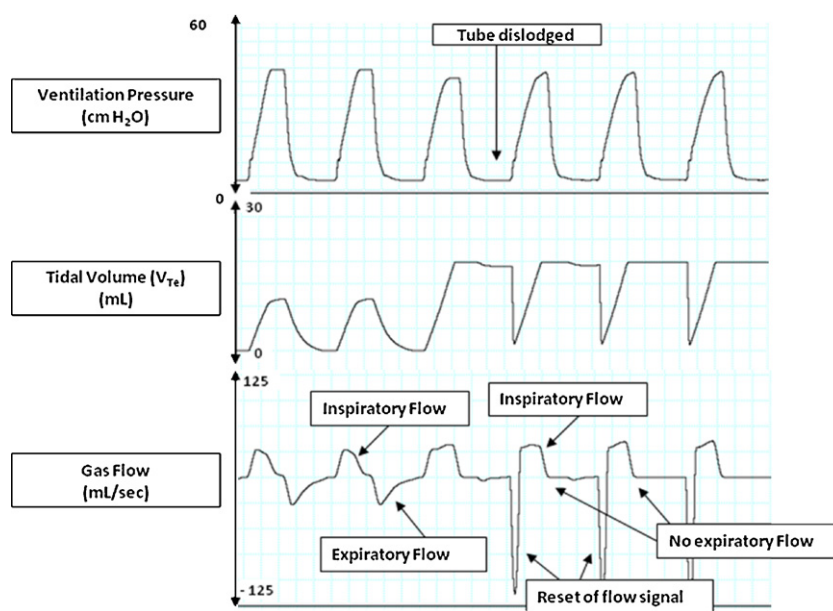
Fig. 2. Dislodgement of ETT from the trachea. Initially, the inspiratory and expiratory flow curves are returning to baseline indicating correct ETT placement. Suddenly, there is no expiratory flow indicating ETT dislodgement from the trachea. This is reflected in the V_T curve displaying almost 100% leak. There is still some gas flow towards the ETT, but no expiratory gas flow.

This can be seen immediately on the flow and volume signals as there is little or no expiratory flow and volume. This may not be detected with the Pedi-Cap®.

The fact that the same observers observed all flow Recordings and the Pedi-Cap® color changes might be weakness of this study. However, inexperience or lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals. Therefore anyone using flow traces must be trained to interpret these signals.[19]

We used an animal model to investigate the usefulness and sensitivity of both devices. Further studies using different interfaces, tidal volumes and lung disease severity are required in order to determine performance during different clinical scenarios.

5. Conclusions

Both devices correctly identified tube position in all cases. The flow sensor was faster (first two inflations) than the Pedi-Cap® (3–10 inflations). Further studies are required to confirm the potential advantages of the flow sensor in conditions of low cardiac output and when tidal volumes are below the threshold of the Pedi-Cap®.

Conflict of interest

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Chapter XIII

Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation

PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter XIII "Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation"

Declaration by candidate

In the case of Chapter XIII the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Idea, protocol design, data collection, data analysis, writing and revising the manuscript	75%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Poulton DA	Helping with data analysis	
COF Kamlin	Help with data collection, revising the manuscript	
Dawson JA	Help with data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature	██████████████	Date 29/10/2010

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	Dept. of Newborn Research, The Royal Women's Hospital, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	███████████	20/7/10
Signature 2	███████████	20/07/2010
Signature 3		
Signature 4	██████	18.7.10
Signature 5	███████	20.7

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PART B: Suggested Declaration for Thesis Chapter

Monash University

Declaration for Thesis Chapter XIII "Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation"

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The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Poulton DA	Helping with data analysis	
COF Kamlin	Help with data collection, revising the manuscript	
Dawson JA	Help with data collection, revising the manuscript	
Morley CJ	Revising the manuscript	
Davis PG	Revising the manuscript	

Candidate's Signature		Date 29/10/2010

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

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13.2 INTRODUCTION

Endotracheal intubation remains a common procedure in the delivery room. However, accidental oesophageal intubation is common, particularly amongst junior medical staff. The International Liaison on Committee on Resuscitation recommends that endotracheal tube (ETT) placement should be confirmed by detection of exhaled CO_2 in addition to clinical assessment is recommended in neonates with spontaneous circulation. An increase in heart rate, visible chest wall movement, visualisation of the ETT passing through the vocal cords during direct laryngoscopy are clinical signs of correct tube placement. However, studies have shown that these clinical signs are unreliable even in experienced hands and recognition of oesophageal intubation may take serval minutes using these clinical signs alone.

Colorimetric carbon dioxide detector can be used to confirm ETT placement as carbon dioxide is exhaled from the lungs at concentrations much higher than in air. However, these detectors can fail to change colour despite correct tube placement. This may occur with low cardiac output or an insufficient inflating pressure to deliver an adequate tidal volume.

In comparison, a flow sensor placed between an ETT and a ventilation device will continuously measure gas flow in and out of the trachea. In *Chapter XII* I have shown that flow waves can be used to correctly identify ETT placement in an animal model. In this Chapter I compared a flow sensor and a colorimetric carbon dioxide detector to identify correct tube placement in the delivery room.

13.3 Assessment of flow waves and colorimetric CO_2 detector for endotracheal tube placement during neonatal resuscitation

The following chapter has been accepted in Resuscitation but is not yet published; the proof for publication is presented in PDF as per Monash University guidelines for thesis by publication.

Assessment of flow waves and colorimetric CO$_2$ detector for endotracheal tube placement during neonatal resuscitation

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Conflict of interest: None

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Abbreviations:

PPV   - Positive pressure ventilation

DR   - Delivery room

CO_2 - Carbon dioxide

V_T - Tidal volume

NICU   - Neonatal intensive care unit

PEEP   - Positive end expiratory pressure

PIP   - Peak inflation pressure

V_{Te} - Expired tidal volume

ETT   - Endotracheal tube

Abstract

Aim

Clinical assessment and end-tidal CO_2 ($ETCO_2$) detectors are routinely used to verify endotracheal tube (ETT) placement. However, $ETCO_2$ detectors may mislead clinicians by failing to identify correct placement under a variety of conditions. A flow sensor measures gas flow in and out of an ETT. We reviewed video recordings of neonatal resuscitations to compare a colorimetric CO_2 detector (Pedi-Cap[®]) with flow sensor recordings for assessing ETT placement.

Methods

We reviewed recordings of infants < 32 weeks gestation born between February 2007 and January 2010. Airway pressures and gas flow were recorded with a respiratory function monitor. Video recording were used i) to identify infants who were intubated in the delivery room and ii) to observe colour change of the $ETCO_2$ detector. Flow sensor recordings were used to confirm whether the tube was in the trachea or not.

Results

Of the 210 infants recorded, 44 infants were intubated in the delivery room. Data from 77 intubation attempts were analysed. In 35 intubations of 20 infants both a PediCap[®] and flow sensor were available for analysis. In 21 (60%) intubations, both methods correctly identified successful ETT placement and in 3 (9%) both indicated the ETT was not in the trachea. In the remaining 11 (31%) intubations the PediCap[®] failed to change colour despite the flow wave indicating correct ETT placement.

Conclusion

Colorimetric CO_2 detectors may mislead clinicians intubating very preterm infants in the delivery room. They may fail to change colour in spite of correct tube placement in up to one third of the cases.

Background

Endotracheal intubation is a common procedure in the delivery room (DR). Accidental oesophageal intubation is common, particularly amongst inexperienced operators(1-4).

An international consensus statement on neonatal resuscitation recommends that endotracheal tube (ETT) placement should be confirmed using clinical signs and detection of exhaled carbon dioxide(5). Clinical signs of correct tube placement include prompt increase in heart rate, chest wall movement, visualisation during direct laryngoscopy of the ETT passing through the vocal cords, presence of breath sounds in the axillae and absence of breath sounds in the epigastrium and condensation in the ETT during expiration(5). These clinical signs are unreliable even in experienced hands(6). Recognition of oesophageal intubation, using clinical signs alone, may take several minutes(2;4;7;8).

Carbon dioxide (CO_2) is exhaled from the lungs at concentrations much higher than in air and can be detected with semi-quantitative colorimetric devices (e.g. Pedi-Cap$^®$)(8;9). Thus, CO_2 detection in expired gas is a useful method for confirming ETT placement(7;8;10;11). However, CO_2-detectors (Pedi-Cap$^®$) can give false negative results i.e. fail to change colour when the tube is in the trachea(8). This may occur when cardiac output is low,(12;13) or the inflating pressure is insufficient to ventilate the lungs(14).

A flow sensor placed immediately proximal to a face mask or an ETT continuously measures gas flow and tidal volume (V_T), which can be displayed on a monitor (Figure 1)(15). We have shown that this can be used to confirm ETT placement in an

animal model(16). Flow sensors are commonly used in neonatal intensive care units (NICU) to guide ventilation(17;18). No study has compared a flow sensor with a colorimetric CO_2 device to identify ETT placement in the delivery room.

The aim of this observational study was to determine the accuracy of a CO_2-detector (PediCap$^{®}$) in identifying ETT position during neonatal resuscitation.

Patients and Methods

All infants were born at The Royal Women's Hospital, Melbourne, Australia, a tertiary perinatal centre where ~ 6000 infants are delivered and > 100 infants < 1000g birth weight are admitted to the NICU annually. Between February 2007 and January 2010, 210 deliveries of infants < 32 weeks gestation were attended by the research team. Clinical care of the infants was provided by a separate team. We reviewed video recordings of infants enrolled in two randomised control trials (Australian and New Zealand Clinical Trials Registry number ACTRN12607000062426 and ACTRN12608000357358) where a Respiratory Function Monitor was used during resuscitation in the delivery room. The first study compared the T-piece (Neopuff; Fisher & Paykel, Auckland, New Zealand) with a self-inflating bag (SIB) (Laerdal 240 mL silicone infant resuscitator; Laerdal, Stavanger, Norway) for resuscitation of infants < 29 weeks gestation. The second investigated the use of the *Florian Respiratory Function Monitor* during PPV and enrolled infants of ≤32 weeks. Both randomised controlled trials were approved by The Royal Women's Hospital Research and Ethics Committees and parental consent to use the recordings was obtained.

Infants <32 weeks gestation who were intubated in the DR and where the research team were present to make physiological recordings were eligible for inclusion. Infants with congenital abnormalities and infants whose parents did not consent were excluded.

Ventilation device

PPV was given with either a T-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) or a self-inflating bag (Laerdal, Stavanger, Norway). The Neopuff is a continuous flow, pressure-limited device with a built-in manometer and a positive end-expiratory pressure (PEEP) valve. The default settings used were a gas flow of 8 L/min, peak inflation pressure (PIP) of 30 cm H_2O and PEEP of 5 cm H_2O. The self-inflating bag was used with 8 L/min gas flow and without a manometer or a PEEP-valve. Staff members attending deliveries were trained to use both devices.

Pedi-Cap[®]

The Pedi-Cap[®] (Nellcor Puritan Bennett, Pleasanton, CA) is a disposable non-invasive semi-quantitative colorimetric CO_2-detector. A pH-sensitive chemical indicator changes colour with each inflation and expiration. It is purple in the absence of CO_2 and changes to yellow in the presence of > 2% CO_2 (according to the manufacturer)(19). A persistent purple colour indicates either that the ETT is not in the trachea(4;7;8;20), the cardiac output is very low(12;13), or tidal volume is very small(14).

Respiratory Function Monitor

A hot-wire anemometer flow sensor (Florian Respiratory Function Monitor, Acutronic Medical Systems AG, Zug, Switzerland) was placed between the ventilation device and the ETT to measure gas flow, tidal volume and airway pressure. The dead space of the flow sensor is approximately 1 mL. The inspiratory and expiratory tidal volumes (V_{Te}) passing through the sensor were automatically calculated by integrating the flow signal. Detection of expiratory flow indicates correct positioning of the ETT (Figure 1) whereas the presence of inspiratory flow with no expiratory flow indicates the ETT is not in the trachea (Figure 2)[15;21].

Pulse Oximeter

A pulse oximeter (Radical 7, Masimo, California, USA), placed on the right hand or wrist, measured heart rate and oxygen saturation throughout the resuscitation. It was set to maximal sensitivity with 2 second averaging[22;23]. Data were collected throughout the resuscitation.

Data Acquisition and Analysis

We reviewed video recordings to identify infants who were intubated in the delivery room. JAD and GMS independently reviewed the videos recordings to identify whether the PediCap® changed colour or not, blinded to the flow waves. The policy in our hospital is to use a PediCap® for identification of ETT placement. However, on many occasions a flow sensor was also connected to the ETT to record respiratory functions. The clinical team was not always able to see the flow wave curves. When both devices were used the Pedi-Cap® and flow sensor were connected in series and maintained in their relative position (i.e. Pedi-Cap® closer to the ventilation

device and the flow sensor closer to the ETT) for each intubation. Pressure, gas flow and tidal volume from the respiratory function monitor were recorded at 200 Hz using a desktop computer with Spectra physiological recording software (Grove Medical, London, UK).

Statistical analysis

The pressure, flow, and tidal volume (V_T) were analyzed and the V_T and mask leak measured until colour change at the PediCap® occurred. If no colour change was observed the number of inflations until the clinical team removed the ETT was calculated. We examined in detail intubation episodes in which the flow sensor detected expiratory flow i.e. correct endotracheal tube placement. The median V_T and leak measured when colour change was seen were compared with values obtained when there was no colour change. Results are presented as mean (SD) for normally distributed continuous variables and median (IQR) for variables with a skewed distribution. Data were analysed using STATA version 10 (Stata Corp, College Station, Texas, US).

Results

Of the 210 deliveries attended, 44 infants were intubated in the DR. In 35 intubations of 20 infants a good quality video image of the PediCap® and a flow sensor recording were available for analysis. These infants had a mean (SD) gestation of 26 (1) weeks and birth weight of 866 (283) g.

In 21 (60%) intubations both flow sensor and PediCap® correctly identified placement in the trachea (Figure 1). In 3 (9%) intubation both the PediCap® and the flow sensor indicated the ETT was not in the trachea (Figure 2). In the remaining 11

(31%) intubations no colour change of the PediCap$^®$ was seen but the flow wave showed correct ETT placement. Positive and negative predictive value, sensitivity and specificity are presented in Table 1.

In all 11 cases where the flow sensor indicated correct position of the ETT but the PediCap did not change colour the clinical team removed the tube and reintubated. The decision to remove the tube was made after a median (IQR) of 14 (8-26) inflations or a median (IQR) of 13 (10-30) seconds. The median (IQR) expired tidal volume (V_{Te}) was 2.0 (1-3.1) mL. In three of these cases the next intubation produced the same result i.e. flow sensor indicated correct position but no colour change. These infants were intubated a third time and colour change was noted. The median (IQR) delivered V_{Te} in the 11 cases when colour change occurred was 5.2 (2.0-9.5) mL (p=0.04). The mean (SD) delivered PIP with no colour change was 29.5 (5.5) cm H_2O compared to 28.1 (4.1) cm H_2O with colour change (p=0.57). The median (IQR) heart rate and oxygen saturation prior to intubation were 143 (118-157) / minute and 56 (34-81) % in these infants.

Discussion

Endotracheal intubation in the delivery room remains a common procedure. However it is technically difficult and oesophageal intubation is common(1-4;24). In addition, several studies have shown that the delay in recognizing oesophageal intubation using clinical assessment may take several minutes(2;4;7;8). To our knowledge, this is the first study comparing flow waves with semi-quantitative colorimetric CO_2 devices to identify ETT position in the delivery room.

We found that the PediCap® incorrectly identified ETT position in up to one third of the analysed intubations with a sensitivity of 65% and a negative predictive value of 21% (Table 1). Although, the PediCap® is not recommended for infants < 1kg, it is widely used to confirm tube placement during neonatal resuscitation(25-28). Garey et al.(9) recently reported the required volume threshold to achieve a colour change at the Pedi-Cap®. In an artificial lung model, charged with 5% CO_2, tidal volumes of > 0.72mL were required to achieve colour change at the PediCap®. We identified two cases in whom colour change of the PediCap® was observed with a delivered V_T below this threshold(9). However, in nine cases the PediCap® remained purple despite delivered V_Ts greater than the reported threshold(9). In the first minutes after birth lung liquid has to be cleared and effective gas exchange needs to be established(29) in order to detect exhaled CO_2. In some infants, concentrations of exhaled CO_2 may have been insufficient to cause colour change of the PediCap®. Kamlin et al. described a difficult resuscitation where the Pedi-Cap did not change colour when the ETT was correctly placed(14). Colour change was only observed after very high pressures were used for 15 seconds. This suggests that the delivered tidal volume might have been too low(30;31). Aziz et al(8) also described failure of colour change of the Pedi-Cap® in three infants with correctly placed ETTs. In these cases the set PIP might have been too low to achieve a V_T sufficient to produce colour change(30;31).

A limitation of a flow sensor is that inexperience and lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals(15). Therefore anyone using this device must be trained to interpret pressure, flow and tidal volume signals(15). Furthermore, a flow sensor will aid the resuscitator but does not provide

interpretation of the signals or a diagnosis. For example the presence of a large leak around an ETT may be interpreted as a misplaced ETT and therefore removed (Figure 4).

The PediCap® manufacturer suggests that assessment of colour change occurs after six inflations(19). However, in some situations the Pedi-Cap® does not change colour despite correct tube placement(8;14). This may due to an inadequate PIP to inflate the lungs, which might occur in both term and preterm newborns. We have recently shown that inadequate V_T can be delivered during mask PPV in the DR(30;31). These observational studies suggest that a single PIP does not always achieve adequate V_T delivery. We suggest that if after six inflations no colour change of the Pedi-Cap® is observed, the PIP is increased by 5 cm H_2O and six further inflations are delivered. This process may be repeated and if the Pedi-Cap® remains purple after a total PIP increase of 10 cm H_2O the ETT position should be either reassessed with direct laryngoscopy or removed and the infant reintubated.

Conclusion

Colorimetric CO_2 detectors may mislead clinicians intubating very preterm infants in the delivery room. They may fail to change colour in spite of correct tube placement in up to one third of the cases. Further trials evaluating the use and limitations of quantitative colorimetric CO_2 devices are indicated.

Table 1: Positive and negative predictive value, sensitivity and specificity

		Flow sensor		Predictive values
		Trachea	**Oesophagus**	
PediCap®	**Trachea**	21	0	**Positive** 100%
	Oesophagus	11	3	**Negative** 21%
		Sensitivity 65%	**Specificity** 100%	

Figure legend

Figure 1: Correct tube placement in 26 week infant

The PediCap® showed colour change after 2 inflations. The flow waves show inspiratory and expiratory flow, which can be already seen with the first inflation. The measured tidal volume during inflations was 5-8 mL/kg.

Figure 2: Oesophageal tube placement in a 25 week infant

The PediCap® showed no colour change. The flow waves show inspiratory flow but no expiratory flow. The tidal volume wave is demonstrating a stepwise increase with each inflation until the flow sensor resets and a further stepwise rise is seen.

Figure 3: Correct tube placement in a 28 week infant

Correct ETT placement is indicated as both inflation and expiratory flow curves return to baseline. The tidal volume curve shows very small tidal volumes entering and leaving the lung. The attached Pedicap® failed to change colour.

Figure 4: > 80% Leak around an endotracheal tube

The area underneath the inflation flow curve is greater than that under the expiratory flow curves. This is reflected in the tidal volume curve, which displays a larger inspiratory tidal volume compared to an expiratory tidal volume. Leak is displayed as a straight line in the tidal volume curve. The attached PediCap® did not change colour. However, the inflation and expiration flow curve indicates correct tube placement of a tube which is too small.

Figure 1
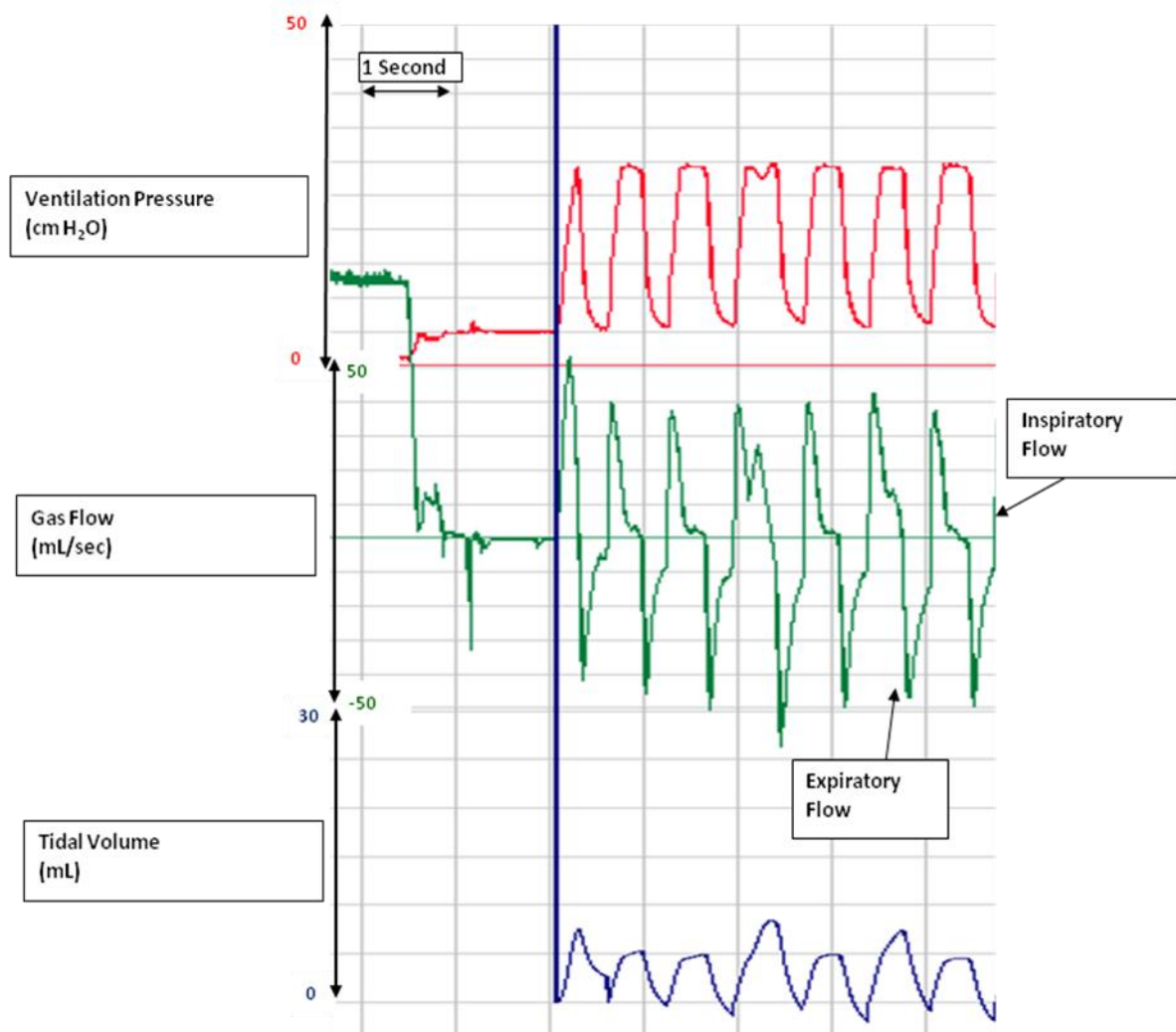
Figure 2
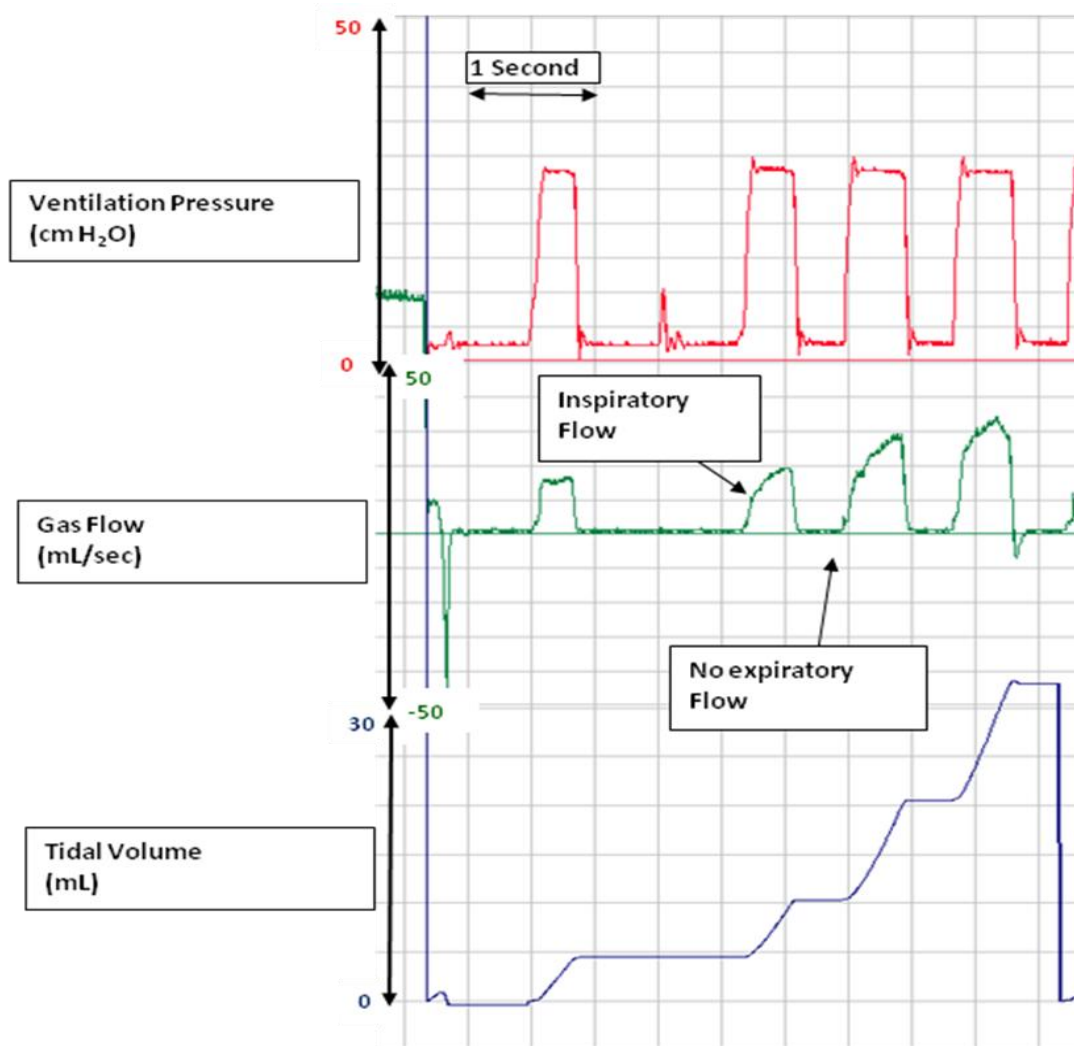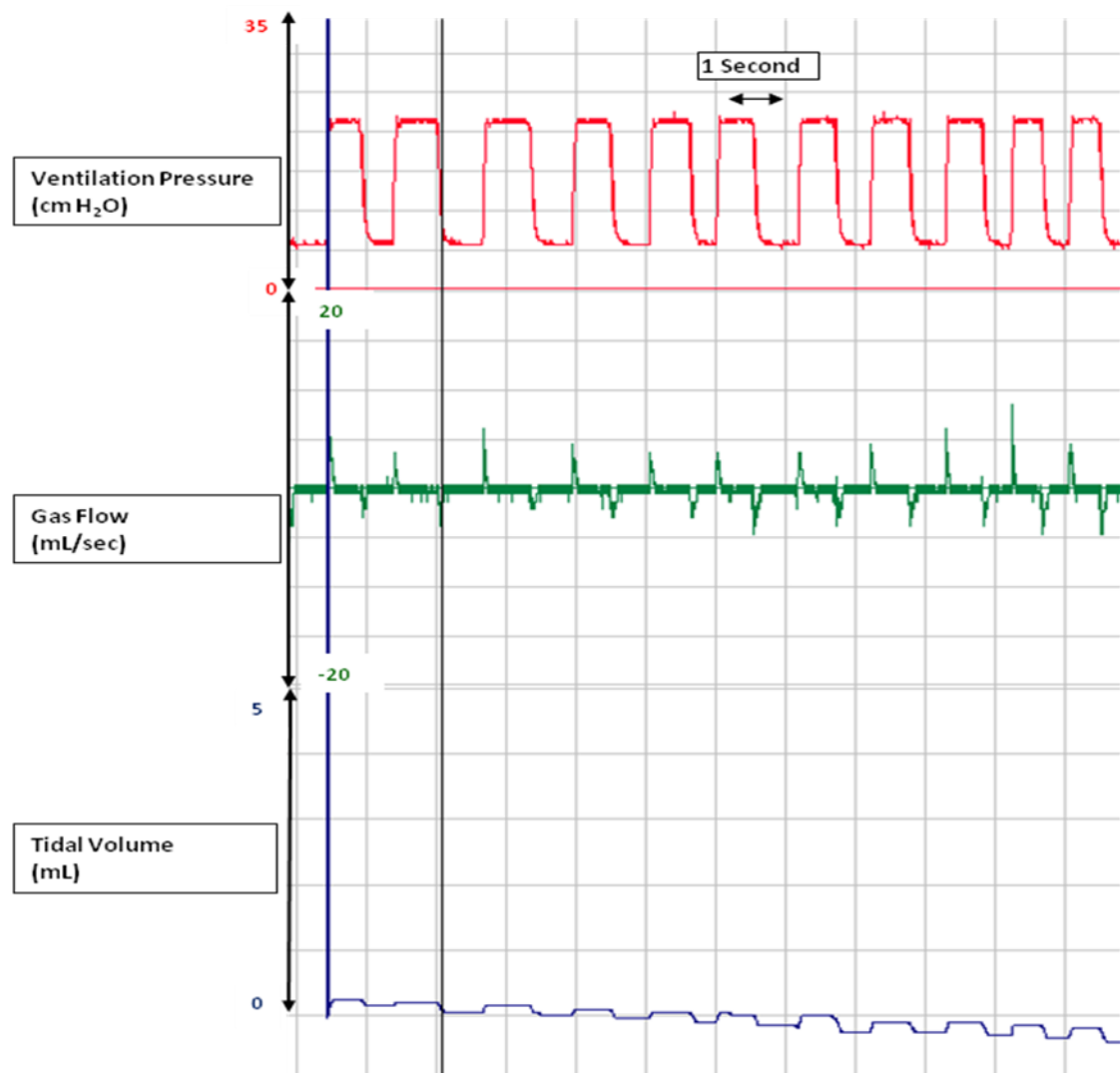
Figure 3

Figure 4
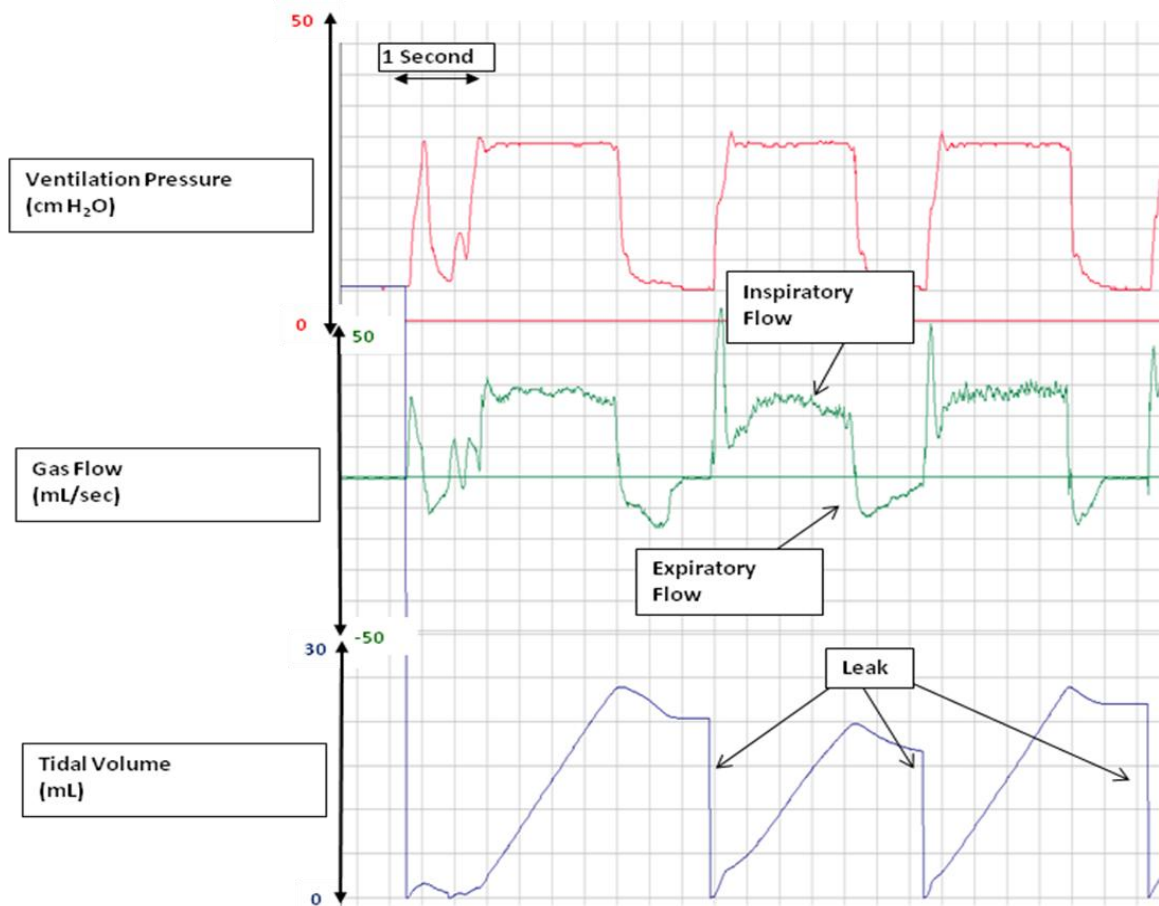
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Chapter XIV

General Discussion

Summary and Conclusions

Approximately 3-6% of all newborn infants require respiratory assistance at birth (Singhal et al., 2001). An internationally agreed consensus statement (ILCOR Part 7: Neonatal resuscitation, 2005a) and various guidelines (Biarent et al., 2005; Morley, 2007b) provide advice regarding techniques and equipment for neonatal resuscitation. They all agree that the key to successful neonatal resuscitation is adequate PPV (Biarent et al., 2005; ILCOR Part 7: Neonatal resuscitation, 2005a; Morley, 2007b). However, PPV can be difficult because the assessment of mask seal (O'Donnell et al., 2005a; Wood et al., 2008b), tidal volume (Roehr et al., 2009; Schmölzer et al., 2010b) and effective ventilation is subjective and relies on an impression of adequate chest wall rise, oxygenation levels and increased heart rate (ILCOR Part 7: Neonatal resuscitation, 2005a).

Until recently, intermittent blood gas measurements and chest wall movements were the only way to assess the adequacy of ventilation in NICUs. Now most neonatal ventilators are equipped with a RFM, which measures and displays many aspects of airway pressure, gas flow and tidal volume (Klimek et al., 2006). This is important information to help clinicians adjust the ventilator settings and assess the adequacy of ventilation (South and Morley, 1986b; Bhutani and Sivieri, 2001; Bhutani, 2002; Keszler, 2005). The significance of the experiments described in this thesis is that applying technologies used in NICUs could improve the effectiveness of ventilation in the DR. The aims of the studies were i) to measure respiratory function during PPV ii) to assess the performance of the resuscitator (*Chapter V, VI,* respectively) and describe the possible usefulness of a RFM (*Chapter III, IV, VII, VIII, IX, XII and XIII* respectively), iii) to assess if a RFM could reduce Morbidity and Mortality during PPV (*Chapter X, XI,* respectively), and iv) determine when gas exchange occurs (*Chapter XIV*)

Assessment of chest wall movements during PPV

An international agreed consensus recommends that infants with inadequate breathing or are bradycardic, should be given mask PPV with a self-inflating bag, flow-inflating bag or T-piece device (ILCOR Part 7: Neonatal resuscitation, 2005b; ILCOR consensus on science: neonatal resuscitation, 2006). The purpose of PPV is to establish and maintain a FRC, deliver an appropriate V_T and facilitate gas exchange (Schmölzer et al., 2008; Te Pas et al., 2008a). A PIP is chosen with the assumption that this will deliver an appropriate V_T (ILCOR Part 7: Neonatal resuscitation, 2005b; ILCOR consensus on science: neonatal resuscitation, 2006). The resuscitator judges the delivered V_T by observing chest wall movements,(ILCOR Part 7: Neonatal resuscitation, 2005b; ILCOR consensus on science: neonatal resuscitation, 2006) but the tidal volumes are not measured. During PPV adequacy of gas exchange is judged by an increase in HR (ILCOR Part 7: Neonatal resuscitation, 2005a. However, if HR does not increase, chest wall movements should be assessed. The current neonatal resuscitation guidelines do not describe how chest wall movements during PPV should be assessed (ILCOR Part 7: Neonatal resuscitation, 2005a).

In *Chapter V,* I hypothesised that resuscitators are unable to accurately assess delivered V_{Te} and mask leak by looking at chest wall movements while performing PPV. I showed that resuscitators were unable to assess chest wall movements during PPV. In addition, they were unable to judge the delivered V_{Te} or mask leak. However, it could be argued that limited experience in neonatal resuscitation was a contributing factor to these results. In addition, assessing chest wall movement during PPV at the infant's head might be difficult because the ventilation device partly obstructs the resuscitators view, the infant is wrapped in plastic or the resuscitator is focused on administering the ventilation. Therefore, I conducted a further observational study comparing the assessment of chest wall movement during PPV simultaneously at the side (side view) and the head (head view) of the infant.

In *Chapter VI,* I hypothesised that a side view may provide a better assessment of V_T delivery by chest rise because this team member can focus on this single task

compared to performing PPV and assessing chest rise simultaneously. I found that neither the observation position nor the level of experience affected the accuracy of estimation of V_{Te} delivery by assessment of chest wall movements.

These two observational studies showed that the assessment of chest wall movements by the resuscitator was an inaccurate measure of V_{Te}. Using a RFM in the delivery room to continuously measure and display the delivered tidal volume might improve the effectiveness of neonatal resuscitation.

Mask hold, mask position and mask leak

Mask leak is both a common and an unrecognized problem during PPV which can lead to failure of ventilation (O'Donnell et al., 2005a; Wood et al., 2008b; Schmölzer et al., 2010a; Schmölzer et al., 2010b). Although neonatal resuscitation teaching programs emphasise the importance of mask ventilation, the evaluation of how well the students apply the mask and ventilate the mannequin is subjective. Recently, a RFM was used to evaluate mask ventilation of mannequins when teaching neonatal resuscitation (O'Donnell et al., 2005d; Wood et al., 2008a; Wood et al., 2008b; Wood et al., 2008c). Many operators had large and unrecognised gas leaks between the face and the mask (Wood et al., 2008b). When the operators used a RFM they were able to adjust the mask position and reduced the leak by more than half (Wood et al., 2008a). These studies have shown that a RFM can be used to find the best technique of positioning, holding and ventilating a mannequin with a face mask.

In *Chapter V,* I measured mask leak during PPV in the DR and compared it with the assessment of the resuscitator (Johnston and Stenson, 2010; Schmölzer et al., 2010b). I found that mask leak varied widely from almost zero to 100%. In addition, resuscitators were unable to accurately self-assess their leak while performing PPV. These findings are consistent with those of the mannequin studies during PPV (O'Donnell et al., 2005a; Wood et al., 2008b).

In *Chapter VII,* the prevalence of mask leak and airway obstruction during the first two minutes of PPV was assessed. I found that 50% of all infants receiving PPV had

large mask leaks. Interestingly, mask leak was more likely to occur at the start of PPV compared to airway obstruction which occurred later. Once PPV was established, leak was less likely to be observed. Procedures such as fitting a hat or putting the infant in a plastic bag contributed to large face mask leak. Furthermore, assessing the infant can distract the resuscitators focus from mask position and mask holding techniques during the initial phase of PPV.

In *Chapter XI,* I hypothesised that a RFM during PPV in the DR will have similar results as shown in mannequin studies. I hypothesised that continuously displaying mask leak and tidal volume delivery during PPV will lead to i) a reduction in mask leak and ii) more adequate tidal volume delivery. In this randomized control trial, preterm infants at <32 weeks gestation were randomly allocated to receive PPV with either the screen of a "Florian respiratory function monitor" visible to assist the resuscitator during PPV ("RFM visible") or the screen of the "Florian respiratory function monitor" was covered during PPV ("RFM masked"). The overall mean (SD) mask leak for all inflations was significantly less in the RFM visible group compared to the RFM masked group 41% (27) versus 43% (28) (p=0.012). However, there was no difference in the mean mask leak of each resuscitator; "RFM visible" 43% (16) versus 48% (20) "RFM masked" (p=0.34). However, the delivered V_{Te} was significantly lower in the "RFM visible" group which will be discussed below.

In summary, mask leak is common and varies during resuscitation due to either spontaneous movements of the baby, movements of the operator and procedures such as changing the wraps or fitting a hat. This means that it is important to have a continuous display to assess whether the leak and tidal volume are changing during the resuscitation and adjust the mask position to compensate. This can be applied in both mannequin teaching and PPV in newborn infants to find the best technique of positioning, holding and ventilating with a face mask.

Evaluating tidal volumes

The purpose of applying a PIP during PPV is to inflate the lungs with an appropriate tidal volume and thereby facilitate gas exchange. The appropriate V_T to be delivered

during various phases of resuscitation is unknown. Tidal volumes that are too high can damage the lungs by over inflation and V_Ts that are too small will result in inadequate gas exchange (Dreyfuss and Saumon, 1993; Bjorklund et al., 1996; Vilstrup et al., 1996; Bjorklund et al., 1997; Wada et al., 1997; Jobe and Ikegami, 1998; Dreyfuss and Saumon, 1998; Bhutani, 2002; Tremblay and Slutsky, 2006; Hillman et al., 2007; Polglase et al., 2008). It has been claimed that adequate tidal volumes for gas exchange are rarely delivered through a facemask in the DR (Milner et al., 1984; Field et al., 1986; Hoskyns et al., 1987).

In *Chapter V* and *Chapter VI,* I have shown that resuscitators delivered highly variable tidal volumes with a self-inflating bag and T-Piece device from almost zero to 31 mL/kg. Human and animal observational studies suggest V_T during resuscitation should be within a range of 4 to 8 mL/kg and that large tidal volumes can damage the lungs by over inflation (Vilstrup et al., 1996; Bjorklund et al., 1997; Wada et al., 1997; Jobe and Ikegami, 1998; Tremblay and Slutsky, 2006; Hillman et al., 2007; Polglase et al., 2008; Te Pas et al., 2008b). Lung compliance and, therefore, the pressures required to deliver an appropriate tidal volume, varies greatly immediately after birth. There are even greater differences *between* infants depending on the immaturity of the lung and their own variable contributions, which are adding to the inconsistency of volumes delivered by a set PIP (Hooper et al., 2007; Schmölzer et al., 2008; Te Pas et al., 2008a). These observations suggest that it is necessary to measure and adjust the delivered tidal volumes during PPV immediately after birth, especially in very preterm infants (Stenson et al., 2006; O'Donnell and Stenson, 2008; Schmölzer et al., 2008; Vento et al., 2008a; Vento et al., 2008b; Kattwinkel et al., 2009b; Johnston and Stenson, 2010; Schmölzer et al., 2010a; Schmölzer et al., 2010b).

In *Chapter X* a systematic review (Cochrane review) is presented which focuses on the use of a RFM to reduce morbidity and mortality in preterm infants. Unfortunately, no study addressing the issue was identified. Therefore I performed a randomised control trial in infants <32 weeks gestation, which were randomly allocated to receive PPV with either the screen of a "Florian respiratory function monitor" visible to assist the resuscitator during PPV ("RFM visible") or the screen of the "Florian respiratory function monitor" was covered during PPV ("RFM masked"). I hypothesised that

continuously display of V_{Te} during PPV will lead to more adequate tidal volume delivery. I found that the overall median (IQR) delivered V_{Te} for all inflations was lower in the "RFM visible group" 5.9 (3.2-9.2) mL/kg compared to 7.9 (5.0-11.0) mL/kg (p=0.0001). In addition, there was a higher proportion of delivered V_{Te} >8 mL/kg in the "RFM masked" group which may have been excessive and caused lung injury. Kattwinel et al (Kattwinkel et al., 2009b). showed similar results in a mannequin study. Operators were able to adjust the delivered PIP faster once compliance changes occurred when V_T was continuously displayed. However, only 40% of all inflations were in the target range of the proposed study (Kattwinkel et al., 2009b).

In summary, I have shown that a RFM can be used during PPV to assess tidal volume delivery. It enables the resuscitator to see and measure the delivered tidal volume and adjust the PIP to ensure a reasonable tidal volume is delivered. Furthermore, it helped to deliver lower V_Ts which may be less injurious.

Assessment of the PIP, PEEP and pressure waveform

With a self inflating bag or a flow inflating bag, the pressure delivered is unknown unless it is measured and displayed using a manometer (Hussey et al., 2004; Bennett et al., 2005; Oddie et al., 2005; O'Donnell et al., 2005b). The applied pressure is usually shown on a dial during PPV with a T-piece device. Although this is useful, the peak pressure rises and falls rapidly and it can be difficult to see the exact peak pressure being delivered (O'Donnell et al., 2005b). It is even harder to see the exact PEEP because with most dials the scale goes from 0 to at least 70 cm H_2O and therefore it is very difficult for the user to determine accurately the exact level of PEEP when it is around 5 cm H_2O. In addition, during difficult resuscitations it can be difficult to watch both the baby and the pressure dial (O'Donnell et al., 2005b).

The optimum PIP will vary between infants and in the same infant over time as the lung aerates and the compliance and resistance changes or when the baby breathes (Lachmann et al., 1979; Suzuki et al., 2005; Hooper et al., 2007; Te Pas et al.,

2008a). Therefore relying on a set PIP might result in over or under ventilation of the lung. Although only measured for 30 seconds, in *Chapter V* and *Chapter VI,* I have shown that V_T varies widely during PPV. In addition, I found that the airway pressure was a poor proxy for the delivered V_T and the set level could usually be achieved despite very large leaks. This has also has been shown in mannequin studies (O'Donnell et al., 2005d). Clinicians should not assume that effective ventilation is occurring when the desired pressures are achieved (O'Donnell et al., 2005a; Finer et al., 2009; Kattwinkel et al., 2009b; Tracy et al., 2010).

Measurement of V_{Te} during PPV may be more useful than relying on an inflating pressure or clinical judgment (Kattwinkel et al., 2009a). ILCOR and various guidelines suggest an initial inflating pressures between 20 and 25 cm H_2O is sufficient to deliver an adequate V_T in preterm infants (Biarent et al., 2005; ILCOR Part 7: Neonatal resuscitation, 2005b; Morley, 2007b). However, I have shown in Chapter V and VI that with a set PIP of 30 cm H_2O the delivered V_{Te} varied widely between inflations with a median (IQR) V_{Te} of 8.7 mL/kg (5.3 to 11.3). Although only measured for 30 seconds of PPV some infants received inflations far above or below the target range of 4-8 mL/kg. These observations suggest that relying on a fixed inflating pressure may be harmful and result in either under- or over-ventilation (Schmölzer et al., 2010b).

In summary, the purpose of the inflating pressure is to deliver an adequate tidal volume. However, using a RFM enables the whole pressure wave to be observed and the values of PIP, PEEP are easily monitored by the resuscitation team (O'Donnell et al., 2005b). The problem, as I have shown, is that the tidal volumes vary and are unknown. A display of PIP and tidal volume allows the resuscitator to alter face mask position to diminish facemask leak and also adjust the PIP to optimise tidal volume delivery.

Airway obstruction

The contribution of an ineffective technique to failure of neonatal resuscitation is unknown. The delivery of adequate PPV in the DR is dependent on good face mask technique. Several factors can reduce the effectiveness of PPV. These include poor

face mask technique resulting in mask leak or airway obstruction, spontaneous movements of the baby, movements by or distraction of the resuscitator, and procedures such as changing the wraps or fitting a hat (Wood et al., 2008a; Wood et al., 2008b; Finer et al., 2009). A cause of inadequate PPV is airway obstruction. I believe airway obstruction can occur in two places. It appears that in the stress of the resuscitation, resuscitators may hold the mask onto the infant's face too tightly and obstruct the nose and mouth so that no gas can enter the lungs. The second cause is that the neck is too flexed and the airway becomes obstructed at the pharynx. Finer et al. recently reported airway obstruction during PPV using a colorimetric CO_2 detector and found airway obstruction in 75% of infants receiving PPV in the DR (Finer et al., 2009). A CO_2 detector is a very useful for assessing effective ventilation, however, it cannot differentiate between an inadequate tidal volume and airway obstruction. In comparison, a RFM displays flow and tidal volume signals allowing the characteristic pattern associated with mask leak and airway obstruction to be identified (Schmölzer et al., 2010a).

In *Chapter VIII,* I present my observation on airway obstruction during PPV. In this study I have shown that significant airway obstruction can occur during the first two minutes in about a quarter of the very preterm infants who received PPV in the DR. Although I observed both obstruction and leak in 8 recordings, in general, large mask leak was observed in twice as many recordings as airway obstruction. Interestingly, in about a third, neither obstruction nor face mask leak occurred. A further interesting observation was that mask leak was more likely to occur at the start of PPV, while airway obstruction more often occurred later on. Some could argue that correcting mask hold contributed to that result. This is supported by a recent mannequin study by Schilleman et al. which showed that operators had frequent airway obstruction once they had adjusted mask hold to correct for leak (Schilleman et al., 2010). Conventional resuscitation training teaches that airway obstruction may be due to manual compression of the soft tissues of the neck and thus the trachea, or hyperextension or flexion of the head (O'Donnell et al., 2005a; Kattwinkel, 2006). However, after examining many recordings I think most obstruction is due to the face mask being held on the face so tightly that it obstructs the mouth and nose. I believe this was the case because the obstruction was resolved by reapplying the face mask

rather than altering the head position. However, I cannot be sure that neck obstruction did not occur in some infants.

In summary, a RFM can be used to identify airway obstruction by observing tidal volume and flow waves. Obstruction can occur in two places. Firstly, it appears that in the stress of the resuscitation, resuscitators may hold the mask onto the infant's face too tightly and obstruct the nose and mouth so that no gas can enter the lungs. This can be differentiated as a cause of obstruction simply by releasing the mask a little and observing the gas flow and tidal volume signals. The second cause of little or no gas flow into the infant during inflations is that the neck is too flexed and the airway becomes obstructed at the pharynx. This can be diagnosed by observing the flow and tidal volume signals as the head is repositioned.

Endotracheal intubation

Endotracheal intubation in the delivery room remains a common procedure, however it is technically difficult and oesophageal intubation is common (Roberts et al., 1995; Falck et al., 2003; Lane et al., 2004; Finer and Rich, 2004; Leone et al., 2005; O'Donnell et al., 2006). In addition, several studies have shown that the delay in recognizing oesophageal intubation using clinical assessment may take several minutes (Roberts et al., 1995; Aziz et al., 1999; Repetto et al., 2001; Lane et al., 2004; O'Donnell et al., 2006). Although a carbon dioxide detector is now the standard of care for assessing the accuracy of intubation during resuscitation (O'Donnell et al., 2004a; O'Donnell et al., 2004b; O'Donnell et al., 2004c; Biarent et al., 2005; Leone et al., 2006; Morley, 2007b) it can take up to six inflations before the colour changes occurs (Aziz et al., 1999; Repetto et al., 2001; Kamlin et al., 2005; Morley, 2007a). A gas flow sensor continuously measures and displays gas flow and V_T in and out of the ETT (Schmölzer et al., 2009). They are increasingly used in NICUs to guide ventilation (South and Morley, 1986a; Bhutani, 2002; Keszler, 2005; Klimek et al., 2006).

In *Chapter XII,* I evaluate the accuracy of a flow sensor in determining tracheal versus oesophageal tube placement and to compare the speed of a flow sensor with

that of a CO_2-detector (Pedi-Cap[®]) in determining correct tube position in a preterm sheep model of neonatal resuscitation. These observations showed that a flow sensor correctly identifies tube placement within the first two inflations in all cases. In comparison, the PediCap[®] required more inflation to correctly identify tube placement. This study showed that a flow sensor can be used to assess tube placement, but more importantly is quicker compared to a PediCap[®].

The next step was to determine the accuracy of a CO_2-detector (PediCap[®]) in identifying ETT position during neonatal resuscitation which is presented in *Chapter XIII*. Although, the PediCap[®] is not recommended for infants < 1kg, it is widely used to confirm tube placement during neonatal resuscitation (O'Donnell et al., 2005c; Leone et al., 2006; Iriondo et al., 2009; Schmölzer et al., 2010d). Garey et al. (Garey et al., 2008) recently reported the required volume threshold to achieve a colour change at the Pedi-Cap[®]. In an artificial lung model, charged with 5% CO_2, tidal volumes of > 0.72mL were required to achieve colour change at the PediCap[®]. I identified 11 cases were no colour change of the PediCap[®] was observed. In two cases the delivered V_T was below the threshold (Garey et al., 2008). However, in nine cases the PediCap[®] remained purple despite V_Ts greater than the reported threshold (Garey et al., 2008). In the first minutes after birth the lung liquid has to be absorbed and effective gas exchange needs to be established (Hooper et al., 2007; Te Pas et al., 2008a; Hooper et al., 2009) before CO_2 appears in the exhaled air. In these nine cases, the lungs might have been only partially aerated despite tidal volumes during PPV within the target range of 4-8 mL/kg (Schmölzer et al., 2008). This is supported by my results in *Chapter XIV*. These results show that exhaled CO_2 is correlated to the delivered V_T. Hence, inadequate amount of exhaled CO_2 to achieve colour change of the PediCap[®] was present. These results suggest that colorimetric CO_2 detectors may mislead clinicians intubating very preterm infants in the delivery room. They may fail to change colour in spite of correct tube placement in up to one third of the cases.

In summary, a RFM will immediately show whether the ETT is in the trachea or in the oesophagus (O'Donnell et al., 2006; Schmölzer et al., 2010c). If no colour change is seen with a CO_2 detector, it may be that although the ETT is correctly placed, the V_{Te} is too low. This is not clear with a CO_2 detector but can be immediately seen with a

RFM and the PIP increased until an appropriate V_T is achieved. Dislodgment of an ETT, large leaks around an ETT or tube obstruction is all easily seen with a RFM.

Further applications of a RFM include observation of ventilation rate, inflation time and expiration time which I report in *Chapter IV* (Schmölzer et al., 2010a). In addition, te Pas et al., described breathing patterns in term and preterm infants in the first 90 seconds after birth and during spontaneous breathing infants supported with CPAP (Te Pas et al., 2008b; Te Pas et al., 2009). Furthermore, te Pas et al., described the use of a RFM during stabilisation of infants with congenital diaphragmatic hernia (Te Pas et al., 2008c). However, these were only observations and further studies assessing whether these technologies can improve outcomes need to be performed.

Possible problems from using a respiration function monitor

Inexperience and lack of knowledge about the displayed waveforms may lead to misinterpretation of the signals. Therefore, anyone using a RFM must be trained to interpret pressure, flow and tidal volume signals. In addition, the attention of an inexperienced user may be diverted from the baby to the monitor screen. With the current available devices, the displayed V_{Te} must be converted to mL/kg (e.g. a displayed V_{Te} of 6 mL/kg for a 560g infant will be V_{Te} of around 12 mL/kg,). For people unfamiliar with the device they may find that placement of a flow sensor between the mask and resuscitation device makes holding the device a little awkward.

Limitations of a respiration function monitor

With the "Florian RFM", the numerical value for leak is averaged over one minute and so cannot be used for individual inflations. A RFM only displays the waves and data to aid the resuscitator and does not provide interpretation of the signals or a diagnosis. For example a signal showing absent V_T may be due to malposition of the face mask, obstruction of the airways or a congenital abnormality.

Conclusions

The studies presented in this thesis show that a RFM can be used during mannequin based neonatal training program to: 1) teach correct mask hold and positioning techniques to diminish leak; 2) teach assessment of PIP and PEEP; 3) teach assessment of tidal volumes and adjustment of PIP to deliver an appropriate tidal volume. During neonatal resuscitation a RFM can provide continuous information about: 1) tidal volume 2) mask or ETT leak, 3) tube placement after endotracheal intubation, 5) the PIP and PEEP being delivered. In addition, I believe it provides valuable information about 1) ventilation rate, 2) inflation and expiration times, 3) the spontaneous breathing patterns, tidal volume and interaction with the inflations.

Future Directions

Approximately 6% of all newborn infants require assistance during neonatal transition. International guidelines recommend adequate positive pressure ventilation to support infants during neonatal transition. I have shown that this can be difficult because the assessment of mask seal, tidal volume and effective ventilation is subjective and relies on an impression of adequate chest wall rise, oxygenation levels and increased heart rate.

I believe that in order to improve neonatal outcomes we have to optimise neonatal mannequin and simulation training as well as our approach to delivery room resuscitation. A better understanding of neonatal transitions and how we can improve short and long term outcomes is needed. The following questions can be answered by performing large clinical randomised control trials.

I. **Neonatal Mannequin and Neonatal Simulation Training**
   a. Using a RFM to identify flaws in mask technique and improve the delivery of PPV of participants
   b. Evaluate if a RFM can be used as a quantitative assessment tool of PPV in resuscitation courses
   c. Identifying alternative methods to assess PPV; which could also be applied to Level I & II units and in developing countries

II. **Neonatal Transition and Resuscitation**
   a. Is there a possibility to assess chest wall movements during PPV?
   b. Does the use of a RFM in the delivery room improve short and long term outcomes?
   c. Are there alternative methods to assess adequate ventilation (e.g.: Heart rate, oxygen saturation, CO_2)?
   d. Are there alternative methods to safely deliver PPV in infants (e.g.: Volume guarantee combined with face mask for PPV)?
   e. What is the optimal device to conform correct tube placement?

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Chapter XV

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