THE RELATIONSHIP BETWEEN THE VOLUME STATE OF THE LUNG, GAS EXCHANGE AND LUNG MECHANICS DURING HIGH-FREQUENCY OSCILLATORY VENTILATION

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Declaration

This is to certify that

(i) the thesis comprises only my original work towards the PhD except where indicated,
(ii) due acknowledgement has been made in the text to all other material used,
(iii) the thesis is less than 100,000 words in length, exclusive of tables, bibliographies and appendices.

David Gerald Tingay
25 March 2008
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Abstract

Introduction

During mechanical ventilation, lung volume is determined by the applied transpulmonary pressure. Inappropriate application of this pressure increases the risk of ventilator-induced lung injury and, in the neonate, chronic lung disease. High-frequency oscillatory ventilation (HFOV) has been advocated as a lung protective mode of ventilation. But, even when HFOV is applied with a high lung volume strategy, the reductions in chronic lung disease are modest at best. In general, this is because standard high lung volume strategies do not account for the complex relationship between pressure and lung volume. In part, this is due to difficulties in determining lung volume at the bedside during HFOV.

The use of ventilation strategies that target the deflation limb of the pressure-volume (PV) relationship by transiently recruiting the lung to total lung capacity (termed open lung ventilation strategies) result in better gas exchange, improved lung mechanics and less ventilator-induced lung injury in laboratory studies. Open lung ventilation strategies, and the relationship between the volume state of the lung, gas exchange and lung mechanics have not been systematically examined in newborn infants receiving HFOV. An understanding of these relationships may improve the application of HFOV in newborn infants.

Aims

The aims of the research described in this thesis were:

- To map the PV relationship of the diseased neonatal human lung during HFOV.
- To systematically describe the relationship between the volumetric behaviour of the lung and indicators of gas exchange and lung mechanics.
- To determine whether any of the above indicators could be used to determine the optimum mean airway pressure ($P_{aw}$).
Methods

Consent for enrolment was obtained from the parents of haemodynamically stable infants receiving HFOV with a Sensormedics 3100A oscillator and muscle relaxants. Pertinent demographic and clinical data were then collected. In each infant, the PV relationship was mapped using an open lung ventilation strategy designed to describe the deflation limb of the PV relationship, and identify total lung capacity and the critical closing pressure of the lung. To achieve this, $P_{aw}$ was sequentially increased by 2 cm H$_2$O every 10 minutes until no further improvement in peripheral oxygen saturation (Sp$_{O2}$), this point representing total lung capacity. Then, $P_{aw}$ was decreased in 1 – 2 cm H$_2$O steps until Sp$_{O2}$ fell below 85% for 5 minutes, this representing the critical closing pressure of the lung. Clinical stability was then restored by reinflating the lung to total lung capacity for ten minutes prior to returning the $P_{aw}$ to the pre-study value. During the study, no changes to inspired oxygen, oscillatory amplitude or frequency were permitted, and the infant was not handled.

At each $P_{aw}$ step, Sp$_{O2}$, transcutaneous carbon dioxide (Tc$_{CO2}$), change in lung volume (using respiratory inductive plethysmography), airway pressure and flow (both at the airway opening) were measured, Sp$_{O2}$ and Tc$_{CO2}$ were recorded minutely. Airway pressure and volume were recorded continuously at 200Hz, and flow at 1000Hz for 20 seconds of each minute.

From these measurements, Sp$_{O2}$, Tc$_{CO2}$, change in lung volume, quasi-static compliance and tidal volume (at the airway opening and derived from RIP) were determined at each $P_{aw}$ step. In each infant, a $P_{aw}$ – lung volume relationship was derived and each of the above parameters plotted against $P_{aw}$ and lung volume. From these plots, the $P_{aw}$ and lung volume resulting in the maximum (optimal) value for each parameter was determined and compared to the values at total lung capacity, critical closing pressure and at commencement of the study. The pooled data, normalised where applicable, were then compared using a quadratic nonlinear regression model to assess the influence of the volume state of the lung on each parameter.
Results

A total of seventeen infants were studied. All completed the study protocol without complications, including cardiovascular instability. In each infant, it was possible to show that lung volume increased as the lung was taken to total lung capacity. The portion of the deflation limb between total lung capacity and critical closing pressure could then be described. In most infants, hysteresis could be demonstrated with maximum lung volume occurring on the deflation limb, often at a lower $P_{aw}$ than at commencement of the study. A sigmoidal mathematical model of the PV relationship could be fitted to the $P_{aw}$ – volume data.

In most infants, there was a relationship between the volume state of the lung and $SpO_2$, $TcCO_2$ and tidal volume that approximated the PV relationship. As the lung was inflated to total lung capacity all parameters initially improved then deteriorated, suggesting that first alveolar recruitment and then overdistension were occurring. Each parameter was optimised on the deflation limb at a point between total lung capacity and critical closing pressure. The relationship between compliance and both $P_{aw}$ and lung volume was particularly variable when ventilation was applied on the deflation limb.

On the deflation limb, optimal $SpO_2$ occurred at a mean [SD] $P_{aw}$ of 66 [23] % of the difference in the $P_{aw}$ at total lung capacity and critical closing pressure, and was closely associated to the point of maximum lung volume. Although, between 25 to 85% of this $P_{aw}$ difference $SpO_2$ differed little from the value at optimal $SpO_2$. In contrast, optimal $TcCO_2$, compliance and tidal volume was more closely related to critical closing pressure and occurred at pressures from 18% to 41% of the $P_{aw}$ difference between total lung capacity and the critical closing pressure. This suggested that the optimal $P_{aw}$ to apply HFOV on the deflation limb occurred at a $P_{aw}$ of approximately 30% of the difference between total lung capacity and critical closing pressure. This finding was supported by the nonlinear quadratic modelling.
Conclusion

In this study, key regions of the PV relationship could be mapped in infants receiving HFOV. Indicators of oxygenation, carbon dioxide, tidal volume and, to a lesser extent, compliance exhibited a relationship with the volume state of the lung. By applying ventilation on the deflation limb of the PV relationship, a higher lung volume, improved gas exchange and better tidal volume resulted, often at a lower $P_{aw}$. The use of $SpO_2$ in conjunction with, at least one indicator of $CO_2$ or tidal volume, may allow determination of the optimal $P_{aw}$ to apply HFOV in newborn infants.
Table of Contents

Acknowledgments .......................................................... ii
Abstract ................................................................................. v
Glossary of Abbreviations .................................................... xxi

Chapter 1. INTRODUCTION .................................................. 1
  1.1 Problem Statement ...................................................... 1
  1.2 Aims ........................................................................... 2
  1.3 Overview of the thesis .................................................. 2
  1.4 Definition of open lung ventilation and the volume state of the lung..... 3

Chapter 2. LITERATURE REVIEW ....................................... 5
  2.1 Introduction ................................................................... 5
  2.2 Relevant principles of Respiratory Physiology ......................... 5
    2.2.1 Lung mechanics ..................................................... 5
    2.2.2 The Pressure-Volume relationship of the lung ................. 6
  2.3 Strategies to reduce ventilator-induced lung injury and optimise mechanical ventilation ................................................................. 11
    2.3.1 Mechanical ventilation and ventilator-induced lung injury in newborn infants .......................................................... 11
    2.3.2 Concept of lung protective ventilation strategies .................. 12
    2.3.3 Alveolar recruitment .................................................. 13
    2.3.4 Open lung ventilation as an optimal lung protective ventilation strategy ........................................................................... 15
  2.4 The use of HFOV to achieve optimal ventilation ....................... 19
    2.4.1 Principles of HFOV .................................................. 19
    2.4.2 Clinical use of HFOV .............................................. 20
    2.4.3 Laboratory evidence of the relationship between the volume state of the lung, gas exchange and lung mechanics .................. 22
    2.4.4 Achieving optimum lung volume during HFOV in human infants ...... 28
  2.5 Determining change in lung volume during HFOV using respiratory inductive plethysmography ....................................................... 30
    2.5.1 Difficulties in directly measuring lung volume in newborn infants during HFOV .......................................................... 30
    2.5.2 History and theory of respiratory inductive plethysmography ...... 31
    2.5.3 DC-coupled output RIP and the assessment of EELV ............ 33
    2.5.4 Limitations of DC-coupled output RIP ................................ 34
    2.5.5 The use of DC-coupled output RIP to measure change in lung volume during HFOV .......................................................... 34
  2.6 Conclusions ....................................................................... 37
Chapter 3 EXPERIMENTAL DESIGN AND METHODS

3.1 Introduction

3.2 Aims and hypotheses

3.2.1 Aims

3.2.2 Hypotheses

3.3 Experimental design background

3.3.1 Development of an open lung ventilation strategy

3.3.2 Preliminary testing of an open lung ventilation strategy and utility of SpO2 monitoring to determine recruitment/derecruitment.

3.4 Study Location

3.5 Study population

3.6 Eligibility Criteria

3.6.1 Inclusion

3.6.2 Exclusion

3.6.3 Cessation criteria

3.7 Methods

3.7.1 Demographic data

3.7.2 Preparation

3.7.3 Open lung ventilation strategy

3.8 Equipment description and experimental measurements

3.8.1 Bedside physiological monitoring

3.8.2 Description of Florian respiratory mechanics monitor

3.8.3 Description of RIP

3.8.4 Data acquisition

3.8.5 Experimental Measurements

3.9 Data collection and statistical analysis

3.9.1 Intra-subject analysis

3.9.2 Inter-subject analysis

3.9.3 Indicators of optimum ventilation

3.9.4 Sample size

3.10 Conclusion
Chapter 4. DESCRIPTION OF STUDY POPULATION, OSCILLATOR PERFORMANCE AND HAEMODYNAMIC RESULTS ............................................................................................... 68
4.1 Introduction ................................................................................................. 68
4.2 Description of study population ................................................................. 68
  4.2.1 Determination of study population ........................................................ 68
  4.2.2 Final study population ......................................................................... 70
4.3 Ventilator settings and data ........................................................................ 74
  4.3.1 Mean airway pressure ........................................................................... 74
  4.3.2 Frequency ............................................................................................... 75
  4.3.3 Amplitude (ΔP) ..................................................................................... 76
  4.3.4 Endotracheal tube leak ......................................................................... 79
4.4 Haemodynamic data .................................................................................. 80
4.5 P aw and SpO2 data at the end of the study ............................................... 83
4.6 Conclusion ................................................................................................ 83

Chapter 5. RELATIONSHIP BETWEEN MEAN AIRWAY PRESSURE AND LUNG VOLUME ..................................................................................... 84
5.1 Introduction ................................................................................................. 84
5.2 Individual P aw – V LRIP relationships ...................................................... 84
5.3 Normalised pressure - volume relationship .............................................. 87
5.4 Mathematical modelling of the normalised pressure – volume relationship ................................................................................................................. 88
5.5 Conclusion ................................................................................................ 90

Chapter 6. RELATIONSHIP BETWEEN OXYGENATION, MEAN AIRWAY PRESSURE AND LUNG VOLUME................................................. 91
6.1 Introduction ................................................................................................. 91
6.2 Relationship between SpO2 and P aw ....................................................... 91
6.3 Relationship between SpO2 and V LRIP .................................................. 94
6.4 Relationship between SpO2 and the PV relationship using normalised data ......................................................................................................................... 96
6.5 Conclusion ................................................................................................ 99

Chapter 7. RELATIONSHIP BETWEEN QUASI-STATIC COMPLIANCE, MEAN AIRWAY PRESSURE AND LUNG VOLUME........................................ 100
7.1 Introduction ............................................................................................... 100
7.2 Relationship between C rs and P aw ........................................................ 101
7.3 Relationship between C rs and V LRIP ..................................................... 103
7.4 Relationship between C rs and the PV relationship using normalised data ......................................................................................................................... 105
7.5 Conclusion ............................................................................................... 108
Chapter 8. RELATIONSHIP BETWEEN TIDAL VOLUME, MEAN AIRWAY PRESSURE AND LUNG VOLUME

8.1 Introduction ........................................................................................................... 109
8.2 Relationship between tidal volume and $P_{aw}$ .................................................. 110
  8.2.1 Relationship between $V_T$ and $P_{aw}$ .......................................................... 110
  8.2.2 Relationship between $V_{TRIP}$ and $P_{aw}$ .................................................... 113
8.3 Relationship between tidal volume and $V_{LRIP}$ .............................................. 116
  8.3.1 Relationship between $V_T$ and $V_{LRIP}$ ....................................................... 116
  8.3.2 Relationship between $V_{TRIP}$ and $V_{LRIP}$ ................................................ 118
8.4 Relationship between tidal volume and the PV relationship using normalised data .......................................................................................................................... 120
8.5 Relationship between $V_T$ and $V_{TRIP}$ ............................................................ 123
8.6 Conclusion ............................................................................................................ 126

Chapter 9. RELATIONSHIP BETWEEN CARBON DIOXIDE, MEAN AIRWAY PRESSURE AND LUNG VOLUME

9.1 Introduction ........................................................................................................... 127
9.2 Relationship between CO$_2$ and $P_{aw}$ ............................................................ 127
9.3 Relationship between CO$_2$ and $V_{LRIP}$ ......................................................... 131
9.4 Relationship between CO$_2$ and the PV relationship using normalised data .......................................................................................................................... 133
9.5 Relationship between CO$_2$ and $V_T$ ............................................................... 136
9.6 Conclusion ............................................................................................................ 138

Chapter 10. DISCUSSION

10.1 Introduction ........................................................................................................... 139
10.2 Mapping of the PV relationship ........................................................................... 139
10.3 Influence of the volume state of the lung on gas exchange and lung mechanics ......................................................................................................................... 142
  10.3.1 Oxygen saturation .......................................................................................... 142
  10.3.2 Quasi-static compliance ................................................................................ 143
  10.3.3 Tidal volume at the airway opening ............................................................... 144
  10.3.4 Tidal volume determined with RIP ............................................................... 145
  10.3.5 Transcutaneous carbon dioxide ................................................................. 145
  10.3.6 Analysing the data using mathematical modelling ....................................... 146
10.4 Identification of optimal ventilation using the parameters studied ................. 147
10.5 Limitations of the study ..................................................................................... 150
  10.5.1 Study population .......................................................................................... 150
  10.5.2 Mapping of the PV relationship .................................................................. 150
  10.5.3 RIP ................................................................................................................. 151
  10.5.4 Indicators of gas exchange and lung mechanics ......................................... 153
10.6 Chapter summary ............................................................................................... 155
List of Tables

Table 2-1. Summary of reported open lung ventilation strategies used during HFOV in newborn infants. .................................................................29

Table 3-1. Demographic characteristics and ventilator parameters at the time of study for the three infants enrolled in pilot study. .........................43

Table 3-2. Characteristics of Respitrace™ 200 monitor respiration signals (Respitrace users manual 2001; unpublished).................................56

Table 3-3. Mean difference and error in known change in lung volume and $\Delta V_{L_{RIP}}$ during a series of known volume changes in a test lung. ........60

Table 4-1. Characteristics of infants requiring assisted respiratory support via an endotracheal tube at the RCH NNU between August 2003 and August 2006 (median and range). .................................................................69

Table 4-2. Subject characteristics.................................................................................................................................71

Table 4-3. Illness severity by primary respiratory diagnosis (all data mean and SD) .................................................................73

Table 4-4. Difference between $P_{aw}$ displayed by Sensormedics 3100A and $P_{aw}$ recorded at airway opening, and agreement of this relationship, as $P_{aw}$ was altered during the study protocol.................75

Table 4-5. A. Relationship between the displayed $\Delta P$ on the Sensormedics 3100A oscillator and the $\Delta P$ at the airway opening measured with a Florian Monitor. B. Summary of the variation in $\Delta P$ recorded at the airway opening between $P_{aw}$ steps in each infant. All values expressed in cm H$_2$O. .................................................77

Table 4-6. Individual heart rate (HR) and mean arterial pressure (MAP) variations during the study. .................................................................81

Table 8-1. Relationship between $P_{aw}$, $V_T$, $V_{TRIP}$ and $\Delta P$ during the entire open lung ventilation strategy in Infant 3 (weight = 2.25 kg). $P_{max}$ is illustrated in grey.................................................................112

Table 8-2. Relationship between $V_T$ and $V_{TRIP}$ during the inflation and deflation series in the 14 infants with complete $V_{TRIP}$ data. ...............124

Table 9-1. Relationship between $P_{aw}$, $T_{cCO2}$, $V_T$, and $\Delta P$ during the open lung ventilation strategy in Infant 3 (weight = 2.25 kg). $P_{max}$ is illustrated in grey.................................................................129

Table 9-2. Relationship between $V_T$ and $T_{cCO2}$ during the inflation and deflation series.................................................................137
List of Figures

Figure 2-1. A quasi-static pressure - volume relationship of the lung from a surfactant-deficient rabbit model of lung injury. The lower inflection point (LIP) on the inflation limb, total lung capacity (TLC) and the critical closing pressure of the lung (CCP) on the deflation limb are shown. Adapted from Figure 6C in Rimensberger et al (1999b) and reproduced with permission from Critical Care Medicine 1999 27(9) page 1950 (© Lippincott Williams & Wilkins). .................................................................7

Figure 2-2. Pressure-volume relationship of a diseased lung illustrating the zones of overdistension and derecruitment/atelectasis. The ‘safe window’ of ventilation proposed by Froese is the region of lung volume between these two zones (Froese 1997). Reproduced with permission from Critical Care Medicine 1997 25(6) page 906 (© Lippincott Williams & Wilkins). .................. ......................................13

Figure 2-3. Relationship between the RIP-derived change in EELV and $P_{\text{aO}_2}$ during mapping of the PV relationship of the lung using HFOV in a piglet model of surfactant-deficient lung disease (Brazelton et al 2001). Reproduced with permission from Critical Care Medicine 2001 29(12) page 2359 (© Lippincott Williams & Wilkins)................37

Figure 3-1. The relationship between $P_{\text{aw}}$ and $\text{SpO}_2$ during an open lung ventilation strategy in three infants enrolled in the pilot study; recruitment series indicated by solid blue and derecruitment by red. The relationship between $P_{\text{aw}}$ and $P_{\text{aO}_2}$ is also shown in infants 3a and 3b; using dashed lines and open symbols to represent the recruitment (blue) and derecruitment (red) series. $\text{SpO}_2$ and $P_{\text{aO}_2}$ Y-axis scales are different in Pilot 3a.........................44

Figure 3-2. Photograph of infant illustrating the position of the chest (RIP_{CH}) and abdominal (RIP_{AB}) RIP transducer bands and Florian respiratory mechanics monitor pneumotach (PNT) and pressure monitoring line ($P_{\text{ao}}$) at airway opening. Oxygen saturation sensor ($\text{SpO}_2$) and transcutaneous electrode (Tc_{CO}_2) also shown......................49

Figure 3-3. Illustration of the pressure strategy used to identify $P_{\text{max}}$ and then $P_{\text{final}}$. An alveolar recruitment manoeuvre (ARM) was applied to restore lung volume on completion of the deflation series. .................................51

Figure 3-4. The relationships between $P_{\text{aw}}$ and Tc_{CO}_2 (solid lines and symbols) and $P_{\text{aCO}_2}$ recorded continuously from the intra-aortic CO$_2$ sensor in the umbilical arterial line (dashed lines and open symbols) in the third infant studied in the pilot study during the acute (Pilot 3a) and recovery (Pilot 3b) phases of respiratory illness. The inflation and deflation series of each open lung strategy is shown in blue and red respectively.........................53
Figure 3-5. A. Photograph of RIP transducer bands secured around the chest and abdomen of an infant. There is a sinusoidal wire embedded in each band. B. Schematic illustration of the relationship between changes in RIP voltage output (V) generated by stretch of the sinusoidal wire secondary to change in lung volume.

Figure 3-6. Relationship between time and RIP signal output (drift) from a fixed volume test lung. Black lines represent recordings at room temperature and red lines under an overhead radiant warmer operating at 37°C.

Figure 3-7. Schematic setup of the bench top system used to assess the accuracy of RIP to determine change in lung volume in a test lung. Two RIP transducer bands were secured around the test lung. Flow (V') and pressure ($P_{aw}$) were measured at the airway opening via a pressure line and pneumotach (PNT) connected to the Florian. The test lung was connected to the 3L and 1L calibrated syringes via leak-free 3-way taps.

Figure 3-8. $\Delta V_{LRIP}$ during a series of 20mL volume changes using a calibrated volume syringe.

Figure 3-9. A. Correlation between $V_T$ (mL) and uncalibrated $V_{TRIP}$ (V); red line represents the line of agreement. B. Bland-Altman plot of $V_T$ and calibrated $V_{TRIP}$ (both mL/kg). Solid line represents mean difference (bias) and dotted lines the 95% limits of agreement.

Figure 4-1. Bland-Altman plot of the difference between the frequency (Hz) displayed on the Sensormedics 3100A and the frequency measured at the airway opening (239 samples from 15 infants). Solid line represents bias (-0.007 Hz) and dotted lines ±2SD.

Figure 4-2. Scatter plot of the relationship between normalised $P_{aw}$ and the difference in the initial $\Delta P$ at the airway opening and the $\Delta P$ recorded at each $P_{aw}$ step during the inflation series (closed circles) and deflation series (open diamonds) in all 15 infants.

Figure 4-3. Scatter plots of $P_{aw}$ against changes in heart rate (A) and mean arterial pressure (B) from the value at $P_{initial}$. There was no relationship between either parameter and $P_{aw}$. In particular, a high $P_{aw}$ did not result in bradycardia or hypotension.

Figure 5-1. Individual $P_{aw} – V_{LRIP}$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis is different in Infants 2, 3, 5, 10 and 14.

Figure 5-2. $P_{aw} – V_{LRIP}$ relationship in 15 infants during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ and $V_{LRIP}$ data. Data expressed as mean and standard error of the mean.
Figure 5-3. Nonlinear regression analysis of deflation (A) and inflation (B) series, using normalised $P_{aw}$ and $V_{LRI}$ data fitted to the sigmoid model of the PV relationship proposed by Venegas et al (1998). Solid line represents the best-fit curve and dotted lines 95% CI of the curve. Small closed circles (A) and open diamonds (B) represent individual PV values. Large closed circles (A) and open diamonds (B) represent mean PV values, and error bars standard error of the mean, as shown in Figure 5-2. 89

Figure 6-1. Individual $P_{aw}$ – $SpO_2$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. 92

Figure 6-2. Individual $V_{LRI}$ – $SpO_2$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X-axis range differ in Infants 2,3,5,7 and 10. 95

Figure 6-3. A. $P_{aw}$ – $SpO_2$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $V_{LRI}$ – $SpO_2$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRI}$ data. Data expressed as mean and standard error of the mean. 97

Figure 6-4. Nonlinear regression analysis of the data presented in Figure 6-3, using the sigmoid model of the PV relationship (blue lines [Venegas et al 1998]) and a quadratic model (red lines). A. Normalised $P_{aw}$ – $SpO_2$ relationship during the inflation series. B. Normalised $P_{aw}$ – $SpO_2$ relationship during the deflation series. C. Normalised $V_{LRI}$ – $SpO_2$ relationship during the inflation series. D. Normalised $V_{LRI}$ – $SpO_2$ relationship during the deflation series. Solid line represents the best fit curve and dotted lines 95% CI of the curve. In all cases, the resultant curves did not significantly deviate from the data ($p$ values 0.191 to 0.743; Runs tests). 98

Figure 7-1. Individual $P_{aw}$ – quasi-static $C_{rs}$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants. 102

Figure 7-2. Individual $V_{LRI}$ – quasi-static $C_{rs}$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X- and Y-axis range differs between infants. 104
Figure 7-3. A. $P_{aw}$ - quasi-static $C_{rs}$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $V_{LRIP}$ – quasi-static $C_{rs}$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ data. Quasi-static $C_{rs}$ data expressed as the change from the value at $P_{initial}$. All data expressed as mean and standard error of the mean.................................................................106

Figure 7-4. Nonlinear regression analysis of the data presented in Figure 7-3 using a quadratic model (red lines). A. Normalised $P_{aw}$ – quasi-static $C_{rs}$ relationship during the inflation series. B. Normalised $P_{aw}$ – quasi-static $C_{rs}$ relationship during the deflation series. C. Normalised $V_{LRIP}$ – quasi-static $C_{rs}$ relationship during the inflation series. D. Normalised $V_{LRIP}$ – quasi-static $C_{rs}$ relationship during the deflation series. Data is also analysed using a sigmoid model of the PV relationship (blue lines; Venegas et al 1998) in Fig 7-4A and 7-4C. Solid lines represent the best-fit curve and dotted lines 95% CI of the curve. In all cases the resultant curves did not significantly deviate from the data (Runs test $p$ values 0.32 to 0.64) ........................................................................................................107

Figure 8-1. Individual $P_{aw}$ – $V_T/\Delta P$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants.................................111

Figure 8-2. Individual $P_{aw}$ – $V_{TRIP}/\Delta P$ relationships for 14 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants.................................114

Figure 8-3. Individual $V_{LRIP}$ – $V_T/\Delta P$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X- and Y-axis range differs between infants.................................117

Figure 8-4. Individual $V_{LRIP}$ – $V_{TRIP}/\Delta P$ relationships for 14 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated on graph. X- and Y-axis range differs between infants.................................................................119
Figure 8-5. A. $P_{aw} - V_t/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $P_{aw} - V_{TRIP}/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. C. $V_{LRIP} - V_t/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ and $V_{TRIP}$ data. D. $V_{LRIP} - V_{TRIP}/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ and $V_{TRIP}$ data. Data expressed as mean and standard error of the mean.................................................................121

Figure 8-6. Non-linear regression analysis of the data presented in Figure 8-3 using a quadratic model (red lines) and normalised $P_{aw}$, $V_{LRIP}$ and $V_{TRIP}$ data. A. $P_{aw} - V_t/\Delta P$ relationship during the deflation series. B. $P_{aw} - V_{TRIP}/\Delta P$ relationship during the deflation series. C. $V_{LRIP} - V_t/\Delta P$ relationship during the deflation series. D. $V_{LRIP} - V_{TRIP}/\Delta P$ relationship during the deflation series. Solid lines represent the curve of best fit and dotted lines 95% CI of the curve. In all cases, the resultant curves did not significantly deviate from the data using Runs test analysis (all Runs test $p$ values > 0.05)..................................................................................................123

Figure 8-7. A. Relationship between $V_t$ and $V_{TRIP}$ during the inflation series for 14 infants. B. Relationship between $V_t$ and $V_{TRIP}$ during the deflation series for 14 infants. In both figures, the linear regression slope of the $V_t - V_{TRIP}$ relationship is shown, and represented by a different colour and symbol for each infant...........125

Figure 9-1. Individual $P_{aw} - Tc_{CO2}/\Delta P$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants. .........................128

Figure 9-2. Individual $V_{LRIP} - Tc_{CO2}/\Delta P$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X- and Y-axis range differs between infants.........................132

Figure 9-3. A. $P_{aw} - Tc_{CO2}/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $V_{LRIP} - Tc_{CO2}/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ data. Data expressed as mean and standard error of the mean.................................................................134
Figure 9-4. Nonlinear regression analysis of the data presented in Figure 9-3 using a quadratic model (red lines). A. Normalised $P_{aw} - T_{cCO2}/\Delta P$ relationship during the inflation series. B. Normalised $P_{aw} - T_{cCO2}/\Delta P$ relationship during the deflation series. C. Normalised $V_{LRIP} - T_{cCO2}/\Delta P$ relationship during the inflation series. D. Normalised $V_{LRIP} - T_{cCO2}/\Delta P$ relationship during the deflation series. Solid lines represent the curve of best fit and dotted lines 95% CI of the curve. In all cases, the resultant curves did not significantly deviate from the data (Runs test $p$ values 0.36 to 0.94).

Figure 10-1. Relationship between the deflation limb of the PV relationship between TLC and CCP (grey line), derived using the mathematical model proposed by Venegas et al (1998), and the optimal $P_{aw}$ for $V_{LRIP}$, $SpO_2$, $V_T$, $C_{rs}$ and $T_{cCO2}$. $P_{initial}$ and the same $P_{aw}$ during the deflation series are also shown. Pressure and volume is expressed using normalised data. Optimal $P_{aw}$ points are mean and error bars standard error of mean.

Figure 10-2. Optimal $P_{aw}$ defined by lung volume ($V_{LRIP}$), oxygen saturation ($SpO_2$), tidal volume ($V_T$ and $V_{TRIP}$), quasi-static compliance ($C_{rs}$) and transcutaneous carbon dioxide ($T_{cCO2}$). Lowest $SpO_2$ represents the lowest $P_{aw}$ that maintains near-optimal $SpO_2$ during the deflation series. All $P_{aw}$ are mean values and referenced to the $P_{aw}$ at $P_{initial}$ (0 cm H$_2$O).
## Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AaDO₂</td>
<td>Alveolar – arterial oxygen gradient</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<tr>
<td>Cₛ</td>
<td>Respiratory system compliance</td>
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<tr>
<td>CCP</td>
<td>Critical closing pressure of the lung</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CLD</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CWM</td>
<td>Chest wall movement</td>
</tr>
<tr>
<td>ETT</td>
<td>Endotracheal tube</td>
</tr>
<tr>
<td>F₁O₂</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>Fr</td>
<td>Frequency</td>
</tr>
<tr>
<td>HFJV</td>
<td>High frequency jet ventilation</td>
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<tr>
<td>HFOV</td>
<td>High-frequency oscillatory ventilation</td>
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<tr>
<td>HLVS</td>
<td>High lung volume strategy</td>
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<tr>
<td>iNO</td>
<td>inhaled nitric oxide</td>
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<tr>
<td>IPPV</td>
<td>Intermittent positive pressure ventilation</td>
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<tr>
<td>LIP</td>
<td>Lower inflection point</td>
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<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MAS</td>
<td>Meconium aspiration syndrome</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>OI</td>
<td>Oxygenation index</td>
</tr>
<tr>
<td>PₐCO₂</td>
<td>Arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PₐO₂</td>
<td>Arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>Pₐo</td>
<td>Pressure at airway opening</td>
</tr>
<tr>
<td>Pₐw</td>
<td>Mean airway pressure</td>
</tr>
<tr>
<td>Pₚfinal</td>
<td>Final mean airway pressure obtained during the study</td>
</tr>
<tr>
<td>Pₚinitial</td>
<td>Mean airway pressure at time of study commencement</td>
</tr>
<tr>
<td>Pₚmax</td>
<td>Maximum mean airway pressure obtained during the study</td>
</tr>
<tr>
<td>Pₚpeak</td>
<td>Peak airway pressure during an oscillatory cycle</td>
</tr>
<tr>
<td>Pₚtrough</td>
<td>Trough airway pressure during an oscillatory cycle</td>
</tr>
<tr>
<td>ΔP</td>
<td>Tidal change, or amplitude, in airway pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive end-expiratory pressure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PIP</td>
<td>Positive inspiratory pressure</td>
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<tr>
<td>PNT</td>
<td>Pneumotach</td>
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<tr>
<td>PPHN</td>
<td>Persistent pulmonary hypertension of the newborn</td>
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<tr>
<td>PV</td>
<td>Pressure-Volume</td>
</tr>
<tr>
<td>RCH</td>
<td>Royal Children’s Hospital</td>
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<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
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<tr>
<td>RIP</td>
<td>Respiratory inductive plethysmography</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SpO2</td>
<td>Peripheral oxygen saturation</td>
</tr>
<tr>
<td>TcCO2</td>
<td>Transcutaneous carbon dioxide</td>
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<tr>
<td>TLC</td>
<td>Total lung capacity</td>
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<tr>
<td>UIP</td>
<td>Upper inflection point</td>
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<tr>
<td>VILI</td>
<td>Ventilator-induced lung injury</td>
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<tr>
<td>V</td>
<td>Gas flow</td>
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<tr>
<td>VL</td>
<td>Lung volume</td>
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<tr>
<td>VLAB</td>
<td>Lung volume measured by abdominal RIP transducer</td>
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<tr>
<td>VLCH</td>
<td>Lung volume measured by chest RIP transducer</td>
</tr>
<tr>
<td>VLRIP</td>
<td>Sum of thoracic gas volume measured by RIP</td>
</tr>
<tr>
<td>VT</td>
<td>Tidal Volume at the airway opening</td>
</tr>
<tr>
<td>VTRIP</td>
<td>Tidal Volume measured by RIP</td>
</tr>
<tr>
<td>ΔVL</td>
<td>Change in lung volume</td>
</tr>
</tbody>
</table>
Chapter 1.

INTRODUCTION

1.1 Problem Statement

Over 3000 newborn infants per year require mechanical ventilation in Australia and New Zealand, the majority being due to prematurity (Donoghue & the ANZNN 2004). High frequency oscillatory ventilation (HFOV) is often used in the sickest newborn infants when other modes of ventilation have failed to provide adequate respiratory support (Tingay et al 2007b). Despite significant advances in neonatal intensive care and improved survival over the last fifteen years, the rate of lung injury remains high. Lung injury has been associated with significant long term morbidities, such as chronic lung disease and neurodevelopmental delay. Mechanical ventilation alone can directly injury the lung; this process is called ventilator-induced lung injury (VILI). Minimising VILI with lung protective ventilation strategies, that is achieving ‘optimal’ ventilation, has the potential to reduce the considerable short and long term healthcare burden of this population.

In general, current ventilation strategies do not account for the complex relationship between applied ventilator pressure and lung volume. In part, this is due to the difficulties in translating the physiological principles confirmed in animal models into clinical practice. Animal studies have identified the need to use pressure strategies that achieve and maintain homogeneous alveolar recruitment, thus reducing the known contributors to VILI (such as atelectasis, overdistension and repetitive shear-force injury).

Open lung ventilation strategies attempt to achieve lung protection by transiently recruiting lung volume to total lung capacity and then applying ventilation on the deflation limb of the pressure-volume (PV) relationship. Laboratory evidence suggests that it is on the deflation limb that lung volume is optimally recruited. In addition to reducing VILI, open lung ventilation strategies improve gas exchange and lung mechanics in animal models of neonatal lung disease. Despite these apparent benefits, ventilation strategies that attempt to achieve, and maintain,
optimal lung volume recruitment (open lung ventilation) have not been widely studied in newborn infants and are limited to anecdotal reports using HFOV.

Understanding the relationship between indicators of lung mechanics and gas exchange, and the PV relationship of the lung at the bedside may assist clinicians to improve the delivery of HFOV.

1.2 Aims

The aim of this research was to investigate the volumetric behaviour and mechanics of the diseased neonatal lung during HFOV in human infants.

This overall aim was divided into four specific aims. These were:

- To describe the PV relationship of the lung during HFOV, using an open lung ventilation strategy, and determine at what point within the PV relationship ventilation was being applied by the clinician.
- In doing so, to identify key regions of the PV relationship in each infant. These were total lung capacity (TLC), the critical closing pressure of the lung (CCP) and the deflation limb of the PV relationship.
- To systematically describe the changes in lung mechanics (quasi-static compliance and tidal volume) and gas exchange (oxygen saturation and transcutaneous carbon dioxide) at different points in the PV relationship.
- To explore whether any, or all, of the above indicators of lung mechanics and gas exchange could be used to determine the optimum mean airway pressure (P_{aw}).

1.3 Overview of the thesis

This thesis is divided into eleven Chapters. Firstly, Chapter 2 examines the existing literature on achieving optimal ventilation with HFOV. Initially, the physiological principles of lung mechanics and the PV relationship of the lung relevant to this thesis are defined. The ventilatory concepts of alveolar recruitment and open lung ventilation are described and the evidence supporting these as methods of optimum lung protective ventilation is presented. Next, the animal studies investigating optimal delivery of HFOV are summarised, in particular the relationship between the volume state of the lung and indicators of lung mechanics and gas exchange. The potential of these relationships to guide the development of an optimal
ventilation strategy during HFOV in animal studies is highlighted. The difficulties in translating these findings into sound clinical practice are then explored. Finally, the difficulty with measuring lung volume in human infants during HFOV, and the ability of respiratory inductive plethysmography (RIP) to measure change in lung volume during HFOV, is discussed.

Chapter 3 develops the hypotheses and the experimental methods by which these are tested.

Chapter 4 describes the study population, haemodynamic data and the performance results of the Sensormedics 3100A oscillators used during the study.

Chapters 5 to 9 describes the results. The relationship between \( P_{aw} \) and lung volume is described in Chapter 5. Chapter 6, 7, 8 and 9 describes the relationship between the PV relationship and oxygenation, quasi-static compliance (\( C_{rs} \)), tidal volume and carbon dioxide (\( CO_2 \)) removal respectively. These results identified relationships between the volume state of the lung and bedside indicators of lung mechanics and gas exchange in human newborn infants, which are discussed in Chapter 10. Conclusions are then drawn in Chapter 11.

1.4 Definition of open lung ventilation and the volume state of the lung

Open lung ventilation is a term that has been used widely, and sometimes inconsistently, in the literature. In this thesis, ‘open lung ventilation’ refers to the ventilation concepts described by Lachmann (Lachmann 1992) and Froese (Froese 2002).

For the purposes of this thesis, the following terms are defined:

*Open lung approach:* This refers to the concept of using a ventilation strategy to apply ventilation at a pressure above the CCP on the deflation limb of the PV relationship after first recruiting the lung through TLC.

*Open lung ventilation strategy:* This refers to a specific pressure and time strategy used to achieve the aims of an open lung approach. Within the literature, a number of open lung ventilation strategies have been described that differ in the details of application but still fulfil the criteria of an open lung approach (De Jaegere et al 2006; Rimensberger et al 2000a).
Volume state of the lung: This term refers to the lung volume that results from applying ventilation at a specific point in the PV relationship. This acknowledges that the lung exhibits hysteresis and, as such, for any given transpulmonary pressure, different lung volumes may result. Atelectasis and overdistension are considered different volume states of the lung. Refer to Chapter 2-2 for a more detailed discussion.
Chapter 2.
LITERATURE REVIEW

2.1 Introduction
This chapter will review the previously published work pertinent to this thesis. Relevant principles of respiratory physiology will be described, in particular lung mechanics and the PV relationship of the lung. The concepts of alveolar recruitment and open lung ventilation during mechanical ventilation will be reviewed within the context of the potential for each to achieve optimum ventilation. The principles, clinical application and current limitations of HFOV in newborn infants will be described. The difficulties in measuring lung volume during HFOV will be highlighted. Finally RIP, as a tool for measuring lung volume in newborn infants, will be reviewed in detail.

The purpose of this chapter is to emphasise the importance of targeting a region of optimum ventilation when delivering HFOV to newborn infants with respiratory failure, and to highlight some of the current practical difficulties in achieving this.

2.2 Relevant principles of Respiratory Physiology

2.2.1 Lung mechanics
The lung is the organ of ventilation. Ventilation requires inspiratory (inflation) and expiratory (deflation) phases during each respiratory cycle. It is well established that the lung possesses mechanical properties that must be overcome for inflation to occur. These include the dynamic forces of elastic recoil, resistance to the conducting airway system and inertance (Mead 1961; Mead & Whittenberger 1953), and determine the applied trans-pulmonary pressure required to achieve gas flow into the lung during inflation. The result of this interaction determines lung volume (Mead 1961; Rahn et al 1956).

Elastic recoil, compliance and resistance
The lung has elastic properties (elastance) which must be overcome to allow inflation. Elastance is influenced not just by the elastic properties of the lung tissue
Literature Review

itself but also the chest wall and the surface forces of the gas – tissue interface (Mead 1961). The pressure required to stretch, or move, the lung (Hooke’s Law), and overcome the elastic recoil of the chest wall, is proportional to the volume of inflation (Rahn et al 1946). Consequently, elastance is the predominant force determining the transpulmonary pressure required to achieve volume change during ventilation.

The inverse of elastance is termed compliance ($C_{rs}$). Lung compliance refers to the proportionality of the relationship between the change in lung volume that results from any given change in pressure (Mead & Whittenberger 1953). The rate of volume change within the lung over time will be influenced by the friction, or resistance, within the respiratory system. For this reason $C_{rs}$ is usually measured at points of zero flow, as the system is effectively static, and independent of time and resistance, and volume change is dependent solely on elastance (Polgar & String 1966).

2.2.2 The Pressure-Volume relationship of the lung

Due to the mechanical behaviour of the lung, the principal determinant of lung volume is the pressure applied upon it. In the case of the mechanical ventilated patient, this is the positive pressure applied at the airway opening. Thus, the bounds of the volume state of the lung can be defined by the static PV relationship during conditions of no flow (Rahn et al 1946). Due to the elastic and resistive properties of the respiratory system, the static pressure – volume relationship is not linear. As shown in Figure 2-1, applying an increasing pressure to the lung from a state of end-expiratory alveolar collapse (such as after disconnection to atmosphere in a mechanically ventilated patient) initially results in minimal volume change. But, once sufficient pressure to overcome the elastic forces of the lung and the high resistance within the respiratory system is applied, then alveoli will progressively open and volume increases. In the diseased lung, the resultant point of curvature change is the lower inflection point (LIP) of the PV relationship, and is determined by the critical opening pressure above which alveolar recruitment commences.

$C_{rs}$ can be measured when the lung is in a static state or during tidal breathing (Stocks et al 1996). In the latter $C_{rs}$ is dynamic and refers to the relationship between changing transpulmonary pressure and resultant magnitude of tidal volume change between end-expiration and end-inspiration at two points of zero flow. The measurement of $C_{rs}$ at zero flow after static changes to applied end-expiratory pressure during tidal ventilation is termed ‘quasi-static’ $C_{rs}$. 

1
Thereafter, the relationship between volume and pressure is approximately linear until a second point of curvature change as TLC is approached. At this point, termed the upper inflection point (UIP), in the diseased lung the majority of alveoli will be recruited and the lung nears the limits of its elasticity and is confined by the chest wall. Further volume gains will result in increasing alveolar overdistension and require relatively higher pressures to be achieved. This relationship between pressure and volume during inflation from residual capacity to TLC is termed the inflation limb of the PV relationship. From the PV relationship, the static $C_{rs}$ can be determined from the slope (Albaiceta et al 2003a; Mead & Whittenberger 1953). During the inflation limb, $C_{rs}$ is greatest during the linear portion (Hickling 2001).

![Figure 2-1. A quasi-static pressure-volume relationship of the lung from a surfactant-deficient rabbit model of lung injury. The lower inflection point (LIP) on the inflation limb, total lung capacity (TLC) and the critical closing pressure of the lung (CCP) on the deflation limb are shown. Adapted from Figure 6C in Rimensberger et al (1999b) and reproduced with permission from Critical Care Medicine 1999 27(9) page 1950 (© Lippincott Williams & Wilkins).](image-url)
From TLC, due to the alinear behaviour of the PV relationship, the lung behaves differently when pressure is withdrawn. This is because, at this point, alveoli are uniformly recruited, airway resistance has been minimised and the applied pressure initially remains sufficient to overcome the viscoelastic forces of the respiratory system. Consequently, initial reductions in pressure do not produce alveolar derecruitment and only small volume changes result. Eventually, as applied pressure is further withdrawn, alveoli will collapse, with resultant increasing volume loss, until the residual lung volume is reached at atmospheric pressure (Figure 2-1). The resultant relationship between pressure and volume is termed the deflation limb. The pressure at which the point of maximal curvature change in the deflation limb occurs is termed the CCP of the lung (Hickling 2001). Whilst the inflation limb is affected by recruitment through out its entirety, the deflation limb is affected by alveolar collapse only at pressures below the CCP (Halter et al 2003; Hickling 2001). At pressures above the CCP, the deflation limb solely reflects the elastic properties of the lung (Mead et al 1957).

**Hysteresis**

The observed difference between the behaviour of the PV relationship during inflation and deflation is termed hysteresis. Hysteresis of the PV relationship was first described in detail by Mead et al (1957) when they demonstrated that the elastic recoil of the lung during inflation was higher than during emptying, or deflation. This results from alveoli recruiting, or ‘opening’, in an irregular fashion during inflation (at a wide range of individual opening pressures) but emptying, or derecruiting and ‘closing’, in a more uniform manner (Crotti et al 2001; Halter et al 2003; Schiller et al 2003).

Hysteresis does not occur in the saline filled lung, indicating that surface forces, and thus surfactant, have some part in determining the mechanical properties of the lung (Mead 1961). This has been further demonstrated in the relatively surfactant-deficient newborn lung with hyaline membrane disease. The static PV relationship of the lung with hyaline membrane disease exhibits less hysteresis than the same lung after exogenous surfactant administration (Göthberg et al 2001; van Kaam et al 2004b). Surface forces alone do not adequately explain the concept of hysteresis. Hysteresis is a result of the complex interaction between resistance, viscoelastic
behaviour and differences in the opening and closing pressures within and throughout lung units (Jonson 2005).

The principal limitation of the static PV relationship is that it is a global measurement of a series of regional changes within lung units, and even alveoli. Alveolar recruitment is an ongoing, and irregular, process during inflation (Anthonisen 1964; Carney et al 1999; Cheng et al 1995; Crotti et al 2001; Frazer et al 1985; Halter et al 2003; Pelosi et al 2001; Smaldone et al 1983). This is because elastic recoil is not uniform between lung units (Mead et al 1957) and the lung tissue and chest wall exert a superimposed hydrostatic pressure (gravity-related) causing compression atelectasis on dependent lung units (Gattinoni et al 1991; Gattinoni et al 1993). Consequently, every lung unit exhibits its own individual PV relationship, resulting in a spectrum of opening and closing pressures throughout the lung, which are normally distributed (Crotti et al 2001; Schiller et al 2003). There is increasing realisation that the inflation limb of the PV relationship represents the range of trans-pulmonary pressures required to open and recruit all alveoli (Albaiceta et al 2004; Jonson 2005). The clinical implications of these principles in achieving optimal ventilation during mechanical ventilation of the diseased lung are discussed in Section 2.3.

It is less clear how alveoli behave during deflation. It has been proposed that alveoli progressively decrease in dimension during deflation (Anthonisen 1964; Forrest 1970; Klingele & Staub 1970). Others have argued that alveolar derecruitment is an important factor in determining volume change during deflation (Bachofen et al 1979; Carney et al 1999; Gil et al 1979; Gil & Weibel 1972; Radford 1962). The likelihood is that both processes occur simultaneously and the predominance of one over the other changes during the deflation limb.

The property of hysteresis, and resultant volume state of the lung, has important clinical significance. For any specific applied pressure during mechanical ventilation, there exists a range of lung volumes that can be achieved. The resultant volume is determined not simply by the applied pressure at that point in time but how the lung has been previously ventilated, termed the volume history of the lung (Mead et al 1957; Mead 1961). Thus, at any given applied pressure, lung volume will be greater on, or near, the deflation limb compared to the inflation limb.
Mathematically defining the pressure-volume relationship of the lung

There have been a number of attempts to describe the PV relationship of the lung mathematically. Fitting a mathematical model to the PV relationship of the lung has the advantage of allowing $C_{rs}$ and other indicators of lung mechanics, to be predicted. Furthermore, the influence of clinical changes which may alter the PV relationship, such as surfactant administration, can be anticipated. The first such mathematical equation to compute lung volume ($V$) during inflation was proposed by Salazar and Knowles (Salazar & Knowles 1964):

$$V = V_{\text{max}} \left[ 1 - e^{-P \left( \frac{\ln \left( \frac{V}{V_{\text{max}}} \right)}{h} \right)} \right]$$

where $V_{\text{max}}$ = maximum lung volume, $P$ = applied pressure and $h$ = half opening pressure.

This equation requires knowledge of $V_{\text{max}}$, or TLC. In clinical practice, TLC is rarely known. A second limitation of this equation is that it is inaccurate at volumes less than 50% of TLC (Saetta & Mortola 1985). A simple, four parameter, second order, sigmoidal model of the PV relationship was proposed by Venegas et al in 1998.

Using this model, lung volume ($V$) is defined as:

$$V = a + \frac{b}{1 + e^{-\left( P - c \right)/d}}$$

where $a$ represents the lower asymptote volume and is equivalent to the residual volume, $b$ is the difference between the volumes at the lower and upper asymptotes points and is equivalent to the vital capacity, $c$ is the pressure at the true inflection point of the sigmoidal curve (where the curvature sign changes and represents the pressure at the highest $C_{rs}$) and $d$ represents the proportion of the pressure range in which the majority of the volume change occurs (Venegas et al 1998). From this equation, the lower and upper corner pressures can be determined from:

$$P_{\text{LIP}} = C_{rs} - 2d \text{ and } P_{\text{UIP}} = C_{rs} + 2d$$

Venegas et al (1998) subsequently showed that this model closely fitted PV relationships in canine models of lung disease and in adults with adult respiratory distress syndrome (ARDS). A limitation of the Venegas et al (1998) model is that
it assumes two symmetrical segments of the inspiratory limb around the pressure defined by \( c \). In humans, the regions below the LIP and above the UIP are usually not symmetrical. Alternative, more sophisticated, five (Heller et al 2002) and six parameter models (Maggiore et al 2001; Svantesson et al 1999) have been proposed to account for this limitation. All of these models produce a closer fit to clinical data than the model proposed by Venegas et al (1998), although the practical benefit of the more complex models is minimal.

2.3 Strategies to reduce ventilator-induced lung injury and optimise mechanical ventilation

2.3.1 Mechanical ventilation and ventilator-induced lung injury in newborn infants

Mechanical ventilation has been used in newborn infants since 1953 (Donald & Lord 1953). As the design of mechanical ventilators developed, it became apparent that they were able to improve survival in newborn infants with respiratory failure (Reid et al 1967). Currently, approximately 3000 newborn infants per year in Australia and New Zealand receive mechanical ventilation delivered via an endotracheal tube (Tingay et al 2007b).

Most neonatal ventilators are time-cycled, pressure-limited devices and deliver an intermittent positive pressure to the lung. By the late 1960’s, it became apparent that some newborn infants receiving mechanical ventilation were developing complications directly related to their treatment. This culminated in the recognition and description of bronchopulmonary dysplasia, a disease characterised by distinctive chest radiograph changes, prolonged respiratory support and oxygen requirement (Avery et al 1987; Northway et al 1967). Over the following decades, the definition of bronchopulmonary dysplasia, or chronic lung disease of the newborn (CLD), has evolved to reflect changes in treatment (Davis et al 2002; Jobe & Bancalari 2001).

Irrespective of the definition of CLD, mechanical ventilation alone can directly injure the lung, a process termed ventilator-induced lung injury (VILI) (Webb & Tierney 1974). VILI is a multifactorial process. Barotrauma (inappropriately high applied inflation pressures) (Corbridge et al 1990; Enhorning & Robertson 1972;
Nilsson et al 1978; Sandhar et al 1988), volutrauma (inappropriately high end-inspiratory volume) (Dreyfuss et al 1985; Dreyfuss et al 1988; Kolobow et al 1987; Tsuno et al 1990), atelectasis (alveoli collapse) (Duggan et al 2003; Meredith et al 1989), shear-force injury (repetitive opening and closing of alveoli) (Copland et al 2004; Muscedere et al 1994; Papadakos & Lachmann 2002; Sandhar et al 1988; Steinberg et al 2004), oxygen toxicity and inflammatory mediated injury (Steinberg et al 2004) have all been implicated as causative mechanisms. It is possible for all or many of these processes to occur simultaneously within the lung. The relatively surfactant-deficient, diseased, newborn lung is particularly prone to these processes. Preterm infants, who have more compliant chest walls and decreased tissue elastic properties, are particularly susceptible to overdistension. In addition, inappropriate application of mechanical ventilation has been associated with other organ injury in newborn infants, in particular neurological damage (HiFi Study Group 1989).

2.3.2 Concept of lung protective ventilation strategies

Interest in applying mechanical ventilation in such a way that it treats respiratory failure whilst protecting the lung from VILI has evolved from the recognition of the injurious potential of mechanical ventilation (Froese 1997; Lachmann 1992). An optimum lung protective ventilation strategy is one which limits high inflation pressures, and volumes, but also prevents repetitive end-expiratory collapse (Lachmann 1992).

Barotrauma, volutrauma, atelectasis and shear-force injury are physical processes directly related to the inappropriate application of a distending pressure during mechanical ventilation. Barotrauma and volutrauma result from the application of too much pressure. This causes overdistension of the lung, a volume state that leads to mechanical disruption of alveoli, surfactant degradation, increased oxygen requirement and oedematous fluid accumulation. Atelectasis, or alveolar collapse, results from too little end-expiratory pressure, causing surfactant inhibition, local tissue hypoxia and stimulation of inflammatory processes. In turn, the repetitive recruitment and derecruitment of alveoli leads to mechanical, or shear-force, injury. Thus, there must be a range of applied pressures greater than the end-expiratory pressure resulting in atelectasis, and less than the pressure causing over
distension, which do not increase VILI. This ‘safe window’ of lung protective ventilation can be considered within the context of the PV relationship of the lung, as illustrated in Figure 2-2, and has been proposed as the goal of any lung protective ventilation strategy (Froese 1997).

Figure 2-2. Pressure-volume relationship of a diseased lung illustrating the zones of overdistension and derecruitment/atelectasis. The ‘safe window’ of ventilation proposed by Froese is the region of lung volume between these two zones (Froese 1997). Reproduced with permission from Critical Care Medicine 1997 25(6) page 906 (© Lippincott Williams & Wilkins).

2.3.3 Alveolar recruitment

Transiently increasing applied pressure to facilitate inspiration will recruit atelectatic lung units and increase lung volume (Gattinoni et al 1995). But the use of positive inspiratory pressure alone does not reduce VILI (Webb & Tierney 1974) and, to maintain adequate ventilation, exposes the lung to barotrauma and sheer-force injury. In contrast, adequate end-expiratory lung volume (EELV), a product of adequate positive end-expiratory pressure (PEEP) during mechanical ventilation, is essential to prevent alveolar collapse and atelectasis (Clark et al 2000; Falke et al 1972; Halter et al 2003; Meredith et al 1989; Probyn et al 2004; Steinberg et al 2004; Webb & Tierney 1974). Without adequate PEEP, a greater applied inspiratory pressure is required to re-open collapsed alveoli (Halter et al 2003; Jonson 2005; Mead et al 1970). The search for methods of defining and determining the adequate, or optimal, PEEP during mechanical ventilation has arisen from the understanding of the role of PEEP to maintain alveolar recruitment.
Initially, ventilating along the linear portion of the inflation limb, with the PEEP at the pressure resulting in the LIP and the positive inspiratory pressure (PIP) set below the pressure resulting in UIP was advocated as an optimal approach to maintaining recruitment and minimising overdistension (Amato et al 1998; Suter et al 1975). But, at LIP, many alveoli will not be kept open (inflated) during expiration (Schiller et al 2003). Thus, it is more appropriate to consider the LIP of the PV relationship as the point where alveolar recruitment begins (Albaiceta et al 2004; Jonson 2005). In the diseased lung, the PEEP that results in all alveoli effectively remaining open at end-expiration (the ‘open–lung PEEP’) will always be greater than LIP (Halter et al 2003; Hickling 2001).

Just as alveoli have different opening pressures, the pressures resulting in alveolar overdistension will differ. Above LIP, the change in lung volume is the result of the sum of volume gains due to overdistension ($\Delta V_{\text{distension}}$) and alveolar recruitment ($\Delta V_{\text{recruitment}}$), and is influenced by time. Hickling (2001) developed a mathematical model accounting for gravitational pressures and the normal distribution of alveolar opening and closing pressures, to explain the process of recruitment during mechanical ventilation (Hickling 2001). From this model, and subsequent laboratory studies that have also accounted for time dependent recruitment, the inflation limb of the PV relationship should be seen as having three distinct zones, each related to the underlying process of volume change and lung mechanics:

1. The region below the LIP, being the region within which the applied pressure is less than the opposing viscoelastic and resistive forces within the respiratory system. In this region, atelectasis predominates and $\Delta V_{\text{recruitment}}$ is minimal.

2. The steep linear region between the LIP and UIP, being the region in which the majority of recruitment occurs and $\Delta V_{\text{recruitment}}$ is greater than $\Delta V_{\text{distension}}$. Overdistension can still occur within this region (Halter et al 2003).

3. The region above the UIP. The UIP represents the point where $\Delta V_{\text{distension}}$ is greater than $\Delta V_{\text{recruitment}}$. Recruitment may still be occurring within the region but the overall contribution to change in lung volume will be minimal (Hickling 2001; Jonson 2005).
This micromechanics concept of recruitment and overdistension being a continual process dependent on time and mechanical properties of the lung has been demonstrated in adult humans (Crotti et al 2001) and animal models of ARDS (Downie et al 2004; Pelosi et al 2001). Using these concepts, it can be seen that, at no point on the inflation limb can all the mechanical causes of VILI be minimised simultaneously. There will always be some, if not many, lung units that are either collapsed or overdistended. Consequently, strategies which target the inflation limb can not result in optimal lung protection.

2.3.4 Open lung ventilation as an optimal lung protective ventilation strategy

**Principles**

Alveolar recruitment is concerned with opening lung units using pressure, thus overcoming inhomogeneity of ventilation. Alveolar recruitment is an inspiratory process in the diseased lung that continues until TLC is reached, not an ideal region to apply ventilation. Preventing repeated collapse, or derecruitment, of lung units during tidal ventilation is an expiratory process and, during mechanical ventilation, is achieved using PEEP. In addition to applied PEEP, derecruitment is influenced by the volume history and super-imposed gravitational pressure (Bachofen et al 1979; Gil et al 1979; Gil & Weibel 1972; Hickling 2001; Nilsson et al 1978; Smaldone et al 1983). Once recruited, alveoli behave differently due to hysteresis (Crotti et al 2001; Saibene & Mead 1969). The pressure required to open lung units exceeds that needed to prevent collapse once lung units are opened (Albaiceta et al 2004; Hickling 2001; Rimensberger et al 2000b). Crotti et al (2001) have shown that, after recruitment, alveolar deflation and derecruitment do not occur in unison in adult ARDS patients; alveolar gas volume is lost without alveolar collapse if PEEP is maintained above the CCP of the lung. Like the LIP, the CCP of lung units is normally distributed (Halter et al 2003). Thus, by exploiting the hysteresis of the lung, alveolar stability can be maintained during expiration on the deflation limb of the PV relationship at a lower PEEP than needed on the inflation limb (Albaiceta et al 2004; Downie et al 2004; Halter et al 2003; Maggiore et al 2001).
An optimum ventilation strategy can be summarised as one which:

1. Recruits atelectatic lung units.
2. Maintains ventilation on, or near, the deflation limb using a PEEP that is above the median threshold of lung unit collapse (CCP) and uses the smallest possible pressure amplitude required to effect CO$_2$ removal (Rouby 2004).
3. Is titrated to the degree of lung disease, recruitment potential and hysteresis of the lung at that point in time
4. Altered frequently in response to changes in lung mechanics.

Lachmann (1992) termed this optimum strategy ‘open lung ventilation’ with the maxim ‘Open up the lung and keep the lung open’ as the goal of lung protective mechanical ventilation. Ventilation strategies targeting the deflation limb were first described in the late 1970’s and 1980’s (Benito et al 1985; Froese & Kinsella 2005; Lachmann 1992; McCulloch et al 1988). Open lung ventilation uses high pressures to initially recruit (or open) as many lung units to ventilation as possible, aiming to transiently place ventilation near TLC. Thereafter, PEEP is reduced to the lowest value that will maintain end-expiratory alveolar recruitment (keeping lung units open), slightly above the CCP of the lung. As the lung exhibits hysteresis, such an approach will place the lung and tidal ventilation on, or near, the deflation limb (Saibene & Mead 1969).

**Evidence that optimum ventilation can be achieved using an open lung approach**

**Oxygenation and ventilator-induced lung injury**

There is a clear relationship between oxygenation and the point of ventilation within the PV relationship in animal models of acute lung injury (Brazelton et al 2001). The response of arterial partial pressure of oxygen ($P_{aO2}$) during sequential increases in pressure is the standard method used to define a recruited lung. McCulloch et al (1988) defined TLC as the pressure required to achieve a $P_{aO2} > 350$ mmHg, whilst a $P_{aO2}/F_{102} > 450$ mmHg was used by Lachmann (1992). Irrespective of the exact definition of TLC, recruitment is determined by the $P_{aO2}$ response to the volume state of the lung. This allows for the pressure required to
achieve homogeneous recruitment to be individualised to the lung pathology at that point in time (Crotti et al 2001; Halter et al 2003; Schiller et al 2003).

After achieving recruitment, the CCP is defined as the pressure required to maintain a $P_{aO_2}/F_{IO_2} \geq 450$ mmHg, for example, during gradual decreases in pressure from TLC (Bohm et al 1998). In surfactant-deficient rabbits, Rimensberger et al demonstrated better oxygenation, which was sustained for four hours, by applying PEEP just above the CCP compared to the LIP, UIP or near TLC (Rimensberger et al 1999a), and irrespective of whether intermittent positive pressure ventilation (IPPV) or HFOV was used (Rimensberger et al 2000b). These findings have been confirmed in animal models of the normal adult lung (Duggan et al 2003), the ARDS lung (Vazquez de Anda et al 1999; Verbrugge et al 1998), neonatal respiratory distress syndrome (van Kaam et al 2003) and meconium aspiration syndrome (MAS) (van Kaam et al 2004a). In all these studies, achieving an open lung resulted in less VILI than targeting the inflation limb or TLC. All these studies delivered IPPV with low tidal volumes, to minimise tidal stretch injury (Copland et al 2004). In some studies (van Kaam et al 2003; van Kaam et al 2004a; Vazquez de Anda et al 1999; Verbrugge et al 1998), IPPV was delivered at rates of 150 breaths per minute. Such fast rates are considered high-frequency ventilation by many clinicians (Donoghue & the ANZNN 2004).

The use of alveolar recruitment followed by the application of an optimal PEEP resulted in better oxygenation than both high PEEP without alveolar recruitment and alveolar recruitment without PEEP in adults post-cardiac surgery (Dyhr et al 2004). In addition, there did not appear to be any deleterious consequences of transiently exposing the non-dependent regions of the lung to overinflation during the recruitment process in adults ventilated with an open lung ventilation strategy (Crotti et al 2001; Ferguson et al 2005).

**Carbon Dioxide removal**

Carbon dioxide removal is improved, and sustained, after alveolar recruitment and application of end-expiratory pressure at or above the CCP in animal models of surfactant-deficient lung disease (Rimensberger et al 2000b; van Kaam et al 2003) and MAS (van Kaam et al 2004a). In the surfactant-deficient, but not the MAS, model HFOV resulted in slightly better CO$_2$ removal than IPPV.
Tidal Volume

Tidal volume appears to be more stable when ventilation is applied on the deflation limb above CCP. During ventilation on the inflation limb, ongoing recruitment causes the tidal PV curve to change shape and position with time. In contrast, whilst the lung remains above the CCP on the deflation limb, tidal PV curves are consistent in magnitude, are superimposed on one another over time and exhibit less tidal recruitment/derecruitment (Downie et al 2004).

Compliance

Compliance is also improved on the deflation limb, compared to the inflation limb, using an open lung approach in animal models of adult (Albaiceta et al 2003a; Downie et al 2004) and neonatal lung disease (Rimensberger et al 1999b; Rimensberger et al 1999a; Rimensberger et al 2000b; van Kaam et al 2003; van Kaam et al 2004a; Vazquez de Anda et al 1999). Compliance was significantly improved at a PEEP of 12 cm H₂O after the application of an alveolar recruitment manoeuvre in adults receiving volume controlled ventilation for ARDS than the use of either intervention alone (Dyhr et al 2004).

Downie et al (2004) identified a ‘bell-shaped’ relationship between pressure and \( C_{rs} \) on the deflation limb, with maximal \( C_{rs} \) at a similar pressure as optimal oxygenation. Although others have suggested that oxygenation and lung mechanics are not necessarily optimised at the same PEEP during open lung ventilation (Lichtwarck-Aschoff et al 1999), this does suggest that \( C_{rs} \) could be used to determine the optimum post-recruitment PEEP during open lung ventilation strategies.

Surfactant

Exogenous surfactant therapy reduces morbidity and mortality in acute neonatal respiratory distress syndrome (Soll 2000). In surfactant-deficient animal models, the use of an open lung ventilation strategy preserves exogenous surfactant function for at least three hours (Verbrugge et al 1999), irrespective of ventilation modality (Vazquez de Anda et al 2000). In comparison, surfactant levels within the lung quickly deteriorate to pre-treatment values during ventilation along the inflation limb (Verbrugge et al 1999). Furthermore, the dose of surfactant needed to improve oxygenation and lung mechanics is less when an open lung ventilation
strategy was used in the same animal model (van Kaam et al 2004b). The presence of interleukin 8, an inflammatory mediator attributed to increased VILI, correlated with higher surfactant doses in this study, indicating a potential secondary lung protective benefit of an open lung approach.

2.4 The use of HFOV to achieve optimal ventilation

2.4.1 Principles of HFOV

HFOV is a ventilation modality that achieves alveolar gas exchange using tidal volumes less than anatomical dead space at frequencies of 3 - 15 Hz (Slutsky et al 1980). During HFOV, ventilation is determined by the stroke volume delivered by the oscillator (expressed as the amplitude of the oscillatory flow rate) (Slutsky et al 1980) and the frequency, which is inversely related (Froese 2002). The mechanisms of gas transport during HFOV are complex, have been reviewed previously (Chang 1984) and are beyond the scope of this review.

After the observation that ventilation could be achieved using small tidal volumes delivered at fast rates, early investigation of HFOV in animal models determined that oxygenation was closely related to the applied mean airway pressure (Thompson et al 1982). It was speculated that this was due to the relationship between $P_{aw}$ and lung volume during HFOV, and later confirmed by Kolton et al (1982) who showed that a sustained static inflation to 30 cm H$_2$O for 10 – 15 seconds improved EELV and oxygenation during HFOV but not IPPV (Kolton et al 1982). Gerstmann et al (1990) then demonstrated that, at any given $P_{aw}$, alveolar pressure was effectively constant during HFOV due to marked attenuation of the oscillatory waveform through the respiratory tree, a potential lung protective benefit of HFOV. This finding identified an additional important difference between HFOV and IPPV, the de-coupling of oxygenation from ventilation. During HFOV, lung volume can be altered by changing $P_{aw}$, without the need for high inspired pressures, whilst frequency and the oscillatory amplitude determine tidal volume and CO$_2$ removal.
2.4.2 Clinical use of HFOV

HFOV was first used to ventilate humans in the early 1980’s (Butler et al 1980). Since then, high-frequency oscillators and ventilation strategies have evolved along with conventional ventilation approaches and other respiratory therapies, such as exogenous surfactant therapy, routine use of antenatal steroids and inhaled nitric oxide (iNO). At present, HFOV is mainly used in the treatment of newborn infants with respiratory failure. The most common oscillator in use world-wide is the Sensormedics 3100 series, a diaphragm oscillator with active inspiratory and expiratory phases. There is some evidence that clinicians generally use HFOV as a rescue therapy, when other modalities have failed, in both preterm and term newborn infants (Tingay et al 2007b). Whilst rescue therapy appears to be a widespread practice, there is little evidence to suggest a benefit over IPPV (Bhuta et al 2001; Bhuta & Henderson-Smart 2000). Only three randomised clinical trials have assessed the use of HFOV against IPPV as a rescue therapy in preterm infants, one in preterm infants (HiFO Study Group 1993) and the other two in term infants (Clark et al 1994; Kinsella et al 1997). HFOV did not confer a benefit in any of these trials and resulted in an increase in intraventricular haemorrhage in the preterm group receiving HFOV (HiFO Study Group 1993). The implications of these studies to current practice are limited as surfactant, antenatal steroids, iNO and recruitment breaths were not routinely used in the earlier two studies (Clark et al 1994; HiFO Study Group 1993).

Interestingly, the early introduction of HFOV, as part of a specific management plan, may result in improved survival in infants with congenital diaphragmatic hernia (Ng et al 2008), a disease in which aggressive recruitment is known to be detrimental, and low \( P_{aw} \) strategies result in better outcome (Bohn 2002).

**Elective use of HFOV to treat pulmonary dysfunction in newborn infants**

Fifteen randomised controlled trials comparing elective HFOV and IPPV in preterm infants have been performed since 1989, including 3585 infants. A detailed description of each trial is beyond the scope of this review, but has been extensively examined by Henderson-Smart et al 2007 and Thome et al 2005. Overall, these trials have failed to show a clear long-term benefit for the elective use of HFOV to treat preterm infants (Henderson-Smart et al 2007) despite the
laboratory evidence to the contrary. Sub-group analysis is more revealing, and highlights the importance of how ventilation is delivered, rather than with which modality. An early clinical trial of HFOV used a low lung volume approach (HiFi Study Group 1989) and resulted in a higher incidence of neurological injury and air leak without any benefit in terms of survival or chronic lung disease. Consequently, the majority of subsequent trials used a high lung volume strategy (HLVS) to deliver HFOV. This approach resulted in a slight, but significant, reduction in death or chronic lung disease compared to IPPV (Henderson-Smart et al 2007). This benefit is increased using diaphragm oscillators and reduced when IPPV is also delivered with a lung protective strategy. There was no difference in neurological complications but an increased risk of air leaks in infants treated with HFOV using a HLVS (Henderson-Smart et al 2007).

When these 15 trials are analysed using cumulative meta-analysis, a method which accounts for the trial heterogeneity and new adjunctive therapies over time, only the use of exogenous surfactant and a lung protective ventilation strategy (irrespective of ventilation modality) reduced CLD and neurological injury (Bollen et al 2003; Thome et al 2005). Most importantly, there was no difference in outcome when both HFOV and IPPV are used with a lung protective strategy (Bollen et al 2003). The only two conclusions that can be made from this large series of randomised controlled trials comparing elective HFOV to IPPV in preterm infants were summarised by Froese and Kinsella (2005):

Firstly, that the strategy used is more important than the machine, and, secondly that the best ventilator strategy is one which is tailored to the patients pathophysiology.

In the case of HFOV, this is unequivocally a HLVS. In their meta-analysis of the available trials Henderson-Smart et al (2007) defined a HLVS as the use of HFOV with two or more of the following:

1. Initial use of a higher $P_{aw}$ than on IPPV.
2. Initial weaning of fraction of inspired oxygen ($F_{IO2}$) before $P_{aw}$.
3. Use of alveolar recruitment manoeuvres.

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This term is not defined by the authors of the most recent Cochrane systematic review of elective high-frequency ventilation to treat respiratory dysfunction in premature infants (Henderson-Smart et al 2007).
This does not define how much higher the $P_{aw}$ at initiation should be, nor is the need for or how to achieve alveolar recruitment defined. This differs from the earlier definition of Bryan (Bryan & Froese 1991), in which achieving and confirming alveolar recruitment (using oxygenation) is given paramount importance.

Recently, this definition of HLVS has been criticised for not being truly lung protective (van Kaam & Rimensberger 2007). Detailed information on the ventilation and oxygenation targets used to define optimal lung volume was lacking in many of the randomised controlled trials comparing HFOV with a HLVS to IPPV. Moreover, when alveolar recruitment was defined, it was only achieved in less than half of the trials, irrespective of ventilation modality (van Kaam & Rimensberger 2007).

Importantly, the comparisons of elective HFOV and IPPV in preterm infants illustrate that all modes of ventilation can injure the lung if applied inappropriately. Achieving an optimal lung protective strategy that adequately maintains alveolar recruitment is more important than the machine that applies it (Bollen et al 2003; Thome et al 2005; van Kaam & Rimensberger 2007).

### 2.4.3 Laboratory evidence of the relationship between the volume state of the lung, gas exchange and lung mechanics

**Relationship between $P_{aw}$, lung volume and oxygenation during HFOV**

It became evident that recruitment using a brief period of higher $P_{aw}$ (sustained inflation) to achieve a higher lung volume was feasible during HFOV, and resulted in rapid and persistent improvements in oxygenation. This was irrespective of whether the recruitment manoeuvre used a static $P_{aw}$ increase (Hamilton et al 1983; Kolton et al 1982; Walsh & Carlo 1988) or whether oscillations were allowed to continue during the sustained inflation (Byford et al 1988). Achieving a high lung volume during HFOV compared to either HFOV with a ‘low lung volume strategy’$^3$ or IPPV (with or without active alveolar recruitment manoeuvres) resulted in reduced VILI (deLemos et al 1989; Froese et al 1993; Walsh & Carlo

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$^3$ Achieving oxygenation with the lowest possible $P_{aw}$ and without any attempt to recruit lung volume is the aim of low lung volume strategies, thus avoiding barotrauma. This concept is based on the finding that equivalent oxygenation can be achieved with a lower $P_{aw}$ during HFOV compared to IPPV.
1988) and greater hysteresis (Bond & Froese 1993; McCulloch et al 1988) in addition to improved oxygenation. In 1991, Bryan and Froese defined optimal ventilation during HFOV in the context of a HLVS:

The hallmark of a high volume strategy is that the achievement of alveolar expansion is given a higher priority than minimisation of applied pressure. Therefore, mean airway pressures early in the treatment of respiratory distress syndrome are often higher than is customary with conventional ventilation. In a ‘high volume’ weaning protocol $F_{O2}$ is decreased first, with pressures being brought down only when such adjustments do not increase the $F_{O2}$ requirement.

Alveolar recruitment is also influenced by the duration of the recruiting pressure during HFOV (Armengol et al 1985; Kolton et al 1982). Sustained inflations of 10 and 15 cm H$_2$O above $P_{aw}$ for 10 or 30 seconds resulted in better oxygenation than a sustained inflation of 5 cm H$_2$O above $P_{aw}$ over any time period, or any $P_{aw}$ for only three seconds in a surfactant-deficient rabbit model (Walsh & Carlo 1988). The prolonged application of a high $P_{aw}$ resulted in significant hypercarbia due to overdistension. Later, Suzuki et al (1992) showed that a time dependent relationship between $P_{aw}$ and lung volume only existed if the $P_{aw}$ was above the LIP. Above this pressure, the relationship between oxygenation and $P_{aw}$ was linear.

The use of a systematic application of $P_{aw}$ to achieve an open lung was first reported by McCulloch et al (1988) in a surfactant-deficient rabbit model. The PV relationship was mapped using a series of 5 cm H$_2$O changes in $P_{aw}$ from 0 to 30 cm H$_2$O, and then back to 0 cm H$_2$O. Such an approach allowed a high lung volume, defined by the $P_{aw}$ resulting in a $P_{aO2} > 350$ mmHg, to be achieved. In addition, this approach achieved better $C_{rs}$, greater hysteresis and less hyaline membrane formation than both IPPV and HFOV without alveolar recruitment.

Importantly for clinical practice, McCulloch et al (1988) showed that the PV relationship could be mapped, and specific points targeted using a ‘quasi-static’ technique with oscillations continuing. By virtue of the small tidal changes in lung volume, HFOV offers the ability to ventilate the lung at specific points within the PV relationship. Subsequently, others have confirmed that the relationship between $P_{aw}$ and $P_{aO2}$ closely resembles the PV relationship of the lung, either directly against a measure of volume (Brazelton et al 2001; Göthberg et al 2001) or indirectly (Lachmann 1992; Rimensberger et al 2000b; van Kaam et al 2003; van
Kaam et al 2004b; Vazquez de Anda et al 1999), allowing identification of LIP, TLC and CCP using oxygenation as a proxy indicator of lung volume during HFOV (Brazelton et al 2001; Göthberg et al 2001; Markhorst et al 2003). In all of these studies, oxygenation was optimised on the deflation limb of the PV relationship and could be maintained if the $P_{aw}$ was above CCP. This animal evidence suggests that oxygenation has utility as a proxy indicator of lung volume and might help clinicians to deliver an optimal ventilation strategy using an open lung approach.

**Relationship between $P_{aw}$ and lung mechanics**

The relationship between $P_{aw}$ and $C_{rs}$ during HFOV is poorly understood. In part, this is due to the difficulties in determining $C_{rs}$. Most established methods of determining $C_{rs}$ (Mead & Whittenberger 1953; Stocks et al 1996) require assessment at two points of zero flow to negate the effect of resistance. Measurement of static $C_{rs}$, requiring cessation of tidal ventilation, is impractical in human infants receiving HFOV. During HFOV, zero flow does not coincide with the trough and peak of the oscillatory pressure wave (Peter Dargaville, personal communication), questioning the validity of dynamic $C_{rs}$ measurement based on the Mead and Whittenberger (1953) method.

Despite this, $C_{rs}$ does appear to be influenced by the volume state of the lung during HFOV. Byford et al (1988) showed that improvements in static and ‘quasi-static’ $C_{rs}$ were directly related to the magnitude of $P_{aw}$ change, and subsequent recruitment achieved, after sustained inflations during HFOV in surfactant-deficient rabbits. Later, Bond and Froese (1993) also reported, in the same animal model, an improvement in $C_{rs}$ after application of a volume recruitment manoeuvre during HFOV.

Optimal $C_{rs}$ occurred on the deflation limb of the PV relationship when HFOV was applied using the open lung approach described by McCulloch et al (1988). This point of optimal static $C_{rs}$ in the recruited lung resulted in improved ventilation homogeneity (Pillow et al 2004) and oxygenation without haemodynamic compromise (Goddon et al 2001; Rimensberger et al 1999a; Rimensberger et al 2000b). In addition, Wood et al (2002) were able to identify atelectasis and overdistension on the inflation limb using static $C_{rs}$. Later Mills, in his PhD study,
was able to demonstrate that the volume history of the lung exerted an independent effect on $C_{rs}$ during HFOV and suggested that ‘quasi-static’ $C_{rs}$ may have utility as an indirect indicator of optimum lung volume during HFOV (Mills 2003 unpublished).

**Relationship between $P_{aw}$ and tidal volume**

Tidal volume during HFOV is principally determined by the amplitude of the oscillatory wave. But there are limited data suggesting that the volume state of the lung also influences tidal volume during HFOV. The study of Mills (2003 unpublished) demonstrated a reduction in tidal volume (measured at the airway opening with a hot-wire anemometer) with mean airway pressures resulting in overdistension and atelectasis, and improved tidal volume after alveolar recruitment in healthy and surfactant-deficient piglets.

In preterm infants commencing rescue HFOV with a HLVS, there is an inverse relationship between tidal volume at the airway opening and oxygenation that is amplitude independent (Dimitriou et al 1998; Zimova-Herknerova & Plavka 2006). Interestingly, in some of the infants studied, the measured tidal volume was greater than the anatomical dead space. Significant changes in the volume state of the lung may be required to noticeably alter tidal volume during HFOV. Chan et al (1993) found no change in tidal volume during small increases in $P_{aw}$ (2 and 5 cm H$_2$O) above that required during IPPV.

Difficulties in measuring tidal volume accurately at fast frequencies and the attenuation of the oscillatory waveform through the respiratory tree have hampered thorough investigation of the relationship between tidal volume and lung volume during HFOV. Pneumotachography has been used to measure tidal volume during HFOV (Boynton et al 1989b; Dimitriou et al 1998; Kamitsuka et al 1990; Watson & Jackson 1984) and correlated well to plethysmographic measurement of tidal volume (Courtney et al 1990). More recently, Scalfaro et al (2001) demonstrated reliable tidal volume measurements at the airway opening during HFOV using a commercially available hot-wire anemometer in an *in vitro* model of the neonatal lung (error range ±10% at frequencies between 8 and 13 Hz). This method has been shown to be feasible and accurate in adults receiving HFOV for ARDS (Hager et al 2006; Hager et al 2007). Measurement of tidal volume at the airway
opening may be a useful relative indicator of the alveolar tidal volume during HFOV.

Clinicians have long used subjective assessment of chest wall movement during HFOV to determine the adequacy of oscillator amplitude. Chest wall movement (CWM) is determined by the delivered tidal volume and the attenuation of the oscillatory amplitude. Pillow et al (2002) showed that attenuation of the oscillatory amplitude was determined by the resistance in the endotracheal tube and lung mechanics of the airways, lung tissue and chest wall (Pillow et al 2002). Increasing alveolar compliance reduced the attenuation whilst increasing chest wall resistance increased it. This suggests CWM may be a proxy indicator of alveolar tidal volume, if it can be accurately quantified. Mills (2003 unpublished), in his study, found a relationship between CWM, measured with fibre optic respiratory plethysmography, and the volume state of the diseased piglet lung during HFOV. This suggests that CWM may be useful as an indirect indicator of lung volume during HFOV.

**Relationship between $P_{aw}$ and carbon dioxide**

During HFOV, CO$_2$ is primarily determined by alveolar ventilation, and is the product of frequency and the square of tidal volume (Rossing et al 1981; Slutsky et al 1981; Wright et al 1981; Zimova-Herknerova & Plavka 2006). Because lung impedance influences the delivered stroke volume for any frequency, some experienced users of HFOV also recommend that when CO$_2$ elimination is a problem the first action must be to ensure adequate recruitment. (Froese & Kinsella 2005). Despite this, the relationship between $P_{aw}$ and CO$_2$ removal is poorly understood and the findings conflicting. In some cases, no relationship between $P_{aw}$ and CO$_2$ could be identified (Slutsky et al 1981; Wright et al 1981). On the one hand this is not surprising given the ‘de-coupling’ of ventilation and oxygenation during HFOV, on the other the relationship between the volume state of the lung and lung mechanics during open lung ventilation (Rimensberger et al 1999b; Rimensberger et al 1999a; Rimensberger et al 2000b) suggests otherwise. The presence of hypercarbia is more likely using a $P_{aw}$ that results in overdistension, in both animal models (Walsh & Carlo 1988; Yamada et al 1986) and preterm infants (Chan & Greenough 1994). In contrast, Breen et al (1984) reported an
improvement in arterial partial pressure of CO\textsubscript{2} ($P_{a\text{CO}_2}$) at higher $P_{aw}$ in the saline-lavaged lung, presumably due to inadequate recruitment at lower $P_{aw}$.

In his study, Mills (2003 unpublished) identified an amplitude- and frequency-independent relationship between $P_{aw}$ and CO\textsubscript{2} removal in the surfactant-deficient piglet, and suggested that $P_{a\text{CO}_2}$ may be used to indicate an optimal $P_{aw}$ during HFOV. In particular, after the application of an alveolar recruitment manoeuvre, $P_{a\text{CO}_2}$ was impaired at both high (overdistension) and low (atelectasis) $P_{aw}$, with a $P_{aw}$ resulting in optimal CO\textsubscript{2} clearance between the two.

**Haemodynamic cost of targeting the deflation limb**

Critics of HFOV have suggested that a high volume approach will have a negative effect on cardiac output (Polglase et al 2005). The majority of laboratory evidence suggests that these concerns are unfounded and cardiac output is unchanged when ventilation is applied on the deflation limb at a reasonable $P_{aw}$ (Brazelton et al 2001; Wood et al 2002). Applying ventilation at TLC does impair cardiac output in disease states associated with low $C_{rs}$ (Traverse et al 1988). The ventilated newborn appears to have greater tolerance to $P_{aw}$ changes during HFOV than animal models, with minimal or no reduction in cardiac output using HFOV with a HLVS compared to IPPV (Cambonie et al 2003; Marchak et al 1981; Osborn & Evans 2003). Cardiac output was reduced by 10.6% during a recruitment manoeuvre ($P_{aw}$ increased by 5 cm H\textsubscript{2}O) in 14 infants less than one year of age receiving HFOV (Gullberg et al 2004). Cardiac output rapidly returned to normal when $P_{aw}$ was then returned to pre-study values. Finally, only six, of a total of 244 sustained inflations to 40 cm H\textsubscript{2}O for 40 seconds each, given to 25 adults with ARDS, needed to be aborted due to hypotension in a RCT of HFOV and IPPV both using an open lung approach (Ferguson et al 2005). In this study, HFOV resulted in a doubling of the $P_{a\text{O}_2}/F_{i\text{O}_2}$ ratio and a significant decrease in average $F_{i\text{O}_2}$ compared to IPPV.
2.4.4 Achieving optimum lung volume during HFOV in human infants

The conflicting clinical experiences with HFOV indicate that an optimal lung protective strategy during HFOV is elusive in neonatal practice. Based on the laboratory evidence, Froese (2002) summarised the optimal lung protective approach to HFOV as follows:

HFOV is most lung protective in animal models when alveolar re-expansion is achieved with a volume recruitment manoeuvre and then maintained with an appropriate $P_{aw}$.

This poses three questions:

1. How best to achieve volume recruitment?
2. What is an appropriate $P_{aw}$ to achieve, and then maintain, volume recruitment?
3. How can clinicians confirm adequate volume recruitment?

Despite these questions, it is apparent that achieving an optimal lung volume must be the goal of any pressure strategy. Open lung ventilation fulfils this goal by virtue of achieving volume recruitment, providing a method of defining the adequacy of recruitment and being repeatable.

Open lung approaches during HFOV in human newborn infants

Determining the optimal $P_{aw}$ prior to commencement of HFOV with a HLVS is difficult, and the degree of recruitment needed to optimise oxygenation variable (Dimitriou et al 2004). For this reason, stepwise increases in $P_{aw}$ at initiation of HFOV were advocated by Chan et al (1994).

The use of a $P_{aw}$ strategy that would constitute an open lung approach during HFOV has only been reported twice in newborn infants (De Jaegere et al 2006; Rimensberger et al 2000a). The ventilation strategies of each are summarised in Table 2-1.
Table 2-1. Summary of reported open lung ventilation strategies used during HFOV in newborn infants.

<table>
<thead>
<tr>
<th></th>
<th>Paw at initiation of HFOV</th>
<th>Definition of TLC</th>
<th>Definition of CCP</th>
<th>Method used to recruit the lung to TLC</th>
<th>Method used to identify optimal lung volume after recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimensberger et al (2000a)</td>
<td>12 – 16 cm H2O</td>
<td>FIO2 ≤ 0.4</td>
<td>Lowest Paw required to maintain FIO2 ≤ 0.4 after TLC obtained</td>
<td>Paw increased by 1 – 2 cm H2O every 1 – 2 minutes (maximum Paw of 25 cm H2O)</td>
<td>Paw decreased by 1 – 2 cm H2O every 1 – 2 minutes until CCP</td>
</tr>
<tr>
<td>De Jaegere et al (2006)</td>
<td>6 – 8 cm H2O</td>
<td>FIO2 ≤ 0.25</td>
<td>Lowest Paw required to maintain FIO2 ≤ 0.3 after TLC obtained</td>
<td>Paw increased by 1 – 2 cm H2O every 2 minutes</td>
<td>Paw decreased by 1 – 2 cm H2O every 2 minutes until CCP. Then Paw transiently increased to reinflate to TLC. Finally, reduced to CCP+2 cm H2O (optimal Paw)</td>
</tr>
</tbody>
</table>

Rimensberger et al (2000a) compared their experience with first intention HFOV using an open lung approach in 32 preterm infants (less than 32 weeks gestation and 1500 gm birth weight) with 39 matched historical controls receiving synchronised IPPV without an open lung approach. The HFOV group required less days of ventilatory support, experienced less oxygen dependency and CLD and had no increase in neurological complications. More recently, De Jaegere et al (2006) showed that an open lung ventilation strategy using oxygenation to guide the recruitment process (see Table 2-1) was feasible and safe during first intention HFOV in 103 preterm infants (less than 37 weeks gestation) with neonatal respiratory distress syndrome (RDS) prior to surfactant therapy. Using this strategy, an FIO2 ≤ 0.25 at optimal Paw could be achieved in 75% of infants and ≤ 0.3 in 98%. The optimal Paw was significantly lower than the Paw at TLC and resulted in a significant reduction in FIO2 compared to before the lung was opened.

Whether one to two minutes is adequate to allow for volume stabilisation after a Paw change is questionable. In some preterm infants, 25 minutes was required for lung volume to stabilise after a Paw change (Thome et al 1998b).
Rimensberger et al (2000a) confirmed that preterm infants could tolerate transient high recruitment pressures of 25 cm H₂O and verified the use of peripheral oxygen saturation (SpO₂) as a proxy indicator of lung volume. De Jaegere et al (2006) illustrated the limitation of solely using oxygenation as a proxy indicator of lung volume. There was a need to transiently expose the lung to collapse and de-oxygenation to identify CCP. In animal models, the $P_{aw}$ resulting in optimal $C_{rs}$, tidal volume and CO₂ appears to be closely related too, but always greater, than CCP. Mills (2003 unpublished) identified a quadratic relationship⁴ between tidal volume, CO₂ and $C_{rs}$ and the volume state of the lung in his study. He suggested that these relationships could be exploited, in conjunction with oxygenation, to identify an optimal $P_{aw}$ on the deflation limb. In addition, De Jaegere et al (2006) noted that the transcutaneous CO₂ ($TcCO₂$) was reduced by 9 mmHg at optimal $P_{aw}$. Whether changes in tidal volume, CO₂ and $C_{rs}$ can assist in identifying the region of optimal ventilation during HFOV has not been evaluated systematically in human infants.

2.5 Determining change in lung volume during HFOV using respiratory inductive plethysmography

2.5.1 Difficulties in directly measuring lung volume in newborn infants during HFOV

Directly determining lung volume during HFOV is difficult due to the fast gas flows, complex mechanism of gas transport and the high degree of illness severity in HFOV recipients.

In clinical practice, chest radiograph is commonly used to estimate lung volume during HFOV. Chest radiography is useful to identify gross overdistension and atelectasis but lacks the precision to determine the volume changes required to identify an optimal volume. Clinical assessment of lung volume during HFOV using chest radiograph correlated poorly, over a wide range of volumes, with thoracic gas volume determined using a SF₆ gas dilution technique (Thome et al 1998a). Inert tracer gas dilution techniques are considered accurate methods of measuring absolute lung volume during mechanical ventilation (Dimitriou et al

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⁴ A relationship resulting in a bell, or U, shaped curve.
2004; Schibler et al 2002; Schibler & Frey 2002). These techniques are problematic during HFOV due to the more complicated gas transport mechanisms and the need to transiently transfer to IPPV (Thome et al 1998b). Similarly, the super syringe method, first described by Harf et al in 1975, used to describe the PV relationship in adults (Albaiceta et al 2003a; Jonson 2005) requires disconnection from ventilation and is not practical in sick infants receiving HFOV.

The use of single slice computerised tomography to assess lung volume during HFOV has been validated in adults (Gattinoni et al 1988) and offers the added advantage of defining regional volume distribution (Crotti et al 2001; Pelosi et al 2001; Albeciata et al 2004). The impracticality of repeated imaging, plus concerns about the radiation exposure in children, limits its utility in newborn infants.

Finally, whole body plethysmography is impractical during the delivery of HFOV in newborn infants. Knowledge of absolute lung volume is not necessary to determine the optimal $P_{aw}$ during HFOV. Simply assessing change in lung volume from a known point in the PV relationship, such as FRC or TLC, is adequate. Inductive plethysmographic devices can measure change in lung volume and are non-invasive. These properties have led to interest in these techniques to determine optimal ventilation strategies during HFOV.

### 2.5.2 History and theory of respiratory inductive plethysmography

Respiratory inductive plethysmography is a method of determining change in lung volume by measuring the changes in both chest and abdominal volume displacement during ventilation.

Historically, reliably determining lung volume change from changes in the chest wall has been difficult due to the motion of different parts of the chest wall in different directions. In 1967, Konno and Mead (Konno & Mead 1967), using the principle that there is a relationship between linear motion and volume displacement, showed that the chest wall operates with two degrees of freedom, irrespective of whether an open or closed system, and two moving parts, the rib cage and the abdomen. Additionally, in terms of motion of their surfaces, there was functional separation between the abdomen and the rib cage during breathing. By utilising the unitary behaviour of these two compartments, volume change of the
chest wall, and thus total thoracic volume$^5$, could be determined from measurement of volume displacement in each separate compartment. During ventilation, the lung will contribute to the majority of thoracic volume change.

Using this principle lung volume ($V_L$) can be mathematically expressed as follows:

$$V_L = V_{LCH} + V_{LAB},$$

where $V_{LCH}$ and $V_{LAB}$ represent volume displacement within the chest and abdominal compartments respectively.

The true practical advantage of Konno and Mead’s observation can be realised by considering the fact that a volume change will result in a change in cross-sectional area within each compartment. Thus, $V_L$ can be considered as:

$$V_L = m(k x \Delta R_{ch} + \Delta R_{ab}),$$

where $R_{ch}$ and $R_{ab}$ are the cross-sectional areas of the chest and abdomen compartments respectively, $k$ represents a calibration factor, representing the proportional contribution of each compartment to total volume, and $m$ scales the sum of the cross-sectional areas to a known volume (Bar-Yishay et al 2003; Sackner et al 1989).

Two dimensional changes are easier to measure than volume in a moving system. In the late 1970’s, the use of electrical inductance change to measure change in cross-sectional area around the chest (rib cage) and abdomen was investigated (Adams 1996) after it was noted that the electrical self-inductance of a sinusoidal coil of wire is altered by the degree of stretch on that wire (Watson et al 1988). In a series of studies on experimental models, Watson et al (1980 and 1988) showed that the inductance increased linearly as a function of cross-sectional area in curved shaped (Adams 1996; Watson et al 1988), but not rectangular objects (Adams 1996; Martinot-Lagarde et al 1988).

These findings lead to the development of the first RIP devices (Adams 1996; Watson et al 1988). Apart from improvements in the processing capacity and greater stability in the transducers to overcome some of the thermal drift noted in earlier devices, the early RIP devices differ little from current ones (Leino et al...

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$^5$ Thoracic volume includes the gas volume within the respiratory tree, blood volume within the chest and the volume of thoracic tissue.
2001). RIP devices employ two transducers that are placed circumferentially around the rib cage (chest) and abdomen. Each transducer consists of a sinusoidal wire embedded in an elastic material. These wires are connected to an electronic oscillator that generates a sine wave of 20 mV at 300 kHz. Changes in cross-sectional area in the transducer will produce variations in self-inductance within the wire and thus frequency. RIP devices demodulate the frequency change to produce an analogue voltage waveform representing the changes in rib cage and abdominal volume change in real-time (Ohms Law).

Whilst RIP produces a plethysmographic recording, it is unable to record absolute lung volume but rather changes in thoracic volume. This offers the ability to non-invasively measure variation in tidal volume and respiratory rate and pattern in clinical situations where change in, rather than absolute, lung volume is required. The first use of RIP to assess these parameters in spontaneously breathing infants was described by Duffy et al in 1981.

A detailed description of the RIP device used in the experimental protocol can be found in Chapter 3.8.3.

### 2.5.3 DC-coupled output RIP and the assessment of EELV

Early RIP devices operated solely in AC-coupled output mode. This was adequate for assessing respiratory rate, tidal volume and synchrony of respiration but the baseline signal was too unstable to assess EELV (Morel et al 1983). Morel et al (1983) were able to show that, when a DC-coupled output was used, the RIP signal was sufficiently stable to allow reliable measurement of changes in EELV. Subsequently, good agreement with whole-body plethysmography (Carry et al 1997) and supersyringe methods (Albaiceta et al 2003a) have been shown.

The first use of DC-coupled output RIP to briefly measure changes in EELV during mechanical ventilation in newborn infants was reported by Choong et al in 2003. This study reported lung volume change during two methods of endotracheal tube suction in fourteen ventilated paediatric patients receiving IPPV, although only two were newborn infants (Choong et al 2003).
2.5.4 Limitations of DC-coupled output RIP

There are a number of limitations to DC-coupled output RIP that need to be considered. The most important of these is the inability to determine the residual volume of the lung and absolute volume change. Furthermore, change in inductance measured by RIP is linearly related to thoracic volume rather than lung volume *per se*. We have noted that RIP detects blood volume change within the chest during intravenous administration of fluid boluses (Tingay unpublished data).

Strict adherence to a standardised method of transducer placement is required to reduce inter-subject variability (Landon 2002). The chest and abdomen are most likely to operate with one degree of freedom when transducers are placed at the level of the nipples and at, or just above, the umbilicus (Konno & Mead 1967).

False estimations of tidal volume and EELV can be made during periods of asynchronous breathing. When the abdominal and chest compartments are completely out of phase, the summated RIP assessments of thoracic volumes will be nil. This is rarely a problem in patients receiving muscle relaxants.

Finally, the disease state of the lung may affect the drift of the RIP signal in adults receiving mechanical ventilation, especially in obstructive pulmonary disease (Neumann et al 1998; Werchowski et al 1990). In the short term, this did not affect the accuracy of RIP to measure PEEP induced changes in EELV in mechanically ventilated adult patients (Valta et al 1992). A more detailed discussion of the specific limitations of DC-coupled output RIP during HFOV can be found in the next section (Chapter 2.5.5).

2.5.5 The use of DC-coupled output RIP to measure change in lung volume during HFOV

Accuracy

The RIP output signal is essentially a dimensionless and arbitrary unit expressed as a voltage. Unfortunately, there is no agreed method of calibrating a RIP signal to a known volume during HFOV. Numerous methods of calibration to flow signals or spirometry during spontaneous breathing (Sackner et al 1989) and conventional mechanical ventilation (Bar-Yishay et al 2003) have been proposed in adults and infants (Dolfin et al 1982), with variable accuracy (Brown et al 1998; Revow et al

During HFOV, calibration to a volume measured at the airway opening does not account for attenuation of flow through the respiratory tree. It is possible to calibrate the RIP voltages to a brief period of conventional breaths (Markhorst et al 2006; Tingay et al 2007a), but this requires transient disconnection from HFOV and is thus invasive. Moreover, calibration accuracy decreases with severity of lung disease (Markhorst et al 2006) and HFOV is rarely used to treat infants with normal lungs (Tingay et al 2007b). The phase deviation in the transducer outputs, and thus the stability of the calibration factor, increases in a linear fashion at frequencies above 10 Hz (Boynton et al 1989a). Finally, during the small volume changes associated with HFOV, the magnitude of any calibration factor errors becomes more significant.

Despite these limitations, Markhorst et al (2006) demonstrated that, when calibrated, the relative measurement error of a modern RIP device operating for short periods of time during HFOV (-2.0 ± 9%; bias ± 2 SD) was less than common commercially available pneumotach systems (Florian Respiratory mechanics monitor and Dräger Babylog 8000; 6.3 ± 5% [Scalfaro et al 2001] and -5.5 ± 3% [Roske et al 1998] respectively) in a piglet model of paediatric lung disease. The reliability of RIP calibration was best when measurements were immediately preceded by calibration, and deteriorated with time.

Even when uncalibrated, RIP still has clinical potential to measure relative change in lung volume during HFOV, and avoids the limitations of calibration (Markhorst et al 2006) On the bench-top, uncalibrated RIP accurately measured relative change in EELV during HFOV between frequencies of 7 to 15 Hz ($r^2 = 0.944$) (Brazelton et al 1999a abstract), and did so with a stable signal for up to four hours in a thermally constant environment, once time dependent drift had stabilised over approximately 30 minutes (Brazelton et al 1999b abstract). Long term signal stability has not been confirmed in human studies.
Uncalibrated RIP has been shown to be a reliable method of assessing relative change in EELV during HFOV in animal models of neonatal lung disease, agreeing with changes in lung volume measured using whole-body plethysmography (Weber et al 2000), super-syringe derived PV relationships (Brazelton et al 2001; Göthberg et al 2001) and single-slice chest computerised tomography (Pellicano et al 2004 abstract).

**Use of RIP to determine optimal ventilation during HFOV**

The first reported use of RIP to record changes in EELV during high-frequency ventilation was by Saari et al (1984) to demonstrate dynamic hyperinflation in seven adult patients receiving high-frequency ventilation. More recently, RIP has been used to describe the PV relationship during HFOV in animal models of surfactant-deficient lung disease.

Weber et al (2000) used RIP to describe the inflation limb in healthy and surfactant-depleted piglet lungs. Lung overdistension could be identified using RIP-derived static $C_{rs}$. In both lung models, the relationship between pressure and $C_{rs}$ fitted a second-order sigmoidal model, with the $P_{aw}$ resulting in overdistension translating to the UIP of the sigmoid curve. The same group then assessed time-based recruitment with RIP during sequential $P_{aw}$ increases (Habib et al 2002). At each $P_{aw}$, the RIP-derived time constant of the lung varied depending on the position within the static inflation limb; shortened during volume recruitment from a collapsed state and then lengthening again with overdistension. The authors concluded that the RIP-derived time constant of the lung could be used to identify the point of optimal ventilation.

RIP has been used to define the effects of applying HFOV with an open lung approach to identify the point of optimum lung volume in a piglet model of paediatric ARDS (Brazelton et al 2001), and term and preterm lambs (Göthberg et al 2001). In both studies, RIP was able to map the entire PV relationship, show hysteresis, and identify TLC and the opening and closing pressures of the lung. Optimum lung volume occurred on the deflation limb and was closely related to the $P_{aw}$ resulting in optimal $P_{aO2}$ (Figure 2-3). In addition, RIP demonstrated improvement in the hysteresis of the lung after administration of exogenous surfactant (Göthberg et al 2001).
To date, the ability of RIP to record lung volume and describe the PV relationship in human infants receiving HFOV has not been described, nor the ability of RIP to determine tidal volume (chest wall movement) or quasi-static $C_{rs}$.

### 2.6 Conclusions

Mechanical ventilation has the potential to treat respiratory failure in newborn infants if applied appropriately. Despite an understanding of the need to achieve a HLVS for lung protection during HFOV, clinical benefit as determined from randomised controlled trials has been minimal.

There is strong evidence in adults, and from experimental animal data, that using an open lung approach results in better oxygenation and lung mechanics with less VILI. Such an approach exploits the hysteresis of the lung to achieve and maintain alveolar recruitment at the lowest possible PEEP, and has been suggested as the best way to deliver a HLVS. The clinical experience with open lung ventilation strategies during HFOV is limited. In part, this is due to difficulties directly determining lung volume at the bedside during HFOV, necessitating the need for indirect indicators of lung volume.
To date a systematic examination of the volume state of the lung during HFOV in newborn infants has not been performed. In particular, it has not been verified whether potential indirect indicators of lung volume (oxygenation, $C_{rs}$, tidal volume, CWM and CO$_2$) can predict the volume state of the lung and point to an optimal region in which to apply ventilation during the clinical use of HFOV.
Chapter 3

EXPERIMENTAL DESIGN AND METHODS

3.1 Introduction

This chapter describes the experimental design and methods used in this thesis. Initially, the aims and hypotheses will be stated. The process by which the hypotheses were developed into an experimental method will be outlined. The means by which the study population was determined will be described. Finally, the experimental design and methods will be described in detail.

3.2 Aims and hypotheses

3.2.1 Aims

The aim of this research was to examine the volumetric behaviour and mechanics of the diseased neonatal lung during HFOV in human infants.

The specific aims of the research were:

- To describe the PV relationship of the lung during HFOV, and to determine at what point within the PV relationship ventilation was being applied by the clinician.
- By doing so, to identify key regions of the PV relationship, these being TLC, CCP and the deflation limb, in each infant.
- To systematically describe the changes in lung mechanics (tidal volume and quasi-static $C_{rs}$) and gas exchange ($S_{PO2}$ and $T_{CCO2}$) at different points in the PV relationship during HFOV.
- To explore whether any of the above measured physiological parameters could be used as indicators of the optimum $P_{aw}$ setting during HFOV.
3.2.2 Hypotheses

The hypotheses to be tested were, that in newborn infants requiring HFOV for respiratory failure:

- It is possible to describe the PV relationship of the lung at the bedside.
- It is possible to identify specific regions of the PV relationship, namely the deflation limb and the points corresponding to TLC and CCP.
- The mechanics of the lung and gas exchange vary at different points within the PV relationship.
- By understanding the interaction between indicators of lung mechanics, gas exchange and the PV relationship an optimum $P_{aw}$ can be identified.

3.3 Experimental design background

Fundamental to this research was the need to accurately describe the PV relationship at the bedside. This required a method of accurately measuring change in lung volume ($\Delta V_L$) during a series of changes in $P_{aw}$. As described in Chapter 2, measurement of absolute lung volume is difficult and invasive during HFOV. Instead, RIP was used to measure relative $\Delta V_L$ in this study. RIP offers the advantage of being non-invasive, but, unlike $Sp_{O2}$, $Tc_{CO2}$, $C_R$ and tidal volume it is not widely used as a monitoring tool in neonatal practice. It has been suggested that there is a relationship between the volume state of the lung and each of oxygenation, carbon dioxide and lung mechanics (De Jaegere et al 2006; Mills 2003 unpublished; Rimensberger et al 1999a; Rimensberger et al 2000b). Thus, $Sp_{O2}$, $Tc_{CO2}$, $C_R$ and tidal volume were recorded simultaneously with $\Delta V_L$ to investigate whether any, or all, may have clinical utility as indirect indicators of lung volume. Serial arterial sampling of $Pa_{O2}$ and $Pa_{CO2}$ during a series of $P_{aw}$ changes was not considered ethical. For this reason $Sp_{O2}$ and $Tc_{CO2}$ were chosen as proxy indicators of gas exchange, both being commonly used as such in clinical practice.

The experimental design was developed into a descriptive physiological study during the application of an open lung ventilation strategy in newborn infants receiving HFOV.
3.3.1 Development of an open lung ventilation strategy

An open lung approach is an established method of mapping key regions of the PV relationship in animal models of neonatal respiratory failure (Brazelton et al 2001; van Kaam et al 2003; van Kaam et al 2004a) and human adults with ARDS (Crotti et al 2001), and can determine TLC and CCP. In addition, there is strong evidence to suggest that optimal ventilation can be applied using an open lung approach (De Jaegere et al 2006; Lachmann 1992). For this reason, an open lung ventilation strategy was developed for this study.

Currently, during the clinical application of HFOV, the point at which ventilation is being applied within the PV relationship is unknown. In most adult and animal model studies of open lung ventilation, the initial lung volume is standardised by transiently disconnecting from mechanical ventilation and allowing passive collapse to end-expiratory residual volume. The resultant atelectasis and hypoxaemia from such an intervention would be unacceptable in the injury-prone neonatal lung. However, $\Delta V_L$ can be referenced to any point within the PV relationship, such as TLC. The mechanical properties of the lung mean that, provided an open lung ventilation strategy commences with a series of incremental $P_{aw}$ changes, the point of TLC will eventually be obtained. Thereafter, lung volume is standardised and subsequent changes will occur along the deflation limb.

3.3.2 Preliminary testing of an open lung ventilation strategy and utility of $SpO_2$ monitoring to determine recruitment/derecruitment.

Previous open lung approaches have used oxygenation as a proxy of lung volume (De Jaegere et al 2006; Lachmann 1992; Rimensberger et al 2000a). This has practical advantages due to the difficulties in measuring lung volume during HFOV. Oxygenation is known to correlate with the PV relationship in animal models (Brazelton et al 2001) and is frequently used to indicate recruitment/derecruitment in animal studies of open lung ventilation (van Kaam et al 2003; van Kaam et al 2004a). It has been suggested that $SpO_2$ is able to indicate regions of the PV relationship (De Jaegere et al 2006; Rimensberger et al 2000a), although this has not been systematically verified in humans. For this reason, the response of $SpO_2$ to determine recruitment and derecruitment during an open lung ventilation strategy aiming to map the PV relationship was tested in a pilot study.
Experimental Design and Methods

An open lung ventilation strategy was performed in three infants. Informed parental consent was obtained in each infant and all met the inclusion criteria of the study (see Chapter 3.6). The demographic characteristics of these infants and ventilatory parameters at the time of study are summarised in Table 3-1. All infants were receiving muscle relaxants and sedation at the time of study. The third infant was studied twice as this infant also had an indwelling continuous umbilical artery blood gas monitor sited in an umbilical arterial line and positioned in the descending aorta (TrendCare continuous monitoring system, Diametrics Medical Ltd, High Wycombe, UK), allowing continuous assessment of the relationship between $\text{SpO}_2$ and $\text{PaO}_2$. The first infant was studied during the acute phase of RDS due to hyaline membrane disease, and the second whilst $P_{aw}$ was being weaned during the recovery phase after surgery to repair a small right congenital diaphragmatic hernia (CDH). The third infant was studied during the acute and recovery phases of RDS.

Commencing at the $P_{aw}$ in clinical use, $P_{aw}$ was increased every ten minutes in 1 to 2 cm H$_2$O increments, until $\text{SpO}_2$ remained unchanged for at least two consecutive $P_{aw}$ values; this indicated that TLC had been obtained (Lachmann 1992). Then $P_{aw}$ was decreased in steps of 1 to 2 cm H$_2$O until $\text{SpO}_2$ began to fall by at least 5% over three pressure decrements (with a $\text{SpO}_2$ of 85% being the lowest acceptable value). Cardiac tolerance was also examined, with heart rate and arterial blood pressure being continuously monitored.

The choice of $P_{aw}$ changes every ten minutes was primarily based on practical considerations. There is some evidence to support the choice of ten minute increments. In a study of thirteen preterm infants, time to stable lung volume after $P_{aw}$ changes during the implementation of a HLVS after commencing HFOV varied (Thomes et al 1998b). The median time to volume stability was 9 minutes (range 1 – 25 minutes), with stable lung volume being achieved in 10 and 15 minutes in 62% and 81% of cases respectively. This study did not account for the influence of volume history on the time constant of the lung (Habib et al 2002), which may explain the wide range of times.
Table 3-1. Demographic characteristics and ventilator parameters at the time of study for the three infants enrolled in pilot study.

<table>
<thead>
<tr>
<th></th>
<th>Age (days)</th>
<th>Gestational age at birth (weeks)</th>
<th>Birth weight (gm)</th>
<th>Diagnosis</th>
<th>$P_{aw}$ (cmH$_2$O)</th>
<th>Fr (Hz)</th>
<th>$\Delta P$ (cmH$_2$O)</th>
<th>$F_{O2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot 1</td>
<td>5</td>
<td>38</td>
<td>4165</td>
<td>RDS and PPHN</td>
<td>16.2</td>
<td>8</td>
<td>31</td>
<td>0.5</td>
</tr>
<tr>
<td>Pilot 2</td>
<td>12</td>
<td>41</td>
<td>3910</td>
<td>Post repair small right CDH</td>
<td>14.1</td>
<td>10</td>
<td>18</td>
<td>0.21</td>
</tr>
<tr>
<td>Pilot 3a</td>
<td>2</td>
<td>37</td>
<td>3280</td>
<td>RDS and PPHN</td>
<td>15.1</td>
<td>8</td>
<td>37</td>
<td>0.65</td>
</tr>
<tr>
<td>Pilot 3b</td>
<td>8</td>
<td>37</td>
<td>3280</td>
<td>RDS and PPHN</td>
<td>12.0</td>
<td>8</td>
<td>22</td>
<td>0.35</td>
</tr>
</tbody>
</table>

CDH = congenital diaphragmatic hernia; PPHN = persistent pulmonary hypertension of the newborn.

On each occasion, the entire protocol was completed and TLC, as defined above, could be determined. The relationship between $P_{aw}$ and $Sp_{O2}$ during the recruitment and derecruitment steps is shown in Figure 3-1. In all infants, a $P_{aw}$ - $Sp_{O2}$ relationship resembling that of the PV relationship could be demonstrated with a distinct inflation and deflation limb and evidence of hysteresis. In each infant, $Sp_{O2}$ values had stabilised before the next $P_{aw}$ step. All infants tolerated the protocol without complications. Heart rate and blood pressure did not vary significantly during the ventilation protocol. The data from the third infant showed that $Pa_{O2}$ and $Sp_{O2}$ behaved similarly during the open lung strategy.
Experimental Design and Methods

Figure 3-1. The relationship between $P_{aw}$ and $SpO_2$ during an open lung ventilation strategy in three infants enrolled in the pilot study; recruitment series indicated by solid blue and derecruitment by red. The relationship between $P_{aw}$ and $P_{aO_2}$ is also shown in infants 3a and 3b; using dashed lines and open symbols to represent the recruitment (blue) and derecruitment (red) series. $SpO_2$ and $P_{aO_2}$ Y-axis scales are different in Pilot 3a.

The pilot data suggested that infants receiving HFOV should tolerate an open lung ventilation strategy involving incremental and decremental $P_{aw}$ changes with a maximum and minimum $P_{aw}$ determined by $SpO_2$. The relationship between $P_{aw}$ and $SpO_2$ during the decremental steps resembled a deflation limb of the PV relationship, the only difference being an initial increase in $SpO_2$ (and $P_{aO_2}$) as the lung was deflated from TLC. The final $SpO_2$ value remained over 85% in three of the four data sets, despite the final $P_{aw}$ being at least 5 cm H$_2$O lower than the starting $P_{aw}$. These preliminary data suggested that defining the final $P_{aw}$ setting as the $P_{aw}$ that resulted in a fall in $SpO_2 <85\%$ would allow description of the upper portion of the deflation limb and allow identification of the CCP.
3.4 Study Location

The study was performed at the Neonatal Unit (NNU) of the Royal Children’s Hospital (RCH; Flemington Road, Parkville, Victoria, Australia), a 22 bed tertiary neonatal intensive care unit with 10 intensive care cots based within a paediatric hospital. This unit is a referral centre for neonatal respiratory disease and has 14 years’ experience with HFOV in both preterm and term infants. All admissions are born at other hospitals and transferred to the NNU for management.

3.5 Study population

The study was approved by the Ethics in Human Research Committee at the RCH (RCH HERC #23022B), and written informed parental consent was obtained for each infant. The study design and implementation conformed to the National Health and Medical Research Council (NHMRC) guidelines for ethical behaviour in human research. Adverse events were defined as per the 1999 NHMRC national statement on ethical conduct in research involving humans (www.nhmrc.gov.au) and any adverse events were reported to the RCH Ethics in Human Research Committee.

It was decided to limit the study population to term, near-term and ex-preterm infants. Barotrauma and volutrauma are well described risk factors for VILI and air leak syndromes in newly-born premature infants. Whilst preterm infants have been exposed to $P_{aw}$ as high as 25 cm H$_2$O during an open lung recruitment strategy without evidence of increased adverse outcomes (Rimensberger et al 2000a), the risk of complications as a result of this study could not be excluded in the preterm infant with hyaline membrane disease.

Animal model and adult studies of open lung ventilation have been conducted in muscle-relaxed and sedated subjects. In an attempt to maintain consistency with these studies, and to minimise the effect of artefact from self-ventilation, only infants receiving muscle-relaxants and sedation as part of their routine clinical care at enrolment were studied.
3.6 Eligibility Criteria

3.6.1 Inclusion

Infants receiving HFOV with a HLVS using the Sensormedics 3100A high frequency oscillator (Sensormedics, Yorba Linda, CA, USA) were considered eligible for enrolment if:

- They were receiving full active intensive care, including an indwelling arterial catheter and adequate sedation.
- They received muscle relaxants as part of their treatment.
- Informed parental consent had been obtained.
- The treating clinician gave consent for the infant’s involvement in the study.

3.6.2 Exclusion

Infants were excluded from study if they had:

- A known chromosomal abnormality.
- Echocardiographically proven cyanotic congenital heart disease.
- A FiO2 greater than 0.9 to maintain pre-ductal SpO2 in the desired range determined by the clinical team.
- Refractory hypotension despite maximal inotrope and fluid support. Refractory hypotension was defined as two standard deviations [SD] below the mean for birth weight (Zubrow et al 1995).
- A base deficit of 15 or more on the most recent arterial blood gas analysis despite maximal inotrope and fluid support.

3.6.3 Cessation criteria

The open lung ventilation strategy was stopped if:

- The infant’s heart rate or blood pressure was below normal limits for gestation and/or age for more than two minutes (Zubrow et al 1995).
3.7 Methods

3.7.1 Demographic data

At the start of each study the following demographic data were collected on specifically designed data collection sheets:

- Infant details
  - Age at time of study
  - Gestational age at birth
  - Birth weight and most recent weight
  - Gender

- Perinatal details
  - Pregnancy complications, mode of delivery and Apgar scores
  - Primary respiratory diagnosis
  - Other relevant conditions
  - Adjunctive medication and dosages that might have affected respiratory function, such as iNO, muscle relaxants, sedation and inotropic agents

- Respiratory support
  - Duration of intubation, endotracheal tube (ETT) size and depth of insertion
  - Duration of HFOV and current HFOV settings ($P_{aw}$, amplitude ($\Delta P$), frequency and $F_{O2}$)
  - Previous modalities of ventilation
  - Time and results of most recent arterial blood gas analyses and corresponding $T_{cO2}$ value
  - Involvement in any other studies or trials which might have affected respiratory function during the study, such as the ‘lavage with exogenous surfactant suspension in meconium aspiration syndrome (lessMAS)’ trial.

Identifiable data (name, hospital identification number, address and parents details) were recorded on the master data collection sheet and stored in a locked cabinet as per NHMRC guidelines.
3.7.2 Preparation

Subject preparation
At least 45 minutes prior to commencement of study, the infant’s nappy was changed and the infant positioned supine. Application of the monitoring equipment listed below was performed at this time.

Approximately 30 minutes prior to each study, ETT suction was performed using a disconnection (open) method, to avoid secretions in the respiratory tree interfering with measurements. ETT suction was performed using a pre-measured 6 FG catheter (Mallinckrodt, Rowville, Australia). After disconnection from ventilation, the catheter was inserted to the tip of the ETT, and suction applied at a pressure of –100 mmHg (13.3 kPa) for six seconds while simultaneously withdrawing the catheter. A second pass was permitted if the treating nursing staff believed that further secretions remained in the ETT. Normal saline lavage and post-suction recruitment manoeuvres were not permitted. The infant was not disturbed for the remainder of the study.

Equipment preparation
The ETT was clamped to prevent lung volume loss, and the ETT connector rapidly changed to one with a Luer Lock side-port (Glaxo, Boronia, Australia) to allow the Florian respiratory mechanics monitor pressure transducer (Acutronic Medical Systems AG, Zug, Switzerland) to be connected at the airway opening via 20FG low compliance plastic tubing. In addition, a dual hot-wire anemometer (pneumotach; PNT), calibrated to zero flow and connected to the Florian respiratory mechanics monitor was incorporated into the ventilator circuit at the airway opening. The ETT was then unclamped. This entire procedure took less than ten seconds.

The size of the ETT leak was determined using the Florian respiratory mechanics monitor, derived from the difference in inspiratory and expiratory tidal volumes recorded at the airway opening. The study was not performed if the displayed ETT leak was >10%.
A pair of RIP transducers (Respibands™, Sensormedics, Yorba Linda, CA, USA) was placed around the chest and abdomen. One band encircled the chest just below the axillae, and the other band encircled the abdomen, with the lower margin 0.5 cm above the umbilicus (Figure 3-2). The Respibands™ are made from self-adherent stretchy material which exhibits Hookian elastic properties. The bands were placed under enough tension so that they felt tight when the investigator’s index finger was placed under each band, but not tight enough to constrain any respiratory movement. To maintain band tension, each band was further secured with tape (see Figure 3-5 for a detailed photograph). The bands were then connected to the Respitrace™ 200 RIP monitor (NIMS, North Bay Village, FL, USA) via the patient interface cable, as per the manufacturer’s instructions (Respitrace users manual 2001, unpublished). Signal drift was allowed to stabilise over at least 40 minutes prior to mapping the PV relationship (See Chapter 3.8.3).

The transcutaneous sensor in clinical use was resited (see Chapter 3.8.2) just prior to a clinically indicated arterial blood gas analysis and Tc\(_{\text{CO}_2}\) calibrated to the corresponding \(P_{\text{aCO}_2}\) value.

![Figure 3-2. Photograph of infant illustrating the position of the chest (RIP\(_{\text{CH}}\)) and abdominal (RIP\(_{\text{AB}}\)) RIP transducer bands and Florian respiratory mechanics monitor pneumotach (PNT) and pressure monitoring line (\(P_{\text{ao}}\)) at airway opening. Oxygen saturation sensor (Sp\(_{\text{O}_2}\)) and transcutaneous electrode (Tc\(_{\text{CO}_2}\)) also shown.](image-url)
In each infant, the $F_{1O2}$ was adjusted to maintain pre-ductal $SpO2$ between 90-94% for 30 minutes, and then not changed during the study. The ventilator $\Delta P$ and frequency had been set by the treating clinicians prior to the study and frequency was not altered. To adjust for the known reduction in delivered $\Delta P$ created by the increased resistance resulting from inclusion of the PNT in the oscillator circuit (Scalfaro et al 2001), $\Delta P$ was increased by 2 cm H$_2$O from that prescribed by the treating clinician. An I/E ratio of 1:2 and an oscillator bias flow of 20 L/min was used in all infants. As per standard care, the inspired gas was warmed and humidified at the airway opening (MR730 Respiratory humidifier, Fisher & Paykel Healthcare Ltd., East Tamaki, New Zealand).

Repeated doses of sedation and muscle relaxation were prescribed if the infant showed evidence of spontaneous breathing or distress.

During the study period the RCH NNU had seven Sensormedics 3100A high frequency oscillators in operation. The study was performed with the oscillator in clinical use at the time. Before use on an infant, the oscillator was checked and calibrated by an Intensive Care Technologist.

3.7.3 Open lung ventilation strategy

Mapping the pressure volume relationship

The experimental protocol was based on the open lung concept described by Lachmann (1992). The open lung ventilation strategy consisted of a quasi-static lung volume optimisation manoeuvre, with a distinct Inflation and Deflation series and a post-study alveolar recruitment manoeuvre, as illustrated in Figure 3-3.

**Inflation Series**

Starting at the $P_{aw}$ set by the clinical team ($P_{initial}$), the $P_{aw}$ was increased by 2 cm H$_2$O every ten minutes until no further increase in $SpO2$ was achieved, or the $SpO2$ decreased over more than two $P_{aw}$ settings ($P_{max}$). Lachmann (1992) has shown that at this $P_{aw}$ the lung should be recruited and near TLC.

At each $P_{aw}$ setting, confirmation of the ventilator amplitude was made to ensure that it remained at the initial study setting. If needed, the amplitude was altered accordingly.
Based on the preliminary data and practical considerations, a ten minute interval between $P_{aw}$ changes was deemed adequate to allow for stabilisation of any lung volume and $SpO_2$ change.

**Deflation Series**

$P_{aw}$ was then decreased every ten minutes, in decrements of 2 cm H$_2$O until $P_{initial} + 2$ cm H$_2$O, and by 1 cm H$_2$O decrements thereafter, until $SpO_2$ fell below 85% for greater than five minutes or $P_{aw}$ reached 5 - 6 cm H$_2$O ($P_{final}$).

**Post study alveolar recruitment manoeuvre**

Once mapping of the PV relationship was completed, alveolar recruitment was re-established by increasing $P_{aw}$ to $P_{max}$ for ten minutes, and then $P_{aw}$ was returned to $P_{initial}$ or, if requested by the treating clinician, an alternative $P_{aw}$. At this stage, the study was complete and the treating clinician informed.

**Figure 3-3. Illustration of the pressure strategy used to identify $P_{max}$ and then $P_{final}$. An alveolar recruitment manoeuvre (ARM) was applied to restore lung volume on completion of the deflation series.**
3.8 Equipment description and experimental measurements

3.8.1 Bedside physiological monitoring

Hewlett-Packard HP48S monitor

Heart rate, arterial blood pressure and SpO2 were recorded using the Hewlett-Packard HP48S (Hewlett Packard, Andover, MA, USA) monitor in use for that infant. The HP48S sampled all parameters continuously. Heart rate was recorded via three electrocardiograph electrodes (Kittycat™ 1050NPSM small, Tyco Healthcare, Mansfield, CT, USA) placed at the right and left shoulders and the left flank. Arterial blood pressure was recorded from the indwelling arterial line (either umbilical or peripheral). The pressure transducer was zeroed to the level of the right atrium prior to commencing each study. The arterial catheter was infused with heparinised saline (5 units/mL). A paediatric oxygen sensor (OxiMax™ paediatric oxygen sensor, Nellcor, Tyco Healthcare Group, Pleasanton, CA, USA) was used to acquire the SpO2 signal.

Transcutaneous carbon dioxide recordings

TcCO2 was recorded using the dedicated modules of the HP48S monitor. Calibration against PaCO2 was performed offline against an arterial blood gas sample. The relationship between transcutaneous and arterial gas values was assumed to be linear for the time the skin sensor was attached to a single site. In the pilot study, TcCO2 correlated with PaCO2 during the open lung ventilation strategy in the third infant studied, as shown in Figure 3-4.

A transcutaneous membrane electrode was applied to the chest or upper abdomen using two drops of contact fluid and a fixation ring (all components; Radiometer Medical ApS, Brønshøj, Denmark) and heated to 43°C. Where possible the sensor was applied to the anterior upper right chest to record pre-ductal values.
3.8.2 Description of Florian respiratory mechanics monitor

The Florian respiratory mechanics monitor is a stand-alone, micro-processor based device which measures flow and pressure at the airway opening. In HFOV mode, it can display peak ($P_{peak}$) and trough ($P_{trough}$) pressure during each oscillatory cycle, $P_{aw}$, flow, frequency, rate, tidal volume at the airway opening ($V_T$), ETT leak and a parameter termed alveolar ventilation (which represents the product of frequency
and $V_T^2$ (Fr.$V_T^2$)). It is approved in Australia by the Therapeutic Goods Administration for use in both infants and adults.

Pressure and flow are measured from independent transducers. The external pressure input and the internal pressure sensor both have a range of -10 to 120 cm H$_2$O. The pressure value has a displayed range of 0 – 120 cm H$_2$O and a resolution of 1 cm H$_2$O. The pressure signal can be exported as an analogue output signal via a dedicated channel (Range -50 to 150 cm H$_2$O with a scale of 1 V = 100 cm H$_2$O).

The analogue output pressure signal delay is ≤ 2 msec.

The Florian respiratory mechanics monitor calculates the $V_T$ of each breath when operating in HFOV mode. The numerical display of $V_T$ and rate represent the average of the previous 15 inflations. A dedicated analogue output channel is allocated to $V_T$. As the analogue output $V_T$ values are 70 msec out of phase from the pressure and flow signal (manufacturer’s user manual), this channel was not sampled during the study.

Percentage of ETT leak is calculated from the inspiratory and expiratory flow signals and displayed on the monitor as a mean value over the preceding 1 minute (range 0 – 50% with a resolution of 1%).

**Description of pneumotach**

Flow was measured at the airway opening using a dedicated PNT which consisted of a dual hot-wire anemometer with a dead space of 1 mL and weighing 10 g. The published operating range in neonatal mode is 0.09 – 32.7 L/min with a manufacturer guaranteed accuracy of ±8% if stored and calibrated correctly.

The flow analogue signal outputs with a delay of ≤ 2 msec and a flow range of ±30 L/min (scale 1 V = 10 L/min).

The flow sensor was calibrated to zero flow prior to insertion into the ventilator circuit using the dedicated calibration function built into the monitor software.
3.8.3 Description of RIP

Description of device

The Respitrace™ 200 is a commercially available, compact, RIP device which generates waveforms in two channels from inductive transducers placed around the chest and abdomen. The inductive transducers determine the change in cross-sectional area of the site enclosed by them (Figure 3-5). The Respitrace™ 200 internally equates the sum of the voltage signal from the chest and abdominal inductive transducers with equal weighting placed on each signal. \( \Delta V_L \) is equal to the change in the summed RIP lung volume (\( V_{L,RIP} \)) signal (Watson et al 1988). The summed \( V_{L,RIP} \) signal was not calibrated to a known volume as there is no accepted method of calibrating RIP during HFOV for prolonged periods of operation (Markhorst et al 2006).

![Figure 3-5. A. Photograph of RIP transducer bands secured around the chest and abdomen of an infant. There is a sinusoidal wire embedded in each band. B. Schematic illustration of the relationship between changes in RIP voltage output (V) generated by stretch of the sinusoidal wire secondary to change in lung volume.](image)
Table 3-2 describes the characteristics of the Respitrace™ 200 device. Both a digital and analogue output can be generated using the Respitrace™ 200. For the purpose of this study, the digital output was only used to set the qualitative calibration factor (50mL = 100% tidal volume) and to centre the baseline gain relative to channel oscillation for the chest and abdominal bands. The gain relative to channel oscillation was set at 1024 count units for each channel.

The DC-coupled analogue signal was used to determine $V_{LRIP}$, tidal volume ($V_{TRIP}$), and $C_{rs}$. The DC-coupled analogue signal was low-pass filtered and expressed as an excitatory voltage for the sum, chest and abdominal signals and recorded using the data acquisition system described below.

The Respitrace 200™ has Therapeutic Goods Administration approval for use as a neonatal monitor in Australia.

Table 3-2. Characteristics of Respitrace™ 200 monitor respiration signals (Respitrace users manual 2001; unpublished).

<table>
<thead>
<tr>
<th>Gain</th>
<th>Range</th>
<th>Linearity</th>
<th>Baseline Recovery</th>
<th>Frequency Response</th>
<th>DC Offset</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mV per 100% $V_T$ after calibration</td>
<td>± 2.048 V</td>
<td>± 10%</td>
<td>Up to 2.5% $V_T$ (or 10 mV) per sec</td>
<td>25 Hz</td>
<td>&lt; 100 mV</td>
</tr>
</tbody>
</table>

Preliminary testing of respiratory inductive plethysmograph

Respiratory inductive plethysmograph signal drift

To determine the reliability of the Respitrace™ 200 to record change in lung volume over time, the drift of the RIP sum signal was investigated in a bench top study. To do so, the $V_{LRIP}$ signal was measured around a rigid plastic right circular cylinder with a fixed cross-sectional area of 123 cm$^2$ and a volume of 1040 cm$^3$. To ensure that no band migration occurred and that the elasticity of the Respibands remained constant, the bands were fixed to the cylinder with adhesive tape. A continuous recording of $V_{LRIP}$ was then made for five hours using the data acquisition system described in 3.9.1 after the Respitrace™ 200 had performed an initial five minute automatic qualitative diagnostic calibration and the gain at commencement had been set to 0 V. The protocol was performed five times at room temperature and twice at 37°C under an Ohio® infant radiant warmer (Ohmeda Medical, Laurel, MS, USA). In all cases, the ambient temperature at the
site of the Respibands™ was recorded 30 minutely (Casio PRG-80T, Casio Corporation, Tokyo, Japan). All electromagnetic field emitting devices within two metres of the Respibands™, except those essential for data collection, were turned off during the recordings.

A drift of ±3% was considered acceptable, this being consistent with other commercially available RIP devices (Brazelton et al 1999a abstract) and the relative measurement error of the Florian monitor (Markhorst et al 2006). In DC-coupled output mode, the maximum potential drift in either direction is 2.048V, hence a 3% drift would equate to a voltage change of ±0.06V over 5 minutes.

The mean [SD] ambient temperature was 23.7 [0.6]°C at room temperature and 36.3 [0.2]°C when the RIP was functioning under the radiant warmer.

The rate of $\Delta V_{\text{RIP}}$ over time is shown in Figure 3-6. In all cases, the RIP device initially demonstrated considerable positive drift. Overall, less than 3% positive drift was obtained by 40 mins with a median time of 30 mins (range 25 to 40 mins). In all cases, a positive drift of less than 1% was occurring by 90 mins, median 60 mins (range 55 to 90 mins). In each case, the relationship between time and $V_{\text{RIP}}$ closely fitted a one phase exponential model ($y=y_{\text{max}}*[1-e^{(-k*x)}]; R^2 = 0.93$ to 0.99).

![Figure 3-6. Relationship between time and RIP signal output (drift) from a fixed volume test lung. Black lines represent recordings at room temperature and red lines under an overhead radiant warmer operating at 37°C.](image-url)
Precision of respiratory inductive plethysmograph to record change in lung volume

To determine the accuracy of the Respitrace™ 200 to measure change in lung volume, a series of known volume changes were made in a test lung.

A two litre rubber hot water bottle was ‘intubated’ with an 8.0 cuffed ETT and a leak free system created by sealing the airway opening with silicon. A pair of RIP bands was secured around the test lung and connected to the RIP monitor. The Florian respiratory mechanics monitor was incorporated into the ventilator circuit at the airway opening (Figure 3-7). The study was performed at 30°C using an Ohio® infant radiant warmer operating in servo control mode.

The proximal end of the PNT was connected to a tracheal tube connector with a Luer Lock side port (GlaxoWelcome, Boronia, Victoria, Australia). A three litre and a one litre (with 20 mL incremental divisions) calibration syringe (Hans Rudolf, Kansas City, KA, USA) were attached to the circuit via leak-free 3-way taps.

Figure 3-7. Schematic setup of the bench top system used to assess the accuracy of RIP to determine change in lung volume in a test lung. Two RIP transducer bands were secured around the test lung. Flow ($V$) and pressure ($P_{ao}$) were measured at the airway opening via a pressure line and pneumotach (PNT) connected to the Florian. The test lung was connected to the 3L and 1L calibrated syringes via leak-free 3-way taps.
Using the three litre syringe, a residual volume of 1.5 litres was created within the test lung. Then a series of five increases and decreases in lung volume were made at two minutely intervals. Each series was performed twice using volume changes of 20mL, 60mL and 100mL. $V_{\text{LRIP}}$ was recorded continuously throughout each series of volume changes.

As illustrated in Figure 3-8, RIP was able to reliably record change in lung volume as the volume was increased and decreased. The mean [SD] overall difference in the known change in lung volume and $\Delta V_{\text{LRIP}}$ for all volume changes and lung volumes was 0.8 [4.1] mL. This resulted in a mean [SD] RIP error of 1.7 [1.9]%, which was independent of the volume and $\Delta V_L$. Table 3-3 summarises the results for each of the 20mL, 60mL and 100mL volume changes. The large SD and error noted during the 60mL series was due to two outlying volume differences (23.2 and -16.6 mL); all other volume differences during this series were ±4 mL of the known volume change.

Figure 3-8. $\Delta V_{\text{LRIP}}$ during a series of 20mL volume changes using a calibrated volume syringe.
Table 3-3. Mean difference and error in known change in lung volume and $\Delta V_{L, RIP}$ during a series of known volume changes in a test lung.

<table>
<thead>
<tr>
<th>Known $\Delta V_L$</th>
<th>Mean (mL)</th>
<th>SD (mL)</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mL</td>
<td>0.2</td>
<td>1.1</td>
<td>1.2 ± 5.7</td>
</tr>
<tr>
<td>60 mL</td>
<td>0.6</td>
<td>9.6</td>
<td>1.0 ± 16.0</td>
</tr>
<tr>
<td>100 mL</td>
<td>1.5</td>
<td>1.6</td>
<td>2.9 ± 2.2</td>
</tr>
</tbody>
</table>

Precision of respiratory inductive plethysmograph to measure tidal volume

There have been concerns about the linearity of RIP in measuring change in tidal volume at different end-expiratory lung volumes, especially when the tidal volume is small (Neumann et al 1998). To examine this, $V_{TRIP}$ was compared to $V_T$ in an animal model of surfactant-deficient lung disease. Two anaesthetised and muscle-relaxed piglets (2-weeks old and 4.2 and 4.6 kg respectively) with a saline lavage model of lung injury were opportunistically studied during another study examining $\Delta V_L$ during ETT suction. This study required description of a quasi-static PV relationship of the lung during IPPV (Bear Cub®, Viasys Healthcare, Yorba Linda, CA, USA). IPPV was delivered with a rate of 40 breaths per minute, inspiratory time 0.5 seconds, $F_{IO2}$ 1.0 and circuit gas flow set at 10L/min. In each piglet, a step-wise change in PIP and PEEP was performed with a constant $\Delta P$ of 15 cm H$_2$O. To do so, the PIP and PEEP were sequentially increased in 5 cm H$_2$O steps from 20/5 cm H$_2$O every two minutes until 40/25 cm H$_2$O respectively, and then decreased in 5 cm H$_2$O steps until the starting pressure was reached again. This resulted in 550 individual breaths over a total of seven pressure changes for each piglet. At each pressure step, $\Delta V_{L, RIP}$, expiratory $V_T$ at the airway opening and $V_{TRIP}$ were recorded. The $V_{TRIP}$ raw signal was calibrated to the $V_T$ over ten stable breaths at PIP/PEEP of 20/5 cm H$_2$O offline and the same calibration factor used throughout the measurement period (Markhorst et al 2005; Markhorst et al 2006).

In both animals, there was no significant difference in $V_T$ and $V_{TRIP}$ at each EELV during mapping of the quasi-static PV relationship. There was good correlation ($r^2 = 0.855$) between the uncalibrated $V_{TRIP}$ values and $V_T$ over the range of tidal volumes recorded (Figure 3-9A). When the $V_T$ was compared with the calibrated $V_{TRIP}$ using the Bland-Altman method (Bland & Altman 1986), the bias was -0.34 mL/kg and the 95% limits of agreement -1.7, 1.0 mL/kg (Figure 3-9B); this is less
than the reported error of the Florian PNT (Scalfaro et al 2001). These data indicate that RIP has the ability to reliably record relative $V_{TRIP}$ over a range of different lung volumes.

![Graph A](image1)

$r^2 = 0.855$

Figure 3-9. A. Correlation between $V_T$ (mL) and uncalibrated $V_{TRIP}$ (V); red line represents the line of agreement. B. Bland-Altman plot of $V_T$ and calibrated $V_{TRIP}$ (both mL/kg). Solid line represents mean difference (bias) and dotted lines the 95% limits of agreement.
3.8.4 Data acquisition

A Pentium 4 laptop computer (IBM corporation, Armonk, NY, USA) running LabVIEW™ (National Instruments, Austin, TX, USA), a graphical programming language, was used for data acquisition, real time display and subsequent analysis. $P_{aw}$, $V_{L, RIP}$, $V_{L, RC}$, $V_{LAB}$ and flow data were digitised and routed to a 16 channel, 12-bit, analogue to digital converter (DAQCard™-6062E, National Instruments, Austin, TX, USA) via a shielded cable using a BNC-terminated adaptor board (BNC-2110, National Instruments, Austin, TX, USA). This system can sample a voltage signal up to 500,000 samples per second (500 kS/s) but for this study a sampling rate of 0.2 – 1 kS/s per channel was deemed adequate to avoid signal aliasing.

3.8.5 Experimental Measurements

At each $P_{aw}$, the following parameters were measured

Recording of ventilator settings

$P_{aw}$ displayed by the Sensormedics 3100A was recorded manually after each change in $P_{aw}$.

Recording of cardiovascular parameters

Heart rate, systolic, diastolic, and mean arterial systemic blood pressure (MAP) were recorded from a Hewlett-Packard HP48S monitor. The displayed heart rate and blood pressure values were recorded on the data collection sheets every minute for the last 5 minutes at each $P_{aw}$.

Recording of indicators of gas exchange

$SpO_2$ and $TcCO_2$ were recorded from the HP48S monitor. The displayed $SpO_2$ and $TcCO_2$ values were manually recorded every minute for the last 5 minutes at each $P_{aw}$. A stop watch was used to ensure time precision.

Recording of airway pressure

Pressure at the airway opening ($P_{aw}$) was recorded using the Florian respiratory mechanics monitor.
At each pressure setting, $P_{ao}$ was sampled continuously at 200Hz (0.2 kS/s) during the last five minutes at each setting using LabVIEW. From the $P_{ao}$ signal, $P_{aw}$, $P_{peak}$ and $P_{trough}$ were determined. The difference between $P_{peak}$ and $P_{trough}$ represented the recorded amplitude of the oscillatory waveform.

**Flow**

Airway flow, measured at the airway opening by the PNT, was recorded using the Florian respiratory mechanics monitor. For the last five minutes at each $P_{aw}$, flow was sampled for the first 20 seconds of every minute at 1000Hz using LabVIEW. Scalforo et al (2001) have previously validated the Florian respiratory mechanics monitor during HFOV within a frequency range of 8 – 13 Hz.

**Calculation of Tidal Volume**

**Tidal Volume at the airway opening ($V_T$)**

The expiratory $V_T$ of each oscillatory breath, measured at the airway opening, was determined by integration of the flow signal from the Florian respiratory mechanics monitor and identification of oscillatory peaks and troughs in the resultant volume signal (analysis program devised by P Dargaville). Scalforo et al (2001) have shown that the Florian monitor allows for reliable $V_T$ estimates at the airway opening during HFOV.

**Tidal Volume as measured by RIP ($V_{TRIP}$)**

The oscillatory peaks and troughs in the $V_{L RIP}$ signal were identified using the same dedicated data analysis program that was used to determine $V_T$. The phase angle of the RIP signals was assumed to be 0° as all infants were receiving muscle relaxants.

**Calculation of compliance ($C_{rs}$)**

Quasi-static $C_{rs}$ was calculated from $V_{L RIP}$ and $P_{ao}$ using the equation $C_{rs} = \Delta V_{L RIP}/\Delta P_{ao}$ (Mead & Whittenberger 1953), where $\Delta V_{L RIP}$ and $\Delta P_{ao}$ represent the difference in each parameter between two consecutive $P_{aw}$ changes.
Recording of change in lung volume ($\Delta V_L$)

Change in lung volume was measured using RIP. The pair of RIP bands were connected to a low-pass filtered, DC coupled, Respirace™ 200 monitor. At least 40 minutes was allowed for thermal and signal stabilisation of the Respitrace™ 200 output (manufacturer’s recommendations and our own bench-top testing).

The RIP monitor was connected to a Pentium 4 laptop computer running RespiPanel V1.4c virtual control panel (NIMS, North Bay Village, FL, USA) via a RS232 cable. Using this program, the qualitative calibration factor was standardised to allow 50 mL to represent 100% tidal volume. After signal stability had been achieved, the outputs were zeroed using the gain control software included with RespiPanel V1.4c. The uncalibrated $V_{LRIP}$ in Volts was derived from the sum of chest and abdominal RIP voltages (Konno & Mead 1967). This $V_{LRIP}$ signal was sampled at 200 Hz (0.2 kS/s) continuously during the last five minutes at each $P_{aw}$ setting using LabVIEW.

3.9 Data collection and statistical analysis

All digitally-recorded raw data were analysed using LabVIEW™. Data were then transposed into a spreadsheet (Microsoft Excel 2003; Microsoft Corporation, Seattle, WA, USA). The final $V_{LRIP}$ at each $P_{aw}$ was defined as the mean end-expiratory voltage during the last, artefact-free, five-second epoch in the five minute recording of $V_{LRIP}$, with the corresponding $P_{aw}$ values being derived from the pressure recordings at the airway opening during the same five-second epoch. Quasi-static $C_{rs}$ was calculated from these values.

$V_T$ and $V_{TRIP}$ at each $P_{aw}$ setting were calculated for each oscillatory cycle during each twenty-second recording. The mean and standard deviation [SD] of $V_T$ and $V_{TRIP}$ were calculated using all the breaths analysed during the twenty-second recordings at each $P_{aw}$ and defined as the final respective value for that parameter at each $P_{aw}$.

All manually recorded data were entered into a spreadsheet. At each $P_{aw}$, the mean and SD of the minutely $\text{SpO}_2$, $\text{TcCO}_2$, heart rate and MAP recordings were calculated. Descriptive statistics for the demographic data were then calculated.
For normally and non-normally distributed data, the mean and SD, and the median and range were used respectively.

The data were then incorporated into either Graph Pad Prism version 4.02 for Windows (Graph Pad Software, San Diego, CA, USA) or Sigmaplot 2000 (Systat Software Inc., San Jose, CA, USA), where appropriate, for statistical analysis. A $p$ value of $<0.05$ was considered significant.

The fundamental questions arising from this study were as follows:

- Could a PV relationship be described in each infant?
- If so, then what was the intra-subject relationship between the parameters recorded and the PV relationship?
- What was the inter-subject relationship between these parameters and the PV relationship within the entire study population?
- Could an optimal $P_{aw}$ (or range of $P_{aw}$) be determined for each parameter?
- Could any of these parameters, or a combination of them, be used to determine an optimal point (or range) within the PV relationship in which to apply ventilation?

### 3.9.1 Intra-subject analysis

A PV relationship (with lung volume expressed in Volts) was plotted for each individual infant. Similarly, the gas exchange and lung mechanics data were plotted against both $P_{aw}$ and $V_{L,RIP}$ for each individual subject.

For each parameter, the values, and corresponding $P_{aw}$ and $V_{L,RIP}$, at the following points within the PV relationship were determined:

- $P_{initial}$
- $P_{final}$
- $P_{max}$
- The $P_{aw}$ during the deflation series which corresponded to that of $P_{initial}$
- The maximum value (optimal point) for that parameter

In the case of $Tc_{CO2}$, the $P_{aw}$ corresponding to the minimum $Tc_{CO2}$ value was used to represent the optimum $P_{aw}$ for CO2 clearance.
3.9.2 Inter-subject analysis

To allow for inter-subject variability, $P_{aw}$ and $V_{LRIP}$ values were normalised by referencing to the corresponding values at $P_{max}$ (100%) and $P_{final}$ (0%), these being the definable upper and lower limits of the deflation series. From these, a PV curve was drawn and compared to the sigmoidal model of the PV relationship proposed by Venegas et al (1998). The coefficient of determination ($R^2$) was used to determine the degree to which this model fitted the data.

The $V_T$ data were referenced to body weight (kg). These data, along with the $C_{rs}$, $V_{TRIP}$ and $T_{cCO2}$ data were referenced to the original value in each infant at $P_{initial}$. No transformation of the $SpO_2$ data was made as $SpO_2$ is expressed in units with a uniform minimum (0%) and maximum (100%) value. The mean and SD at each normalised $P_{aw}$ and $V_{LRIP}$ value were then calculated and plotted for each of the parameters to determine the overall relationship between a particular parameter and the PV relationship. To compare relative change in quasi-static $C_{rs}$ between infants, the normalised PV data were used to calculate $C_{rs}$.

The $P_{aw}$ and $V_{LRIP}$ resulting in the optimum point for each parameter were compared using mean differences and 95% confidence intervals (CI). Unless otherwise indicated all results are presented as mean (95% CI).

3.9.3 Indicators of optimum ventilation

Nonlinear regression analysis, utilising a second order polynomial (or ‘quadratic’) model ($y=a+bx+cx^2$), was used to assess the utility of each parameter to indicate a point (or region) of optimum ventilation within the PV relationship. The presence of a ‘bell-shaped’ relationship between the parameter of interest and $P_{aw}$ or $V_{LRIP}$ was taken to indicate that an optimal point could be predicted for that parameter. The $R^2$ value was calculated to determine the goodness-of-fit of the quadratic model to the data. Runs test analysis was performed to determine whether the curve deviated systematically from the data. Using Runs test analysis, a significant difference ($p$ value <0.05) between the data and the nonlinear model would indicate that the model was inappropriate for the data.
3.9.4 Sample size

Being a descriptive physiological study, the true relationship between the measured parameters and the PV relationship was unknown. Consequently, a sample size of fifteen was chosen based on a judgement that this number would allow adequate exploration of the PV relationship in this group of patients, and on feasibility considerations.

3.10 Conclusion

In this chapter, the aims and hypotheses of this study have been stated and the methods and experimental design used to test these hypotheses described. An open lung ventilation strategy was applied to fifteen newborn infants receiving HFOV in an attempt to describe the clinically relevant regions of the PV relationship. The effect on gas exchange and lung mechanics was examined at each applied $P_{aw}$ during the open lung ventilation strategy. The following six chapters describe the results of this study.
Chapter 4.
DESCRIPTION OF STUDY POPULATION,
OSCILLATOR PERFORMANCE AND
HAEMODYNAMIC RESULTS

4.1 Introduction

The purpose of this chapter is to describe the study population, oscillator performance and haemodynamic results. Initially, the study population is compared to the population of infants at the RCH NNU that received HFOV during the period of enrolment. Secondly, the characteristics of each enrolled subject are described in detail.

The results reported in the subsequent chapters depend on some assumptions with respect to the performance of the Sensormedics 3100A oscillator. Therefore, in each infant, $P_{aw}$, frequency, $\Delta P$ and leak are examined in detail to identify any variation that may have occurred throughout the study period, and to determine any discrepancies between the values displayed by the Sensormedics 3100A oscillator and those recorded using the Florian respiratory mechanics monitor.

The heart rate and MAP results are reported as indicators of haemodynamic stability during the studies. Finally, the $P_{aw}$ and $SpO_2$ data following the alveolar recruitment manoeuvre applied at the end of the study are described.

4.2 Description of study population

4.2.1 Determination of study population

Study enrolment was from 1st of August 2003 until 31st of July 2006. During this period a total of 575 infants were admitted to the RCH NNU for mechanical ventilation via an ETT. Table 4-1 describes the population of intubated infants managed for respiratory failure using the three methods of mechanical ventilation available during the study period; these were IPPV, HFOV and/or high-frequency jet ventilation (HFJV). There was heterogeneity in the characteristics of the infants in each ventilator cohort. There was no significant difference in the demographic
characteristics and time on respiratory support between those infants who received HFOV and those treated solely with IPPV. HFJV was used to treat older but more preterm, and smaller infants who required long periods of HJFV support. This is not unexpected, as it is the practice at the RCH NNU to use HFJV as a rescue therapy when IPPV or HFOV have failed. HFJV is principally used to treat conditions associated with gas trapping, such as pulmonary interstitial emphysema. These conditions are commonly associated with complications of prematurity.

Table 4-1. Characteristics of infants requiring assisted respiratory support via an endotracheal tube at the RCH NNU between August 2003 and August 2006 (median and range).

<table>
<thead>
<tr>
<th></th>
<th>IPPV*</th>
<th>HFOV</th>
<th>HFJV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 440</td>
<td>n = 112</td>
<td>n = 44</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>36 (24, 42)</td>
<td>37 (23, 42)</td>
<td>28 (23, 41)</td>
</tr>
<tr>
<td>Age at admission (days)</td>
<td>1 (0, 237)</td>
<td>1 (0, 151)</td>
<td>15.5 (0, 244)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2600 (519, 5440)</td>
<td>2780 (474, 4400)</td>
<td>1033 (419, 4700)</td>
</tr>
<tr>
<td>Admission weight (g)</td>
<td>2710 (519, 5774)</td>
<td>2828 (474, 4500)</td>
<td>1482 (550, 5015)</td>
</tr>
<tr>
<td>Time on specific type of ventilator (h)</td>
<td>77.5 (0, 3677)</td>
<td>108 (1, 813)</td>
<td>243 (1, 1802)</td>
</tr>
</tbody>
</table>

* limited to infants that received IPPV only. 21 infants received HFOV and HFJV.

Of these 575 intubated infants, 112 (19.5%) infants received HFOV. From these 112 infants, 49 met the study eligibility criteria (See Chapter 3.6). The reasons why 65 were excluded are as follows: 24 had CDH; one had cyanotic heart disease; 38 did not have arterial access or were not receiving a muscle relaxant. Of the 49 eligible infants, the parents of 19 were approached to consent to participation in the study. Generally, the remaining 30 eligible infants were not approached because of lack of availability of the investigator or an essential assistant (for example a translator in the case of non-english speaking families). In some cases, the treating clinician requested the family not be approached. The parents of two eligible infants declined to participate in the study, giving a final study population of 17 infants.
4.2.2 Final study population

Of the 17 infants enrolled, the first and third infants enrolled were excluded due to incomplete $V_{L,RIP}$ data. In the case of the first infant, the RIP was inadvertently set to AC-coupled analogue output, rather than DC-coupled output. In the third infant studied the RIP cable was faulty and a noisy $V_{L,RIP}$ signal was recorded, resulting in meaningless data. The demographic characteristics of the remaining 15 infants are described in Table 4-2.

Gestational age

All infants were term, or near term for corrected gestational age, at the time of enrolment. Three infants were born prematurely and were enrolled at least three weeks after their birth. At the time of enrolment, none of these premature infants had hyaline membrane disease.

Primary Respiratory diagnosis

Meconium aspiration syndrome was the most common primary respiratory diagnosis (seven infants). This condition presents with severe respiratory disease soon after birth in term infants (Dargaville & Copnell 2006). HFOV is increasingly being used early in the management of meconium aspiration syndrome (Tingay et al 2007b). Consequently, the seven infants enrolled with meconium aspiration syndrome were within two days of birth when studied and had a gestational age approximating term (range 39 – 42 weeks). Of these seven infants, three were also enrolled in the ‘lavage with exogenous surfactant suspension in meconium aspiration syndrome (lessMAS)’ trial and randomised to the lavage arm of that study. This involved a dilute surfactant (5 mg/mL of Survanta™) lung lavage of 30 mL/kg in two aliquots. Lung lavage was performed 3.5, 17 and 40 hours prior to the study protocol in Infants 9, 4 and 14 respectively.

Four infants had chest radiographic features of pneumonia. Respiratory syncitial virus and chlamydia were identified in Infants 2 and 12 respectively. No causative organism was identified in the other two infants. Two of these infants were studied when they were more than 28 days old.
Table 4-2. Subject characteristics

<table>
<thead>
<tr>
<th>Infant</th>
<th>Diagnosis</th>
<th>Age (days)</th>
<th>Birth weight (g)</th>
<th>Weight (g)</th>
<th>GA (weeks)</th>
<th>Time on HFOV (hr)</th>
<th>$P_{aw}$ (cm H$_2$O)</th>
<th>$\Delta P$ (cm H$_2$O)</th>
<th>Fr (Hz)</th>
<th>$F_{\text{IO}_2}$</th>
<th>$P_{\text{aCO}_2}$ (mmHg)</th>
<th>BE</th>
<th>$\text{AaDO}_2$ (mmHg)</th>
<th>OI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RDS + PPHN</td>
<td>2</td>
<td>4130</td>
<td>4200</td>
<td>38</td>
<td>29</td>
<td>16.7</td>
<td>35</td>
<td>8</td>
<td>0.40</td>
<td>55</td>
<td>1.0</td>
<td>164</td>
<td>12.8</td>
</tr>
<tr>
<td>2</td>
<td>Pneumonia</td>
<td>42</td>
<td>2310</td>
<td>2700</td>
<td>33</td>
<td>52</td>
<td>13.8</td>
<td>33</td>
<td>7</td>
<td>0.50</td>
<td>57</td>
<td>0.0</td>
<td>197</td>
<td>7.8</td>
</tr>
<tr>
<td>3</td>
<td>Pulmonary oedema</td>
<td>15</td>
<td>2250</td>
<td>2300</td>
<td>40</td>
<td>46</td>
<td>13.5</td>
<td>45</td>
<td>9</td>
<td>0.50</td>
<td>56</td>
<td>1.0</td>
<td>211</td>
<td>8.9</td>
</tr>
<tr>
<td>4</td>
<td>MAS + PPHN</td>
<td>1</td>
<td>3500</td>
<td>3500</td>
<td>42</td>
<td>23</td>
<td>9.8</td>
<td>33</td>
<td>8</td>
<td>0.50</td>
<td>48</td>
<td>-7.0</td>
<td>126</td>
<td>7.8</td>
</tr>
<tr>
<td>5</td>
<td>Pneumonia</td>
<td>32</td>
<td>720</td>
<td>1100</td>
<td>23</td>
<td>22</td>
<td>10.0</td>
<td>26</td>
<td>12</td>
<td>0.35</td>
<td>37</td>
<td>-3.0</td>
<td>153</td>
<td>7.0</td>
</tr>
<tr>
<td>6</td>
<td>Post surgical</td>
<td>7</td>
<td>2100</td>
<td>2100</td>
<td>37</td>
<td>22</td>
<td>14.6</td>
<td>22</td>
<td>9</td>
<td>0.21</td>
<td>45</td>
<td>-3.0</td>
<td>35</td>
<td>6.8</td>
</tr>
<tr>
<td>7</td>
<td>Post surgical</td>
<td>24</td>
<td>910</td>
<td>1100</td>
<td>25</td>
<td>4</td>
<td>10.0</td>
<td>21</td>
<td>12</td>
<td>0.28</td>
<td>47</td>
<td>0.2</td>
<td>53</td>
<td>5.5</td>
</tr>
<tr>
<td>8</td>
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<td>1</td>
<td>3600</td>
<td>3600</td>
<td>39</td>
<td>28</td>
<td>14.3</td>
<td>28</td>
<td>8</td>
<td>0.40</td>
<td>57</td>
<td>-4.0</td>
<td>130</td>
<td>11.0</td>
</tr>
<tr>
<td>9</td>
<td>MAS</td>
<td>2</td>
<td>3430</td>
<td>3400</td>
<td>41</td>
<td>21</td>
<td>17.4</td>
<td>35</td>
<td>6</td>
<td>0.70</td>
<td>38</td>
<td>-3.0</td>
<td>388</td>
<td>19.0</td>
</tr>
<tr>
<td>10</td>
<td>Pneumonia + PPHN</td>
<td>1</td>
<td>3490</td>
<td>3500</td>
<td>42</td>
<td>15</td>
<td>13.4</td>
<td>40</td>
<td>8</td>
<td>0.90</td>
<td>49</td>
<td>-7.0</td>
<td>401</td>
<td>6.7</td>
</tr>
<tr>
<td>11</td>
<td>MAS + PPHN</td>
<td>2</td>
<td>3290</td>
<td>3300</td>
<td>40</td>
<td>41</td>
<td>16.5</td>
<td>35</td>
<td>7</td>
<td>0.35</td>
<td>48</td>
<td>0.0</td>
<td>130</td>
<td>9.6</td>
</tr>
<tr>
<td>12</td>
<td>Pneumonia</td>
<td>12</td>
<td>3120</td>
<td>3500</td>
<td>40</td>
<td>54</td>
<td>11.3</td>
<td>34</td>
<td>8</td>
<td>0.55</td>
<td>100</td>
<td>5.0</td>
<td>207</td>
<td>10.4</td>
</tr>
<tr>
<td>13</td>
<td>MAS + PPHN</td>
<td>2</td>
<td>3340</td>
<td>3340</td>
<td>40</td>
<td>24</td>
<td>15.0</td>
<td>26</td>
<td>8</td>
<td>0.45</td>
<td>37</td>
<td>-5.0</td>
<td>235</td>
<td>19.9</td>
</tr>
<tr>
<td>14</td>
<td>MAS + PPHN</td>
<td>2</td>
<td>3050</td>
<td>3500</td>
<td>40</td>
<td>43</td>
<td>16.0</td>
<td>34</td>
<td>6</td>
<td>0.90</td>
<td>55</td>
<td>-3.0</td>
<td>526</td>
<td>30.6</td>
</tr>
<tr>
<td>15</td>
<td>MAS + PPHN</td>
<td>2</td>
<td>3700</td>
<td>3700</td>
<td>41</td>
<td>44</td>
<td>17.0</td>
<td>42</td>
<td>7</td>
<td>0.80</td>
<td>46</td>
<td>0.0</td>
<td>470</td>
<td>31.6</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>2</td>
<td>3340</td>
<td>3400</td>
<td>40</td>
<td>28</td>
<td>16.0</td>
<td>34</td>
<td>8.0</td>
<td>0.5</td>
<td>48</td>
<td>-3.0</td>
<td>197</td>
<td>9.6</td>
</tr>
</tbody>
</table>

PPHN = Persistent pulmonary hypertension of the newborn requiring inhaled nitric oxide; RDS = Respiratory distress syndrome; MAS = Meconium aspiration syndrome; GA = gestational age; $\Delta P$ = Amplitude; Fr = Frequency; BE = arterial base excess; $\text{AaDO}_2$ = alveolar-arterial oxygen difference; OI = oxygenation index
The remaining four infants had a variety of primary respiratory diagnoses. Infant 1 was a term infant who presented with acute respiratory distress, with chest radiograph features consistent with RDS, and persistent pulmonary hypertension of the newborn (PPHN) after an elective caesarean section. Infant 3 had pulmonary oedema secondary to cardiac failure. Infant 6 had gastroschisis complicated by necrotising enterocolitis. This infant had minimal lung disease at the time of study. Infant 7 was an ex-preterm infant with evolving CLD and was post-surgical repair of a perforated small intestine secondary to necrotising enterocolitis. Both Infants 6 and 7 were commenced on HFOV due to inadequate CO\textsubscript{2} removal on IPPV.

**Pulmonary hypertension**

Eight infants were also receiving iNO (median dose 15 [range 10 to 20] ppm) to treat echocardiographically proven PPHN. In all infants this had improved prior to the study. The alveolar – arterial oxygen gradient (AaDO\textsubscript{2}) and oxygenation index (OI) were greater in the infants receiving iNO compared to those infants that were not (mean difference 165 [95% CI 23, 307] mm Hg and 9.1 [0.9, 17.2] respectively; unpaired \(t\) test).

The RCH NNU has a standardised approach to the management of PPHN. This includes maintaining normothermia, adequate analgesia, and strict control of blood glucose, calcium and magnesium, as well as the use of iNO. All aspects of this standardised management were being met in the eight infants with PPHN. Prostaglandin E1 was not being used in the management of any of the infants enrolled in the study.

**Illness severity**

Illness severity varied considerably amongst the study population, reflecting the heterogeneous respiratory pathologies. Some infants were enrolled during the acute phase of their illness and others during weaning. There was a wide variation in AaDO\textsubscript{2} and OI values (the median [range] AaDO\textsubscript{2} and OI were 197 [35 to 526] mm Hg and 9.6 [5.5 to 31.6] respectively).
Table 4-3 summarises the illness severity by respiratory diagnosis. Infants with MAS had the greatest illness severity at the time of study. Despite this, on statistical analysis, AaDO$_2$, OI, F$_{I02}$ and $P_{initial}$ were not influenced by primary respiratory diagnosis (one-way ANOVA), although the small numbers in each category may have limited the ability to identify any statistical difference. Similarly, age at recruitment did not significantly influence illness severity. This diversity of respiratory diagnoses and illness states is consistent with the current use of HFOV to treat term and near-term infants in Australia and New Zealand (Tingay et al 2007b).

Table 4-3. Illness severity by primary respiratory diagnosis (all data mean and SD).

<table>
<thead>
<tr>
<th>Primary Respiratory Diagnosis (n)</th>
<th>AaDO$_2$ (mm Hg)</th>
<th>Oxygenation Index</th>
<th>F$_{I02}$</th>
<th>$P_{initial}$ (cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAS (7)</td>
<td>286 (173)</td>
<td>18.5 (9.7)</td>
<td>0.59 (0.21)</td>
<td>15.0 (2.6)</td>
</tr>
<tr>
<td>Pneumonia (4)</td>
<td>240 (110)</td>
<td>8.0 (1.7)</td>
<td>0.58 (0.24)</td>
<td>12.1 (1.8)</td>
</tr>
<tr>
<td>Other Respiratory (2)</td>
<td>188 (33)</td>
<td>10.9 (2.8)</td>
<td>0.45 (0.07)</td>
<td>15.0 (2.3)</td>
</tr>
<tr>
<td>Post surgical (2)</td>
<td>44 (13)</td>
<td>6.2 (0.9)</td>
<td>0.25 (0.05)</td>
<td>12.3 (3.3)</td>
</tr>
</tbody>
</table>

Ten infants were receiving at least one inotropic agent for circulatory support. Three were receiving a single inotropic agent and seven two inotropes at the time of enrolment. Dopamine was the most commonly used inotrope, being used in eight infants. Of these eight infants, six required a second inotrope at the time of enrolment, five were also receiving dobutamine and one infant adrenaline. A total of seven infants were receiving a dobutamine infusion. In one of these infants adrenaline was also being used. All infants were adequately volume filled at the time of study. The haemodynamic data for each infant are described in Chapter 4.4.

The use of continuous analgesia during HFOV is standard policy at the RCH NNU for infants receiving muscle relaxants. All infants were receiving a continuous infusion of morphine at the time of enrolment (median dose 35 micrograms/kg/hour; range 20 to 40 micrograms/kg/hour). Two infants (Infants 2 and 7) also received a midazolam infusion at 1 microgram/kg/hour.
Serious Adverse Events

Two infants died within two days of participating in the study. In the case of Infant 2, a serious chromosomal abnormality was identified the day after study. The family then elected to withdraw intensive care.

Infant 14 sustained a prolonged period of bradycardia following re-intubation the day after study, from which he could not be resuscitated. This infant had severe MAS with significant gas trapping and was being transferred to HFJV. An autopsy determined that the primary cause of death was severe MAS.

Both deaths were reported to the RCH Ethics in Human Research Committee as potential serious adverse events. The Ethics in Human Research Committee determined that participation in the study did not contribute to the deaths of either infant.

There were no other adverse events identified.

4.3 Ventilator settings and data

4.3.1 Mean airway pressure

The median (range) of $P_{aw}$ changes during each study protocol was 16 (13 to 21). A median of 5 (4 to 7) $P_{aw}$ changes were made during the inflation series and 11 (8 to 14) during the deflation series in each infant. The details of the individual $P_{aw}$ steps in each infant are described in Chapter 5.

There was good correlation between the $P_{aw}$ displayed on the oscillator and the recorded $P_{ao}$ during the study protocol in each infant (Table 4-4). However, in all but Infant 6, the $P_{ao}$ was less than that displayed on the oscillator. In these infants, the $P_{ao}$ underestimated the displayed $P_{aw}$ by a mean [SD] of 2.0 [0.9] cm H$_2$O. In Infant 6, the $P_{ao}$ was an average of 2.2 cm H$_2$O above the displayed $P_{aw}$. This discrepancy in Infant 6 can only be explained by an error in the calibration of the Sensormedics 3100A oscillator. In all cases, there was clinically acceptable agreement between the measured and displayed $P_{aw}$, as determined by the Bland – Altman method (Bland & Altman 1986), as the $P_{aw}$ was changed during the study protocol (Table 4-4). In all infants, the $P_{aw}$ derived from the $P_{ao}$ signal was used.
Description of Study Population

Table 4-4. Difference between $P_{aw}$ displayed by Sensormedics 3100A and $P_{aw}$ recorded at airway opening, and agreement of this relationship, as $P_{aw}$ was altered during the study protocol.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Mean Difference (cm H$_2$O)</th>
<th>95% Limits of agreement</th>
<th>Slope</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.6</td>
<td>2.3, 3.0</td>
<td>1.044 ± 0.010</td>
<td>0.999</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>1.2, 2.8</td>
<td>0.972 ± 0.016</td>
<td>0.996</td>
</tr>
<tr>
<td>3</td>
<td>2.8</td>
<td>1.8, 3.8</td>
<td>1.081 ± 0.021</td>
<td>0.995</td>
</tr>
<tr>
<td>4</td>
<td>3.1</td>
<td>2.2, 4.0</td>
<td>0.998 ± 0.025</td>
<td>0.991</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>1.4, 2.5</td>
<td>1.044 ± 0.016</td>
<td>0.997</td>
</tr>
<tr>
<td>6</td>
<td>-2.2</td>
<td>-1.3, -3.1</td>
<td>1.110 ± 0.015</td>
<td>0.997</td>
</tr>
<tr>
<td>7</td>
<td>1.3</td>
<td>0.7, 2.0</td>
<td>0.939 ± 0.014</td>
<td>0.997</td>
</tr>
<tr>
<td>8</td>
<td>1.6</td>
<td>1.0, 2.2</td>
<td>0.975 ± 0.015</td>
<td>0.996</td>
</tr>
<tr>
<td>9</td>
<td>3.1</td>
<td>1.8, 4.5</td>
<td>0.886 ± 0.017</td>
<td>0.995</td>
</tr>
<tr>
<td>10</td>
<td>1.8</td>
<td>0.4, 3.2</td>
<td>0.949 ± 0.033</td>
<td>0.981</td>
</tr>
<tr>
<td>11</td>
<td>1.9</td>
<td>1.1, 2.8</td>
<td>0.945 ± 0.022</td>
<td>0.993</td>
</tr>
<tr>
<td>12</td>
<td>1.2</td>
<td>0.4, 2.0</td>
<td>1.037 ± 0.016</td>
<td>0.996</td>
</tr>
<tr>
<td>13</td>
<td>0.3</td>
<td>-0.3, 0.8</td>
<td>0.993 ± 0.012</td>
<td>0.997</td>
</tr>
<tr>
<td>14</td>
<td>1.2</td>
<td>0.3, 2.1</td>
<td>0.899 ± 0.022</td>
<td>0.994</td>
</tr>
<tr>
<td>15</td>
<td>3.5</td>
<td>1.8, 5.2</td>
<td>0.850 ± 0.021</td>
<td>0.992</td>
</tr>
</tbody>
</table>

4.3.2 Frequency

Table 4-2 describes the frequency in use during the study for each infant. The frequency set on the Sensormedics 3100A oscillator was held constant throughout the study protocol. Any variation in the frequency during the study protocol would represent a source of error by virtue of varying the delivered tidal volume. During the application of the open lung ventilation strategy the intra-subject variation in recorded frequency at each $P_{aw}$ step varied by less than 0.5 Hz in each infant.

Figure 4-1 shows the difference between the displayed and the mean measured frequency, at the airway opening, for each infant. Overall, there was no difference between the frequency displayed by the Sensormedics 3100A oscillator and the frequency measured by the Florian respiratory mechanics monitor (bias -0.007 Hz; 95% limits of agreement -0.577, 0.564 Hz; Bland-Altman method).
4.3.3 Amplitude ($\Delta P$)

The $\Delta P$ delivered by the Sensormedics 3100A oscillator is influenced by changes in the $P_{aw}$ and the oscillator amplitude setting. During these studies, attempts were made to maintain a constant displayed $\Delta P$ by manually altering the amplitude setting as needed with each $P_{aw}$ change. This was done to standardise the delivered tidal volume. The Sensormedics 3100A cannot display $\Delta P$ in increments of less than 1 cm H$_2$O.

There was significant difference in the $\Delta P$ displayed by the Sensormedics 3100A and that recorded at the airway opening at the start of each study (Table 4-5A). Only in Infant 12 did the displayed $\Delta P$ equal the recorded $\Delta P$. In all other infants, the recorded $\Delta P$ was less than the displayed $\Delta P$. This difference was not constant and the mean [SD] was 5.7 [4.7] cm H$_2$O and ranged from 0 to 14.7 cm H$_2$O. The finding of a difference in $\Delta P$, measured by different devices at different points within the ventilator circuit, is not surprising as the amplitude of the oscillatory
Description of Study Population

wave form is known to attenuate through the respiratory tree (Gerstmann et al 1990). This attenuation is further exaggerated by the insertion of the Florian pneumotach into the ventilator circuit immediately proximal to the airway opening. The variation of the difference is surprising and was not influenced by the magnitude of the displayed \( \Delta P \).

Table 4-5. A. Relationship between the displayed \( \Delta P \) on the Sensormedics 3100A oscillator and the \( \Delta P \) at the airway opening measured with a Florian Monitor. B. Summary of the variation in \( \Delta P \) recorded at the airway opening between \( P_{aw} \) steps in each infant. All values expressed in cm H\(_2\)O.

<table>
<thead>
<tr>
<th>Infant</th>
<th>A. ( \Delta P ) at study commencement</th>
<th>B. Measured ( \Delta P ) at each ( P_{aw} ) during the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Displayed ( \Delta P )</td>
<td>Recorded ( \Delta P )</td>
</tr>
<tr>
<td>1</td>
<td>35</td>
<td>28.9</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>22.0</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>44.4</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>26.3</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>13.4</td>
</tr>
<tr>
<td>6</td>
<td>22</td>
<td>7.3</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>16.2</td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>24.7</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>31.1</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>31.5</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>33.5</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>34.0</td>
</tr>
<tr>
<td>13</td>
<td>26</td>
<td>25.4</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>32.6</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>32.1</td>
</tr>
</tbody>
</table>
For this study, the ΔP measured by the Florian monitor at the airway opening was used. The presence of intra-subject variation in recorded ΔP between $P_{aw}$ steps is of greater importance to the subsequent analysis of the lung mechanics data than any difference between displayed and measured ΔP. Amplitude is the greatest determinant of tidal volume and CO$_2$ removal during HFOV, and the study aim was to determine the influence of the volume state of the lung on these parameters by holding ΔP and frequency constant, thus negating the influence of these ventilator parameters. There are natural fluctuations in the delivered ΔP on the Sensormedics 3100A oscillator and clinicians usually change ΔP in gradations of at least 2 cm H$_2$O. Consequently, an intra-subject variation in ΔP of less than ±2 cm H$_2$O is unlikely to influence the interpretation of change in tidal volume and CO$_2$.

There was intra-subject variation in ΔP measured by the Florian monitor between $P_{aw}$ steps. In only Infant 10 did the maximum and minimum ΔP during the study differ by less than 2 cm H$_2$O. In six infants the ΔP varied between 2 and 5 cm H$_2$O. It was greater than 5 cm H$_2$O in the remaining eight infants. The greatest variation, of 10 cm H$_2$O, occurred in Infant 15.

Figure 4-2 shows the relationship between normalised $P_{aw}$ (see Chapter 3.9.2) and the difference between the initial ΔP, at the airway opening, and the ΔP at each $P_{aw}$ step. The mean [SD] difference was 0.82 [2.86] cm H$_2$O. There was no significant difference between the inflation and deflation series ($p=0.401$; unpaired t test) and the magnitude of $P_{aw}$ did not influence any variability in recorded ΔP.
Description of Study Population

Figure 4-2. Scatter plot of the relationship between normalised $P_{aw}$ and the difference in the initial $\Delta P$ at the airway opening and the $\Delta P$ recorded at each $P_{aw}$ step during the inflation series (closed circles) and deflation series (open diamonds) in all 15 infants.

The reasons for these differences could not be determined. It is possible that the variations were due to human factors or natural fluctuations within the delivered $P_{aw}$ and $\Delta P$. It would be unlikely that changing lung mechanics could exert such an influence on the recorded $\Delta P$.

To account for the variability in $\Delta P$ between $P_{aw}$ steps, the $V_T$, $V_{TRIP}$ and CO$_2$ data have been referenced to the corresponding $\Delta P$, where applicable.

4.3.4 Endotracheal tube leak

All infants were ventilated via an uncuffed ETT. Lung mechanics data measured at the airway opening were made during expiration and the presence of an ETT leak may have influenced the reliability of these data. Endotracheal tube leak, as determined by the Florian monitor was nearly always less than 10% throughout the study in all infants. The mean [SD] ETT leak was 6.7 [3.0] %. In the case of Infant 7, the ETT leak was 17.8% and 18.8% at two $P_{aw}$ steps during the inflation series.
Generally, there was no significant intra-subject variability in leak during the study. It is unlikely that an endotracheal tube leak of less than 10% would influence the lung mechanics data measured.

4.4 Haemodynamic data

All infants tolerated the study protocol well and no infant met cessation criteria because of low heart rate or blood pressure. Table 4-6 summarises the individual heart rate and blood pressure variations during the study.

There was no consistent relationship between $P_{aw}$ and either heart rate or blood pressure during the study protocol (Figure 4-3). The mean [SD] heart rate recorded for the entire study population was 156 [18.6] beats per minute. When heart rate at each $P_{aw}$ step was expressed as the change in heart rate from the heart rate at $P_{initial}$ the mean [SD] change was -1.8 [10.7] beats per minute. Whilst there was a wide range between the lowest and highest recorded change in heart rate, most values were closely related to the heart rate at $P_{initial}$. Overall, 68% of heart rate measurements were between ±10 beats per minute of the heart rate at $P_{initial}$ and 81% were between ±15 beats per minute of the heart rate at $P_{initial}$. The mean [SD] heart rate at $P_{final}$ was -4.1 [13] beats per minute lower than at $P_{initial}$.

In three infants (Table 4-6), complete arterial blood pressure data could not be collected due to difficulties with the indwelling arterial line. In the other 12 infants, MAP behaved in a similar manner as heart rate during the application of the open lung ventilation strategy. Overall, the mean [SD] MAP was 47.2 [6.9] mm Hg. When the MAP at each $P_{aw}$ step was expressed as the change from MAP at $P_{initial}$, the mean [SD] change was 0.8 [5.2] mm Hg, with 45% of all changes in MAP being within ±2 mmHg of the MAP at $P_{initial}$ and 75% within ±5 mmHg. The mean [SD] MAP at $P_{final}$ was 2.0 [7.0] mmHg above that at $P_{initial}$.
Table 4-6. Individual heart rate (HR) and mean arterial pressure (MAP) variations during the study.

<table>
<thead>
<tr>
<th>Infant</th>
<th>Initial HR</th>
<th>Mean (SD) change in HR from $P_{\text{initial}}$</th>
<th>Initial MAP</th>
<th>Mean (SD) of change in MAP from $P_{\text{initial}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>156</td>
<td>11 (8)</td>
<td>48</td>
<td>-1 (3)</td>
</tr>
<tr>
<td>2</td>
<td>133</td>
<td>-2 (4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>156</td>
<td>-5 (4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>165</td>
<td>-11 (13)</td>
<td>41</td>
<td>8 (8)</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>-8 (9)</td>
<td>30</td>
<td>3 (2)</td>
</tr>
<tr>
<td>6</td>
<td>159</td>
<td>6 (7)</td>
<td>47</td>
<td>0 (4)</td>
</tr>
<tr>
<td>7</td>
<td>162</td>
<td>-5 (2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>178</td>
<td>-4 (5)</td>
<td>46</td>
<td>-2 (3)</td>
</tr>
<tr>
<td>9</td>
<td>158</td>
<td>1 (18)</td>
<td>57</td>
<td>-1 (7)</td>
</tr>
<tr>
<td>10</td>
<td>118</td>
<td>4 (11)</td>
<td>48</td>
<td>-5 (5)</td>
</tr>
<tr>
<td>11</td>
<td>133</td>
<td>12 (6)</td>
<td>49</td>
<td>3 (4)</td>
</tr>
<tr>
<td>12</td>
<td>189</td>
<td>-6 (4)</td>
<td>52</td>
<td>3 (3)</td>
</tr>
<tr>
<td>13</td>
<td>158</td>
<td>-3 (8)</td>
<td>44</td>
<td>2 (2)</td>
</tr>
<tr>
<td>14</td>
<td>175</td>
<td>-7 (4)</td>
<td>44</td>
<td>1 (1)</td>
</tr>
<tr>
<td>15</td>
<td>176</td>
<td>11 (6)</td>
<td>48</td>
<td>-2 (3)</td>
</tr>
</tbody>
</table>

NA = incomplete MAP data
Figure 4-3. Scatter plots of $P_{aw}$ against changes in heart rate (A) and mean arterial pressure (B) from the value at $P_{initial}$. There was no relationship between either parameter and $P_{aw}$. In particular, a high $P_{aw}$ did not result in bradycardia or hypotension.
4.5 $P_{aw}$ and $SpO_2$ data at the end of the study

After the alveolar recruitment manoeuvre, at the end of the study, the mean [SD] final $P_{aw}$ was -1.2 [1.3] cm H$_2$O lower than at $P_{initial}$. The $SpO_2$ on completion of the study (after the post-study alveolar recruitment manoeuvre) was either the same or better than that at $P_{initial}$. The mean [SD] difference between the $SpO_2$ on completion of the study and the $SpO_2$ at $P_{initial}$ was 2.3 [3.1] %. The treating clinical team were not blinded to the results of the study. In all cases, it was the treating clinical team that determined the final $P_{aw}$ setting. This decision was made at the bedside after review of the preliminary oxygenation results.

4.6 Conclusion

In this chapter, the final study population reported in this thesis has been described. The group consisted of a heterogeneous population of 15 predominantly term infants receiving muscle relaxants and sedation. The heart rate and blood pressure data recorded during the study were described. No infant developed significant bradycardia or hypotension during the study protocol.

There was variability in the $\Delta P$ during each study protocol and, as a consequence, this will be accounted for in subsequent data analysis of measurements of $V_T$, $V_{TRIP}$, $C_t$, and $Tc_{CO2}$. In the subsequent five chapters the relationship between pressure, lung volume, gas exchange and lung mechanics data will be examined.
Chapter 5.
RELATIONSHIP BETWEEN MEAN AIRWAY PRESSURE AND LUNG VOLUME

5.1 Introduction
This chapter describes the relationship between $P_{aw}$ and change in lung volume, measured with RIP, during the application of the open lung ventilation strategy. Firstly, the raw data are presented for each individual infant, and then as pooled data. Secondly, the combined PV relationship from all infants is described using the normalised data. Finally, the goodness-of-fit between the combined data and a mathematical model of the PV relationship (Venegas et al 1998) is examined using nonlinear regression analysis.


5.2 Individual $P_{aw}$ – $V_{LRIP}$ relationships
Figure 5-1 shows the relationship between $P_{aw}$ and $V_{LRIP}$ in each infant. In each case $V_{LRIP}$, and thus relative lung volume, increased during the inflation series until $P_{max}$. When the data from all infants was pooled the $\Delta V_{LRIP}$ during the inflation series was significant with the mean [95% CI] $\Delta V_{LRIP}$ between $V_{LRIP}$ at $P_{max}$ and at $P_{initial}$ being 0.51 [0.33, 0.69] V. As the point within the PV relationship at commencement of the study was unknown, there was considerable variation in the number of $P_{aw}$ increases required to obtain $P_{max}$. The mean difference between the $P_{aw}$ at $P_{max}$ and $P_{initial}$ was 8.3 [6.6, 10.0] cm H$_2$O.

After identifying $P_{max}$, it was then possible to delineate a distinct deflation limb in each infant (Figure 5-1). Apart from Infants 1 and 13, all PV relationships exhibited hysteresis, with $V_{LRIP}$ values during the deflation series being greater than at the same $P_{aw}$ during the inflation series. The mean difference in $V_{LRIP}$ at $P_{initial}$ and at the same $P_{aw}$ during the deflation series was -0.34 [-0.17, -0.51] V. As
would be expected in a population with considerable heterogeneity in severity and type of lung disease, the degree of hysteresis was variable.

Figure 5-1. Individual $P_{aw}$ – $V_{LRIP}$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis is different in Infants 2, 3, 5, 10 and 14.
Of interest is that the greatest lung volume did not occur at $P_{\text{max}}$ in nine infants. In Infant 1, the greatest $V_{\text{LRIP}}$ value occurred during the inflation series at a $P_{\text{aw}}$ only 0.8 cm H$_2$O below $P_{\text{max}}$. In the other eight infants, the greatest $V_{\text{LRIP}}$ value occurred during the deflation series between 2.4 and 8.5 cm H$_2$O below the $P_{\text{aw}}$ resulting in $P_{\text{max}}$. Within the population as a whole, the mean $P_{\text{aw}}$ resulting in the greatest $V_{\text{LRIP}}$ value was 2.5 [0.9, 4.0] cm H$_2$O below $P_{\text{max}}$. The difference between the greatest $V_{\text{LRIP}}$ and the $V_{\text{LRIP}}$ at $P_{\text{max}}$ just reached significance; mean difference 0.03 [0.01, 0.06] V. In those infants in whom the greatest $V_{\text{LRIP}}$ did not occur at $P_{\text{max}}$, the mean difference was 0.05 [0.01, 0.09] V above the $V_{\text{LRIP}}$ value at $P_{\text{max}}$.

In many infants, lung volume remained close to the $V_{\text{LRIP}}$ value at $P_{\text{max}}$ over a wide range of mean airway pressures during the deflation series, as would be expected if ventilation was being applied near or on the deflation limb, and above the CCP of the lung. Overall, the first $P_{\text{aw}}$ value in which $V_{\text{LRIP}}$ was less than that at $P_{\text{max}}$ occurred at a mean of 5.0 [2.8, 7.1] cm H$_2$O below that of $P_{\text{max}}$. Furthermore, it was not until a mean $P_{\text{aw}}$ of 7.3 [5.4, 9.2] cm H$_2$O below that at $P_{\text{max}}$ that $V_{\text{LRIP}}$ had fallen to <85% of its value at $P_{\text{max}}$, this being a difference in which volume change could be considered clinically significant.

In 13 infants it was possible to identify a point of maximum curvature during the deflation series, the exceptions being Infants 13 and 15. This occurred at a mean [SD] $P_{\text{aw}}$ of 12.5 [2.8] cm H$_2$O, or -1.6 [3.0] cm H$_2$O below $P_{\text{initial}}$.

A large range of $P_{\text{aw}}$ settings were examined during the deflation series with the mean [SD] difference between $P_{\text{max}}$ and $P_{\text{final}}$ being 14.5 [2.8] cm H$_2$O. In three infants (Infants 2, 3 and 12), a lower $P_{\text{final}}$ may have been possible as, in these infants, $P_{\text{final}}$ was defined by reaching the lowest deliverable $P_{\text{aw}}$ on the oscillator, rather than oxygen desaturation (see Chapter 6). These infants were older infants in whom ventilation was being weaned.

The mean $P_{\text{aw}}$ at $P_{\text{final}}$ was 6.3 [5.3, 7.2] cm H$_2$O less than $P_{\text{initial}}$, with a range of 4.0 to 9.9 cm H$_2$O. Despite this difference, in nine infants lung volume was greater at $P_{\text{final}}$ than at $P_{\text{initial}}$, with the mean difference in $V_{\text{LRIP}}$ being 0.17 [0.07, 0.28] V. In the other six infants, the $P_{\text{aw}}$ during the deflation series in which $V_{\text{LRIP}}$ first fell below that at $P_{\text{initial}}$ was 1.6 [7.2, 4.0] cm H$_2$O less than $P_{\text{initial}}$, although the range of this difference was -6.7 to 8.2 cm H$_2$O.

86
5.3 Normalised pressure - volume relationship

To account for the variability in $P_{\text{initial}}$, $P_{\text{max}}$ and severity of lung disease, the airway pressure and volume data for each infant were normalised using the points of $P_{\text{max}}$ and $P_{\text{final}}$ as 100% and 0% respectively. Figure 5-2 shows the PV relationship, using normalised data, for all fifteen infants. This clearly illustrates the recruitment of lung volume during the inflation series, as the lung was taken to $P_{\text{max}}$. Thereafter, hysteresis was demonstrated and, at any given $P_{\text{aw}}$ value, $V_{LRIP}$ values were greater during the deflation series. The mean difference in the normalised $V_{LRIP}$ at the $P_{\text{aw}}$ during the deflation series that approximated $P_{\text{initial}}$, and the $V_{LRIP}$ at $P_{\text{initial}}$ was 80.8 [44.0, 117.6] % of the difference between the $V_{LRIP}$ at $P_{\text{max}}$ and $P_{\text{final}}$. There was no difference in the $P_{\text{aw}}$ values at these two points (mean difference -1.1 [-0.6, 2.8] %).

![Graph showing normalised $P_{aw}$ and $V_{LRIP}$ relationship](image.png)

**Figure 5-2.** $P_{aw} - V_{LRIP}$ relationship in 15 infants during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ and $V_{LRIP}$ data. Data expressed as mean and standard error of the mean.
The greatest $V_{LRIP}$ value (mean [SD] = 107.6 [12.3] %) did not occur at $P_{\text{max}}$ but at a $P_{aw}$ of 82.2 [18.8] % of $P_{\text{max}}$. During the deflation series, lung volume could be maintained at, or near to, $V_{LRIP}$ at $P_{\text{max}}$ over a wide range of airway pressures. $V_{LRIP}$ did not fall below that at $P_{\text{max}}$ until a mean [SD] $P_{aw}$ of 68.2 [23.3] % of $P_{\text{max}}$, and 85% of that at $P_{\text{max}}$ until a $P_{aw}$ of 52.2 [20.1] % of $P_{\text{max}}$. The point of maximum curvature occurred at a mean [SD] $P_{aw}$ resulting in 47.0 [1.7] % of the $P_{aw}$ difference between $P_{\text{max}}$ and $P_{\text{final}}$.

Once ventilation was applied on the deflation limb, a greater lung volume could be maintained, using a lower $P_{aw}$, than elsewhere within the PV relationship. The mean [SD] $V_{LRIP}$ at $P_{\text{final}}$ was 8.9 [56.8] % greater than at $P_{\text{initial}}$. This is despite the $P_{aw}$ at $P_{\text{initial}}$ being 44.4 [13.8] % greater than $P_{\text{final}}$, using the normalised data.

### 5.4 Mathematical modelling of the normalised pressure – volume relationship

During the deflation series, the normalised $P_{aw} – V_{LRIP}$ relationship appeared similar to the upper portion of a PV curve, and could be defined with a model of the PV relationship (Venegas et al 1998) using nonlinear regression analysis ($R^2 = 0.967$; Runs test $p$ value = 0.319), as shown in Figure 5-3A. It is possible, therefore, to conclude that during the deflation series ventilation was being applied on, or near, a portion of the deflation limb of the PV relationship.

This mathematical model could also be used to explain the inflation series data (Figure 5-3B); $R^2=0.987$ (Runs test $p = 1.0$). Unlike the deflation series, the starting point of the inflation series was not standardised. Thus, $P_{\text{initial}}$ may have been at any point within the PV relationship. This, and the smaller data set, limits the interpretation of this modelling.
Figure 5-3. Nonlinear regression analysis of deflation (A) and inflation (B) series, using normalised $P_{aw}$ and $V_{LRIP}$ data fitted to the sigmoid model of the PV relationship proposed by Venegas et al (1998). Solid line represents the best-fit curve and dotted lines 95% CI of the curve. Small closed circles (A) and open diamonds (B) represent individual PV values. Large closed circles (A) and open diamonds (B) represent mean PV values, and error bars standard error of the mean, as shown in Figure 5-2.
5.5 Conclusion

In this chapter, the $P_{aw}$ and $\Delta V_{LRIP}$ data, and the relationship between these two parameters, has been described. During the application of an open lung strategy, it was possible to show that lung volume increased until $P_{max}$. Thereafter, a portion of the deflation limb of the PV relationship could be mapped. The PV relationship in most infants demonstrated hysteresis, such that, at any given $P_{aw}$, lung volume was greater on the deflation limb than during the inflation series. In many cases, by applying ventilation on the deflation limb, a better lung volume could be achieved using a lower $P_{aw}$ than at $P_{initial}$. Once upon the deflation limb, recruited lung volume could be maintained over a wide range of $P_{aw}$ values.
Chapter 6.

RELATIONSHIP BETWEEN OXYGENATION, MEAN AIRWAY PRESSURE AND LUNG VOLUME

6.1 Introduction

This chapter describes the relationship between oxygenation, expressed as SpO₂, and both Paw and lung volume during the application of the open lung ventilation strategy. Firstly, the raw Paw – SpO₂ and Vₐₑₑ₀ – SpO₂ data are presented for each infant, and then as pooled results. Secondly, the combined relationships from all infants are described using the normalised PV data. Finally, the potential of the proposed mathematical models to define the Paw – SpO₂ and Vₐₑₑ₀ – SpO₂ relationships are examined using nonlinear regression analysis.


6.2 Relationship between SpO₂ and Paw

In Figure 6-1, the plots of Paw against SpO₂ from each infant are shown. The relationship between Paw and SpO₂ was variable. Generally, the greatest SpO₂ occurred during the deflation series, but not at Pₘₐₓ. In ten of the infants, the relationship between Paw and SpO₂ resembled a typical PV relationship. In most infants, during the inflation series, SpO₂ initially improved as Paw was increased, although this was not the case in five infants. Like the PV relationships shown in Figure 5-1, hysteresis was demonstrated in many of the Paw – SpO₂ relationships. This is reflected by a mean improvement in SpO₂ of 2.7 [1.1, 4.3] % from Paw when ventilation was applied at the same Paw during the deflation series.
Figure 6-1. Individual $P_{aw}$ – $SpO_2$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph.
The maximum $\text{SpO}_2$ occurred during the deflation series in all but two infants (Infant 4 and 7), and was better than that at $P_{\text{initial}}$ in all but Infant 7. In these two infants, the greatest $\text{SpO}_2$ value occurring during the deflation series was very close to the overall maximum $\text{SpO}_2$ value obtained during the study. There was no difference in the mean [SD] maximum $\text{SpO}_2$ of 96.5 [2.8] % recorded from only the deflation series data and the mean [SD] maximum $\text{SpO}_2$ from the entire data series of 96.9 [2.6] %.

In most infants, a bell-shaped relationship between $P_{aw}$ and $\text{SpO}_2$ existed during the deflation series, such that $\text{SpO}_2$ initially improved as $P_{aw}$ was decreased from $P_{\text{max}}$, and then deteriorated from the maximum value as $P_{aw}$ approached $P_{\text{final}}$. The mean maximum $\text{SpO}_2$ identified during the deflation series was 2.7 [1.3, 4.1] % greater than the $\text{SpO}_2$ at $P_{\text{max}}$.

In some infants, once ventilation was applied on the deflation limb, $\text{SpO}_2$ changed very little until the $P_{aw}$ neared $P_{\text{final}}$ (Figure 6-1). In many infants, this resulted in $\text{SpO}_2$ remaining close, or equal, to the value at the maximum $\text{SpO}_2$ obtained through a wide range of $P_{aw}$ values, rather than at a discrete single $P_{aw}$. $\text{SpO}_2$ differed from the maximum $\text{SpO}_2$ by <1% for more than five consecutive $P_{aw}$ changes in six infants (Infants 2, 3, 6, 12 and 13). In most infants, the range of pressures resulting in essentially maximum $\text{SpO}_2$ did not include $P_{\text{max}}$. Using the pooled data, the upper and lower $P_{aw}$ defining the range of pressures that resulted in near-maximum $\text{SpO}_2$ were 4.9 [3.1, 6.7] cm H$_2$O and 6.6 [4.3, 8.8] cm H$_2$O below $P_{\text{max}}$. This translated to a $P_{aw}$ range of 8.0 [5.6, 10.3] cm H$_2$O to 9.6 [7.3, 12.0] cm H$_2$O above $P_{\text{final}}$.

Overall, once ventilation was being applied on the deflation limb, a better $\text{SpO}_2$ could be achieved at a lower $P_{aw}$. After the maximum $\text{SpO}_2$ was obtained during the deflation series, $\text{SpO}_2$ did not fall below the $\text{SpO}_2$ at $P_{\text{initial}}$ until a mean [SD] $P_{aw}$ that was 4.3 [2.6] cm H$_2$O less than $P_{\text{initial}}$. In three infants (Infants 2, 3 and 12), $\text{SpO}_2$ remained above 90%, and above $\text{SpO}_2$ at $P_{\text{initial}}$ during the entire deflation series, despite $P_{\text{final}}$ representing the lowest possible $P_{aw}$ setting on the oscillator.
6.3 *Relationship between* \( \text{SpO}_2 \) *and* \( V_{LRIP} \)

The individual \( V_{LRIP} - \text{SpO}_2 \) plots are shown in Figure 6-2. During the inflation series, the relationship between \( \text{SpO}_2 \) and \( V_{LRIP} \) was variable. In ten infants, \( \text{SpO}_2 \) increased as lung volume increased, suggesting alveolar recruitment. In the other six infants, \( \text{SpO}_2 \) decreased, possibly due to overdistension.

During the deflation series, the relationship between \( V_{LRIP} \) and \( \text{SpO}_2 \) was not linear. After the maximum \( V_{LRIP} \) value was obtained, \( \text{SpO}_2 \) continued to increase, such that the maximum \( \text{SpO}_2 \) value was always at a lung volume less than that at the maximum \( V_{LRIP} \). The mean difference in these volumes was 0.06 [0.03, 0.08] V, and resulted in a mean increase in \( \text{SpO}_2 \) of 1.1 [0.5, 1.7] %. The mean [SD] \( P_{aw} \) resulting in the upper and lower range of near-maximum \( \text{SpO}_2 \) was 2.8 [1.8] cm H\(_2\)O to 4.1 [3.0] cm H\(_2\)O below the \( P_{aw} \) resulting in the greatest \( V_{LRIP} \) value.

In many infants, it was possible to use \( \text{SpO}_2 \) as a proxy indicator of derecruitment as \( P_{aw} \) was being withdrawn from the recruited lung. After the maximum \( \text{SpO}_2 \) was obtained, \( \text{SpO}_2 \) fell as \( V_{LRIP} \) decreased until \( P_{\text{final}} \). The rate of decline in \( \text{SpO}_2 \) was variable but in many infants it was possible to determine a distinct lung volume at which the slope of the \( V_{LRIP} - \text{SpO}_2 \) relationship changed, as would be expected if the lung was being ventilated close to the CCP.
Figure 6-2. Individual $V_{LRIP}$ – $Sp_{O2}$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X-axis range differ in Infants 2, 3, 5, 7 and 10.
6.4 Relationship between \( \text{SpO}_2 \) and the PV relationship using normalised data

The relationship between \( \text{SpO}_2 \) and both \( P_{aw} \) and \( V_{LRIP} \), using normalised data, is shown in Figures 6-3A and 6-3B respectively. The normalised \( P_{aw} - \text{SpO}_2 \) relationship closely resembled a PV relationship. The only major difference being that the point of maximum curvature during the deflation series occurred at a \( P_{aw} \) approximately 25% of the \( P_{aw} \) difference between \( P_{\text{max}} \) and \( P_{\text{final}} \). \( \text{SpO}_2 \) remained essentially the same over a wide range of pressures from \( P_{\text{max}} \) until the point of maximum curvature during the deflation series. At pressures of between 20 and 85% of \( P_{\text{max}} \), the \( \text{SpO}_2 \) values were between 94% and 96%. During the same \( P_{aw} \) range, \( V_{LRIP} \) decreased from 100% to 49% of the \( V_{LRIP} \) difference between \( P_{\text{max}} \) and \( P_{\text{final}} \). This suggests that, whilst a good indicator of atelectasis and overdistension, \( \text{SpO}_2 \) lacks the precision to reliably determine a distinct point of optimal ventilation upon the deflation limb.

During the initial stages of the inflation series, \( \text{SpO}_2 \) increased with normalised volume, suggesting alveolar recruitment. Later in the inflation series, there was no gain in \( \text{SpO}_2 \) with increasing volume. This implies that overdistension was likely to be the prominent process as the lung approached the volume at \( P_{\text{max}} \). The normalised \( V_{LRIP} - \text{SpO}_2 \) relationship was different during the deflation series. As shown in Figure 6-3B, \( \text{SpO}_2 \) was essentially unchanged during the deflation series until a \( V_{LRIP} \) of 48% of the \( V_{LRIP} \) difference between \( P_{\text{max}} \) and \( P_{\text{final}} \). At this point, there was a distinct change in the slope of the relationship such that \( \text{SpO}_2 \) deteriorated with each fall in volume.

The normalised \( P_{aw} - \text{SpO}_2 \) data could be fitted to the mathematical model proposed by Venegas et al (1998) using nonlinear regression during the inflation \( (R^2 = 0.916) \) and deflation \( (R^2 = 0.869) \) series (Figure 6-4 A and B). This model also closely fitted the normalised \( V_{LRIP} - \text{SpO}_2 \) data during the inflation series \( (R^2 = 0.917) \) and deflation series \( (R^2 = 0.831) \). The 95% CI widened at \( P_{aw} \) and \( V_{LRIP} \) values near \( P_{\text{final}} \). This can be explained by the failure of \( \text{SpO}_2 \) to fall below 85% at \( P_{\text{final}} \) in some infants. Furthermore, the use of the Venegas et al (1998) model to explain the relationship between \( \text{SpO}_2 \) and the volume state of the lung has limited clinical utility, as it does not identify an optimal point, or region, of ventilation and is dependent on identifying the CCP.
Relationship between $\text{SpO}_2$, $P_{aw}$, and $V_{LRIP}$

Figure 6-3. A. $P_{aw}$ - $\text{SpO}_2$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $V_{LRIP}$ - $\text{SpO}_2$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ data. Data expressed as mean and standard error of the mean.
The $P_{aw} - \text{SpO}_2$ and $V_{LRIP} - \text{SpO}_2$ relationships could also be defined using a quadratic model, as shown in Figures 6-4. During the deflation series, nonlinear regression analysis indicated a bell-shaped relationship between $\text{SpO}_2$ and both $P_{aw}$ and $V_{LRIP}$, with a strong goodness-of-fit ($R^2 = 0.778$ and 0.838 respectively). Importantly, using the quadratic model, the 95% CI (Figure 6-4 B and D) remained tight throughout the entire deflation series data range. This suggests that clinicians could exploit these bell-shaped relationships to identify a region of optimum ventilation, once ventilation is being applied on the deflation limb.

**Figure 6-4.** Nonlinear regression analysis of the data presented in Figure 6-3, using the sigmoid model of the PV relationship (blue lines [Venegas et al 1998]) and a quadratic model (red lines). A. Normalised $P_{aw} - \text{SpO}_2$ relationship during the inflation series. B. Normalised $P_{aw} - \text{SpO}_2$ relationship during the deflation series. C. Normalised $V_{LRIP} - \text{SpO}_2$ relationship during the inflation series. D. Normalised $V_{LRIP} - \text{SpO}_2$ relationship during the deflation series. Solid line represents the best fit curve and dotted lines 95% CI of the curve. In all cases, the resultant curves did not significantly deviate from the data ($p$ values 0.191 to 0.743; Runs tests).
6.5 Conclusion

In this chapter, the relationships between oxygenation, and both $P_{aw}$ and lung volume are described whilst the lung was taken through an open lung ventilation strategy. During inflation to TLC, $SpO_2$ initially improved but then deteriorated. This suggests that $SpO_2$ may aid clinicians determine when recruitment ceases to be the major contributor to volume change, and overdistension predominates. Oxygenation was influenced by hysteresis such that, once ventilation was applied on the deflation limb, $SpO_2$ was better than during the inflation series and, in most infants, remained so between TLC and CCP.

Nonlinear regression analysis confirmed that $SpO_2$ was dependent on the volume state of the lung. In most infants, $SpO_2$ could be used as a proxy for lung volume during HFOV in infants. There was little difference in oxygenation between the pressures defining 25 – 85% of the $P_{aw}$ difference between TLC and CCP. This indicates that, whilst a good indicator of recruitment, overdistension and atelectasis, SpO$_2$ does not have the precision to identify a distinct point of optimum ventilation.
Chapter 7.

RELATIONSHIP BETWEEN QUASI-STATIC COMPLIANCE, MEAN AIRWAY PRESSURE AND LUNG VOLUME

7.1 Introduction

This chapter describes the relationship between an indicator of quasi-static $C_{rs}$ and both $P_{aw}$ and lung volume during the application of the open lung ventilation strategy. Firstly, the raw data for the relationships between $C_{rs}$, $P_{aw}$ and $V_{LRIP}$ are presented for each infant, and then the pooled results are described. Secondly, the combined relationships from all infants are described using the normalised PV data. Finally, the ability of nonlinear models to define the relationships between $C_{rs}$ and both $P_{aw}$ and $V_{LRIP}$ are examined.

As detailed in Chapter 3.8.5, quasi-static $C_{rs}$ was calculated using the Mead – Whittenberger equation ($C_{rs} = \Delta V_L/\Delta P$). In this study, absolute lung volume was not measured. Rather, $\Delta V_L$ from a baseline lung volume at $P_{initial}$ was measured using uncalibrated RIP in Volts. As a result, comparison of lung volume in mL, and thus $C_{rs}$ in mL/cm H$_2$O, was not possible.

Furthermore, using uncalibrated RIP data does not necessarily allow consistent inter-subject comparison. To combine these data, $C_{rs}$ has been expressed using the normalised $V_{LRIP}$ and $P_{aw}$ data, both expressed as a percentage, for the purpose of generating and combining the combined data. This method still does not allow comparison of absolute $C_{rs}$ but rather indicates relative change in $C_{rs}$ through the PV relationship. As an example, for Infant 1 during the inflation series, when $P_{aw}$ was increased from 18.4 to 19.8 cm H$_2$O the resultant $V_{LRIP}$ increased from 0.6 to 0.7 V.

Thus, $C_{rs} = (0.7 – 0.6) V/(19.8 – 18.4) \text{ cm H}_2\text{O}$.

This would result in a quasi-static $C_{rs}$ of 0.071 V/cm H$_2$O.
Using the normalised data for the same data points, the $P_{aw}$ changed from 72.9 to 86.6% of the $P_{aw}$ difference between $P_{max}$ and $P_{final}$. This resulted in a volume increase from 81.7 to 98.5% of the $V_{LRIP}$ difference between $P_{max}$ and $P_{final}$.

Using these normalised data:

$$C_{rs} = \frac{[98.5-81.7]}{[86.6-72.9]} \%$$

$$C_{rs} = 1.2$$

This is a value without units rather than a percentage. To prevent confusion, the $C_{rs}$ data is expressed as ‘arbitrary units’ (a.u.), a similar method has been employed previously by Brazelton et al (2001) and Weber et al (2000) to describe uncalibrated RIP data. The $C_{rs}$ at $P_{initial}$ has been nominally termed 0 a.u. and, thus, all $C_{rs}$ data can be expressed as the change from $C_{rs}$ at $P_{initial}$.

### 7.2 Relationship between $C_{rs}$ and $P_{aw}$

In Figure 7-1, the plots of $P_{aw}$ against $C_{rs}$ for each infant are shown. The individual $P_{aw}$ - $C_{rs}$ relationships were variable. In particular, there were outlying data points in some infants (as illustrated in Infant 15) that may represent erroneous data.

In all infants, $C_{rs}$ increased during the inflation series, such that $C_{rs}$ at $P_{initial}$ was the lowest value, or close to it, during the inflation series. Despite this, $C_{rs}$ at $P_{max}$ was not the maximum $C_{rs}$ during the inflation series in 13 infants. This may have been due to overdistension occurring near $P_{max}$ in these infants, although the changes were small and $C_{rs}$ at $P_{max}$ was not significantly different from the $C_{rs}$ at $P_{initial}$; mean difference 0.06 (-0.04, 0.16) V/cm H$_2$O.

Unlike the other parameters measured, hysteresis was not clearly identifiable in the $P_{aw}$ - $C_{rs}$ relationships after the lung was recruited to $P_{max}$. The mean $C_{rs}$ at $P_{initial}$ was -0.04 (-0.14, 0.06) V/cm H$_2$O less than at the same $P_{aw}$ during the deflation series. In all but Infant 13, $C_{rs}$ during the deflation series was initially less than during the inflation series. Regardless of this, $C_{rs}$ generally increased during the deflation series, with the maximum $C_{rs}$ occurring near $P_{final}$, even accounting for outliers. The mean [SD] maximum $C_{rs}$ was 0.22 [0.19] V/cm H$_2$O. This was not significantly different from the mean [SD] maximum $C_{rs}$ during the deflation series of 0.21 [0.19] V/cm H$_2$O. The maximum $C_{rs}$ during the deflation series was significantly higher than the $C_{rs}$ at $P_{initial}$; mean difference 0.21 (0.11, 0.31) V/cm
**Relationship between $C_{rs}$, $P_{aw}$ and $V_{LRIP}$**

H$_2$O. Maximum $C_{rs}$ during the deflation series was more than double the $C_{rs}$ at both $P_{\text{max}}$ and $P_{\text{final}}$; mean difference 0.15 (0.05, 0.25) V/cm H$_2$O and 0.14 (0.04, 0.24) V/cm H$_2$O, respectively.

Figure 7-1. Individual $P_{aw}$ – quasi-static $C_{rs}$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants.
Relationship between $C_{rs}$, $P_{aw}$ and $V_{LRIP}$

The $P_{aw}$ resulting in the maximum $C_{rs}$ during the deflation series was 9.3 (5.4, 13.2) cm H$_2$O less than $P_{max}$, and 5.2 (1.3, 9.1) cm H$_2$O greater than $P_{final}$. This $P_{aw}$ was not significantly different from either $P_{initial}$ or the same $P_{aw}$ as $P_{initial}$ during the deflation series; mean difference -1.1 (-5.0, 2.9) cm H$_2$O and -0.9 (-4.8, 3.0) cm H$_2$O respectively. The $P_{aw}$ resulting in the optimal Sp$_{O2}$ during the deflation series was 4.7 (0.8, 8.6) cm H$_2$O greater than the $P_{aw}$ resulting in the maximum $C_{rs}$. The point of optimal Sp$_{O2}$ resulted in a $C_{rs}$ that was 0.21 (0.11, 0.31) V/cm H$_2$O less than the maximum $C_{rs}$ during the deflation series.

7.3 Relationship between $C_{rs}$ and $V_{LRIP}$

The individual $V_{LRIP}$ - $C_{rs}$ relationships are shown in Figure 7-2. There was considerable variability within and between individual infants. Overall, the relationships were similar to the $P_{aw}$ - $C_{rs}$ plots shown in Figure 7-1. In all infants, $C_{rs}$ initially increased during the inflation series, from the value at $P_{initial}$, as $V_{LRIP}$ increased. Only in Infant 15, did the $V_{LRIP}$ at $P_{max}$ correspond to the maximum $C_{rs}$ during the inflation series. This suggests that, in the other 14 infants, alveolar recruitment was occurring in the early phases of the inflation series. Later in the inflation series, as the lung approached $P_{max}$, the gains in $V_{LRIP}$ were most likely associated with overdistension.

There was minimal, if any, improvement in $C_{rs}$ during the deflation series compared to the inflation series. In most infants, $C_{rs}$ improved sequentially as $V_{LRIP}$ decreased during the deflation series, with the $V_{LRIP}$ at the point of maximum $C_{rs}$ being more closely related to the $V_{LRIP}$ at $P_{final}$ than the $V_{LRIP}$ at $P_{max}$; mean difference 0.20 (0.01, 0.39) V and -0.30 (-0.11, -0.49) V respectively. During the deflation series, the point of maximum $V_{LRIP}$ was 0.32 (0.14, 0.51) V greater than the $V_{LRIP}$ at the point of maximum $C_{rs}$. But, the $C_{rs}$ at the point of maximum $V_{LRIP}$ was 0.19 (0.09, 0.29) V/cm H$_2$O less than the maximum $C_{rs}$. There was no difference in the $C_{rs}$ at the point of maximum $V_{LRIP}$ and optimal Sp$_{O2}$ during the deflation series.
Figure 7-2. Individual $V_{LRIP}$ – quasi-static $C_{rs}$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X- and Y-axis range differs between infants.
7.4 Relationship between \( C_{rs} \) and the PV relationship using normalised data

The relationships between change in quasi-static \( C_{rs} \), and both \( P_{aw} \) and \( V_{L RIP} \), using normalised data from all 15 infants, are shown in Figures 7-3A and 7-3B respectively. The inflation series data illustrate the response seen in many of the individual plots, \( C_{rs} \) initially increased as both \( P_{aw} \) and \( V_{L RIP} \) were increased from the values at \( P_{initial} \). Later in the inflation series, \( C_{rs} \) then decreased as the \( P_{aw} \) and \( V_{L RIP} \) approached \( P_{max} \). This was particularly evident in the \( V_{L RIP} - C_{rs} \) relationship. The mean [SD] maximum change in \( C_{rs} \) during the inflation series of 3.1 [2.5] a.u. occurred at a pressure and volume of 78.2 [1.9]% and 57.1 [16.8]% of each value’s respective difference between \( P_{max} \) and \( P_{final} \).

During the deflation series, quasi-static \( C_{rs} \) improved as \( P_{aw} \), and consequently \( V_{L RIP} \), were decreased from the resultant values at \( P_{max} \). The mean [SD] maximum change in \( C_{rs} \) from \( P_{initial} \) of 3.2 [1.8] a.u. occurred during the deflation series at a mean [SD] \( P_{aw} \) and \( V_{L RIP} \) of 38.5 [1.0]% and 53.7 [15.2]% of each value’s respective difference between \( P_{max} \) and \( P_{final} \). It is possible that the point of maximum change in \( C_{rs} \) from \( P_{initial} \) was influenced by the outlier data noted in Figures 7-1 and 7-2. The next highest \( C_{rs} \) result of 3.0 [2.7] a.u. occurred at a \( P_{aw} \) and \( V_{L RIP} \) of 4.5 [1.2]% and 7.0 [4.8]% of the respective values at \( P_{max} \). This point appears more consistent with the general trend, and the \( C_{rs} \) values at neighbouring \( P_{aw} \) and \( V_{L RIP} \) points within the deflation series. Whilst it appears that the \( C_{rs} \) at \( P_{final} \) was less than the preceding values, it is impossible to determine whether this represents the fall in \( C_{rs} \) expected at the CCP or is simply due to the variability within the data set.

During the deflation series, \( C_{rs} \) was generally lower at pressures greater than 50% of the \( P_{aw} \) difference between \( P_{max} \) and \( P_{final} \). This suggests that, once ventilation is applied on the deflation limb, clinicians should target a \( P_{aw} \) between \( P_{final} \) and 50% of the \( P_{aw} \) difference between \( P_{max} \) and \( P_{final} \) to optimise \( C_{rs} \). More specifically, in these data, targeting a \( P_{aw} \) of between 20 – 50% of the \( P_{aw} \) difference between \( P_{max} \) and \( P_{final} \) would result in ventilation approaching both optimal \( C_{rs} \) and the lower range of pressures that optimised \( \text{SpO}_2 \).
Figure 7-3. A. $P_{aw}$ - quasi-static $C_{rs}$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $V_{LRIP}$ – quasi-static $C_{rs}$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ data. Quasi-static $C_{rs}$ data expressed as the change from the value at $P_{initial}$. All data expressed as mean and standard error of the mean.
The inflation series $P_{aw} - C_{rs}$ and $V_{LRIP} - C_{rs}$ data were poorly defined by the model proposed by Venegas et al (1998); $R^2$ of 0.547 and 0.621 respectively (Figure 8-4A and C). This model could not be fitted to the deflation series data.

Figure 7-4. Nonlinear regression analysis of the data presented in Figure 7-3 using a quadratic model (red lines). A. Normalised $P_{aw}$ – quasi-static $C_{rs}$ relationship during the inflation series. B. Normalised $P_{aw}$ – quasi-static $C_{rs}$ relationship during the deflation series. C. Normalised $V_{LRIP}$ – quasi-static $C_{rs}$ relationship during the inflation series. D. Normalised $V_{LRIP}$ – quasi-static $C_{rs}$ relationship during the deflation series. Data is also analysed using a sigmoid model of the PV relationship (blue lines; Venegas et al 1998) in Fig 7-4A and 7-4C. Solid lines represent the best-fit curve and dotted lines 95% CI of the curve. In all cases the resultant curves did not significantly deviate from the data (Runs test $p$ values 0.32 to 0.64)
The quadratic model could be used to define the quasi-static $C_{rs}$ data with tight 95% confidence intervals, but the resultant goodness-of-fit was poor (Figure 8-4 A–D). Nonlinear regression analysis of the quadratic model resulted in $R^2$ values of 0.585 and 0.674 for the $P_{aw} - C_{rs}$ and $V_{LRIP} - C_{rs}$ inflation series data. During the deflation series, the quadratic model resulted in $R^2$ values of 0.507 and 0.477 for the respective $P_{aw} - C_{rs}$ and $V_{LRIP} - C_{rs}$ relationships. The quadratic model produced a U-shaped curve rather than the predicted bell-shaped relationship during the deflation series $P_{aw} - C_{rs}$ data. This result was surprising but is explained by the early deterioration in $C_{rs}$ during the deflation series. The $V_{LRIP} - C_{rs}$ data does not appear to be consistent with any nonlinear mathematical model.

7.5 Conclusion

In this chapter, the relationships between an indicator of quasi-static $C_{rs}$ and both $P_{aw}$ and $V_{LRIP}$ have been described whilst the lung was taken through an open lung ventilation strategy. The $P_{aw} - C_{rs}$ and $V_{LRIP} - C_{rs}$ relationships were variable between infants. In many infants, there was minimal change in $C_{rs}$ throughout the portion of the PV relationship described and the data were compromised by outlying values. Despite the minimal change in $C_{rs}$ during the open lung ventilation strategy, some trends were apparent. During the inflation series, $C_{rs}$ initially improved then deteriorated as $P_{aw}$ increased, suggesting a change from alveolar recruitment to overdistension. Generally, during the deflation series, $C_{rs}$ improved as $P_{aw}$ was decreased from $P_{max}$ with the maximum $C_{rs}$ being achieved at $P_{aw}$ values associated with $P_{final}$ and the lower pressures that resulted in optimal oxygenation.

Whether these trends in relative $C_{rs}$ translate to clinically important differences cannot be determined from this study. The inconsistencies noted within the $C_{rs}$ data, and the difficulties in determining $C_{rs}$ at the bedside during HFOV, currently limit the application of this parameter as an aid to determining the optimal point of ventilation in clinical practice.
Chapter 8.

RELATIONSHIP BETWEEN TIDAL VOLUME, MEAN AIRWAY PRESSURE AND LUNG VOLUME

8.1 Introduction

This chapter describes the relationship between tidal volume and both $P_{aw}$ and lung volume during the application of the open lung ventilation strategy. The data for tidal volume measured at the airway opening during expiration ($V_T$) and from RIP ($V_{TRIP}$) are presented. Unlike conventional modalities of ventilation, during HFOV the tidal variation in peak to trough volume is attenuated down the tracheobronchial tree (Gerstmann et al 1990). Hence, $V_T$ cannot be considered the same as the alveolar tidal volume. Despite this, $V_T$ has been validated as a reliable indicator of relative change in alveolar tidal volume during HFOV (Scalfaro et al 2001). RIP has been used to measure tidal ventilation in self-ventilating infants (Dolfin et al 1982; Duffty et al 1981) and it is reasonable to expect that RIP should be able to do so during HFOV. RIP allows breath to breath measurement of relative change in lung volume, and bench-testing showed that it could detect small tidal volume changes (see Chapter 3.8.3).

For both $V_T$ and $V_{TRIP}$, firstly the raw data for the relationship between tidal volume and $P_{aw}$, and tidal volume and $V_{LRIP}$ are presented for each individual infant, and then the pooled results are described. Tidal volume is expressed as mL/kg in the case of the $V_T$ data and voltages (from the uncalibrated RIP) in the case of $V_{TRIP}$. To account for any intra-subject variation in $\Delta P$, both the $V_T$ and $V_{TRIP}$ data have been defined as the ratio between the tidal volume parameter and $\Delta P$.

Secondly, the combined relationships from all infants are described using the normalised PV data. To allow inter-subject comparison, the combined $V_{TRIP}$ data have been normalised, with 100% representing the maximum $V_{TRIP}$ value and 0% the minimum $V_{TRIP}$ value occurring for each infant during the application of the open lung ventilation strategy. The ability of a quadratic model to define the relationships between the two measures of tidal volume, $P_{aw}$ and $V_{LRIP}$ is then described. Finally, the $V_T$ and $V_{TRIP}$ data are compared in each infant using linear regression.
8.2 Relationship between tidal volume and $P_{aw}$

8.2.1 Relationship between $V_T$ and $P_{aw}$

In Figure 8-1, the $P_{aw} - V_T/\Delta P$ plots for each infant are shown. In all but Infants 1 and 5, the maximum $V_T/\Delta P$ value during the inflation series did not occur at $P_{max}$. This suggests overdistension and impairment of tidal ventilation at high $P_{aw}$ values in these 13 infants. In eight of these infants, $V_T$ decreased as $P_{aw}$ was sequentially increased to $P_{max}$. In five infants (3, 4, 6, 8 and 12), $V_T$ initially improved with increasing $P_{aw}$ but deteriorated as $P_{max}$ was approached. In Infant 1, there was no discernable variation in $V_T$ during the inflation series. Overall, the mean $V_T/\Delta P$ at $P_{max}$ was 0.01 (-0.03, 0.03) mL.kg$^{-1}$/cm H$_2$O lower than at $P_{initial}$. This does not translate to a clinically significant difference, as illustrated in Table 8-1.

In only one infant (Infant 7) was the $V_T$ lower during the entire deflation series than the inflation series. In all other infants, $V_T$ exhibited a varying degree of hysteresis. In seven infants, the $V_T$ was greater during the entire deflation series compared to the inflation series. In the remaining six infants, there was an improvement in $V_T$ within a small range of $P_{aw}$ during the deflation series. The maximum $V_T/\Delta P$ value for the entire data set occurred during the deflation series in all but Infant 12. The mean [SD] maximum $V_T/\Delta P$ value from the entire data set of 0.14 [0.07] mL.kg$^{-1}$/cm H$_2$O was the same as the mean [SD] maximum $V_T/\Delta P$ value from the deflation series data alone. The mean difference between the maximum $V_T/\Delta P$ during the deflation series and the value at $P_{initial}$ was 0.03 (0.00, 0.05) mL.kg$^{-1}$/cm H$_2$O. Using the median $\Delta P$ from the entire subject population of 34 cm H$_2$O as a clinical example, this difference translates to an improvement in $V_T$ of 1.0 mL/kg, or an increase of 30% from the median $V_T$ at $P_{initial}$, from all 15 infants, of 2.4 mL/kg.
Figure 8-1. Individual $P_{aw}$ – $V_T/\Delta P$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants.
Table 8-1. Relationship between $P_{aw}$, $V_T$, $V_{TRIP}$ and $\Delta P$ during the entire open lung ventilation strategy in Infant 3 (weight = 2.25 kg). $P_{max}$ is illustrated in grey.

<table>
<thead>
<tr>
<th>$P_{aw}$ (cm H$_2$O)</th>
<th>$V_T$ (mL)</th>
<th>$V_{TRIP}$ (V)</th>
<th>$\Delta P$ (cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5</td>
<td>5.0</td>
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<td>44.4</td>
</tr>
<tr>
<td>15.4</td>
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<td>16.5</td>
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<td>43.2</td>
</tr>
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<td>40.9</td>
</tr>
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<td>0.07</td>
<td>39.3</td>
</tr>
<tr>
<td>18.7†</td>
<td>6.6</td>
<td>0.09‡</td>
<td>39.5</td>
</tr>
<tr>
<td>16.7</td>
<td>6.7*</td>
<td>0.09‡</td>
<td>39.3</td>
</tr>
<tr>
<td>14.5</td>
<td>6.5</td>
<td>0.09‡</td>
<td>40.9</td>
</tr>
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<td>6.2</td>
<td>0.08</td>
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<td>5.8</td>
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<td>7.2</td>
<td>5.0</td>
<td>0.07</td>
<td>45.3</td>
</tr>
<tr>
<td>6.2</td>
<td>5.1</td>
<td>0.05</td>
<td>45.8</td>
</tr>
</tbody>
</table>

The maximum $V_T$ (*) occurred during the deflation series. This was 1.7 mL better than the initial $V_T$. † Indicates the $P_{aw}$ that resulted in the maximum $V_{LRIP}$. ‡ Indicates the $P_{aw}$ resulting in the maximum $V_{TRIP}$.

In none of the infants did the maximum $V_T/\Delta P$ value during the deflation series occur at $P_{max}$. In 13 of the 14 infants in whom hysteresis was demonstrated, the relationship between $P_{aw}$ and $V_T$ during the deflation series was bell-shaped with the maximum $V_T/\Delta P$ occurring between, but not at, $P_{max}$ and $P_{final}$. The exception was Infant 1, in whom the maximum $V_T/\Delta P$ value occurred at $P_{final}$ and there was a U-shaped, or inverse bell-shaped, relationship between $P_{aw}$ and $V_T$. The mean maximum $V_T/\Delta P$ value during the deflation series was significantly greater than the $V_T/\Delta P$ value at $P_{max}$ and $P_{final}$: mean difference 0.03 (0.01, 0.05) mL.kg$^{-1}$/cm H$_2$O and 0.03 (0.01, 0.06) mL.kg$^{-1}$/cm H$_2$O respectively. There was no difference between the $V_T$ values at $P_{max}$ and $P_{final}$. 

112
The difference between the $P_{aw}$ resulting in optimum $V_T/\Delta P$ during the deflation series, and the $V_T/\Delta P$ at $P_{max}$ and $P_{final}$ was significant; mean difference -9.4 (-12.7, 6.1) cm H$_2$O and 5.1 (1.8, 8.4) cm H$_2$O respectively. The mean $P_{aw}$ resulting in optimum $V_T$ during the deflation series was 4.8 (1.5, 8.0) cm H$_2$O lower than the $P_{aw}$ resulting in the optimum $Sp_{O2}$. This resulted in an improvement in $V_T/\Delta P$ of 0.02 (0.01, 0.04) mL.kg$^{-1}$/cm H$_2$O from the $V_T/\Delta P$ at the point of maximum $Sp_{O2}$, or 0.58 (0.36, 0.77) mL/kg using the earlier example with a $\Delta P$ of 34 cm H$_2$O. The mean [SD] $Sp_{O2}$ at the point of optimum $V_T$ was 92.4 [6.2] %, which was 4.1 (1.5, 6.7) % lower than the point of maximum $Sp_{O2}$. As described in Chapter 6, during the deflation series the $Sp_{O2}$ remained at, or near, its maximum value over a range of $P_{aw}$ values. Using the lowest possible $P_{aw}$ in this range of near-maximum $Sp_{O2}$, there was no difference in this $P_{aw}$ and the $P_{aw}$ resulting in the optimum $V_T/\Delta P$; mean difference 2.9 (-0.8, 6.5) cm H$_2$O. However, the difference in $V_T/\Delta P$ between these two points remained significantly lower; mean difference -0.02 (-0.03, -0.01) mL.kg$^{-1}$/cm H$_2$O.

The $P_{aw}$ resulting in optimum $V_T/\Delta P$ was closely related to the $P_{aw}$ resulting in the optimum quasi-static $C_{rs}$; mean difference 2.4 (-1.5, 6.4) cm H$_2$O. The resultant $V_T/\Delta P$ values were not different; mean difference 0.02 (0.00, 0.05) mL.kg$^{-1}$/cm H$_2$O.

### 8.2.2 Relationship between $V_{TRIP}$ and $P_{aw}$

The $P_{aw} - V_{TRIP}/\Delta P$ relationships for each infant during the open lung ventilation strategy are shown in Figure 8-2. Complete data on $V_{TRIP}$ could not be collected from Infant 13 due to a fault in the RIP chest lead cable. In the remaining 14 infants, the $P_{aw} - V_{TRIP}/\Delta P$ relationships varied, but were the same, or very similar, to the corresponding $P_{aw} - V_T/\Delta P$ plots in 11 infants, differing only in Infants 1, 4 and 12.
Figure 8-2. Individual $P_{aw}$ – $V_{TRIP}/\Delta P$ relationships for 14 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants.
In ten infants, $V_{TRIP}$ decreased as $P_{aw}$ was increased to $P_{max}$ during the inflation series, and the lowest $V_{TRIP}$ during the inflation series occurred at $P_{max}$. In Infant 3, $V_{TRIP}$ initially increased with increasing $P_{aw}$ but then deteriorated as the lung approached $P_{max}$. In the remaining three infants (Infants 5, 6 and 7), the maximum $V_{TRIP}$ did not occur at $P_{max}$, although the $V_{TRIP}$ generally increased through the inflation series. There was no difference in the $V_{TRIP}/\Delta P$ at $P_{initial}$ and $P_{max}$; mean difference 15.5 (-21.5, 52.4)%.

During the deflation series, $V_{TRIP}$ increased from the value at $P_{max}$ in 11 infants. In nine of these, there appeared to be a bell-shaped $P_{aw} - V_{TRIP}/\Delta P$ relationship, with the maximal $V_{TRIP}/\Delta P$ value occurring between $P_{max}$ and $P_{final}$. In Infant 7, there was a U-shaped (or inverse bell-shaped) relationship between $P_{aw}$ and $V_{TRIP}$ during the deflation series. In the other four infants, $V_{TRIP}$ either increased (Infant 1 and 14) or decreased (Infant 4 and 5) sequentially as $P_{aw}$ was reduced from $P_{max}$ to $P_{final}$.

Hysteresis was not as apparent in many of the $P_{aw} - V_{TRIP}/\Delta P$ relationships. Unmistakable hysteresis was only demonstrated in Infants 3, 6, 8 and 15. In the majority of infants, there was some improvement in $V_{TRIP}$ during the deflation series compared to the inflation series. The mean [SD] maximum $V_{TRIP}/\Delta P$, using the deflation series data alone, was 94.3 [11.2]% of the maximum $V_{TRIP}/\Delta P$ value from the entire data set. The $V_{TRIP}/\Delta P$ at $P_{initial}$ was 49.2 (12.2, 86.1) % lower than the maximum $V_{TRIP}/\Delta P$ during the deflation series.

The maximum $V_{TRIP}/\Delta P$ during the deflation series was 44.5 (7.5, 81.5)% and 58.9 (21.9, 95.9)% greater than the $V_{TRIP}/\Delta P$ at $P_{final}$ and $P_{max}$ respectively. The $P_{aw}$ resulting in the maximum $V_{TRIP}/\Delta P$ during the deflation series was 8.3 (4.5, 12.2) cm H$_2$O lower than $P_{max}$ and 5.9 (2.1, 9.8) cm H$_2$O greater than $P_{final}$. The point of optimal $SpO2$ during the deflation series occurred at a $P_{aw}$ that was 4.2 (0.4, 8.1) cm H$_2$O greater than the point of maximum $V_{TRIP}$. This resulted in a decrease in $V_{TRIP}/\Delta P$ of 41.2 (4.2, 78.1)% from the maximum $V_{TRIP}/\Delta P$ during the deflation series.
The points of maximum \( V_T \) and \( V_{TRIP} \) were closely related. The \( V_{TRIP}/\Delta P \) at the point of maximum \( V_T \) was 19.9 (-17.1, 56.9)% lower than the maximum \( V_{TRIP} \). Both points occurred at a similar \( P_{aw} \); mean difference -0.6 (-4.4, 3.3) cm H\(_2\)O. Consequently, there was also no significant difference in the points of maximum \( V_{TRIP} \) and quasi-static \( C_{rs} \).

**8.3 Relationship between tidal volume and \( V_{LRIP} \)**

**8.3.1 Relationship between \( V_T \) and \( V_{LRIP} \)**

The individual \( V_{LRIP} - V_T/\Delta P \) plots are shown in Figure 8-3. These were similar to the \( P_{aw} - V_T/\Delta P \) relationships described in Figure 8-1 and, again, there was considerable variability between infants. In 10 infants, \( V_T/\Delta P \) decreased with increasing \( V_{LRIP} \) during the inflation series, implying overdistension was, at least in part, contributing to the increasing \( V_{LRIP} \). \( V_T/\Delta P \) increased with increasing \( V_{LRIP} \) during the inflation series in Infants 3, 4 and 12. In Infants 1 and 5, there was essentially no change in the \( V_T/\Delta P \) as lung volume increased.

Hysteresis in the \( V_{LRIP} - V_T/\Delta P \) relationships could be identified in 12 infants. In these infants, the \( V_T/\Delta P \) values were greater during all or part of the deflation series compared to the same \( V_{LRIP} \) values during the inflation series. In Infants 3 and 13, there was essentially no difference in the inflation and deflation series. The mean \( V_{LRIP} \) resulting in the optimum \( V_T/\Delta P \) was 0.25 (0.05, 0.45) V greater than the mean \( V_{LRIP} \) at \( P_{initial} \).

The relationship between \( V_{LRIP} \) and \( V_T/\Delta P \) during the deflation series was bell-shaped in all but four infants. In these infants, the relationships appeared linear. In Infant 3 and 5, \( V_T/\Delta P \) decreased from the \( V_{LRIP} \) at \( P_{max} \). In Infant 1 and 7, \( V_T/\Delta P \) generally increased as the lung was taken from \( P_{max} \) to \( P_{final} \), although the magnitude of change was minimal in the case of Infant 1. Overall, the mean \( V_{LRIP} \) resulting in the optimum \( V_T/\Delta P \) was 0.24 (0.04, 0.44) V greater than the \( V_{LRIP} \) at \( P_{final} \) and 0.26 (0.06, 0.46) V less than the \( V_{LRIP} \) at \( P_{max} \).
Figure 8-3. Individual $V_{LRIP} - V_T/\Delta P$ relationships for the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X- and Y-axis range differs between infants.
The point of optimum $V_T/\Delta P$ during the deflation series occurred at a mean [SD] $V_{LRIP}$ of 0.25 [0.38] V. This was significantly lower than the $V_{LRIP}$ that resulted in maximum lung volume; mean difference 0.28 (0.08, 0.48) V. The optimum $V_T/\Delta P$ during the deflation series was 0.02 (0.00, 0.04) mL.kg$^{-1}$/cm H$_2$O greater than the $V_T/\Delta P$ at maximum $V_{LRIP}$. Using the earlier example of a $\Delta P$ of 34 cm H$_2$O, the optimal $V_T$ during the deflation series would be 0.7 mL/kg greater than the $V_T$ at the maximum $V_{LRIP}$. The $V_{LRIP}$ at optimum $V_T/\Delta P$ was related to the $V_{LRIP}$ that resulted in the optimum quasi-static $C_{rs}$; mean difference 0.04 (-0.18, 0.26) V.

8.3.2 Relationship between $V_{TRIP}$ and $V_{LRIP}$

The relationship between $V_{LRIP}$ and $V_{TRIP}/\Delta P$ for each infant is shown in Figure 8.4. These relationships varied considerably between infants. During the inflation series, $V_{TRIP}$ decreased with increasing $V_{LRIP}$ in nine infants, although the pattern was not consistent. In some infants (2, 4 and 14), $V_{TRIP}$ decreased sequentially whilst in others (1, 7, 9, 10, 11 and 12) $V_{TRIP}$ did not decrease until at higher lung volumes, suggesting that overdistension was occurring late in the inflation series in these infants. In the case of Infants 3, 5 and 6, $V_{TRIP}$ generally increased with increasing $V_{LRIP}$ during the inflation series. There was minimal change in $V_{TRIP}$ during the inflation series in Infant 15.

Hysteresis occurred in six infants. In another five infants (Infants 1, 2, 3, 10 and 12), there was minimal change in $V_{TRIP}$ during the inflation and deflation series. The $V_{TRIP}$ during the inflation series was greater than the deflation series data in the remaining three infants (Infants 4, 5 and 7). Overall, the $V_{LRIP}$ resulting in the maximum $V_{TRIP}/\Delta P$ was 0.20 (-0.01, 0.42) V less than the $V_{LRIP}$ at $P_{initial}$. Whilst this difference was not significant, the difference between the $V_{LRIP}$ at maximum $V_{TRIP}/\Delta P$, using the deflation series alone, was significantly greater than the $V_{LRIP}$ at $P_{initial}$; mean difference 0.29 (0.08, 0.50) V.
Figure 8-4. Individual $V_{LRIP} - V_{TRIP}/\Delta P$ relationships for 14 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated on graph. X- and Y-axis range differs between infants.
The relationship between $V_{L RIP}$ and $V_{TRIP}/\Delta P$ during the deflation series was bell-shaped in eight infants. In Infants 3, 4 and 5, $V_{TRIP}$ decreased with decreasing $V_{L RIP}$ during the entire deflation series and increased in Infants 10 and 14. In the case of Infant 7, there was a U-shaped (or inverse bell-shaped) relationship between $V_{L RIP}$ and $V_{TRIP}$ during the deflation series. The $V_{L RIP}$ that resulted in the maximum $V_{TRIP}/\Delta P$ during the deflation series occurred at a $V_{L RIP}$ that was 0.25 (0.03, 0.46) V less than the $V_{L RIP}$ at $P_{\text{max}}$, and 0.24 (0.03, 0.45) V greater than the $V_{L RIP}$ at $P_{\text{final}}$. The maximum $V_{L RIP}$ during the deflation series was 0.27 (0.06, 0.49) V greater than the $V_{L RIP}$ at maximum $V_{TRIP}/\Delta P$ during the deflation series. This resulted in a $V_{TRIP}/\Delta P$ at maximum $V_{L RIP}$ that was 45.2 (8.2, 82.11) % less than the maximum $V_{TRIP}/\Delta P$ during the deflation series.

There was no difference in the $V_{L RIP}$ that resulted in the maximum $V_{TRIP}$ and $V_T$; mean difference 0.00 (-0.21, 0.22) V. Consequently, there was also no difference in the $V_{L RIP}$ resulting in maximum $V_{TRIP}$ and optimum quasi-static $C_{rs}$. The mean $V_{L RIP}$ resulting in optimum $\text{SpO}_2$ was 0.27 (0.06, 0.49) V greater than the $V_{L RIP}$ resulting in the maximum $V_{TRIP}$ during the deflation series.

### 8.4 Relationship between tidal volume and the PV relationship using normalised data

The relationships between $V_T/\Delta P$ and $V_{TRIP}/\Delta P$, and $P_{aw}$ and $V_{L RIP}$, using pooled normalised data, are shown in Figures 8-5 A – D. The $V_T$ values changed little during the inflation series as $P_{aw}$ increased to $P_{\text{max}}$ (Figure 8-5 A). Conversely, normalised $V_{TRIP}$ generally decreased during the inflation series with increasing $P_{aw}$ (Figure 8-5 B). In both cases, there was greater variability in the tidal volume values at higher $P_{aw}$ values. The volume state of the lung was not standardised at $P_{\text{initial}}$. Thus, in some infants, it was likely that overdistension was occurring as the lung was taken to $P_{\text{max}}$. In others, alveolar recruitment appeared to be the prominent process throughout the inflation series. Alveolar recruitment should improve, whilst overdistension impede, tidal volume. There was a similar degree of variability in the $V_{L RIP} – V_T/\Delta P$ (Figure 8-5C) and $V_{L RIP} – V_{TRIP}/\Delta P$ (Figure 8-5D) relationships during the deflation series, using normalised $V_{L RIP}$ and $V_{TRIP}$ data.
Relationship between $V_T$, $P_{aw}$ and $V_{LRIP}$

Figure 8-5. A. $P_{aw} - V_T/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. B. $P_{aw} - V_{TRIP}/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $P_{aw}$ data. C. $V_{LRIP} - V_T/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ and $V_{TRIP}$ data. D. $V_{LRIP} - V_{TRIP}/\Delta P$ relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised $V_{LRIP}$ and $V_{TRIP}$ data. Data expressed as mean and standard error of the mean.

During the deflation series, the $P_{aw} - V_T/\Delta P$ and $V_{LRIP} - V_T/\Delta P$ relationships were bell-shaped. Hysteresis was expressed, such that $V_T$ was generally better during the deflation rather than inflation series. The point of optimal $V_T/\Delta P$ occurred at a mean [SD] $P_{aw}$ of 52.5 [1.5]% of the difference in $P_{aw}$ between $P_{max}$ and $P_{final}$. This value, and the data at a normalised $P_{aw}$ of 38.5%, may represent outlying data. Removing these data it appears that $V_T/\Delta P$ was near the maximal value over the range of pressures between 16.7 [1.4]% and 65.7 [2.5]% of the $P_{aw}$ difference between $P_{max}$ and $P_{final}$. This translated to lung volumes that ranged from 85.1 [31.3]% to 38.5 [25.4]% of the $V_{LRIP}$ at $P_{max}$. 
There was little difference between the normalised inflation and deflation series data for the $P_{aw} - V_{TRIP}/\Delta P$ and $V_{LRIP} - V_{TRIP}/\Delta P$ relationships (Figures 8-5 B and D). Despite this, during the deflation series, there was a bell-shaped relationship between $V_{TRIP}$ and both $P_{aw}$ and $V_{LRIP}$ that was similar to the relationship seen with the $V_T$ data. The region of optimum $V_{TRIP}/\Delta P$ during the deflation series was more closely related to the $P_{aw}$ at $P_{final}$ than the $V_T$ data, occurring at a $P_{aw}$ between 7.7 [1.7]% and 16.7 [1.4]% of the $P_{aw}$ at $P_{max}$, and a $V_{LRIP}$ of between 18.4 [12.0]% and 38.5 [25.4]% of the $V_{LRIP}$ at $P_{max}$.

The bell-shaped relationship between $P_{aw}$, using the normalised data, and both $V_T$ and $V_{TRIP}$ during the deflation series could be shown using the proposed quadratic model (Figures 8-6 A and B). The model produced a clear bell-shaped curve with narrow 95% confidence intervals and a peak, or maximum, tidal volume occurring at a $P_{aw}$ of 48% and 23% of the difference between $P_{max}$ and $P_{final}$ for the $V_T$ and $V_{TRIP}$ data respectively. However, the goodness-of-fit for both relationships was poor ($R^2 = 0.411$ and 0.450 respectively). When the two outlying values, at pressures of 38.5% and 52.5%, were removed from the $P_{aw} - V_T/\Delta P$ relationship, the goodness-of-fit of the quadratic model improved considerably ($R^2 = 0.721$). A similar improvement resulted when the three outlier values were removed from the $P_{aw} - V_{TRIP}/\Delta P$ relationship ($R^2 = 0.654$).

The quadratic model could not be fitted to any of the inflation series relationships ($R^2 0.010$ to 0.277; all permutations).
8.5 Relationship between $V_T$ and $V_{TRIP}$

The assessment of tidal volume during HFOV is difficult. Unlike conventional ventilation, there is no gold standard measure of tidal volume. Assessment at the airway opening is complicated by the magnitude of the ETT leak and attenuation of the oscillatory pressure wave through the respiratory tree. RIP, which measures the magnitude of chest wall movement during tidal ventilation, has been validated as a measure of tidal volume during normal breathing but not HFOV. Thus, in this study, both $V_T$ and $V_{TRIP}$ should be considered relative indicators of alveolar tidal volume. As the RIP signals were not calibrated during the experimental protocol, the $V_{TRIP}$ cannot be directly compared to $V_T$. As such, to determine whether $V_T$ and $V_{TRIP}$ behaved similarly during the open lung ventilation strategy, the $V_T$ and $V_{TRIP}$ data in each infant were compared using linear regression.
The relationships between $V_T$ and $V_{TRIP}$ during the inflation series, for the 14 infants with complete $V_{TRIP}$ data, are shown in Figure 8-7A. Linear regression of each $V_T$ – $V_{TRIP}$ relationship is described in Table 8-2. During the inflation series, there was a strong correlation in only five infants ($r^2 > 0.7$; Infants 3, 9, 10, 11 and 14). In the remaining nine infants, the correlation between $V_T$ and $V_{TRIP}$ was weak ($r^2 < 0.6$). Furthermore, in five of these infants (Infants 4, 5, 6, 7 and 8) the relationship was negative.

**Table 8-2. Relationship between $V_T$ and $V_{TRIP}$ during the inflation and deflation series in the 14 infants with complete $V_{TRIP}$ data.**

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<th>Deflation series</th>
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</tr>
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</table>

*Indicates slope is positive and significantly non-zero (p<0.05). $r^2$ values have not been calculated (N/A) if the correlation coefficient was negative.
Relationship between $V_T$, $P_{aw}$ and $V_{LRIP}$

Figure 8-7. A. Relationship between $V_T$ and $V_{TRIP}$ during the inflation series for 14 infants. B. Relationship between $V_T$ and $V_{TRIP}$ during the deflation series for 14 infants. In both figures, the linear regression slope of the $V_T - V_{TRIP}$ relationship is shown, and represented by a different colour and symbol for each infant.

There was a closer relationship between $V_T$ and $V_{TRIP}$ during the deflation series (Figure 8-7B). In six infants, there was a strong correlation between $V_T$ and $V_{TRIP}$ and the resultant linear regression slope was significantly linear ($r^2 > 0.7$; Infants 3, 8, 9, 11, 14, 15). In the remaining eight infants, the correlation was poor in five infants ($r^2 < 0.4$) and negative in the case of Infant 7.
It was expected that both indicators of $V_T$ and $V_{TRIP}$ would correlate well. The reasons for the lack of linear correlation between $V_T$ and $V_{TRIP}$ in many of the infants are unclear. It may be that the differences represent an error within one or both of the measurement techniques (see Chapter 10.3.3 and 10.3.4), or physical changes in the infant’s respiratory system during the open lung strategy (for example airway compression from overdistension).

8.6 Conclusion

In this chapter, the relationships between indicators of tidal volume and both $P_{aw}$ and $V_{LRIP}$ have been described whilst the lung was taken through an open lung ventilation strategy. In many infants, even after accounting for any variability in $\Delta P$, the volume state of the lung independently influenced $V_T$ and $V_{TRIP}$ to some degree. Overall, $V_T$ and $V_{TRIP}$ were impaired as the lung was taken to TLC, likely due to increasing overdistension. Thereafter, hysteresis could be demonstrated in many infants, allowing the region of optimal $V_T$ and $V_{TRIP}$ to be defined on the deflation limb of the PV relationship. Generally, there was a bell-shaped relationship between both indicators of tidal volume, $P_{aw}$ and $V_{LRIP}$. This bell-shaped relationship varied between infants and, consequently, the proposed quadratic mathematical model resulted in a moderate goodness-of-fit with the pooled normalised data, although this improved when outlying data points were removed. Overall, the bell-shaped relationship during the deflation series allowed identification of the optimal region for tidal volume, this being at a $P_{aw}$ of 20 – 50% of the difference between $P_{max}$ and $P_{final}$. This was closely associated with the region of optimal quasi-static $C_{rs}$, and the lower portion of the region resulting in optimal $SpO_2$. These results indicate that using indicators of tidal volume may have some value in identifying the region of optimal ventilation, without the need to identify the CCP and expose the lung to transient atelectasis.

Measurement of tidal volume during HFOV is complex and these results identify the need for further study to understand the interaction between measurement of tidal volume at different sites within the ventilator circuit and respiratory tree.
Chapter 9.

RELATIONSHIP BETWEEN CARBON DIOXIDE, MEAN AIRWAY PRESSURE AND LUNG VOLUME

9.1 Introduction
This chapter describes the relationship between CO$_2$ and both $P_{aw}$ and $V_{LRIP}$ during the application of the open lung ventilation strategy. CO$_2$ was measured by the transcutaneous method and, to account for any fluctuations in $\Delta P$ that may directly influence $Tc_{CO2}$, expressed as the ratio between $Tc_{CO2}$ and $\Delta P$. Firstly, the raw data for the relationships between $Tc_{CO2}/\Delta P$, $P_{aw}$ and $V_{LRIP}$ are presented for each infant, and then the pooled results described. Secondly, the combined relationships from all infants are described using the normalised PV data. Finally, the ability of a nonlinear model to define the relationships between $Tc_{CO2}$, $P_{aw}$ and $V_{LRIP}$ are examined. In this chapter optimal CO$_2$ is defined as the minimum $Tc_{CO2}$ value obtained, representing the point where CO$_2$ clearance will be greatest.

9.2 Relationship between CO$_2$ and $P_{aw}$
In Figure 9-1, the plots of $P_{aw}$ against $Tc_{CO2}/\Delta P$ from each infant are shown. The individual relationships between $P_{aw}$ and $Tc_{CO2}/\Delta P$ were variable. In 11 infants, $Tc_{CO2}/\Delta P$ increased during the inflation series, indicating a worsening of CO$_2$. In two of the remaining four infants (Infants 1 and 12), $Tc_{CO2}/\Delta P$ remained essentially unchanged, or increased only slightly. In the final two infants (Infants 3 and 5), $Tc_{CO2}/\Delta P$ decreased as the lung was taken to TLC. The mean $Tc_{CO2}/\Delta P$ at $P_{max}$ was 0.7 (0.1, 1.3) mmHg/cm H$_2$O greater than at $P_{initial}$. Using the earlier example in Chapter 8.2.1 of a $\Delta P$ of 34 cm H$_2$O, the $Tc_{CO2}$ at $P_{max}$ would be 23 mmHg greater than at $P_{initial}$, a highly significant clinical difference.
Relationship between CO$_2$, \( P_{aw} \), and \( V_{LRIP} \)

Figure 9-1. Individual \( P_{aw} \) – \( Tc_{CO2}/\Delta P \) relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number is indicated in the top left hand corner of each graph. Y-axis range differs between infants.
In eleven infants, there was hysteresis demonstrated in the $P_{aw}$ - Tc$_{CO_2}$/ΔP relationships with Tc$_{CO_2}$/ΔP improving after the lung was recruited to $P_{max}$. In Infant 12, there was little difference between the Tc$_{CO_2}$/ΔP during the deflation and inflation series. In three infants (Infants 1, 14 and 15), Tc$_{CO_2}$/ΔP was worse during the entire deflation series compared to the inflation series. The mean [SD] minimum Tc$_{CO_2}$/ΔP from the entire data set was 1.8 [1.2] mmHg/cm H$_2$O. This did not differ from the mean [SD] minimum Tc$_{CO_2}$/ΔP during the deflation series of 1.9 [1.2] mmHg/cm H$_2$O. There was no difference between the Tc$_{CO_2}$/ΔP at $P_{initial}$ and the same $P_{aw}$ during the deflation series; mean difference 0.0 (-0.7, 0.7) mmHg/cm H$_2$O. Although this difference was not significant, the difference between the Tc$_{CO_2}$/ΔP at $P_{initial}$ and the minimum Tc$_{CO_2}$/ΔP value during the deflation series was significant; mean difference 0.5 (0.2, 0.8) mmHg/cm H$_2$O, or 17 (10, 22) mmHg using the example ΔP of 34 cm H$_2$O. This is further illustrated in Table 9-1, which shows the Tc$_{CO_2}$ data during the study from Infant 3.

Table 9-1. Relationship between $P_{aw}$, Tc$_{CO_2}$, $V_T$, and ΔP during the open lung ventilation strategy in Infant 3 (weight = 2.25 kg). $P_{max}$ is illustrated in grey.

<table>
<thead>
<tr>
<th>$P_{aw}$ (cm H$_2$O)</th>
<th>$V_T$ (mL)</th>
<th>Tc$_{CO_2}$ (mmHg)</th>
<th>ΔP (cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5</td>
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<td>6.2</td>
<td>5.1</td>
<td>58.6</td>
<td>45.8</td>
</tr>
</tbody>
</table>

* The maximum $V_T$ occurred during the deflation series and was 1.7 mL greater than the initial $V_T$. † Indicates the $P_{aw}$ that resulted in the minimum Tc$_{CO_2}$, which was 14 mmHg less than $P_{initial}$. 

129
In 14 infants, TcCO2/ΔP improved during the deflation series as Paw was decreased from P_max. In nine of these 14 infants, the relationship between TcCO2/ΔP and Paw was U-shaped during the deflation series, such that the minimum TcCO2/ΔP value occurred at a Paw between P_max and P_final. In Infants 4 and 6, the minimum TcCO2/ΔP value was similar to the value at P_final and occurred at a Paw closely related to P_final. It is possible that further decreases in Paw beyond P_final would have resulted in the U-shaped relationship seen in the other nine infants. In three infants (Infant 10, 14 and 15), the minimum TcCO2/ΔP value occurred at P_final. In Infant 1, TcCO2/ΔP increased with each Paw step during the deflation series such that the maximum TcCO2/ΔP occurred at P_final.

The point of optimum CO2, as expressed by the minimum TcCO2/ΔP, during the deflation series was significantly lower than the TcCO2/ΔP at P_max; mean difference 1.2 (0.6, 1. 8) mmHg/cm H2O. The mean TcCO2/ΔP value at P_final was 0.3 (-0.3, 0.9) mmHg/cm H2O greater than that at the point of optimum CO2, a difference that was not significant. The difference in the Paw resulting in the point of optimum CO2 did not differ significantly from P_final; mean difference 2.7 (-0.8, 6.2) cm H2O. There was a significant difference between P_max and the Paw resulting in the minimum TcCO2/ΔP; mean difference 11.9 (8.4, 15.3) cm H2O. Importantly, this indicated that, in many infants, the Paw resulting in the optimal CO2 was closely related to, but greater than, the CCP. The Paw – TcCO2 relationship may offer utility in mapping the deflation limb of the PV relationship, by identifying when the lung is approaching the CCP.

The Paw resulting in optimal CO2 did not differ significantly from the Paw resulting in the optimal VT (and VTRIP) and maximal Crs; mean difference -1.5 (-5.0, 2.0) cm H2O and -1.8 (-6.0, 2.4) cm H2O respectively. In contrast, the Paw resulting in the optimal SpO2 was significantly greater than the Paw resulting in optimum CO2; mean difference 7.2 (3.7, 10.7) cm H2O. The TcCO2/ΔP at the point of optimum SpO2 was 0.7 (0.1, 1.3) mmHg/cm H2O greater than the optimal CO2 value. This is important, as SpO2 values remained close to the optimal SpO2 through a wide range of pressures during the deflation series (see Figure 6-3A). Thus, targeting the Paw resulting in optimal CO2 may not come at the cost of impaired oxygenation.
9.3 Relationship between CO$_2$ and V$_{LRIP}$

The individual V$_{LRIP}$ - Tc$_{CO2}/\Delta P$ relationships are shown in Figure 9-2. Similar to the $P_{aw}$ - Tc$_{CO2}/\Delta P$ relationships shown in Figure 9-1, there was considerable variability. During the inflation series, the Tc$_{CO2}/\Delta P$ increased with increasing V$_{LRIP}$ in 11 infants. In many of these 11 infants there was a distinct change in the slope of the V$_{LRIP}$ – Tc$_{CO2}/\Delta P$ relationship during the inflation series. This may represent the point at which overdistension rather than volume recruitment became the prominent process determining $\Delta V_L$. In the case of Infants 1, 3 and 5, the Tc$_{CO2}/\Delta P$ decreased as V$_{LRIP}$ increased suggesting that lung volume recruitment was occurring, resulting in better CO$_2$ clearance. In Infant 7, Tc$_{CO2}/\Delta P$ remained essentially unchanged during the inflation series.

In most infants, the relationship between V$_{LRIP}$ and Tc$_{CO2}/\Delta P$ during the deflation series was not linear. In eight infants, there was a distinct U-shaped relationship during the deflation series, with the V$_{LRIP}$ resulting in the optimal CO$_2$ occurring between $P_{max}$ and $P_{final}$. In five infants, Tc$_{CO2}/\Delta P$ improved throughout the entire deflation series such that the V$_{LRIP}$ resulting in the optimum CO$_2$ occurred at, or near, the V$_{LRIP}$ at $P_{final}$. In three of these five infants (Infants 4, 10 and 11), the relationship approached a U-shaped relationship. In the other two (Infants 8, 15), a linear relationship was noted. Finally, in Infant 1 and 14, the Tc$_{CO2}/\Delta P$ either remained unchanged, or increased linearly, throughout the entire deflation series.

The point of optimum CO$_2$ occurred at a mean [SD] V$_{LRIP}$ of 0.20 [0.27] V. This did not differ significantly from the mean [SD] V$_{LRIP}$ that resulted in the optimal CO$_2$ of 0.17 [0.28] V during the deflation series. There was no difference in the mean V$_{LRIP}$ that resulted in the optimal CO$_2$ and the V$_{LRIP}$ at $P_{initial}$; mean difference 0.20 (-0.40, 0.01) V. During the deflation series, the V$_{LRIP}$ resulting in the optimal CO$_2$ was 0.34 (0.13, 0.55) V less than the V$_{LRIP}$ at $P_{max}$, and 0.37 (0.16, 0.58) V less than the maximum V$_{LRIP}$. This resulted in an improvement in Tc$_{CO2}/\Delta P$ of 0.9 (0.3, 1.4) mmHg/cm H$_2$O when ventilation was applied at the point of optimal CO$_2$ rather than maximum V$_{LRIP}$. The V$_{LRIP}$ resulting in the optimal CO$_2$ during the deflation series was closely related to the V$_{LRIP}$ at $P_{final}$; mean difference -0.16 (-0.37, 0.05) V.
During the deflation series, there was a close relationship between the $V_{LRIP}$ resulting in optimal CO$_2$, $V_T$, $V_{TRIP}$ and $C_{rs}$. The $V_{LRIP}$ resulting in the optimal CO$_2$ was 0.05 (-0.26, 0.16) V and 0.04 V (-0.19, 0.26) less than the $V_{LRIP}$ at optimal $V_T$ (and $V_{TRIP}$) and $C_{rs}$, respectively. During the deflation series, CO$_2$ was optimised at a lower $V_{LRIP}$ than Sp$_{O2}$; mean difference 0.27 (0.06, 0.49) V.

Figure 9-2. Individual $V_{LRIP}$ – $Tc_{CO2}/\Delta P$ relationships from the 15 infants during an inflation (open diamonds) and deflation (closed circles) series. Infant number indicated in the top left hand corner of each graph. X- and Y-axis range differs between infants.
9.4 Relationship between CO$_2$ and the PV relationship using normalised data

The relationships between Tc$_{CO2}$/$\Delta P$ and both $P_{aw}$ and $V_{LRIP}$, using pooled normalised data, are shown in Figures 9-3A and 9-3B respectively. During the inflation series, Tc$_{CO2}$/$\Delta P$ deteriorated as both $P_{aw}$ and $V_{LRIP}$ increased, with the greatest Tc$_{CO2}$/$\Delta P$ occurring at $P_{max}$. In addition, this relationship between $P_{aw}$ and Tc$_{CO2}$/$\Delta P$ was not linear. Initially, there was little change in Tc$_{CO2}$/$\Delta P$ with increasing $P_{aw}$ but, at a normalised $P_{aw}$ of 63%, the slope of the relationship changed. Thereafter, Tc$_{CO2}$/$\Delta P$ increased with increasing $P_{aw}$ until $P_{max}$. Similarly, Tc$_{CO2}$/$\Delta P$ remained static with increasing $V_{LRIP}$, until a normalised $V_{LRIP}$ of 30%, after which further gains in $V_{LRIP}$ resulted in increasing Tc$_{CO2}$/$\Delta P$. This change in the behaviour of Tc$_{CO2}$/$\Delta P$ suggests that overdistension is likely to be an important contributor to any further $\Delta V_L$, above a normalised $P_{aw}$ and $V_{LRIP}$ of approximately 60% and 30% of the values at $P_{max}$ respectively. A similar observation was reported with the Sp$_{O2}$ data in Chapter 6.4.

During the deflation series, Tc$_{CO2}$/$\Delta P$ improved as the $P_{aw}$ was reduced from $P_{max}$ until a region of optimal CO$_2$ was obtained. This occurred at pressures of between 10% and 30% of the $P_{aw}$ difference between $P_{max}$ and $P_{final}$. Tc$_{CO2}$/$\Delta P$ values then increased again as $P_{aw}$ was decreased to $P_{final}$. This region of optimal CO$_2$ occurred at volumes 20% to 60% of the $V_{LRIP}$ difference between $P_{max}$ and $P_{final}$. The region of optimal CO$_2$ occurred within a narrower range of pressures and volumes than the region of optimal Sp$_{O2}$ described in Chapter 6.

During the deflation series, the region of optimal CO$_2$ corresponded to the $P_{aw}$ and $V_{LRIP}$ resulting in the lower portion of the region of optimal Sp$_{O2}$. This suggests that the point of optimal CO$_2$ may represent the optimal point at which to apply ventilation after lung recruitment. The point of optimal CO$_2$ defines the lowest $P_{aw}$, and $V_{LRIP}$, resulting in the best balance of CO$_2$ and Sp$_{O2}$, whilst avoiding pressures that result in atelectasis and overdistension. These data also indicate that clinicians should use more than just oxygenation to determine optimum $P_{aw}$ when implementing an open lung ventilation strategy.
Relationship between CO\textsubscript{2}, P\textsubscript{aw} and V\textsubscript{LRIP}

Figure 9-3. A. P\textsubscript{aw} - T\textsubscript{cCO₂}/ΔP relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised P\textsubscript{aw} data. B. V\textsubscript{LRIP} - T\textsubscript{cCO₂}/ΔP relationship during the inflation (open diamonds) and deflation (closed circles) series, using normalised V\textsubscript{LRIP} data. Data expressed as mean and standard error of the mean.
The inflation series normalised $P_{aw} - \frac{Tc_{CO2}}{\Delta P}$ data could be fitted with the quadratic model ($R^2 = 0.561$; Figure 9-4A), although with only a moderate goodness-of-fit. This model could also closely define the normalised $V_{LRIP} - \frac{Tc_{CO2}}{\Delta P}$ relationship during the inflation series ($R^2 = 0.983$; Figure 9-4C). The correlation between the inflation series data and the quadratic model was better than expected. This can be explained by the distinct point of curvature change seen in the data (Figure 9-3 A and C), and the supposition that the volume state of the lung changed during the inflation series, as the lung approached TLC.

Figure 9-4. Nonlinear regression analysis of the data presented in Figure 9-3 using a quadratic model (red lines). A. Normalised $P_{aw} - \frac{Tc_{CO2}}{\Delta P}$ relationship during the inflation series. B. Normalised $P_{aw} - \frac{Tc_{CO2}}{\Delta P}$ relationship during the deflation series. C. Normalised $V_{LRIP} - \frac{Tc_{CO2}}{\Delta P}$ relationship during the inflation series. D. Normalised $V_{LRIP} - \frac{Tc_{CO2}}{\Delta P}$ relationship during the deflation series. Solid lines represent the curve of best fit and dotted lines 95% CI of the curve. In all cases, the resultant curves did not significantly deviate from the data (Runs test $p$ values 0.36 to 0.94).
The quadratic model could also be fitted to the normalised $P_{aw} - \text{TcCO}_2/\Delta P$ data during the deflation series ($R^2 = 0.893$; Figure 9-4B). This indicates that the relationship between $P_{aw}$ and $\text{TcCO}_2$ is U-shaped. Using this model, the $P_{aw}$ resulting in the optimal CO$_2$ occurs at 4.0% of the $P_{aw}$ difference between $P_{max}$ and $P_{final}$, a value that is very closely associated with $P_{final}$. This point occurred at a lower $P_{aw}$ value than that identified from the normalised data (see Figure 9-3A). This is due to the three infants in whom optimal CO$_2$ occurred at $P_{final}$. This model could also be used to define the relationship between normalised $V_{LRIP}$ and $\text{TcCO}_2/\Delta P$ ($R^2 = 0.803$; Figure 9-4D), with the $V_{LRIP}$ resulting in the optimal CO$_2$ occurring at 33% of the $V_{LRIP}$ difference between $P_{max}$ and $P_{final}$. This equates to a normalised $P_{aw}$ of 15% of the $P_{aw}$ at $P_{max}$.

The nonlinear regression modelling confirmed the results of the normalised data, in particular the U-shaped relationship between $P_{aw}$ and $\text{TcCO}_2$ during the deflation series. This relationship could have been exploited to anticipate the $P_{aw}$ corresponding to the CCP in many of the infants studied. The trough of the U-shaped curve, which corresponded to the point of optimal CO$_2$, occurred very close to $P_{final}$ and, thus, the $P_{aw}$ in which rapid deoxygenation commenced. By using $\text{TcCO}_2$, further decreases in $P_{aw}$ would be unnecessary once the rise in $\text{TcCO}_2$, after the point of optimal CO$_2$, was realised. This would avoid the lung from being placed at $P_{final}$, or below, and the transient deoxygenation and subsequent re-recruitment to $P_{max}$ associated with this.

9.5 Relationship between CO$_2$ and $V_T$

CO$_2$ clearance is influenced by minute ventilation. Thus, CO$_2$ should be inversely proportional to $V_T$. The relationships between $\text{TcCO}_2$ and $V_T$, during the inflation and deflation series, were analysed using linear regression in each infant. Table 9-2 shows the correlation coefficient and goodness-of-fit for each relationship. During the inflation series there was a close inverse relationship ($r^2 >0.7$) in eight infants, and, in a further two, the $r^2$ was >0.5. In five infants, there was a close inverse relationship ($r^2 >0.7$) between CO$_2$ and $V_T$ during the deflation series, and the $r^2$ was >0.5 in three other infants. The correlation coefficient was positive or close to zero in the respective five and six remaining infants. The variability in the correlation between $V_T$ and $\text{TcCO}_2$ may be due to the practical limitations of each
Relationship between $CO_2$, $P_{aw}$ and $V_{LRIP}$ technique. For example, the accuracy of $Tc_{CO2}$ diminishes over time and can be influenced by tissue perfusion. The limitations of each technique are discussed in more detail in Chapter 10.4.4.

Table 9-2. Relationship between $V_T$ and $Tc_{CO2}$ during the inflation and deflation series.

<table>
<thead>
<tr>
<th>Infant</th>
<th>Correlation coefficient</th>
<th>$r^2$</th>
<th>Correlation coefficient</th>
<th>$r^2$</th>
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* Indicates slope is positive and significantly non-zero ($p<0.05$).
9.6 Conclusion

In this chapter, the relationship between CO₂ clearance and both $P_{aw}$ and $V_{LRIP}$ has been described whilst the lung was taken through an open lung ventilation strategy. Generally, CO₂ clearance was impaired as $P_{aw}$ was increased to TLC, likely secondary to lung overdistension. The PV relationship of the lung influenced CO₂ clearance, which exhibited its own hysteresis and was independent of $\Delta P$. That is, once lung volume was recruited, the $Tc_{CO2}$ was usually better than prior to recruitment, and remained so until the CCP. During the deflation series, the behaviour of CO₂ clearance against $P_{aw}$ and $V_{LRIP}$ exhibited a U-shaped relationship, fitting a quadratic model with a distinct region of optimal CO₂ occurring within a narrow range of pressures and volumes. This optimal region occurred at a $P_{aw}$ just greater than the CCP, and was closely associated with the lowest acceptable $P_{aw}$ resulting in optimal oxygenation. These results indicate that CO₂ may have utility in aiding the identification of a better point of optimum ventilation than the use of oxygenation alone.
10.1 Introduction

In this chapter, the results will be summarised and discussed as they relate to each of the primary aims. Initially, the use of the open lung ventilation strategy, in conjunction with RIP, to map the PV relationship during HFOV will be examined. Secondly, the influence of the volume state of the lung on gas exchange and lung mechanics will be discussed. This will highlight the potential for oxygenation, carbon dioxide and tidal volume to indicate volume response during $P_{aw}$ changes. Then, the ability to determine an optimal region of ventilation will be considered. In particular, that this region should be defined in the context of optimal lung mechanics as well as oxygenation. Using such an approach, the optimal region of ventilation occurred on the deflation limb, and is closely associated with the CCP. Finally, the limitations of this study, not previously mentioned, will be described in detail.

10.2 Mapping of the PV relationship

In this study, it was possible to describe, or map, the clinically important regions of the PV relationship of the lung during HFOV. This was achieved using an open lung ventilation strategy designed to maximise alveolar recruitment by inflation to TLC. Thereafter, the hysteresis of the lung was exploited to allow systematic description of the deflation limb between TLC and CCP. To do this, RIP was used to measure relative $\Delta V_L$.

The use of open lung approaches in the application of mechanical ventilation is not new (McCulloch et al 1988). There is now a considerable body of evidence to suggest that open lung approaches can define the PV relationship and guide the application of optimal ventilation in animal models (Rimensberger et al 1999b; Rimensberger et al 1999a; Rimensberger et al 2000b; van Kaam et al 2003) and adults humans (Albaiceta et al 2003b; Dyhr et al 2004; Ferguson et al 2005; Gattinoni et al 1995; Pelosi et al 2001). This study is the first to systematically describe the PV relationship in human newborn infants during mechanical ventilation.
Discussion

ventilation. Understanding the relationship between lung volume and the pressure applied to the lung is a critical step in developing physiologically sound strategies to reduce VILI. In this study, none of the infants were being ventilated on the deflation limb before commencing PV mapping, although clinicians were attempting to achieve a HLVS (Henderson-Smart et al 2007). Despite this, in the infants studied, it was feasible to apply ventilation on the deflation limb. This resulted in an increased lung volume, often at the same or lower $P_{aw}$.

To achieve ventilation on the deflation limb, lung volume was recruited to TLC. In this study, a series of stepwise $P_{aw}$ increases was used, a method that is practical and feasible across a variety of different pathophysologies. This incremental approach to achieve alveolar recruitment has been applied in animals (Brazelton et al 2001; van Kaam et al 2003; van Kaam et al 2004a), adults (Albaiceta et al 2004; Maggiore et al 2001) and newborn infants (De Jaegere et al 2006; Rimensberger et al 2000a). The incremental approach was chosen as it allows for the time-based component of recruitment, and allows consideration of the complex micromechanics of alveolar recruitment (Copland et al 2004; Halter et al 2003; Hickling 2001; Schiller et al 2003). Alveolar recruitment has also been achieved with rapid sustained (Kolton et al 1982) and dynamic (Byford et al 1988) inflations. There is emerging evidence that an incremental approach achieves better recruitment than sustained and dynamic inflations (Pellicano et al 2004 abstract).

Historically, clinicians have been reluctant to use a transient high $P_{aw}$ to recruit the lung during HFOV, due to concerns that such an approach would cause barotrauma and haemodynamic compromise. In some infants studied, a $P_{aw}$ as high as 27 cm H$_2$O was used to recruit the lung to TLC and, on average, $P_{max}$ was 8.3 cm H$_2$O greater than $P_{initial}$. These transient high $P_{aw}$ were applied without resultant heart rate or blood pressure compromise. Rimensberger et al (2000) also found that transiently applying a recruiting $P_{aw}$ of up to 25 cm H$_2$O was well tolerated in 32 preterm infants receiving first-intention HFOV. Transient recruitment to TLC during first-intention HFOV, using a similar open lung approach to that employed in this study, was also well tolerated in a prospective study of 103 preterm infants (De Jaegere et al 2006).
Discussion

There are two important differences between this study and those of Rimensberger et al (2000) and De Jaegere et al (2006). Firstly, confirmation of the resultant relationship between lung volume and $P_{aw}$ was made directly using RIP, rather than indirectly with oxygenation. Secondly, the use of RIP, and a longer time at each $P_{aw}$ step, allowed confirmation that lung volume had stabilised after each $P_{aw}$ change.

Currently, no reliable bedside tool exists to measure absolute lung volume during HFOV. As detailed in Chapter 2.4.3, chest radiography is not a reliable indicator of lung volume during HFOV (Thome et al 1998a), is impractical for frequent measurement and does not indicate the point within the PV relationship that ventilation is being applied. This study showed that RIP is a practical technique for determining relative $\Delta V_L$ during HFOV. RIP has the advantage of being noninvasive, unaffected by ETT leak and is simple to use without the need to interrupt mechanical ventilation. Uncalibrated DC-coupled RIP has been validated in animal studies as a measure of change in thoracic gas volume, allowing the complete PV relationship of the lung to be described and optimum lung volume, and $P_{aw}$, to be determined during HFOV in animal models (Brazelton et al 2001; Göthberg et al 2001; Markhorst et al 2006; Weber et al 2000). The $P_{aw} – V_{LRIP}$ relationships described in this study were similar to the $P_{aw} – V_{LRIP}$ plots reported in these animal studies.

The combined $P_{aw} - V_{LRIP}$ data from this study fitted the mathematical model proposed by Venegas et al (1998). This model assumes TLC to be the point of greatest lung volume. The finding that, in nine infants, the maximum $V_{LRIP}$ did not occur at $P_{max}$ is curious. Brazelton et al (2001) reported a similar finding in piglets receiving HFOV, with the maximum $V_{LRIP}$ occurring on the deflation limb, but not at TLC. They attributed this finding to overdistension at TLC. There are other possible explanations for this finding. Firstly, changes in intrathoracic blood volume and impaired cardiac output may have occurred at $P_{max}$ (Gullberg et al 2004). RIP would be unable to distinguish this effect from a change in lung volume. Secondly, alveolar recruitment is not uniform, even at high airway pressures. Alveolar opening pressures vary and overdistension of some alveoli may compress adjacent, collapsed alveoli at $P_{max}$ (Halter et al 2003; Schiller et al 2003; Steinberg et al 2004). Only at pressures below TLC may these compressed alveoli
be able to open after alveolar recruitment. Finally, it is likely that absolute TLC was not achieved at $P_{\text{max}}$ in this study, and that further time dependent recruitment was occurring after the mapping of the deflation series commenced. As absolute lung volume was not measured during this study, this final explanation cannot be excluded. But, if true, it is of limited practical significance. In this study, $P_{\text{max}}$ was defined by the presence of no further increase, or a deterioration, in $SpO_2$. Further increases in $P_{aw}$ above $P_{\text{max}}$ would not achieve any clinical benefit, even if the lung was not approaching absolute TLC.

Hysteresis was variable, not an unexpected finding given the heterogeneity of lung disease between infants. The PV data during the deflation series closely resembled the portion of the deflation limb of the PV relationship between TLC and CCP. This indicates that any resultant change in lung mechanics or gas exchange during the deflation series should be a result of a change in the volume state of the lung (Rimensberger et al 2000b; van Kaam et al 2003).

In summary, the use of the open lung ventilation strategy, and RIP to measure $\Delta V_L$, were able to define the key regions of the PV relationship in each infant. This suggests that a HLVS can be achieved using an open lung approach. By virtue of allowing a high lung volume to be maintained with a relatively low $P_{aw}$, open lung ventilation strategies may be a preferable approach to achieving a HLVS than currently used ventilation strategies.

10.3 Influence of the volume state of the lung on gas exchange and lung mechanics

10.3.1 Oxygen saturation

There was a close intra- and inter-subject relationship between $SpO_2$ and the volume state of the lung. Generally, during the inflation series, $SpO_2$ initially increased as $P_{aw}$ was increased from $P_{\text{initial}}$, presumably due to lung volume recruitment. As the lung approached TLC, $SpO_2$ usually started to fall, most likely secondary to overdistension. $SpO_2$ also deteriorated with falling $V_{L,RIP}$ during the deflation series, presumably due to increasing derecruitment. These data are similar to the $PaO_2$ response to the open lung approaches used in the animal studies of Vazquez et al (1999a, 1999b), van Kaam et al (2003, 2004), Rimensberger et al
Discussion

(1999b, 2000) and the earlier work, exploring alveolar recruitment during HFOV, of Kolton et al (1982). The ability of $\text{SpO}_2$ to act as a proxy indicator of lung volume during HFOV in this study was confirmed by the close fit of the mathematical model of the PV relationship (Venegas et al 1998) to the $P_{aw} - \text{SpO}_2$ and $V_{LRIP} - \text{SpO}_2$ data. Despite this, in three infants it was not possible to identify derecruitment near $P_{\text{final}}$ using $\text{SpO}_2$, even at a $P_{aw}$ of 6 cm $\text{H}_2\text{O}$ or less. This is likely due to the $P_{aw}$ at $P_{\text{final}}$ being above the CCP of the lung.

It should be noted, that the open lung ventilation strategy developed for this study differed from that described by Lachmann (1992), and later used in the clinical studies of Rimensberger et al (2000) and De Jaegere et al (2006). In these studies, a target $\text{SpO}_2$ range was set and recruitment/derecruitment identified from the change in required $\text{FIO}_2$. This approach is more practical than the method used in this study, and acknowledges the increasing awareness of the dangers of hyperoxia (Askie et al 2003), but it assumes that $\text{SpO}_2$ can accurately approximate $P_{\text{aO}_2}$ over a range of different lung volumes in newborn infants receiving HFOV. This has not been verified in human infants.

10.3.2 Quasi-static compliance

Compliance has never been systematically described in human infants receiving HFOV. The PV mapping procedure used in this study allowed description of a relationship between an indicator of quasi-static $C_{rs}$ and the volume state of the lung in many infants, but often this was variable.

It was during the inflation series that the relationship between $C_{rs}$ and the volume state of the lung was most reliable. In most infants, $C_{rs}$ improved early in the inflation series, presumably due to recruitment, but then deteriorated at higher $P_{aw}$. The latter is likely to be caused by overdistension as the lung approached TLC. These findings are consistent with the animal studies of Weber et al (2000), Wood et al (2002), and Habib et al (2002), all of whom showed that $C_{rs}$ can define the inflation limb, and identify recruitment and overdistension. Weber et al (2000) and Habib et al (2002) were also using RIP to define static $C_{rs}$. 

In most infants, there was minimal change in individual $P_{aw} - C_{rs}$ and $V_{LRIP} - C_{rs}$ relationships during the deflation series, and the variability between infants was wide. This limits the ability to generalise the $C_{rs}$ results during the deflation series. The difficulties in determining $C_{rs}$ during HFOV in human infants also warrants consideration. Thus, this study suggests that quasi-static $C_{rs}$ may offer utility in determining adequate recruitment during open lung HFOV strategies, but is of limited value in defining the change in volume state after recruitment has been obtained.

10.3.3 Tidal volume at the airway opening

Measurement of $V_T$ has become standard neonatal practice during IPPV in infants, and is often used to guide ventilatory management. Given the clinical familiarity with this technique, and the relative ease of use, it is surprising that the use of $V_T$ during HFOV has not been more thoroughly examined, even if to simply aid determination of an appropriate $\Delta P$ or frequency. The results in this study were very similar to the results reported by Mills in his PhD thesis (2003 unpublished). Mills identified a relationship between $V_T$ and the volume state of the lung that was independent of $\Delta P$ and frequency in a piglet model of surfactant-deficient lung disease. For most infants in this study, $V_T$ was able to identify overdistension and atelectasis, as well as demonstrating hysteresis. This is not surprising, as there is no reason to expect that the general principles of lung mechanics differ between HFOV and IPPV.

The $V_T$ values recorded in this study were frequently greater than expected, a finding that had been identified earlier in preterm infants (Dimitriou et al 1998; Zimova-Herknerova & Plavka 2006). Both these studies suggested that, in some situations, tidal volume at the airway opening maybe greater than the presumed anatomical dead space during HFOV. Whether the tidal volumes in the alveoli were also this great in the 15 infants studied is unclear. Irrespective of this concern, these studies suggest that the relative change in displayed $V_T$ may aid determination of the volume state of the lung.
10.3.4 Tidal volume determined with RIP

Like $V_T$, $V_{TRIP}$ was also influenced by the volume state of the lung. This finding is consistent with the limited animal (Mills 2003 unpublished; Pillow et al 2002) and bench top (Pillow et al 2002) data that exists. The use of RIP to assess tidal volume during HFOV has not been reported before in humans. RIP measures breath-to-breath CWM. In most situations, the greatest contributor to CWM will be tidal volume change in the distal respiratory tree. Due to this, and the fact that $V_{TRIP}$ is independent of ETT leak, the potential of RIP to measure tidal volume during HFOV is appealing.

Experienced clinicians often use visual assessment of CWM to determine $\Delta P$ during HFOV. $V_{TRIP}$ may be a quantifiable method of assessing CWM. Pillow et al (2002) identified that CWM was dependent on the volume state of the lung in a preterm lamb model of surfactant-deficient lung disease. Mills (2003 unpublished) also reported a similar relationship in a piglet model of surfactant-deficient lung disease in his PhD thesis. This study is the first to quantify CWM in human infants receiving HFOV and, to a limited degree, justifies the subjective visual assessment of CWM to determine tidal volume.

10.3.5 Transcutaneous carbon dioxide

$T_{cCO_2}$ is frequently used to guide $\Delta P$ and frequency during HFOV. This is the first study to systematically describe CO$_2$ removal throughout the PV relationship in human infants. In most infants, there was a close relationship between $T_{cCO_2}$ and the volume state of the lung, which was independent of $\Delta P$ and frequency. Also, $T_{cCO_2}$ was generally lower on the deflation series after transient impairment during recruitment to TLC than during the inflation series. This suggests that CO$_2$ removal may aid clinicians determine recruitment and an optimal $P_{aw}$. A relationship between CO$_2$ and the volume state of the lung, that was $\Delta P$ and frequency independent, was reported by Mills (2003 unpublished) in his PhD thesis. Incidentally, De Jaegere et al (2006) reported a decrease in $T_{cCO_2}$ of 9 mmHg when HFOV was applied at a $P_{aw}$ 2 cm H$_2$O above CCP, after lung recruitment with an open lung approach.
10.3.6 Analysing the data using mathematical modelling

To allow for inter-subject comparison, some of the data were normalised. After data normalisation, it was possible to fit a quadratic model to the pooled data sets with either a strong ($SpO_2$, $VT$, $TcCO_2$) or moderate ($VT_{RIP}$, $C_{rs}$) goodness-of-fit.

A strong fit of the quadratic model to the data, in this study of a small and heterogeneous group, suggests a relationship that may be reproducible in the wider population. A quadratic model was chosen as it results in a bell- or U-shaped relationship. This may allow identification of an optimal point (peak or trough) within the data range (see Chapter 10.3). Moreover, this model was also used by Mills (2003 unpublished) in his PhD thesis, to describe the relationship between the volume state of the lung, gas exchange and lung mechanics during HFOV in an animal study.

Habib et al (2002) was able to show that $C_{rs}$ followed a second-order sigmoid relationship during recruitment along the inflation limb. In addition to the difficulties with $C_{rs}$ calculation, the fact that only part of the PV relationship was mapped in this study may explain the poor correlation between $C_{rs}$ data and the model of the PV relationship proposed by Venegas et al (1998). This model assumes the data represents the entire inflation or deflation limb and attempts to fit the data with a symmetrical second order sigmoidal model.

In summary, it was generally possible to identify a relationship between the volume state of the lung and the indicators of gas exchange and lung mechanics studied during mapping of the PV relationship. These results suggest that an open lung ventilation strategy may aid clinicians in optimising ventilation. There was considerable inter-subject variability in the results. The causes are likely multifactorial, but mostly due to the inherent limitations of the methods used to describe gas exchange and lung mechanics and the heterogeneity of the study population (Chapter 10.4).
10.4 Identification of optimal ventilation using the parameters studied

In most infants, it was possible to identify a range of $P_{aw}$ that optimised each of $V_{L,RIP}$, $\text{SpO}_2$, $T_c\text{CO}_2$, $C_{rs}$, $V_T$ and $V_{TRIP}$. For all of these parameters, this was on the deflation limb between TLC and CCP. The optimal $P_{aw}$ for each parameter differed in each infant. Thus, defining optimal ventilation based on one single parameter may be misleading. In this study, no single common numerical $P_{aw}$ value could be identified that universally resulted in alveolar recruitment and optimal ventilation for each infant. It may be more appropriate to consider the region of optimal ventilation within the bounds of each infant’s PV relationship at that point in time, a method that accounts for individual differences.

Traditionally, optimal ventilation has been solely defined by the response to oxygenation (De Jaegere et al 2006; Lachmann 1992; McCulloch et al 1988; Rimensberger et al 2000a). Although oxygenation was the most robust indirect parameter tested in this study, there was often no appreciable single $P_{aw}$ that resulted in optimal $\text{SpO}_2$ in most infants. Rather, the best $\text{SpO}_2$ value that could be obtained occurred over a wide range of pressures. This resulted in $\text{SpO}_2$ changing little during the deflation series, until the $P_{aw}$ fell below 25% of the value at $P_{\text{max}}$, or an average of 4.8 cm H$_2$O above $P_{\text{final}}$. Usually, this occurred at a lower $P_{aw}$ than $P_{\text{initial}}$. Brazelton et al (2001) also found that $P_{a\text{O}_2}$ approximated optimal $P_{a\text{O}_2}$ over a wide range of pressures between TLC (40 cm H$_2$O) and CCP, in the surfactant-deficient piglet. Consequently, there appears to be no practical benefit in applying ventilation above the lowest $P_{aw}$ that maintains optimal $\text{SpO}_2$, once ventilation is applied on the deflation limb.

This leads to the question of how best to clinically define a range of $P_{aw}$ that results in optimal ventilation on the deflation limb?

It may be argued that optimal ventilation should be defined by the $P_{aw}$, or range of $P_{aw}$, where gas exchange and lung mechanics are all optimised.
In most infants, the optimal $P_{aw}$ for each of $C_{rs}$, $V_T$, $V_{TRIP}$ and $Tc_{CO2}$ differed significantly from that for $Sp_{O2}$. As shown in Figure 10-1, the optimal point for each of these was more closely related to each other, and $P_{final}$, than optimal $Sp_{O2}$. The optimal point of ventilation for $C_{rs}$, $V_T$, $V_{TRIP}$ and $Tc_{CO2}$ was closely related to the lowest $P_{aw}$ that resulted in near-maximum $Sp_{O2}$ during the deflation series (normalised $P_{aw}$ of 25%). Targeting a higher $P_{aw}$, to achieve slight gains in $Sp_{O2}$, would be at the expense of impaired $C_{rs}$, tidal volume and $CO_2$ removal. This suggests that a $P_{aw}$ of 30% of the pressure difference between TLC and CCP may represent the optimal point of ventilation, in most infants.

![Figure 10-1. Relationship between the deflation limb of the PV relationship between TLC and CCP (grey line), derived using the mathematical model proposed by Venegas et al (1998), and the optimal $P_{aw}$ for $V_{LRIP}$, $Sp_{O2}$, $V_{TRIP}$, $V_T$, $C_{rs}$ and $Tc_{CO2}$, $P_{initial}$ and the same $P_{aw}$ during the deflation series are also shown. Pressure and volume is expressed using normalised data. Optimal $P_{aw}$ points are mean and error bars standard error of mean.](image)
Identifying TLC and CCP is critical to all open lung ventilation strategies (Lachmann 1992). The use of oxygenation alone to determine these points requires the need to transiently de-recruit the lung to identify CCP (De Jaegere et al 2006; Lachmann 1992). The impact of repeatedly doing this on the neonatal lung has not been studied in detail. It may be safer to define CCP using techniques that do not require transient derecruitment.

The finding of optimal lung mechanics and $T_c CO_2$ close to, but above, the CCP may obviate the need to de-recruit the lung. This could be achieved by exploiting the quadratic relationship between the volume state of the lung and $T_c CO_2$, $V_T$ and, to a lesser extent, $V_{TRIP}$. Figure 10-2 illustrates how these principles might apply to an individual in clinical practice. Using the overall mean $P_{aw}$ data from all 15 infants, the $P_{aw}$ resulting in optimal $C_{rs}$ and $V_T$ would be 5.2 cm H$_2$O above $P_{final}$. $V_{TRIP}$ and $T_c CO_2$ are optimised at 5.7 cm H$_2$O and 2.8 cm H$_2$O above $P_{final}$, respectively. These values are also closely related to the lowest $P_{aw}$ that maintained optimal $SpO_2$. Thus, in this hypothetical infant, optimal ventilation is achieved at a $P_{aw}$ of approximately 4 cm H$_2$O above $P_{final}$.

![Figure 10-2](image_url)

**Figure 10-2.** Optimal $P_{aw}$ defined by lung volume ($V_{LRIP}$), oxygen saturation ($SpO_2$), tidal volume ($V_T$ and $V_{TRIP}$), quasi-static compliance ($C_{rs}$) and transcutaneous carbon dioxide ($T_c CO_2$). Lowest $SpO_2$ represents the lowest $P_{aw}$ that maintains near-optimal $SpO_2$ during the deflation series. All $P_{aw}$ are mean values and referenced to the $P_{aw}$ at $P_{initial}$ (0 cm H$_2$O).

By observing the behaviour of CO$_2$ removal and lung mechanics during the deflation series, there is no need to decrease $P_{aw}$ to CCP. After the optimal $P_{aw}$ for each has been obtained, further decreases in $P_{aw}$ are likely to result in impairment of each parameter. This would alert the clinician that the lung is almost at its CCP. Further decreases in $P_{aw}$ would be unnecessary.
In summary, these data suggest that ventilation can be optimised by targeting the deflation limb of the PV relationship at a $P_{aw}$ that approximates 30% of the pressure difference between TLC and CCP, rather than the higher $P_{aw}$ needed to achieve optimal oxygenation. The use of indicators of lung mechanics and CO$_2$ at the bedside, and an understanding of their relationship with lung volume, may also allow clinicians to refine the delivery of an open lung ventilation strategy.

10.5 Limitations of the study

There are a number of limitations to this study that need to be considered.

10.5.1 Study population

This study only examined fifteen infants in detail. The study population was also heterogeneous and did not include any extremely preterm infants with hyaline membrane disease, who constitute the largest group receiving HFOV in Australia and New Zealand (Tingay et al 2007b). Due to feasibility and safety concerns, these limitations were self-imposed.

All infants enrolled in this study were also receiving muscle relaxants, a practice that is not routine in the acute respiratory management of preterm infants. The lung mechanics of this population may be different from those of self-ventilating infants receiving HFOV. The exclusion of self-ventilating infants was intentional to minimize the effect of spontaneous ventilation and movement artefact, and to reproduce the optimal ventilation strategy identified in animal studies (Rimensberger et al 1999b; Rimensberger et al 1999a; Rimensberger et al 2000b; van Kaam et al 2003; van Kaam et al 2004a; Vazquez de Anda et al 1999). Generalisation of these results to the wider newborn population, in particular the preterm infant, must be undertaken with caution.

10.5.2 Mapping of the PV relationship

Unlike adult patients (Albaiceta et al 2004), constructing a complete PV relationship is not possible in human infants. In this study, for reasons of safety, the lung was not allowed to passively deflate prior to commencing PV mapping, nor was the lung allowed to fully deflate beyond the CCP. Thus, the inspiratory limb of the PV relationship and the final section of the deflation limb, beyond
CCP, are incompletely mapped. Even so, the data obtained closely resembled the PV relationships described by Brazelton et al (2001) using RIP in piglets receiving HFOV. The $P_{aw} - V_{L,RIP}$ data also conformed to the mathematical model proposed by Venegas et al (1998). Even incomplete mapping of the PV relationship in human infants is of practical value, as it allows the deflation limb to be accurately defined within the confines of a clinically acceptable $SpO_2$ range.

Similarly, it is possible that $P_{max}$ and $P_{final}$ did not truly represent TLC and CCP, especially in this population with heterogeneous lung disease and variable pulmonary blood flow. Ideally, these points can only be defined during a series of known volume changes. In this study, they were defined using oxygenation as a proxy indicator of lung volume. Thus, it is more appropriate to view $P_{max}$ and $P_{final}$ as practical definitions of TLC and CCP. It is unlikely that clinicians would willingly expose the lung to a $P_{aw}$ above $P_{max}$, or below $P_{final}$, given the knowledge that these represent the absolute bounds of acceptable oxygenation.

It is possible that ventilation was being applied closer to the deflation limb prior to the episode of ETT suction performed before commencing each study. ETT suction, especially methods that involve disconnection from mechanical ventilation, is known to result in transient derecruitment of lung volume (Choong et al 2003; Hoellering et al 2008). Despite its wide spread use in clinical practice, an alveolar recruitment manoeuvre was not applied immediately after these episodes of ETT suction as pre-suction lung volume was unknown. Instead, commencement of the study was deferred for thirty minutes to allow for passive, time-based recruitment to restore lung volume. There is limited data to suggest that, even in infants receiving muscle relaxants, lung volume returns to pre-suction values within a few minutes of ETT suction (Hoellering et al 2008; Tingay et al 2007).

10.5.3 RIP

The concerns relating to RIP calibration during HFOV (Markhorst et al 2006), drift of the $\Delta V_L$ voltage signal (Brazelton et al 1999b abstract) and accuracy to measure very small $\Delta V_L$ at fast rates (Markhorst et al 2006) are pertinent to this study. A detailed discussion of the general limitations of RIP can be found in Chapter 2.5.3. Attempts were made to reduce these errors by using an uncalibrated raw RIP
Discussion

voltage signal and determining the drift and accuracy of the RIP device before data collection. Despite this, it is acknowledged that RIP was not compared to a standardised method of assessing lung volume in this study, such as whole body plethysmography. These comparisons have been made previously (Albaiceta et al 2003a; Carry et al 1997).

In this study, assessment of lung volume using RIP was made on infants receiving muscle relaxants. Whether RIP has the ability to reliably determine change in lung volume over prolonged periods of time in self-ventilating infants receiving HFOV, especially those preterm, is unknown. Recently, RIP has been successfully used to determine $\Delta V_L$ immediately before, during and for five minutes after ETT suction in self-ventilating infants receiving both HFOV and conventional mechanical ventilation (Hoellering et al 2008).

Most RIP software has been developed largely for application in sleep medicine. There is currently no integrated RIP software available to track neonatal lung volume during mechanical ventilation, hampering the progression of RIP from a research to a clinical tool.

The limitation of RIP to distinguish between change in gas, blood or tissue volume within the thorax has been discussed previously. RIP simply provides an estimation of global thoracic volume. RIP is unable to distinguish between alveolar recruitment and overdistension, both of which would result in an increase in $V_{L RIP}$. RIP is also unable to determine differences in regional lung volume in the heterogeneous and gravity-dependent diseased lung. In this study, RIP could not confirm that homogeneous recruitment was achieved in all parts of the lung at $P_{max}$. It is possible, although unlikely due to the gas exchange and lung mechanics results, that the regional volume state at $P_{max}$, or elsewhere on the deflation limb, represented overdistension of less dependent lung units with ongoing collapse of dependent units. Such a volume state could not be considered lung protective. The incremental recruitment strategy used in this study was similar to studies in adults (Albaiceta et al 2004) and neonatal piglets (Pellicano et al 2004 abstract) that used computerised tomography to confirm homogeneous alveolar recruitment.
Since commencing this study, a new non-invasive technique to assess lung volume has become available, called electrical impedance tomography (EIT). EIT allows measurement of regional volume differences and global volume changes within the lung (Wolf & Arnold 2005). EIT has been validated as a measure of regional change in EELV and tidal volume during open lung ventilation in surfactant-deficient animal models (Frerichs et al 2006), and during HFOV in preterm infants (Dunlop et al 2006). EIT offers potential as a future alternative to RIP and would have been a potent adjunct to RIP had it been available at the commencement of this study.

10.5.4 Indicators of gas exchange and lung mechanics

The techniques used to assess gas exchange and lung mechanics in this study relied upon indirect measures of the parameter in question. The limitation of each measurement needs to be considered if they are to be used as proxy indicators of optimum lung volume. It should be noted, however, that at present no other feasible bedside alternatives exist for many of these indirect measures of gas exchange and lung mechanics.

**SpO₂ as a proxy indicator of PaO₂**

Whilst SpO₂ monitoring is the most commonly used bedside indicator of oxygenation it has limitations as a proxy of PaO₂. Transcutaneous pulse oximetry is known to have an error of ± 4-6% in relation to the true arterial oxygen saturation (Poets & Martin 1996). SpO₂ values are influenced by tissue perfusion and any given SpO₂ reading may represent a wide range of PaO₂ values. For example, SpO₂ is unable to identify any further improvement in oxygenation once a SpO₂ of 100% is obtained. This limitation is noticeable in the Paw - SpO₂ curves of subjects 3 and 12 (Figure 6-1) and the general variability in the Paw - SpO₂ relationships compared to the PV relationships. The close association with PaO₂ in the pilot study is reassuring but, in hindsight, sampling of PaO₂ at critical points during each open lung ventilation strategy (such as P_initial, P_max and P_final) would have been useful.

In clinical practice, the response of oxygenation to applied pressure may be altered by other factors apart from lung volume, such as alterations in pulmonary blood flow and pulmonary vascular resistance (Dimitriou et al 2004; Markhorst 2005 unpublished). In this study, eight infants had PPHN being treated with iNO, and
ten required inotropic support. It is possible that the presence of PPHN in some infants accounted for the variability in the results in individual patients. Interestingly, the relationship between $\text{SpO}_2$ and the volume state of the lung in these infants did not differ from those without pulmonary hypertension or cardiac failure. In all infants, cardiac failure or PPHN was stable at the time of study. This may explain these findings. It has been speculated that pulmonary hypertension and cardiac failure are less important during HFOV with a HLVS than IPPV, due to better lung recruitment with HFOV (Dobyns et al 2002). In a study of 108 paediatric patients with acute hypoxic respiratory failure, Dobyns et al (2002) found that HFOV, with or without iNO, resulted in better ventilation to perfusion matching than IPPV with iNO.

**Determination of $C_{rs}$ during HFOV**

The difficulties in measuring $C_{rs}$ during HFOV have been discussed previously. The heterogeneous quasi-static $C_{rs}$ results found in this study are most likely due to these practical difficulties. The present inadequacy of the RIP software also limits the use of RIP-derived $C_{rs}$.

Assessment of dynamic $C_{rs}$ at the airway opening is possible with a PNT during IPPV. Using this method, $C_{rs}$ is determined from $\Delta V/\Delta P$ where $\Delta V$ is the tidal volume at the airway opening and $\Delta P$ is derived from the difference in $P_{\text{peak}}$ and $P_{\text{trough}}$. Unfortunately, these pressure points do not occur at zero flow during HFOV (Dargaville, personal communication). Whether this method may allow relative assessment of $C_{rs}$ during HFOV remains to be clarified.

**Difficulties determining tidal volume during HFOV**

Neither method of assessing tidal volume used in this study is without its faults. Both measurements of tidal volume can only be viewed as relative indicators of true alveolar tidal volume during HFOV. PNT assessment of $V_T$ is leak dependent and the oscillatory amplitude is attenuated through the respiratory tree during HFOV. A linear relationship between the PNT assessment of $V_T$ and alveolar tidal volume has been shown in bench-top (Scalfaro et al 2001) and animal studies (Courtney et al 1990), but has yet to be confirmed in human studies.
It is possible that RIP assessment of alveolar tidal volume results in a closer approximation of alveolar tidal volume (see Chapter 10.3.4). Unfortunately, the inability to reliably calibrate the signal during HFOV limits inter-subject comparison.

**TcCO2 as a proxy indicator of PaCO2**

TcCO2 is a proxy of PaCO2. TcCO2 is the most commonly used bedside indicator of CO2 in newborn infants, and is more reliable than end-tidal CO2 as an indicator of PaCO2 in newborn infants with respiratory failure (Sivan et al 1992; Tingay et al 2005). Whilst TcCO2 has been shown to reliably monitor CO2 trends over time (Huch 1995; Poets & Martin 1996; Tingay et al 2005), the method is limited by skin perfusion (which may be altered by oedema, hypovolaemia and vasoconstrictive agents) and a slow response time (30 – 50 seconds) (Schibler & Frey 2002). TcCO2 reliability decreases with time and resiting of the transcutaneous electrode every two hours is recommended by most manufacturers. In this study, Pfinal was frequently not obtained until more than two hours after the study commenced and the electrode was often left in situ. This and a potential lag in TcCO2 expressing any change in volume state, may explain some of the variability seen in individual Paw - TcCO2 relationships. Again, intermittent sampling of PaCO2 at critical points during the open lung ventilation strategy would have been beneficial.

**10.6 Chapter summary**

In this chapter, the results of the study, as they related to the aims, have been discussed. In this study, it was possible to map the PV relationship of the lung using an open lung ventilation strategy in infants receiving HFOV, and describe the relationship between the volume state of the lung and bedside indicators of gas exchange and lung mechanics. The potential to use these relationships to identify an optimal point of ventilation was examined. Finally, the limitations of the study were considered.

The conclusions that can be drawn from these results, and the implications for future research arising from this study, are stated in the following chapter.
Chapter 11.

CONCLUSIONS

11.1 Introduction

The purpose of this chapter is to summarise the conclusions that can be drawn from this thesis and outline the implications for future research.

11.2 Major Findings

This study is the first in human infants to systematically describe the quasi-static PV relationship of the lung at the bedside during HFOV. To do so, a ventilation strategy based on the open lung approach was developed and tested. During this process, potential indirect indicators of lung volume were measured. These were then compared to the volume state of the lung, to determine any relationship that clinicians could exploit to optimise ventilation.

The major findings of this study were:

1. Mapping the key regions of the PV relationship was practical, repeatable and well tolerated in the infants studied.
2. RIP can non-invasively measure relative $\Delta V_L$ in newborn infants during HFOV and aid identification of the volume state of the lung, in particular recruitment and derecruitment.
3. Bedside measures of oxygenation, carbon dioxide, tidal volume, and to a lesser extent, quasi-static compliance exhibit a relationship with the volume state of the lung which could be exploited to identify overdistension and atelectasis.
4. Using an open lung approach to target the deflation limb of the PV relationship resulted in a higher lung volume, improved gas exchange and better tidal volume than was being achieved with current ‘high lung volume’ strategies, and often at a lower $P_{aw}$.
5. A HLVS, as is currently practised, may not result in HFOV being applied optimally.
6. Using $Sp_{O_2}$, with at least one of $Tc_{CO_2}$, $V_T$, $V_{TRIP}$ and $C_{rs}$, enabled identification of the region of optimal ventilation on the deflation limb. In conjunction, these
parameters may allow determination of the optimal $P_{aw}$ to apply HFOV in human infants.

11.3 Future implications

This study has raised additional questions which justify future research.

This study could not define regional volume behaviour. The need to quantify the regional volume distribution during recruitment to TLC and mapping of the deflation limb with an open lung approach is required. In particular, to determine whether the open lung ventilation strategy tested in this study results in homogenous alveolar recruitment rather than overdistension.

There is no reason why IPPV cannot be delivered with an open lung approach in human infants. Whether HFOV may offer any benefit in achieving homogeneous recruitment compared to IPPV warrants investigation. A future series of experiments, using EIT and RIP, is being developed to investigate regional distribution of EELV and tidal volume during synchronised volume-targeted IPPV and HFOV, both delivered with an open lung approach. This will initially require study in animal models to refine an open lung ventilation strategy during IPPV. Later, this series of experiments will involve premature infants with hyaline membrane disease, an important diagnostic group omitted in this thesis.

It is hoped that future studies will allow further quantification of the relationship between the volume state of the lung and the indirect parameters tested in this thesis. Of major interest is whether the changes believed to be due to overdistension, collapse or recruitment of lung volume are confirmed to be so using EIT.

Time is often a neglected consideration in the development of recruitment strategies. Comparing relatively rapid recruitment strategies, such as those used by Rimensberger et al (2000) and De Jaegere et al (2006), to slow strategies, such as the approach used in this thesis, is needed before open lung ventilation strategies can be used in the wider neonatal population. A series of experiments is being planned to test this in animal models of term and preterm neonatal lung disease.
A further aspect of time dependent alveolar recruitment requires investigation. This thesis did not assess how to maintain the optimal ventilation point once it had been achieved on the deflation limb, but it did identify that the volume state of the lung was a dynamic entity. Determining when to repeat recruitment and mapping of the PV relationship is required. In future studies of open lung ventilation, it is proposed that the lung be held at the optimal point after an open lung is achieved, and the behaviour of lung volume, gas exchange and lung mechanics at that point observed over time.

By addressing these questions it is hoped that practical ventilation strategies, that aim to optimise ventilation and reduce VILI, can be developed and tested in wider neonatal populations.
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Publications and presentations arising from this thesis

Publications


Presentations

Pediatric Academic Societies Annual Scientific meetings

**14 – 17 May 2005 in Washington D.C., USA**


**29 April – 2 May 2006 in San Francisco, CA, USA**

European conference on Paediatric and Neonatal Ventilation

**7th Conference held in Montreux, Switzerland on 24 – 27 March 2004**
Publications and Presentations arising from this Thesis

7th Conference held in Montreux, Switzerland on 29 March – 1 April 2006

Perinatal Society of Australia and New Zealand Annual Congress
8th Annual Congress held in Sydney, NSW, Australia on 15 – 18 March 2004


9th Annual congress held in Adelaide, SA, Australia on 2005


Australian and New Zealand Intensive Care Society
31st Annual Scientific meeting held in Hobart, Tasmania, Australia on 12 – 15 October 2006
30th Annual scientific meeting held in Adelaide, SA, Australia on 20 – 23 October 2005

Describing the deflation limb of the pressure-volume (PV) relationship in infants receiving High Frequency Oscillatory Ventilation (HFOV). Tingay D, Dargaville PA, Pellicano A, Morley CJ, Mills JF. *Oral presentation awarded ‘Paediatric best medical paper’.*
Appendix

ROYAL CHILDREN’S HOSPITAL

PARENT/GUARDIAN INFORMATION STATEMENT

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Title of Project
Optimising the clinical application of high frequency oscillatory ventilation using techniques which describe lung mechanics

Thank you for taking the time to read this Information Statement.
This information statement is 4 pages long. Please make sure you have all the pages.
Your child is invited to participate in a Research Project that is explained below.

What is the Research Project about?
Some newborn babies develop difficulty with breathing at or soon after birth, which may require the assistance of a breathing machine (ventilator). “Conventional” ventilators imitate a baby’s normal breathing pattern and, while they help save lives, they may cause damage to the fragile lining of the lungs. Another type of breathing machine has been developed called a high frequency oscillator that may cause less damage to the lungs than a conventional ventilator. High frequency oscillatory ventilation (HFOV) works by giving lots of little breaths much faster than babies normally breathe (over 600 breaths each minute), and at a lower pressure than is needed during conventional ventilation.

HFOV is frequently used in the Neonatal Unit, Royal Children’s Hospital and in many other neonatal intensive care units in Australia and the rest of the world. It is most often used when a sick baby is not getting better on a conventional ventilator. For HFOV to be used safely and effectively, the pressure delivered by the ventilator needs to be within a narrow range; too much pressure and a baby’s lungs are too expanded, too little and they are not expanded enough. If HFOV is not used within this narrow range of pressure settings, the lining of the lungs may be damaged and the chance of bleeding inside the brain may be increased.

In this project, we are interested in finding out the best pressure to use when a baby is receiving HFOV. At the moment, we use the amount of oxygen a baby needs and the size of the lungs on an X-ray to guide us in finding the correct pressure. Unfortunately these methods are imprecise and may result in too much pressure being used. Research in this hospital and overseas suggests that HFOV may be safer if a lower pressure is used than would be suggested by the indicators mentioned above. Recently, we have discovered some new ways of identifying this lower pressure level during HFOV. These include measuring the tidal volume (the amount of air a baby breathes in and out with each breath), the amount of chest wall movement (the amount a baby’s chest moves with each breath), and the level of carbon dioxide (a gas that babies breathe out through the lungs) in the blood. The tidal volume and chest wall movement of a baby receiving HFOV can easily be measured using a device called a Respitrace. It consists of two small stretchy bands that
are placed around the baby’s chest and stomach. This device has already been tested overseas on many newborn babies and the Australian Therapeutic Goods Administration (TGA) has approved its use on newborn babies in Australia. The carbon dioxide level in the blood is already routinely monitored in all babies receiving HFOV. We think that these new measurements may be a more reliable guide to the correct pressure whilst on HFOV than the ones we currently use but we don’t know for certain. In this project, we aim to find out whether the old or the new measurements are the best.

Who are the Researchers?
Dr David Tingay, Dr John Mills, Dr Peter Dargaville and Prof Colin Morley

Why am I and my child being asked to be in this research project?
Your baby is already receiving HFOV as part of his/her treatment. This is an important research project to help us find out how to improve the care of babies who are receiving HFOV. The research can only be done by carefully studying the way HFOV affects a baby’s lungs.

What does my child need to do to be in this research project?
We will need to place two small stretchy bands around your baby’s chest and stomach (the Respitrace). This allows us to measure how your baby’s lungs change during HFOV. In addition, we will need to connect a pressure-measuring device (Florian monitor) between the HFOV machine and the breathing tube going into your baby’s lungs. Neither will restrict your baby’s breathing nor cause discomfort. All other treatment will continue uninterrupted. We will then steadily decrease the pressure delivered by the ventilator and simultaneously measure the tidal volume, chest wall movement and carbon dioxide level. This process will take approximately 120 - 180 minutes. When all the measurements have been taken, we will restore the HFOV settings to those used prior to the study.

Is there likely to be a benefit to my child?
Your baby will receive the best possible care that we can give. Your baby is already receiving HFOV and we know this treatment is very effective. It is possible that your baby may receive HFOV more effectively as a result of the study.

Is there likely to be a benefit to other children in the future?
This research should help us improve our understanding of HFOV. The results of this study will certainly be important in helping improve the care of critically ill babies needing HFOV in the future.

What are the possible risks and/or side effects for my child?
HFOV is a form of treatment that has become standard in many neonatal intensive care units for babies with respiratory difficulties. There should be no more risks for your baby in this study than are possible for any baby needing intensive care. As we slowly decrease the pressure that your baby receives, there is the possibility that he/she may need more oxygen, or that there may be a change in blood pressure or heart rate. If any of these occur, we will stop the study and restore the previous HFOV settings.

What are the possible discomforts and/or inconveniences for me or my child?
Apart from the results collected from the Respitrace, all the other data will be collected by recordings from the monitors or from devices that we will connect directly to the HFOV machine. There should be no discomforts or inconveniences.

What will be done to make sure the information is confidential?
Your baby’s privacy is important to us. If your agree for your baby to take part in this study, your baby’s medical records may be inspected by regulatory authorities, such as the Australian Therapeutic Goods Administration (TGA) as well as the Royal Children’s Hospital Ethics Committee in order to check that the study is being carried out correctly.
Your baby’s name, however, will not be disclosed by the hospital. All documents collected will contain a subject number (which will be allocated on enrolment in the research project) and your baby’s initials only. All data will be recorded using the study number rather than your baby’s name. These documents are stored in a locked cupboard and computer data protected with a password only known to the researchers.

By signing the consent form you are giving authority for the release of or access to confidential information to relevant study personnel and regulatory authorities for the verification of study data and procedures.

**Will I be informed of the results when the research project is finished?**

If you wish to be informed of the results when the research project is finished, please tell Dr David Tingay, who will contact you with the results. A report about the whole study can be sent to you if you wish.

**You can decide whether or not you give permission for your child to take part in this research project.**

**You can decide whether or not you would like to withdraw your child from this research project at any time. No explanation is needed.**

You may like to discuss your participation in this research project with your family and with your doctor. You can ask for further information before deciding if your child will take part.

The name and telephone number of the person to contact for more information or in an emergency is:

**Dr David Tingay on (03) 93455000, or on (03) 93455522 and pager 4500.**

For parents/guardians who speak languages other than English

**If you would also like Information about the research and the Consent Form in your language, please ask for it to be provided.**

**What are my child’s rights as a Participant?**

1. I am informed that except where stated above, no information regarding my child’s medical history will be released. This is subject to legal requirements.
2. I am informed that the results of any tests involving my child will not be published so as to reveal my child’s identity. This is subject to legal requirements.
3. The detail of the procedure proposed has also been explained to me. This includes how long it will take, how often the procedure will be performed and whether any discomfort will result.
4. It has also been explained that my child’s involvement in the research may not be of any benefit to him or her. I understand that the purpose of this research project is to improve the quality of medical care in the future.
5. I have been asked if I would like to have a family member or a friend with me while the project is explained to me.
6. I understand that this project follows the guidelines of the National Statement on Ethical Conduct in Research Involving Humans (1999).
7. I understand that this research project has been approved by the Royal Children’s Hospital Ethics in Human Research Committee on behalf of Women’s and Children’s Health Board.
8. I have received a copy of this document.

**If you have any questions about patient rights contact**

<table>
<thead>
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<th>The RCH Patient Representative</th>
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<tr>
<td>RCH Hospital Support Unit</td>
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<tr>
<td>Phone 9345 5676</td>
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186
STANDARD INFORMED CONSENT
FOR PARENT / GUARDIAN TO GIVE CONSENT
FOR THEIR CHILD TO PARTICIPATE IN A RESEARCH PROJECT

Title of Project
Optimising the clinical application of high frequency oscillatory ventilation using techniques which describe lung mechanics.

Principal Investigator(s) Dr David Tingay, Dr John Mills, Dr Peter Dargaville, Prof Colin Morley

Brief outline of research project including benefits, possible risks, inconveniences and discomforts
HFOV is a special form of breathing machine (ventilator) used in the Neonatal Unit, Royal Children’s Hospital for babies with breathing difficulties. For HFOV to be used safely and effectively, the pressure delivered by the ventilator needs to be within a narrow range. In this project, we are interested in finding out the best pressure to use when a baby is receiving HFOV. Recent research has suggested that there may be better ways to guide us in finding the correct pressure than those we currently use. We will compare the new ways with the old ways by using a special pressure-measuring device and the Respitrace device. Neither will interrupt nor interfere with your baby’s treatment. We will need to steadily decrease the pressure delivered by the ventilator and simultaneously measuring the new and old parameters. This process will take approximately 120 – 180 minutes. When all the measurements have been taken, we will restore the HFOV settings to those used prior to the study. There should be no inconveniences or discomforts to your baby and we will stop the study if you baby becomes unwell. Although your baby is unlikely to benefit from the project, this project should help improve the care of babies needing HFOV in the future.

I (Parent/Guardian name) ______________________________
Parent / Guardian of (child’s name) ______________________________
voluntarily consent to him / her taking part in the above titled Research Project, explained to me by
Mr / Ms / Dr / Professor ______________________________

I have received a Parent/Guardian Information Statement to keep and I believe I understand the purpose, extent and possible effects of my child’s involvement. I have been asked if I would like to have a family member or friend with me while the project was explained.
I understand that if I refuse to consent, or withdraw my child from the study at any time without explanation, this will not affect my child’s access to the best available treatment and care from the Royal Children's Hospital.

I understand I will receive a copy of this consent form.

PARENT GUARDIAN SIGNATURE ______________________________ Date __________

I have explained the study to the participant who has signed above, and believe that they understand the purpose, extent and possible effects of their involvement in this study.

RESEARCHER’S SIGNATURE ______________________________ Date __________
Author/s: Tingay, David Gerald

Title: The relationship between the volume state of the lung, gas exchange and lung mechanics during high-frequency oscillatory ventilation

Date: 2008

Citation: Tingay, D. G. (2008). The relationship between the volume state of the lung, gas exchange and lung mechanics during high-frequency oscillatory ventilation. PhD thesis, Faculty of Medicine, Dentistry & Health Sciences, Paediatrics Royal Children’s Hospital, University of Melbourne.

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