AN INVESTIGATION INTO REGIONAL VENTILATION IN INFANTS AND CHILDREN; ITS DISTRIBUTION AND DETERMINANTS

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DECLARATION

I, *Alison Lupton-Smith*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Title: **An investigation into regional ventilation in infants and children; its distribution and determinants**

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Changing body position is commonly used in the management of individuals with respiratory diseases and those receiving mechanical ventilation, in order to optimise ventilation and oxygenation. In acute respiratory distress syndrome (ARDS), prone positioning is reported to improve oxygenation by recruiting collapsed dorsal lung regions, although this has not been confirmed in children. Ventilation distribution is well established in adults as being gravity dependent. Clinical practice in the paediatric population has been guided by the notion that all children, irrespective of the presence or absence of disease and age, consistently demonstrate the opposite ventilation distribution pattern to adults and this pattern is said to occur until the second decade of life. Studies in the paediatric population are limited to a few reported from the 1980's, on very heterogeneous populations. With advances in technology, new methods of examining regional ventilation, such as electrical impedance tomography (EIT), have become available. Recent neonatal studies using EIT have reported a dissimilar ventilation distribution to the conventional paediatric pattern. Despite a growing number of studies examining the effects of various interventions on ventilation distribution, very few exist in infants and children older than 6 months of age. Furthermore, differing methodologies and the manner in which ventilation distribution is described and analysed makes pooling the available data in the paediatric population extremely difficult. An understanding of how ventilation is distributed under normal conditions is imperative when examining the effects of different interventions and medical conditions on ventilation distribution.

This thesis aimed to describe the effects of body position, head position, age, and respiratory muscle activity on ventilation distribution in children between six months and nine years of age under normal conditions, with respiratory disease, neuromuscular disease, and during mechanical ventilation. Furthermore, the effect on ventilation distribution of prone positioning in children with ARDS was evaluated.

Regional ventilation distribution was measured using thoracic EIT and respiratory muscle activity was measured using surface electromyography (sEMG) using standardised methodology.

Results of a series of sub-studies indicate that ventilation distribution is more complex and variable than previously thought, with no standard “paediatric pattern” of ventilation. Overall, greater ventilation occurred in the right and dorsal lungs, respectively, in different positions. Head position did not affect regional ventilation in the children studied. Age had a variable effect on ventilation distribution, with healthy children under 12 months of age more likely to follow the paediatric pattern, particularly in side lying positions; however, the response was not uniform. The presence of mechanical ventilation, disease state and respiratory muscle activity did not affect ventilation distribution with these children also showing variable patterns of regional ventilation distribution. Data suggests that turning children with ARDS into the prone position does not result in recruitment of the dorsal lung regions, but rather more homogenous ventilation throughout the lungs. Furthermore, results suggest that children with greater ventilation inhomogeneity at baseline are more likely to respond positively (improvement in oxygenation index) to prone positioning.

This research provides novel insights into ventilation distribution and respiratory muscle activity in infants and children older than six months of age under a number of different conditions. These results contribute to a better understanding of the factors influencing the distribution of regional ventilation and the mechanisms by which prone positioning in ARDS may improve oxygenation in this population. These findings have potentially important clinical implications, as well as providing baseline data for future clinical studies.

Given the variability observed, these studies highlight the potential clinical utility of EIT to monitor different interventions and outcomes. An important strength of the studies presented in this thesis, is that they were performed in a standardised manner, using relatively homogenous individual populations and validated measures of describing ventilation distribution. This methodology could provide a template for future studies in the paediatric population, to allow for comparison between studies.

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ABBREVIATIONS

ABG	Arterial blood gas
AC	Alternating current
AECC	American-European Consensus Conference
ALI	Acute lung injury
ANOVA	Analysis of variance
Ar	Argon
ARDS	Acute respiratory distress syndrome
ATS	American Thoracic Society
AUC	Area under the curve
BP	Blood pressure
CF	Cystic fibrosis
CH_4	Methane
CI	Confidence interval
CLD	Chronic lung disease
CMD	Congenital Muscular Dystrophy
CMRR	Common mode rejection ratio
CMV	Continuous mandatory ventilation
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPT	Chest physiotherapy
CT	Computed tomography
CV	Coefficient of variation
DSP	Digital signal processor
DTPA	Diethylenetriamine penta-acetic acid
EBCT	Electron beam computed tomography
ECG	Electrocardiogram
EELV	End expiratory lung volume
EIT	Electrical impedance tomography
EMG	Electromyography
ERS	European Respiratory Society
ERT	Extubation readiness test
fEIT	Functional electrical impedance tomography
FEV_1	Forced expiratory volume in one second
FI	Filling index
FiO2	Fraction of inspired oxygen
FRC	Functional residual capacity
FVC	Forced vital capacity
GBS	Guillian Barré Syndrome
GI	Global inhomogeneity index

He	Helium
HR	Heart rate
HRCT	High resolution computed tomography
ICC	Intra-class correlation co-efficient
ICU	Intensive care unit
IPPV	Intermittent positive pressure ventilation
IQR	Interquartile range
LCI	Lung clearance index
LOA	Limits of agreement
MAA	Macro aggregated albumin
MABP	Mean arterial blood pressure
MAP	Mean airway pressure
MBW	Multiple breath washout
MEF_{25}	Maximal expiratory flow at 25% of forced vital capacity
MEF_{75}	Maximal expiratory flow at 75% of forced vital capacity
MR	Moments ratio
MS	Microsoft
MV	Mechanically ventilated infants/children
N_2	Nitrogen
NMD	Neuromuscular disease
NREM	Non-rapid eye movement
OI	Oxygenation index
OR	Odds ratio
OSI	Oxygen saturation index
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PARDS	Paediatric acute respiratory distress syndrome
PC	Pressure controlled
Pdi	Transdiaphragmatic pressure
PEEP	Positive end expiratory pressure
PET	Positron emission tomography
PF	Partial pressure of oxygen/fraction of inspired oxygen
PICU	Paediatric intensive care unit
PIP	Peak inspiratory pressure
PL	Prone position with head turned to left
PR	Prone position with head turned to right
RCWMCH	Red Cross War Memorial Children's Hospital
RD	Respiratory disease
REM	Rapid eye movement

ROC	Receiver operator curves
ROI	Region of interest
RR	Respiratory rate
RV	Residual volume
RVD	Regional ventilation delay
SB	Spontaneously breathing infants/children
SD	Standard deviation
sEMG	Surface electromyography
SF	Pulse oximetric saturation/fraction of inspired oxygen
SF_6	Sulphur hexafluoride
SIMV	Synchronised intermittent mandatory ventilation
SL	Supine position with head turned to left
SM	Supine position with head in midline
SR	Supine position with head turned to right
TLC	Total lung capacity
USFM	Ultrasonic flow meter
VC	Vital capacity
VILI	Ventilator induced lung injury
VQ	Ventilation/Perfusion
^{133}Xe	Xenon-133
^{81m}Kr	Krypton-81m
^{99m}Tc	Technetium-99m

Chapter 1 Introduction

Respiratory disease is one of the leading causes of mortality in infants and children worldwide and in South Africa the impact of respiratory disease is further exacerbated by lower socioeconomic conditions and where tuberculosis and human immunodeficiency virus are prevalent (Msemburi et al., 2014; WHO, 2014; Groenewald, Bradshaw & Msemburi, 2012). Acute and chronic respiratory tract infections account for a considerable portion of healthcare utilisation (Nair et al., 2013). In countries such as South Africa, where there is a high demand for healthcare but limited resources, it is particularly important that interventions provided are evidence based in order to provide the most effective patient treatment whilst minimising the use of futile and potentially harmful interventions.

Chest physiotherapy (CPT) is frequently prescribed for infants and children with respiratory disease with the primary aims of facilitating airway clearance, improving lung volumes and optimising ventilation-perfusion matching (Krause & Hoehn, 2000; Oberwaldner, 2000). Although CPT is commonly used in clinical practice, there is limited and at times conflicting evidence supporting its use. This is largely due to the fact that CPT seldom consists of a single technique used in isolation, but rather a bundle of techniques. Since CPT is assessed as a bundle it is difficult to determine the efficacy of specific techniques and whether some are more or less associated with the observed outcomes than others. Therefore, determining efficacy of the various individual components of the chest physiotherapy "bundle" may aid the development/implementation of more effective treatment bundles. Furthermore, while there are many studies in adult and neonatal populations, there are relatively few studies examining the effect of cardiopulmonary physiotherapeutic modalities in conditions other than cystic fibrosis in older infants and children.

One of the key interventions used in CPT is body positioning (Dean, 1985). This may be used to improve ventilation-perfusion matching by positioning a child in such a way as to maximise ventilation to the "healthier" lung or to improve ventilation to atelectactic lung regions to facilitate re-expansion (Pryor & Prasad, 2002; Op'tHolt, 2003). Positioning is also used to facilitate drainage of secretions using gravity, commonly termed gravity-assisted positioning or postural drainage (Stiller, 2000). Other benefits of body positioning include minimising the occurrence of pressure sores and the development of postural deformities, optimising cardiovascular function, minimising gastroesophageal reflux (Curley, Quigley & Lin, 2003; Martin-Du Pan, Benoit & Girardier, 2004).

Traditionally, the choice of positioning for optimising ventilation or for ventilation/perfusion (V/Q) matching has been based on the premise that the non-dependent lung is preferentially ventilated in *all* infants and children (Heaf et al., 1983; Davies et al., 1985). This is

commonly referred to as the “paediatric pattern” of ventilation distribution. Based on this, for many years teaching and clinical practice has been that infants and children should be positioned with the “healthier” lung regions uppermost to improve oxygenation, or with the affected (collapsed) lung uppermost to improve expansion and ventilation of that lung. Despite the widespread use of body positioning to improve ventilation to specific lung regions, the effects of choice of positioning have not been examined with regards to short and medium term clinical outcomes. Furthermore, using the “paediatric pattern” premise in choosing body positioning to improve V/Q matching poses several problems. It is well established that perfusion is gravity dependent regardless of age and body position (West & Dollery, 1960). Therefore, positioning a child with the “healthier” lung uppermost i.e. the “paediatric pattern”, whilst greatest perfusion is in the dependent (diseased) lung may result in a V/Q mismatch, particularly in the presence of severe lung disease. Additionally, if gravity assisted positioning was used; the non-dependent, diseased lung would then be uppermost and according to present knowledge be preferentially ventilated. Depending on the severity of the disease, this could potentially result in impaired oxygenation. Recently questions as to whether the preferential distribution of ventilation to the non-dependent lung is applicable to all neonates and infants (up to 6 months of age) have been raised (Frerichs et al., 2003; Schibler et al., 2009; Pham et al., 2011), with recent studies using newer technology reporting dissimilar results to those of Davies et al., (1985) and Heaf et al., (1983). Whether this “paediatric pattern” is consistently followed in infants (defined as older than 28 days but less than one year of age) and children (defined as older than one year) has not been examined. It is clearly not appropriate to apply the findings from neonatal studies to older infants and children given the differences in anatomy and physiology that exist. Furthermore, no recent studies have examined the effect of different conditions (e.g. normal lungs, respiratory disease and mechanical ventilation) on the distribution of ventilation. In order to guide clinical practice and deliver the most effective treatment techniques, a clearer understanding of the effects of body position and disease state on ventilation distribution is imperative.

Body positioning is frequently used by various members of the medical team in the management of children with respiratory conditions, particularly in the paediatric intensive care unit (PICU). It is possible that inexpensive and low-risk interventions, such as positioning, may limit the child’s exposure to interventions, such as invasive mechanical ventilation, which carry more risk to the developing lung (Gillies, Wells & Bhandari, 2012). Prone positioning in acute respiratory distress syndrome (ARDS) has been shown to result in significant short term and long term improvements in clinical outcomes, such as survival, in the adult population (Gattinoni et al., 2003; Guerin et al., 2004). The effect of prone positioning in ARDS on lung inflation has been well studied in the adult population (Gattinoni et al., 1991; Pelosi et al., 1998; Gattinoni et al., 2001; Pelosi, Brazzi & Gattinoni, 2002).

However, imaging devices (computed tomography), used in adult studies require repeated radiation exposure and cannot be performed at the bedside. As a result, there is little reported on the effect of prone positioning on lung inflation and ventilation in paediatric ARDS. While prone positioning may be beneficial in terms of improved oxygenation in children with ARDS, not everyone responds positively to prone positioning and the reasons for this are unknown (Curley et al., 2005). Whether non-response is due to specific anomalies in lung mechanics and ventilation distribution has not been studied in the paediatric population.

This thesis, therefore, aims to investigate distribution of ventilation in infants and children and explore possible factors that may influence ventilation distribution. The background to the principles underpinning ventilation distribution and factors which may influence it are discussed in Chapter Two. Based on these principles and factors, the hypothesis, aims and objectives of the studies examined in this thesis are presented at the end of the chapter. Chapter Three presents an overview of previous methods of determining ventilation distribution and discusses the outcome measures which were used in this thesis. The methodology for the four studies examining the effect of body position on the distribution of ventilation under different health conditions is presented in Chapter Four. Included in the methodology is the study design; details regarding the participants; specific technical details regarding the outcome measures, data acquisition and analysis; and ethical considerations. Results of the four positioning studies in healthy children, mechanically ventilated children, children with neuromuscular disease and, lastly, children with respiratory disease are presented in Chapter Five. The results of each study are followed by a brief discussion, study limitations and clinical implications. Chapter Six presents a final clinical study examining the effect of prone positioning in mechanically ventilated infants and children with ARDS. In this chapter, specific methodology is followed by the results and a brief discussion, limitations and clinical implications. Final conclusions, limitations, clinical implications and directions for future research are presented in Chapter Seven.

Chapter 2 Background

One of the aims in the management of adults and children with pulmonary disease and critical illness is to optimise ventilation and oxygenation where these are compromised (Gosselink et al., 2008; Gillies, Wells & Bhandari, 2012). There are different methods of achieving this, some of which include mechanical ventilation, body positioning and prone positioning in ARDS. Different body positions may optimise V/Q matching and thereby improve oxygenation (Dean, 1985). In addition to V/Q matching, positioning may facilitate the drainage of secretions and compliment other medical interventions which aim to improve gaseous exchange and oxygenation (Dean, 1985). In order to ensure the correct and most effective position is chosen for individual patients, an understanding of how ventilation is distributed is essential. While ventilation distribution has been studied extensively in animal, adult and, more recently, neonatal populations, there is a paucity of studies in the paediatric population. The principles upon which the choice of position is chosen in order to improve regional ventilation to specific lung regions in the neonatal population and infants up to six months of age have recently been queried based a number of recent studies in the neonatal population (Frerichs et al., 2003; Heinrich et al., 2006; Schibler et al., 2009; Pham et al., 2011; Hough et al., 2012; Hough et al., 2013), which report dissimilar ventilation distribution to the conventional ”paediatric” pattern. Newer technology, such as electrical impedance tomography (EIT), has improved the feasibility of studying the distribution of regional ventilation in infants and children and may provide a clearer understanding which can help correctly guide and inform clinical practice.

This Chapter aims to provide background to important differences that exist between adults' and children's respiratory systems. The principles underpinning ventilation distribution and factors which may influence it are discussed. The current knowledge of regional ventilation distribution in the paediatric population is discussed. The current literature on non-invasive respiratory muscle monitoring and respiratory muscle activity in children is discussed. Lastly, the use of positioning as a therapeutic modality in both children with respiratory disease and those with ARDS is discussed.

2.1 How infants differ from adults

When considering distribution of ventilation, and the effects of respiratory disease and mechanical ventilation in the paediatric population, it is important to note that infants and children differ from adults with regard to anatomy, physiology and respiratory mechanics. Some of these differences could have a significant impact on ventilation and ventilation distribution, therefore principles that apply to adults may not apply to infants and young children.

Infants and young children have a compliant chest wall relative to lung compliance (Agostoni, 1959; Papastamelos et al., 1995). The chest wall compliance has been shown to reduce rapidly within the first two years of life, after which it is similar to that of adults (Papastamelos, Panitch & Allen, 1996). As a result of the imbalance between the lower elastic recoil pressure of the lungs and more compliant chest wall in infants, the volume of air remaining in the lungs at the end of expiration, functional residual capacity (FRC), is reduced (Stocks, 1977). In infants and young children (<6 years), the lower FRC may approach closing volumes (volume at which small airways tend to close) (Agostoni, 1959; Mansell, Bryan & Levison, 1972; Heaf et al., 1983; Davies et al., 1985; Papastamelos, Panitch & Allen, 1996; Schechter, 2007; Wheeler, Wong & Zingarelli, 2011). Consequently, this results in a greater tendency for airway closure and a greater propensity for lung collapse (Schechter, 2007), unless expiration is controlled by mechanisms such as laryngeal braking or tonic diaphragm activity to maintain a higher FRC (Papastamelos, Panitch & Allen, 1996). Owing to the co-operation challenges of performing lung function tests in infants and young children, there is a paucity of longitudinal normative values and therefore it is unclear as to when the FRC (relative to weight/height) reaches adult values. It has been reported that FRC exceeds closing capacity after six years of age (Krause & Hoehn, 2000).

The airways in neonates and infants tend to be more “floppy” as a result of the still developing cartilage and smooth muscle, and therefore there is a greater tendency for airway collapse due to dynamic airway compression during manoeuvres which result in increased expiratory flow rates such as coughing (Hislop & Haworth, 1989; Schechter, 2007; Wheeler, Wong & Zingarelli, 2011). The airways of infants and young children are also narrower than those of adults. As a result, a small amount of inflammation or obstruction results in a marked increase in airway resistance (Poiseuille’s Law) (Schechter, 2007). Collateral channels of ventilation are only fully developed by approximately 6 years of age. The absence or immaturity of these channels may result in collapse of alveoli distal to an obstruction; this can result in a reduced surface area for gaseous exchange and negatively affect oxygenation (Hislop & Haworth, 1989).

The horizontal configuration of the ribs in infants limits the ability of the thorax to expand in the anteroposterior direction (Openshaw, Edwards & Helms, 1984; Hatch & Fletcher, 1992). In conditions which reduce lung compliance, the horizontal configuration of the ribs together with the greater tendency for airway collapse, place infants at children at higher risk of developing respiratory failure (Wheeler, Wong & Zingarelli, 2011). Furthermore, the horizontal rib configuration places the intercostal muscles at a mechanical disadvantage, making the diaphragm the primary muscle of respiration in infants. Due to the more horizontal insertion of the diaphragm, the zone of apposition is relatively small, placing it too at a mechanical disadvantage (Gaultier, 1995). Additionally, the diaphragm has fewer type

one muscle fibres, making it more susceptible to fatigue during increased ventilatory demand (Keens et al., 1978). The configuration of the rib cage and chest wall mechanics are said to change as infants assume a more upright position and are similar to that of adults by the age of two years, coinciding with infants and children assuming a more upright, anti-gravity posture (Openshaw, Edwards & Helms, 1984; Gaultier, 1995).

The differences outlined above are said to contribute to the pattern of greater ventilation in the non-dependent lung regions in infants and children (Heaf et al., 1983; Davies et al., 1985).

2.2 Ventilation distribution

2.2.1 Determinants of ventilation distribution in the adult population

Distribution of ventilation is determined by a multifaceted interaction between chest wall, lung mechanics and airway geometry (Chang, 1999; Glenny, 2009). Gravity and the body's orientation to it is one of the primary determinants of ventilation distribution within the lung (Bryan, Milic-Emili & Pengelly, 1966).

2.2.1.1 Gravity

A number of experimental studies have described a pleural pressure gradient within the lung in an upright posture. The pleural pressure, and thereby transpulmonary pressure, becomes progressively greater (less sub-atmospheric) from the non-dependent to the dependent regions of the lung at the end of expiration (Mead, 1961; Daly & Bondurant, 1963; Bryan, Milic-Emili & Pengelly, 1966; Milic-Emili et al., 1966). In the upright man the intrapleural pressure is approximately -10cmH_2O at the apex of lung and -2.5cmH_2O at the base of the lung at the end of expiration and becomes more negative during inspiration (West, 1978). The differences in pleural pressure are likely due to the weight of the lung which results in increased superimposed hydrostatic pressures in the dependent regions (Milic-Emili, Mead & Turner, 1964; Bryan, Milic-Emili & Pengelly, 1966).

As a consequence of this non-uniform intrapleural pressure gradient, different lung regions have different resting volumes. Using the ^{133}Xe technique in adults, it was shown that the upper (non-dependent) lung regions have higher resting volumes (FRC) and residual volumes (RV), which become progressively lower as the vertical distance from the top of the lung increases (Kaneko et al., 1966; Milic-Emili et al., 1966). Conversely, the lower (dependent) lung regions have higher vital and inspiratory capacities than the upper zones. The combination of these factors results in the lower lung regions being more compliant than the upper lung regions under normal conditions. Thus, the lower lung regions will have a greater volume change for a given change in transpulmonary pressure than the upper lung regions. Consequently, ventilation distribution is gravity dependent with greater ventilation occurring in the dependent lung regions.

This gravity dependent pattern of ventilation distribution in different body positions has been repeatedly demonstrated in more recent adult studies using non-invasive measures such as EIT (Frerichs, Hahn & Hellige, 1996; Frerichs et al., 2001; Frerichs et al., 2004; Riedel, Richards & Schibler, 2005)

2.2.1.2 Lung volumes

The volume at which breathing occurs, as well as the tidal volume, also influences the distribution of ventilation. Breathing from low lung volumes results in greater ventilation in the upper lung regions. This is likely the result of airway closure at low lung volumes in the lower regions as a result of the lower resting volumes (Kaneko et al., 1966; Milic-Emili et al., 1966). When breathing from higher lung volumes, greater ventilation is seen in the lower regions. This is the result of the non-uniformity of transpulmonary pressures throughout the lung (Kaneko et al., 1966; Milic-Emili et al., 1966). As the volumes approach total lung capacity (TLC), the distribution becomes more even between upper and lower lung regions.

The effect of lung volume on ventilation distribution has been confirmed by several relatively recent adult studies using EIT. Frerichs et al. (2001 & 2004) have confirmed greater ventilation in the dependent lung regions during vital capacity (VC) and forced vital capacity (FVC) manoeuvres. Similar results were found by Riedel, Richards & Schibler (2005). A separate study, using EIT, examining the effect of breathing from different end-expiratory lung volumes (EELV) and at different tidal volumes, confirmed that when breathing from low EELV at small or normal tidal volumes, greater ventilation occurs in the upper lung regions and as the EELV increases ventilation distribution becomes more equal between dependent and non-dependent lung regions (Schnidrig et al., 2013). At higher than normal tidal volumes, ventilation and regional filling was greater in the lower lung.

2.2.1.3 Flow rates

Flow rates have also been shown to affect the distribution of ventilation due to differences in regional compliance and airway resistance (Robertson, Anthonisen & Ross, 1969; Bake et al., 1974; Chang, 1999). Low flow rates result in greater ventilation in the lower lung regions as a consequence of the more compliant alveoli and lower distending pressures (Grant, Jones & Hughes, 1974). As flow rates increase there is progressively greater ventilation of the upper lung regions (Pedley, Sudlow & Milic-Emili, 1972; Bake et al., 1974). At high flow rates ventilation distribution between upper and lower lung regions becomes more uniform (Bake et al., 1974; Schnidrig et al., 2013).

2.2.1.4 Age

The impact of age on ventilation distribution is primarily the result of changes in chest wall and lung compliance. Using ventilation scintigraphy, Holland et al. (1968) described reduced ventilation to the dependent lung regions in elderly subjects during normal tidal breathing.

This has been confirmed more recently by Frerichs et al. (2004) who showed that in elderly adults, ventilation distribution becomes more equal and may even shift towards greater ventilation in the non-dependent lung in different body positions. These differences in ventilation distribution in the elderly were attributed, in part, to a stiffer chest wall and more compliant lungs which may have resulted in early airway closure in the dependent lung regions.

2.2.2 Ventilation distribution in the paediatric population

It has been postulated that children do not have the same pattern of ventilation distribution as adults. It has been suggested that due to the more compliant chest wall, less compliant lungs and "floppy" airways, and therefore lower FRC, airway closure occurs in the dependent lung regions resulting in greater ventilation in the non-dependent lung regions (Heaf et al., 1983; Davies et al., 1985). This "paediatric pattern" of ventilation was said to extend into the second decade of life (Davies, Helms & Gordon, 1992). However, recent studies have suggested that ventilation distribution in the neonatal population is no different to adults; implying age may not affect ventilation distribution (Schibler et al. 2009, Pham et al. 2011). These studies only examined either supine position only or supine and prone positions and the effect of other body positions on ventilation distribution was not studied. A summary of the available studies in the paediatric population is presented in Table 2.2.1.

Table 2.2.1 Summary of studies examining ventilation distribution in the paediatric population.

Study	Sample	Respiratory support	Outcome measures used	Procedure	Methods of describing ventilation distribution	Conclusion
Heaf et al., 1983	Total sample: 10 Age (mean): 45 days (range 2 days-8 months) Condition: Unilateral lung disease (congenital diaphragmatic hernias, hypoplastic lungs and atelectasis)	None: n = 5 IPPV: n = 3 CPAP: n = 2	Radionuclide scanning (n=4) Transcutaneous measures of oxygenation	Positions: supine, left and right side lying. Order of positions: randomised Time in positions: 10 minutes	Proportion of ventilation	Ventilation increased in the "good" lung when non-dependent associated with increased transcutaneous oxygenation.
Davies et al., 1985	Total sample: 18 Age: 11 days – 27 months Condition: Unilateral lung disease; bilateral lung disease; and "normal "based radiographic findings but including conditions which usually affect respiratory mechanics (e.g. cystic fibrosis, exomphalos, leukodystrophy)	None: n = 15 Ventilatory support (not specified): n = 3	Radionuclide scanning	Positions: supine, left and right side lying Order of positions: unspecified Time in position: not reported	Proportion of ventilation in right lung	Ventilation in the right lung was greatest when the right lung was non-dependent. Ventilation was unaffected by radiographic findings ALL children showed a reversal of the adult pattern.
Bhuyan et al., 1989	Total sample: 18 Age: 5 months to 11 years Condition: Mixed respiratory conditions, postural deformities	Not specified	Radionuclide scanning	Positions: supine, side lying: unspecified Order of positions: supine – side lying Time in positions: unspecified	Proportion of ventilation	Ventilation to the dependent lung decreased when moving from supine to dependent position.
Davies et al., 1992	Total sample: 43 Age (mean): 11 years (range 2-17 years) Condition: Unilateral lung disease; bilateral lung disease based radiographic findings.	None	Radionuclide scanning	Positions: supine, left and right side lying Order of positions: unspecified Time in position: not reported	Proportion of ventilation to right lung	Ventilation was greater in the right lung when the right lung was non-dependent in most children < 18 years of age, but was not the case in all children. Those older than 18 showed mixed patterns of ventilation distribution.

Study	Sample	Respiratory support	Outcome measures used	Procedure	Methods of describing ventilation distribution	Conclusion
Frerichs et al., 2003	Total sample: 12 Age: 23 ± 12 days Condition: Healthy pre-term and term neonates (mean gestational age 34 weeks)	None	Electrical impedance tomography (EIT)	Positions: supine, prone and right side lying Time in position: not reported Order of positions: Supine, right side lying, prone, supine	Relative tidal impedance change (ROI – left and right lung) Proportion of ventilation	The right lung showed greater ventilation when non-dependent (NS), this was reversed during sighs. The contribution of the right lung to ventilation was greater than the left.
Heinrich et al., 2006	Total sample: 20 Age: Healthy (n=10) – 13 ± 11 days Mechanically ventilated (n=10) – 59 ± 36 days Condition: Healthy, congenital hernias (unspecified)	None: n = 10 Mechanical ventilation (unspecified): n = 10	EIT	Positions: supine with the head in midline and turned to the left and right; and prone with head turned to the left and right Time in position: not reported Order of positions: randomised to either supine-prone or prone-supine	Relative tidal impedance change (ROI – left and right lung) Proportion of ventilation	Head position to the left or right reduced ventilation in the left lung.
Schibler et al., 2009	Total sample: 24 neonates and 13 adults Age (mean): Neonates: 14.3 ± 0.6 days; Adults: 36 years (24-48 years) Condition: Healthy	None	EIT	Positions: supine and prone Time in position: 10 minutes Order of positions: not specified Measurements in neonates taken during NREM sleep.	Impedance profiles (ROI – 32 slices from anterior to posterior) Geometric centre of ventilation Phase angles/Time course analysis	Impedance profiles did not differ significantly between neonates and adults. A central pattern (anterior-posterior direction) of ventilation was seen in neonates and adults. No significant differences in filling of the ventral or dorsal lung regions between groups.

Study	Sample	Respiratory support	Outcome measures used	Procedure	Methods of describing ventilation distribution	Conclusion
Hough et al., 2012	Total sample: 30 Age: Healthy: 1.8 ± 1.2 days; RDS – 4.7 ± 3.8 days Condition: Healthy (n=6); Respiratory distress syndrome (n=24)	None: n = 6 CPAP: n = 24	EIT	Positions: supine, prone and quarter turn prone Time in position: 30 minutes Order of positions: randomised	Relative tidal impedance change (ROI- left, right, anterior and posterior regions) Global inhomogeneity (GI) index Phase angle /time course analysis	Significantly greater ventilation and faster filling in the dorsal lung regions in supine position. Dorsal lung showed greater ventilation then the anterior lung in all positions in infants on CPAP. Greater ventilation in the right lung compared to the left in all positions in both groups.
Pham et al., 2011	Total sample: Measurement one:32; measurement two – 24; measurement three: 26 Age: Measurement one:13.7 ± 3 days; measurement two – 97 ± 8 days; measurement three – 187 ± 6 days Condition: Healthy, term infants	None	EIT	Position: supine Time in position: 10 minutes Measurements taken at 2 weeks (measurement 1), 3 months (measurement 2) and 6 months (measurement 3) after birth	Impedance amplitudes (ROI – 6 slices from anterior to posterior and left to right respectively) Phase angles/time course analysis	Impedance amplitudes increased with age, with the greatest increase in the dorsal lung regions. Regional filling was faster in the dependent lung at all ages.
Humphreys et al., 2011	Total sample: 38 Age (median): 13 (IQR 1.5 – 168) months Condition: Cardiac defects requiring surgery	Transition from spontaneous breathing to mechanical ventilation	EIT	EIT measurements taken in supine position during: Spontaneous breathing; induction of anaesthesia; mechanical ventilation	End expiratory lung volume (EELV) Geometric centre of ventilation Global inhomogeneity index Filling index	EELV decreased during induction and intubation. Shift in the geometric centre of ventilation from posterior to anterior during induction. During spontaneous breathing posterior regions had slower initial filling; filling became relatively equal during induction. Ventilation was more homogenous during induction and mechanical ventilation.

Study	Sample	Respiratory support	Outcome measures used	Procedure	Methods of describing ventilation distribution	Conclusion
Hough et al., 2013	Total sample: 30 Age: Healthy 1.8 ± 1.2 days; RDS – 1.7 ± 1.0 days Condition: Healthy (n=6); RDS (n=24)	None: n=6 IPPV: n=24	EIT	Positions: supine, prone and quarter turn prone Time in position: 30 minutes Order of positions: randomised	Relative tidal impedance change (ROI- left, right, anterior and posterior regions) Global inhomogeneity (GI) index Phase angle /time course analysis	No difference in regional ventilation between lung regions in infants receiving IPPV. Greater ventilation was seen in the dorsal and right lung regions in the healthy neonates. No difference in filling between anterior and posterior lung regions and the right lung filled significantly faster than the left in infants on IPPV.
Van der Burg et al., 2015	Total sample: 15 Age(median): 12.7 days Condition: preterm neonates	CPAP: n=7 Nasal cannula: n=8	EIT	Positions: supine, left and right side lying Time in position: 180 minutes Order of positions: convenience Measurements taken in supine and at 0, 30, 60, 120, 150 and 180 minutes in the side lying position	EELV Relative impedance change (ROI – left and right regions) Geometric centre of ventilation	Global EELV increase in side lying positions, mostly as a result of EELV in non-dependent lung volumes. Dependent pattern of ventilation particularly in right side lying. Shift in the geometric centre of ventilation to the dependent lung regions

2.2.2.1 Under normal conditions

In comparison to the adult population, there are few studies which provide insight into regional ventilation distribution in the paediatric population. This is likely due to the invasive nature of earlier testing procedures and exposure to radiation, making studies in this vulnerable population ethically difficult. Furthermore, it is likely that the previously used techniques would have required sedation and application of face masks which have the potential to alter normal breathing patterns, therefore may not truly reflect what occurs under "normal" conditions. As a result of these ethical and technical difficulties, normative data for ventilation distribution in response to body positioning in the paediatric population is lacking.

Several studies performed in the 1980's have formed the basis of clinical teaching and practice in the paediatric population (Heaf et al., 1983; Davies et al., 1985; Bhuyan et al., 1989). Authors of these studies proposed that children, up until the second decade of life and irrespective of the presence of lung disease, preferentially ventilate the non-dependent lung regions. The majority of these studies were, however, performed on heterogeneous population groups, where the age did not exceed 27 months and the infants or children had respiratory disease or required ventilatory support. Both Heaf et al. (1983) and Davies et al. (1985) used krypton-81m ventilation scanning to determine the proportion of ventilation occurring in the left and right lungs in the supine position and left and right side lying positions. These authors concluded that ventilation distribution and gaseous exchange are affected by position change (greater in the non-dependent lung) (Heaf et al., 1983; Davies et al., 1985) and "the reversal of the adult pattern of regional ventilation is universal in infants and very young children" (Davies et al., 1985). There were, however, a number of methodological limitations to these studies that limit the generalisability of their results. Infants and children in both studies had conditions, such as congenital diaphragmatic hernia with accompanying lung hypoplasia and atelectasis, cystic fibrosis, histiocytosis x, exomphalos and leukodystrophy, which will inevitably alter respiratory mechanics and consequently impact on ventilation distribution. In addition, some of the infants or children were receiving mechanical ventilation which may also impact on ventilation distribution. Sample sizes were small with only four infants undergoing ventilation scanning in the study by Heaf et al., (1983) and 18 in the study by Davies et al., (1985). The extent to which ventilation scanning truly represents tidal volume change, and therefore ventilation, is also questionable. Although authors reported krypton-81m scanning is representative of tidal volume, other studies (Lythgoe et al., 1992; Ciofetta et al., 2007), which are discussed in Section 3.1.1, have shown it may more accurately be representative of both lung volume and tidal volume especially in infants where respiratory rates are higher than adults (Bhuyan et al., 1989).

Similar results were observed in older children by Bhuyan et al. (1989) and Davies, Helms & Gordon (1992). Bhuyan et al. (1989) reported a decrease in the proportion of ventilation in the dependent lung when moving from supine to side lying. Using slightly different methodology of reporting ventilation distribution, Davies, Helms & Gordon (1992), reported greatest ventilation in the non-dependent lung in side lying positions. Whilst no apparent effect of age was seen up until the age of 11 (Bhuyan et al., 1989), not all children beyond 11 years of age had greater ventilation of the non-dependent lung and beyond 18 years of age the "pattern" of ventilation became more variable within and between individuals (Davies, Helms & Gordon, 1992). Whether there were underlying conditions affecting respiratory mechanics in these studies was unclear, however, these results have been inferred to the general paediatric population.

Over the last 15 years there have been a growing number of studies examining the distribution of regional ventilation in response to body position, particularly in the neonatal population in both healthy and diseased lungs. The development of non-invasive, radiation-free imaging tools, such as EIT, has made studies in this vulnerable population feasible and ethically permissible. These more recent studies have raised the question as to whether *all* infants and children *always* preferentially ventilate the non-dependent lung (following the "paediatric pattern") irrespective of age and the presence of lung disease or mechanical ventilation. While these recent studies (discussed below) have provided new insight into an area which has been difficult to study, differing study methodologies make it difficult to draw direct comparison between studies and adequately describe "normal' ventilation distribution in the neonates and young infants. These differences include study procedures, such as participants recruited and relatively small numbers of homogenous study populations; positions studied and time spent in positions; how a region of interest in defined (i.e. which regions of the lungs are studied); and how ventilation distribution was described, measured and analysed (Table 2.2.1).

Frerichs et al. (2003) studied 12 spontaneously breathing neonates (mean age 23 ± 12 days) with no respiratory disease. EIT measurements were taken in the supine position, right side lying and prone positions whilst the neonate was sleeping. It is unclear for how long each position was maintained, however authors note that the total study time was 50-60 minutes. Ventilation distribution was determined for both a tidal breath and a deep inspiration (sigh) in each position and were described using relative tidal impedance change and the proportion of ventilation in a specified region. EIT images were generated using only one breath. It was found that spontaneously breathing neonates demonstrated better ventilation of the non-dependent lung in right side lying during tidal breathing; however, this difference was not significant. During deep inspirations (sighs) there was a significantly greater proportion of ventilation in the dependent (right) lung region. It was also reported

that the right lung region had a greater contribution to ventilation than the left lung region in right side lying, supine and prone positions, however this was only significant in the prone position during tidal breathing and in right side lying during deep inspirations (Frerichs et al., 2003). Whether similar patterns were seen in left side lying, as well as the effect of supine and prone positions on ventilation in the ventral and dorsal lung regions were not examined.

Table 2.2.2 Summary of different methods used to describe and analyse ventilation distribution in the EIT studies

Method used	Details	Studies used in
Relative tidal impedance change	This is closely related to tidal volume and describes the difference in impedance values from the end of expiration to the end of inspiration.	Frerichs et al., 2003; Heinrich et al., 2006; Hough et al., 2012; Hough et al., 2013; Van der Burg et al., 2015
Proportion of ventilation	Describes the proportion of tidal ventilation in a specified region in relation to global tidal ventilation. This allows for inter-individual comparison.	Frerichs et al., 2003; Heinrich et al., 2006
Impedance profiles	These are plots of relative impedance change for specified regions of interest (usually slices from anterior to posterior or left to right)	Schibler et al., 2009; Pham et al., 2011
Geometric centre of ventilation	This describes where the centre of ventilation (calculated using the balanced average of pixel values) on either the anterior to posterior or left to right axis.	Schibler et al., 2009; Humphreys et al., 2011; Van der Burg et al., 2015
Global inhomogeneity index	This is a single index which describes ventilation homogeneity throughout the lungs. It allows for inter-individual comparison (refer to Section 4.5.1.1.4).	Hough et al., 2012; Humphreys et al., 2011; Hough et al., 2013
Phase angle analysis	This describes the rate of filing or emptying of one lung region relative to another.	Schibler et al., 2009; Hough et al., 2012; Pham et al., 2011; Hough et al., 2013
Filling indices	This describes the rate of filling and emptying of a lung region relative to global filling and emptying (refer to Section 4.5.1.1.3).	Humphreys et al., 2011
End expiratory lung volume (EELV)	This is calculated using the relative impedance values at the end of expiration. It can be normalised by using the EELV of a region in relation to the global EELV or relative to body weight to allow for inter-individual comparison.	Humphreys et al., 2011; Van der Burg et al., 2015

Building on the study by Frerichs et al. (2003), Heinrich et al. (2006) examined the effect of head position on the distribution of ventilation in spontaneously breathing, healthy neonates (n=10, mean age 13 ± 11 days) and mechanically ventilated neonates (n=10, mean age 58 ±

36 days) in the supine and prone positions using EIT. The most common reason for requiring mechanical ventilation was following surgical repair of congenital diaphragmatic hernias. The neonates were randomly assigned to either supine-prone position or prone-supine position. In the supine position, the following head positions were assessed: head in the midline, head turned to the left and head turned to the right; and in prone position head turned to the left and right were assessed. The time spent in each position was not reported; however, the total measurement time was 40 minutes for healthy neonates and 20 minutes for mechanically ventilated neonates. Four to six breaths were used from the 60 second EIT recording for analysis. The mean relative impedance change and proportion of ventilation occurring in the left and right lung regions was assessed. Authors reported that head position significantly affected the distribution of ventilation in the left and right lung regions in the supine and prone positions in both spontaneously breathing and mechanically ventilated neonates. Head rotation to the left (supine and prone positions) or right (prone position only) resulted in smaller tidal volumes in the left lung region. This change was greatest when the head was turned to the left in the prone position. It was postulated that shifts in organs and tissues occur with head rotation resulted in reduced gas flow to the left main bronchus (Heinrich et al., 2006). Similar to the findings of Frerichs et al. (2003), authors reported that the right lung region was larger than the left in both spontaneously breathing and mechanically ventilated neonates. Mechanically ventilated neonates demonstrated greater tidal volumes than spontaneously breathing neonates in all positions.

A study by Schibler et al. (2009) examined the distribution of ventilation, using EIT, in healthy, spontaneously breathing neonates (n=24, mean age 14.3 ± 0.6 days) in the supine and prone positions and compared them to a cohort of healthy adults (n=13, mean age of 36 years (24-48 years)). Neonates were all examined during non-rapid eye movement (NREM) sleep. Each position was maintained for 10 minutes in both adults and neonates. In neonates, tidal breathing and sighs were used for analysis and compared to adult data. EIT data was presented as impedance profiles, which consisted of 32 profiles (ROI) which were arranged from either non-dependent to dependent or left to right. In addition, the geometric centre of ventilation and phase angles were reported. Briefly, the geometric centre of ventilation is calculated using the balanced average of pixel values in either the anterior to posterior or left to right directions (Schibler et al., 2009). Phase angle analysis provides information regarding regional filling relative to either other lung regions or the entire lung region (Schibler et al., 2009). Both neonates and adults displayed a “central” pattern of ventilation in the supine and prone positions as was evident from the similar geometric centres of ventilation in the anterior to posterior direction. The profiles of impedance change differed slightly (not statistically significant), with neonates demonstrating a more pyramidal shaped profile, whilst adult profiles were less pyramidal in shape. Ventilation in the ventral lung region was significantly greater when in the non-dependent position in neonates. The

ventral lung region demonstrated faster filling and emptying than the dorsal lung region in both positions in neonates, whereas the dorsal lung regions tended to show faster filling, particularly in supine position, in adults. None of the differences in filling characteristics were reported to be significant. Authors concluded that the distribution of ventilation in healthy neonates and adults is no different; however, they only reported on global ventilation in supine and prone positions, therefore it remains unclear whether regional differences in each position exist.

In a small cohort of healthy, spontaneously breathing neonates (n=6, age 1.8 ± 1.2 days), EIT measurements were taken in supine, prone and quarter prone positions, the order of which was randomised and measurements were taken after the neonate had been in the position for 30 minutes. Regional ventilation was determined by calculating the average impedance change during tidal breathing, for the left, right, anterior and posterior lung regions (Hough et al., 2012). In addition, regional filling characteristics, which describe the filling and emptying of one lung region relative to another, were calculated. Spontaneously breathing neonates showed significantly greater ventilation of the dorsal lung compared the ventral lung, as well as significantly earlier filling of the dorsal lung regions in the supine position. Ventilation in the right lung was significantly greater than the left lung (Hough et al., 2012). While this was a very small sample; the findings of greater ventilation in the right lung region was similar to that described by Frerichs et al. (2003) and Heinrich et al. (2006).

A longitudinal study in healthy term infants, in which measurements in the supine position were taken at two weeks after birth (n=32, age 13.7 ± 3 days), three months (n=24, 97 ± 8 days) and six months (n=26, 187 ± 6 days) of age, aimed to describe regional impedance changes with age (Pham et al., 2011). Measurements were taken for 10 minutes and both tidal breaths (≥ 10 breaths) and sighs were used in the analysis. Impedance amplitudes were calculated for six regions of interest in the anterior to posterior and left to right directions and regional filling characteristics were studied. Impedance amplitudes in the anterior-posterior direction increased with age, with the greatest increase occurring between two weeks and three months. The greatest change in amplitude was found in the dorsal lung, increasing in increments of approximately 10 at each measurement point. Authors reported that the dependent (dorsal) lung was better ventilated than the non-dependent (ventral) lung, however, evidence of this comparison and the significance level was not reported. The dependent lung filled significantly faster than the non-dependent lung regardless of age (Pham et al., 2011). These findings are in keeping with those of Hough et al. (2012); however, whether a similar distribution occurred in the prone position was not examined.

In summary, recent studies using EIT have shown that healthy, spontaneously breathing neonates and infants up to six months of age do not always preferentially ventilate the non-

dependent lung in different body positions. Although most of the recent studies have been limited to supine and prone positions and have different study methodology, relatively small sample sizes and different definitions of regional ventilation and the analysis thereof, the results indicate that determinants of ventilation distribution may be more complex. No recent studies exist that describe ventilation distribution in infants and children older than six months of age.

2.2.2.2 During mechanical ventilation

In mechanically ventilated patients a number of factors, such as ventilatory parameters, level of sedation, underlying respiratory conditions and body position may influence the distribution of ventilation (Frerichs et al., 2002a). Ventilation is not always homogenously distributed during mechanical ventilation. This is may be due to differences in regional compliance and resistance, and chest wall compliance which results in differing rates of filling and emptying in the lungs (Riedel, Richards & Schibler, 2005). These differences in regional compliance can be further amplified in the presence of respiratory disease or muscle paralysis (Gattinoni et al., 1993). A number of studies have examined the effect of different ventilator settings and manoeuvres on ventilation distribution in children, however there are only a few examining regional ventilation distribution and the effect of body position during mechanical ventilation (Wolf et al., 2007; Humphreys et al., 2011; Wolf et al., 2012). Furthermore, to the best of my knowledge, there are no recent studies describing ventilation distribution in mechanically ventilated children beyond neonatal age, who are not anaesthetised or paralysed.

2.2.2.2.1 <u>During anaesthesia and/or paralysis</u>

During anaesthesia and/or paralysis alterations in chest wall and thoraco-abdominal mechanics occur which in turn affect the distribution of ventilation (Froese & Bryan, 1974; Rehder & Marsh, 2011). The abdominal contents and the diaphragm also contribute to pleural pressure gradients and thereby affect ventilation distribution in the horizontal postures (Agostoni, D'angelo & Bonanni, 1970); therefore, muscle paralysis can have significant effects on ventilation distribution.

During anaesthesia, with or without paralysis, cephalad displacement of the dependent portion of the diaphragm may be observed as a result of increased intra-abdominal hydrostatic pressures in the dependent regions and consequently a lower FRC which nears or reaches closing volumes resulting in airway closure in the dependent lung regions (Bryan, 1974; Froese & Bryan, 1974; Kleinman et al., 2002; von Ungern-Sternberg et al., 2006). During anaesthesia alone, where spontaneous breathing occurs, despite the cephalad shift in the diaphragm, greatest diaphragm movement occurs in the dependent portion, which may help prevent airway closure in the dependent lung regions. Conversely, during paralysis greatest movement occurs in the non-dependent portion of the diaphragm (Froese

& Bryan, 1974). With the positive pressure support given during mechanical ventilation air is directed to areas of higher compliance, therefore with collapse of dependent lung regions, ventilation of the non-dependent lung regions will be favoured (Riedel, Richards & Schibler, 2005).

A recent study, using EIT, examined the effects of anaesthesia and conventional mandatory ventilation (CMV) on regional ventilation distribution in 38 infants and children (median age 13.0 (1.5 – 168.0) months) undergoing elective cardiac surgery (Humphreys et al., 2011). Anaesthesia was induced using inhaled Sevoflurane in oxygen and Pancuronium which was administered intravenously. Infants and children were undergoing elective cardiac surgery for ventricular septal defects (n=10), atrioventricular septal defects (n=5), atrial septal defects (n=6), tetralogy of Fallot (n=8), cavopulmonary shunts (n=6); and mixed congenital heart defects (n=3). EIT measurements were taken before anaesthetic induction (spontaneously breathing), during the entire induction process and during CMV. Changes in EELV, ventilation distribution (described using the geometric centre of ventilation and global inhomogeneity (GI) index) and regional filling characteristics were determined for five time points (spontaneously breathing, hand bagging with muscle paralysis, intubation, hand bagging with endotracheal tube in situ, and CMV). All measurements were taken in the supine position. Relative to the spontaneously breathing period, EELV significantly reduced in the anterior and global regions during intubation. Global and posterior EELV also showed a significant reduction during the induction phases, which improved after intubation. The geometric centre of ventilation showed a significant shift from posterior (dependent) to anterior (non-dependent) lung regions during the induction phases. During spontaneous breathing the posterior lung regions showed slower initial filling which accelerated (relative to global filling) towards the end of inspiration (filling index of <1), whilst the opposite was observed in the anterior lung region (filling index>1). During induction, the filling indices in both lung regions approached 1.0, indicating relatively equal rates of filling relative to global, this difference was significant compared to the spontaneously breathing values. Ventilation became more homogenous during induction and CMV; this postulated to be due to the application of positive end expiratory pressure (PEEP) during the induction phases and CMV. Children included in this study all had cardiac conditions which are likely to be associated with cardiomegaly, lung disease and alterations in pulmonary blood flow which may have significant effects on ventilation distribution, therefore whether similar changes occur in children without respiratory involvement needs to be confirmed. The shift in greater ventilation from dependent to non-dependent lung regions is similar to that seen in adults who are anaesthetised and mechanically ventilated (Rehder et al., 1972; Frerichs et al., 1998). It has been demonstrated that by applying PEEP, and therefore minimising collapse of the dependent lung regions by increasing FRC, this deviation from gravity-dependent ventilation distribution can be partially reversed (Hinz et al., 2005; Frerichs et al., 2007).

This finding suggests that airway closure in the dependent lung regions, which is ameliorated by the application of PEEP, may account for the changes in ventilation distribution seen. Frerichs et al. (1998) also reported that following anaesthesia and CMV in adults, there was a progressive shift of ventilation back towards the dependent lung regions coinciding with more spontaneously breathing efforts whilst still intubated and ventilated. This is in keeping with greater excursion of the dependent regions of the diaphragm seen with spontaneous breathing efforts in mechanically ventilated patients (Froese & Bryan, 1974).

2.2.2.2.2 Without anaesthesia and/or paralysis

While a reversal in the gravity dependent ventilation distribution is seen during mechanical ventilation with paralysis, given the important changes that occur in thoraco-abdominal mechanics, this reversal cannot be said to occur during mechanical ventilation without paralysis.

Hough et al. (2012 & 2013), in two separate studies, examined the effects of body position (supine, prone and quarter prone positions) on ventilation distribution in preterm neonates receiving either CPAP (n = 24, mean postnatal age 4.7 ± 3.8 days, mean gestational age 28.7 ± 1.8 weeks) or IPPV (n = 24, mean postnatal age 1.7 ± 1.0 days, mean gestational age 27.4 ± 1.9) for respiratory distress syndrome. In both studies, the order of positions was randomised and EIT measurements were taken 30 minutes after the neonate had been placed in the position. Regular tidal breathing periods were used for analysis. Ventilation distribution was described using regional (anterior, posterior, left and right lung regions) impedance amplitudes, GI index and regional filling described by phase angle analysis. Infants receiving CPAP, with pressures of 6-8cmH_2O, showed greater ventilation of the posterior compared to the anterior lung ($F_{(1,124)}$=8.55, p<0.01) and the right lung compared to the left lung region ($F_{(1,124)}$=5.94, p<0.02) irrespective of the body position (Hough et al., 2012). Compared to controls (n=6 spontaneously breathing neonates), neonates receiving CPAP had a greater degree of ventilation inhomogeneity ($F_{(1,89)}$=31.56, p<0.01). No difference in regional filling was found between anterior and posterior lung regions ($F_{(1,122)}$=0.01, p=0.95). Unlike those receiving CPAP, neonates receiving IPPV showed no differences between posterior and anterior lung regions ($F_{(2,134)}$=2.79, p=0.87) or left and right lung regions ($F_{(1,134)}$=0.41, p=0.52). The distribution of ventilation was unaffected by body position ($F_{(2,134)}$=0.15, p=0.87). Ventilation inhomogeneity was greater in neonates receiving IPPV compared to six healthy controls ($F_{(1,102)}$=62.50, p<0.01) and was unaffected by body position. Similarly to neonates receiving CPAP, regional filling was similar between anterior and posterior lung regions in those receiving IPPV ($F_{(1,52)}$=0.31, p=0.37). The right lung region filled significantly faster that the left lung in all positions ($F_{(1,134)}$=7.91, p<0.01). The amount of ventilatory support neonates on IPPV were receiving was not reported, this

may have provided further insight into similarities and differences observed between those receiving CPAP and the healthy controls (discussed in Section 2.2.2.1). Authors conclude that ventilation distribution in neonates receiving CPAP or IPPV is not gravity dependent (Hough et al., 2012; Hough et al., 2013), however whether this apparent lack of gravitational effect extends to side lying positions was not studied.

The effect of side lying positions was examined in 15 preterm neonates (median postnatal age 12.7 days, median gestational age 28.9 weeks) (van der Burg et al., 2016). Neonates were either on non-invasive CPAP (n=8) or nasal cannula (n=7). Following a 30 minute period in supine position, neonates were turned onto their left (n=8) or right (n=7) side (depending on their position prior to being in the supine position). They remained in this position for 180 minutes. EIT measurements were taken in supine position and at 0, 30, 60, 120, 150 and 180 minutes in the side lying position. Measurements were only taken in one side lying position for each neonate, this position depended on their position prior to study enrolment (i.e. if they were in left side lying before being placed in the supine position, measurements were taken in right side lying). At each measurement point EELV, relative impedance change in the left and right lungs and the geometric centre of ventilation were determined. A dependent or non-dependent orientation of ventilation distribution was described using a 50% cut-off, i.e. if less than 50% of the ventilation occurs in the non-dependent lung there is a dependent orientation of ventilation distribution. Turning neonates, on either CPAP or nasal cannula, from the supine position to side lying positions resulted in an immediate shift of greater ventilation to the dependent lung, which was seen predominately seen in right side lying (ventilation in the non-dependent lung decreased from 48.3 ± 4.4% before turning to 40.2 ± 6.0% immediately after turning, $p<0.05$) (van der Burg et al., 2016). This shift in ventilation was no longer significant after three hours in the position. Although not significant, a greater proportion of ventilation occurred in the dependent (right) lung region in right side lying, whilst the opposite was seen with greater ventilation in the non-dependent lung in left side lying. Global EELV increased immediately after being turned into the lateral position and stabilised after 30 minutes. This increase may be attributable to the significant increase in EELV in the non-dependent lung since EELV in the dependent lung remained relatively stable. This change in EELV may explain the reports of greater ventilation distribution in non-dependent lung regions in earlier studies using 81m-krypton scanning (Heaf et al., 1983; Davies et al., 1985), where it is likely that measurements reflected both lung volume and tidal volume change, leading to a possible over-estimation of volume change in the non-dependent lung regions. Since positions were not randomised, rather one of convenience, this may have introduced a degree of bias. This study only examined neonates in one side lying position, therefore it remains unclear as to whether the same behaviour exists in the other position. This is a relatively small sample of

respiratory stable neonates and therefore these findings may not be applicable to the greater neonatal population and those requiring more ventilatory support or with respiratory disease.

To the best of my knowledge there are no recent studies investigating ventilation distribution in older infants/children receiving mechanical ventilation without anaesthesia or paralysis or during recruitment manoeuvres.

Adult studies have also reported gravity-dependent ventilation distribution during mechanical ventilation without anaesthesia/paralysis (Frerichs et al., 1998; Bein et al., 2010). In an animal study using single photon emission tomography, ventilation was greater in the dependent lung regions during spontaneous breathing whilst receiving mechanical ventilation (Neumann et al., 2005). The gravity-dependent ventilation distribution appears to be associated with spontaneous breathing efforts and is likely the result of greater displacement of the dependent diaphragm that occurs during spontaneous breathing preventing airway closure in the dependent lung regions (Froese & Bryan, 1974; Krayer et al., 1989; Neumann et al., 2005).

2.2.2.3 In the presence of respiratory and neuromuscular disease

2.2.2.3.1 Respiratory disease

Respiratory disease is one of the leading causes of mortality in children under the age of five years (Liu et al., 2012). Common conditions include pneumonia, bronchiolitis, asthma and cystic fibrosis. Alterations in regional compliance, airway resistance and altered flow rates that accompany respiratory disease are likely to result in a more heterogeneous ventilation distribution (Aurora et al., 2005; Zhao et al., 2012; Simpson et al., 2015). Time constants of regional filling and emptying are likely to have greater differences in the presence of disease which will likely result in a heterogeneous distribution of ventilation. Zhao et al. (2012) demonstrated improved ventilation homogeneity in patients with cystic fibrosis at higher inspiratory volumes, supporting the notion of different time constants. There are a limited number of studies examining the regional distribution of ventilation in children with respiratory disease. This is probably due to the nature of testing procedures, which require co-operation, may be invasive or require sedation and result in radiation exposure, which make studies in children difficult. The first studies examining the effects of body position and regional ventilation distribution were performed in the 1980's and have guided practice in the paediatric population since (Heaf et al., 1983; Davies et al., 1985). Using radionuclide scanning, it was concluded that irrespective of radiographic findings (normal, unilateral and bilateral infiltrates) there was always preferential ventilation to the non-dependent lung in different body positions, implying respiratory disease has no effect on ventilation distribution. The limitations of these studies have been discussed in previous sections, but briefly even children who had "normal" chest radiographs had underlying conditions likely to alter lung

and/or chest wall mechanics, therefore it is not appropriate to suggest that these findings are universally applicable. Another major limitation of these studies is that the radionuclide scanning technique used may not only represent tidal volume change but also static lung volume and is therefore not necessarily representative of “dynamic” ventilation distribution.

To the best of my knowledge there are no recent studies examining the effects of body position on regional ventilation distribution in the presence of respiratory disease.

2.2.2.3.2 Neuromuscular disease

There are many neuromuscular diseases (NMD) which may be acute or chronic, acquired or hereditary. NMD can be classified into five broad categories: muscular dystrophies, congenital and metabolic myopathies, disorders of the neuromuscular junction, peripheral neuropathies and anterior horn cell diseases (Gozal, 2000). Respiratory insufficiency is one of the primary causes of morbidity and mortality in children with NMD (Gozal, 2000; Boitano, 2006). Respiratory insufficiency is the result of either acute or chronic respiratory disease or, more commonly, a result of respiratory pump failure (Panitch, 2009).

Differences in chest wall and lung mechanics in children with NMD may have a significant impact on ventilation distribution. Accompanying the associated muscle weakness, reduced chest wall compliance (in later years) as a result of fibrotic changes and deformities, and reduced lung compliance contribute to a restrictive pattern of respiratory disease in these children (Gibson et al., 1977; Estenne et al., 1983; Redding et al., 2008). The reduction in total lung capacity and vital capacity is associated with disease progression and aging (Inkley, Oldenburg & Vignos, 1974; Samaha et al., 1994). In infants and younger children with NMD, chest wall compliance is similar to that of new-borns, where the chest wall is prone to deformation during respiratory efforts, resulting in reduced lung volumes (Papastamelos, Panitch & Allen, 1996; Lissoni et al., 1998). Furthermore, the efficacy of diaphragmatic contraction is compromised by the distortion of the compliant chest wall. The more compliant chest wall may be the result of reduced muscle tone, as well as the lack of mobility and weight bearing which leads to structural changes in the connective tissue (Papastamelos, Panitch & Allen, 1996). As with new-borns and infants, the more compliant chest wall results in a lower FRC and predisposes these children to atelectasis, particularly of the dependent lung regions. The distortion of the chest wall can result in chest wall deformities, such as pectus excavatum, which in turn limit lung growth and contribute to reduced lung volumes (Panitch, 2006; Sharma, 2009).

In addition to the changes seen in chest wall mechanics, several other factors may contribute to ventilation distribution in these children. Depending on the degree of muscle weakness, flow rates, either inspiratory, expiratory or both may be reduced (Gozal, 2000). This may favour ventilation of the non-dependent lung. Reduced expiratory flow rates,

together with low lung volumes, are associated with an inadequate cough, making these children prone to respiratory infections and mucus plugging, with resulting atelectasis (Panitch, 2006). The micro-atelectasis that is frequently seen in NMD may contribute significantly to the lower lung compliance that is observed (Carbonara & Eidelman, 2005). Low tidal volume breathing commonly occurs due to muscle weakness and the restrictive changes that occur in the chest wall. This further amplifies the potential for the development of atelectasis (Panitch, 2006).

The presence of postural and chest wall deformities may have a significant impact on ventilation distribution. A ventilation scintigraphy study in children with scoliosis showed marked disparities between ventilation in the left and right lungs (Redding et al., 2008). The effect of body position on the distribution of ventilation in children with neuromuscular disease is unclear.

To the best of my knowledge there are no recent studies examining the effects of body position on regional ventilation distribution in the presence of NMD.

2.3 Respiratory muscle activity

The primary muscles of inspiration are the diaphragm and external intercostal muscles. The diaphragm is the main inspiratory muscle; accounting for ~70% of minute ventilation under normal conditions (Vassilakopoulos, 2012). It can be divided into the costal and crural portions, based on their point of origin (Vassilakopoulos, 2012); and consists of left and right hemi-diaphragms, which are innervated separately. Contraction of the diaphragm results in its caudal displacement which increases the diameter of the thoracic cavity in the craniocaudal axis. The force generating capacity of a muscle is determined by the resting length (Pengelly, Alderson & Milic-Emili, 1971; Braun, Arora & Rochester, 1982). The resting length of the diaphragm is determined by the balance of elastic forces between the chest wall and lungs (i.e. resting volumes). Optimal resting length for the diaphragm is just below FRC (Evanich, Franco & Lourenco, 1973). The external intercostal muscles aid in the elevation of the ribcage, increasing the anteroposterior diameter of the thoracic cavity, however under normal conditions the primary action of the external intercostal muscles is to stabilise the rib cage during inspiration (De Troyer & Sampson, 1982; De Troyer, Kirkwood & Wilson, 2005).

The ability of the respiratory muscles to generate sufficient force for respiration depends on the balance that exists between the load that must be overcome and the force generating capacity (neuromuscular competence) of the respiratory muscles (Vassilakopoulos, 2012). Factors that contribute to the overall load that must be overcome include lung and chest wall elastic loads, and airway and tissue resistive loads. The capacity of the respiratory muscles is dependent on central drive, neural and neuromuscular transmission and muscle strength.

Under normal conditions, there is reserve capacity in order to adjust to increased load. However, where this reserve is insufficient or the load is too great, muscle fatigue can occur. Respiratory muscle fatigue can be classified as either central or peripheral fatigue. Central fatigue is when the maximal voluntary contraction generates less force than that of a maximal electrical stimulation; this is tested by measuring the transdiaphragmatic pressure (Pdi) during phrenic nerve stimulation (Vassilakopoulos, 2012). It is postulated that central fatigue may result from the central drive not fully activating all motor units of the diaphragm, whilst peripheral fatigue results from impairments at the neuromuscular junction, usually related to the failure of impulse propagation within the muscle fibres (Vassilakopoulos, 2012).

The first successful report of non-invasive monitoring of diaphragm activity in infants was by Hagan et al. (1977). Following on from this, Prechtl, Van Eykern & O'Brien (1977) described a method for monitoring diaphragmatic activity in newborns non-invasively using pairs of electrodes. There have since been a number of studies using surface electromyography (sEMG) to monitor respiratory muscle activity in infants and children under various conditions. A number of studies have investigated the effect of respiratory muscle activity on tidal flow and end expiratory lung volumes in infants (Maarsingh et al., 2004; Maarsingh et al., 2006; Hutten, van Eykern & Latzin, 2008; Hutten, 2009; Hutten et al., 2010).

In a cohort of 20 term infants (mean age 44 (range 41.9-48.9) weeks) breath-by-breath variability of diaphragm and intercostal muscle activity as well as the impact of respiratory muscle activity on EELV and ventilation inhomogeneity was investigated (Hutten et al., 2008). Measurements were taken during quiet sleep in the supine position. Muscle activity (diaphragm and intercostals) was measured using sEMG and EELV and ventilation inhomogeneity was determined using the multiple breath SF_6 washout technique (performed using a face mask, the average of three washouts was used). During inspiration, intercostal activity began before diaphragm activity and both intercostals and the diaphragm reached their peak activity level after maximal flow was achieved. The contribution of intercostal and diaphragm activity to flow varied on a breath by breath basis, as was seen from the relatively high coefficients of variation (CV) for the relative contribution of intercostal (14.2 ± 6.6%) and diaphragm (32.9 ± 9.4%) activity to tidal flow. The contribution to flow for both muscles became less variable with increased load, albeit a non-significant reduction. Inspiratory muscles maintained a degree of activity during expiration which was weakly correlated with FRC ($r=0.52$, $r^2=0.27$, $p<0.01$). Since this was a small study in healthy infants, the findings may not be applicable to preterm infants, those with respiratory disease or conditions impacting on respiratory mechanics. Furthermore, the impact of potential crosstalk from other muscle groups was not examined. Since measurements were taken during quiet sleep, crosstalk may have been minimised. The placement of the electrodes for diaphragm

activity is above the insertion of the abdominals and reports have shown that during rapid eye movement (REM) sleep in infants there is minimal abdominal muscle activity (Hutten et al. 2007), whether infants were in REM sleep in this study is unclear. A clearer description of sleep state i.e. REM or NREM rather than "quiet" sleep is necessary to adequately interpret these results as sleep state has the potential to alter respiratory mechanics. It is possible that crosstalk from underlying intercostal muscles could have contaminated the diaphragm readings; this was not addressed or examined in the study.

Building on previous findings, Hutten et al. (2010), examined the effect of respiratory muscle activity on flow rates in preterm infants (n=19, median gestational age 27.3 (24.0 - 36.7) weeks, median postnatal age 44.6 (43.4 - 51.1)) compared to healthy age matched controls (n=39, median gestational age 39.9 (37.0 - 41.7) weeks, median postnatal age 44.4 (41.9 - 48.1)). The study methodology was similar to that previously discussed (Hutten et al., 2008). Preterm infants showed significantly less variability in the contributions of intercostal (CV 11.2%) and diaphragm (CV 22.6%, p=0.03) muscle to inspiratory flow compared to the controls. Differences in timing of activity were found between the two groups, with inspiratory muscle activity starting much earlier in expiration in preterm infants compared to controls. Weak correlations were found when respiratory muscle activity was compared to FRC in both groups. Longer post-inspiratory activity was weakly associated with a higher FRC in the control group ($r=0.34$, $r^2=0.12$, $p=0.001$), while a weak negative correlation was found in the preterm infants ($r=0.33$, $r^2=0.11$, $p=0.001$) (Hutten et al., 2010). Methodological limitations are similar to those previously discussed.

During a histamine challenge in 20 pre-school children, diagnosed with asthma, between the ages of 2-6 years, respiratory muscle activity was associated with the degree of airflow limitation (Maarsingh et al., 2004). Diaphragm activity increased by a factor of 2.7 (0.43 ± 0.18, $p =0.004$) and intercostal activity increased by a factor of 3.2 (0.51 ± 0.34, $p=0.005$) with increasing clinical airflow limitation (i.e. the presence of wheeze, persistent cough, prolonged expiration, and increase in the respiratory rate) (Maarsingh et al., 2002; Maarsingh et al., 2004). Respiratory muscle activity returned to baseline values 10 minutes after the administration of salbutamol. Since airflow limitation was determined clinically and not by direct measures of lung function, the relationship between respiratory muscle activity and airflow limitation could not be determined.

In the critical care setting it is well established that mechanical ventilation and critical illness have a significant effect on diaphragm structure and function (Radell et al., 2002; Sassoon et al., 2002; Bernard et al., 2003; Capdevila et al., 2003; Levine et al., 2008; Hussain et al., 2010). This diaphragm dysfunction is typically determined by ultrasonography and measures of muscle strength (namely Pdi). More recent studies in the paediatric population using oesophageal EMG have shown markedly reduced diaphragm activity during

mechanical ventilation which improved significantly after extubation (Emeriaud et al., 2014). studied a total of 55 infants and young children at four time points during their PICU stay: acute phase (n=52, median age 9 (1-35) months), pre-extubation (n=23, median age 4 (2-63) months), post-extubation (n=26, median age 3 (1-56) months), and PICU discharge (n=23, median age 8 (2-49) months). Peak inspiratory activity was significantly higher in children intubated with respiratory disease ($p<0.01$) at all measurement points. Low levels of peak diaphragm activity (<2μV) were common in the acute phase (33%) and pre-extubation phase (24%). Measurements were obtained in 18 children for both the pre-extubation and post-extubation phases. In these patients, peak diaphragm activity increased by 116% (IQR 25-218%). Driving pressures, ventilatory mode and sedation did not impact on diaphragm activity. The reduction in diaphragm activity is likely to occur as a result of reduced respiratory drive related to the amount and duration of mechanical assistance the child was receiving (the first reading was taken a median of 3 (IQR 1-7) days after intubation) as well as the underlying medical conditions (Emeriaud et al., 2014; Vaschetto et al., 2014). Although sedation was found not to affect diaphragm activity, the effect of deeper sedation or neuromuscular blocking agents prior to the first recording may have impacted on diaphragm activity. Owing to the small sample size, stratification of children based on age, amount of sedation, amount of ventilatory support and disease type or severity was not possible, however these factors would need to be considered in future studies investigating factors influencing respiratory muscle activity. Unfortunately, incomplete diaphragm activity measurements were obtained in six children that failed extubation, this data may have given an indication of the relationship (if any) between extubation success or failure.

Wolf et al. (2011) investigated diaphragm activity during an extubation readiness test (ERT) in 20 children (median 5.7 years (range of 4 days – 16 years)). Diaphragm activity was measured using oesophageal EMG before the ERT, one hour into the ERT and after extubation. Extubation failure was defined as requiring re-intubation or non-invasive ventilator support within 24 hours of extubation. Twelve children passed the ERT on the first attempt, six were successfully extubated, four required non-invasive ventilatory support and two required re-intubation. A significantly lower ratio of tidal volume to muscle activity ($p=0.02$) was seen in children who were successfully extubated (24.8 ± 20.9mL/μV) compared to those that failed extubation (67.2 ± 27 mL/μV). Children who passed ERT also showed a significant reduction ($p=0.02$) in the ratio of tidal volume to muscle activity from before the ERT (67.0 ± 92.7 mL/μV) to after one hour of the ERT (24.8 ± 20.9 mL/μV), possibly indicating preserved diaphragm function. A significant correlation was found between diaphragm activity and airway opening pressure ($r=0.68$, $p<0.001$) with increased diaphragm activity resulting in smaller airway opening pressures. This study was limited by a small sample size and rather heterogeneous population. The duration of ventilation, level of previous ventilatory support and use of sedation prior to undergoing the ERT was not

reported, these factors may account for some of the differences between those who passed and failed extubation.

There are no studies, to the best of my knowledge, examining respiratory muscle activity in the older paediatric population in health and disease states and the consequent effect on ventilation distribution. Respiratory muscle activity, like ventilation distribution, is affected by a number of factors, such as respiratory disease, the integrity of the nervous system, and factors related to respiration such as flow rates and airway resistance. Presently, there are a limited number of studies, mostly in neonatal populations, with relatively small sample sizes and heterogeneous population groups and therefore no normal data exists.

2.4 Positioning as a therapeutic modality

Therapeutic positioning is used as therapy by many members of the multidisciplinary team particularly in the presence of respiratory distress and disease. Positioning is thought to augment oxygenation by optimising ventilation to healthy lung regions and improving ventilation-perfusion matching (Dean, 1985; Fink, 2002). In clinical practice positioning is also used to re-expand atelectactic lung regions. This is achieved by placing the atelectactic lung uppermost (based on the findings of Heaf et al. (1983) and Davies et al. (1985)) in order to facilitate greater ventilation to this region. This positioning for atelectasis is frequently used despite little evidence to support its use. Not only does positioning aid in improving ventilation and oxygenation, but it may minimise the risk of developing pressure sores, deep vein thrombosis, atelectasis and pneumonia (Hewitt, Bucknall & Glanville, 2016). Since positioning is relatively inexpensive and non-invasive it is an attractive intervention to achieve improved oxygenation and in turn potentially reduce the amount of time that more invasive interventions, such as mechanical ventilation, are required (Gillies, Wells & Bhandari, 2012). Furthermore, the correct choice and use of positioning can augment the effects of other interventions, such as cardiopulmonary physiotherapy (Dean, 1985). Although therapeutic positioning may have beneficial effects, it also carries some risk, particularly in critically ill infants and children. These include accidental removal of invasive lines, accidental extubation, haemodynamic instability, and pressure ulceration if positions are maintained for extended periods of time (Curley, 1999). Determining the effects and possible risks of positioning is therefore important to ensure both safe and effective practice.

The vast majority of studies examining positioning as a therapeutic modality are in preterm infants (Rivas-Fernandez et al., 2016), with very few studies examining the effects in the older paediatric population (Curley, Thompson & Arnold, 2000; Kornecki et al., 2001; Curley et al., 2005). In addition, the majority of participants in previous studies were mechanically ventilated and the most common positions examined were supine and prone positions. Studies, particularly of prone positioning, report improved oxygenation, improvement in respiratory parameters, improved breathing synchrony and improved respiratory mechanics

(Wagaman et al., 1979; Wolfson et al., 1992; Maynard, Bignall & Kitchen, 2000). Side lying positions offered no additional benefit over the supine or prone positions in improving oxygenation in preterm infants (Gillies, Wells & Bhandari, 2012). Of the available studies in the older paediatric population (over one year of age) (Murdoch & Storman, 1994; Kornecki et al., 2001; Curley et al., 2005), the majority only examined the effects of prone and supine positions in mechanically ventilated children with ARDS, reporting improved oxygenation in the prone position (refer to Section 2.5.2.2 for further detail).

Positioning is a commonly used component of cardiopulmonary physiotherapy; however, our understanding the effects of positioning, particularly positions other than supine and prone positions, on ventilation distribution and clinical benefits in the older paediatric population is limited.

2.5 Prone positioning in acute respiratory distress syndrome

2.5.1 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is characterised by widespread inflammation and oedema in the lungs, resulting in impaired oxygenation and stiff lungs (Gattinoni et al., 2006). ARDS was first defined in 1994 by the American-European Consensus Conference (AECC) (Bernard et al., 1994). This definition classified ARDS as acute hypoxaemia, based on the ratio of partial pressure of oxygen in the blood and the fraction of inspired oxygen the patient is receiving (PF ratio) of <200mmHg, with bilateral infiltrates on the chest radiograph and the absence of left atrial hypertension. A second category, acute lung injury (ALI), was also identified and was determined by a PF ratio of <300mmHg. In 2011, the definition of ARDS was revised and the Berlin Definition was developed. The Berlin Definition of ARDS has three classifications of severity (mild, moderate or severe) based on the degree oxygen impairment (Table 2.5.1) and takes several other factors, such as radiological severity, respiratory system compliance, positive end expiratory pressure levels and expired volume/minute volume into account (Force, 2012).

The AECC and Berlin classifications of ARDS which were developed for adult patients have been extrapolated to the paediatric population. Based on the AECC classification the estimated incidence of ARDS in the paediatric population is between 2.2 to 12.8 per 100 000 person-years in the United States, Europe, Australia and New Zealand (Bindl, Dresbach & Lentze, 2005; Erickson et al., 2007; Kneyber et al., 2008; Zimmerman et al., 2009; Lopez-Fernandez et al., 2012). A recent meta-analysis by Schouten et al. (2016) reported a pooled population based incidence of 3.5 per 100 000 person-years (95% CI, 2.2-5.7) in children. The overall pooled weighted mortality for paediatric ARDS is 33.7% (95% CI, 28.6-39.7%), it must be noted that the pooled weighted mortality was higher in Asian studies (51.0%; 95% CI, 41.5-62.7%) compared to Western studies (27.3%; 95% CI, 22.5-33.5%), likely due to

differing study methodologies (Schouten et al., 2016). An international multicentre study evaluated the revised Berlin definition in the paediatric population and found it to be valid (De Luca et al., 2013). Authors concluded that it may be more suited for use in the paediatric population than the previous AECC definition as the addition of the "severe" ARDS category may better predict mortality (hazard ratio (HR) for moderate ARDS 0.8 (95% CI 0.3 – 2.5) p=0.77 vs HR for severe ARDS 2.7 (95% CI 1.1 – 7.1) p=0.02) and the likelihood of requiring extracorporeal membrane oxygenation (ECMO) (HR for moderate ARDS 0.8 (95% CI 0.3 – 2.4) p=0.71 vs HR severe ARDS 3.0 (95% CI 1.9- 7.9) p=0.02) in children (De Luca et al., 2013).

Table 2.5.1 Classification of ARDS based on PF ratio using the Berlin Definition

ARDS classification	**PaO_2/FiO_2**
Mild	$200 < PaO_2/FiO_2 < 300$
Moderate	$100 < PaO_2/FiO_2 < 200$
Severe	$100 > PaO_2/FiO_2$

Although the revised Berlin definition has been validated against the AECC definition in children, important differences between adults and children were not considered. These differences, as described by Khemani et al. (2015), include:

- Age or stage of lung development
- The reliability and sensitivity of radiographic features (specifically bilateral infiltrates)
- Criteria for determining severity and risk stratification
- The more frequent use of non-invasive mechanical ventilation in the paediatric population
- The presence of cardiac and underlying respiratory conditions

Subsequently, a paediatric specific definition was developed based on the existing Berlin definition but considering these differences between children and adults with ARDS (Figure 2.5.1). Major differences to the adult definition (Berlin) include the presence of new infiltrates (not necessarily bilateral) on chest radiographs, the inclusion of known cardiac or lung disease, and the use of oxygenation index (OI) over PF ratio in the classification of paediatric ARDS (Khemani et al., 2015). Yehya, Servaes & Thomas (2015) suggested that classification of ARDS, using the OI or PF ratio, should be made either after 24 hours of stabilisation or using the worst value, as these were both significantly associated with mortality and the number of ventilator free days, whilst the OI or PF values were not predictive of either. Based on combined data from the studies of Erickson et al. (2007) and Khemani et al. (2009a) it has been suggested that children may progress from a less to more severe classification of ARDS over several days of mechanical ventilation (Khemani et

al., 2015). In addition, based on this pooled data, the worst OI value over three days appears to better predict mortality when compared to the worst PF value over the three days (p=0.02) (Khemani et al., 2015).

Age	Exclude patients with peri-natal related lung disease			
Timing	Within 7 days of known clinical insult			
Origin of Edema	Respiratory failure not fully explained by cardiac failure or fluid overload			
Chest Imaging	Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease			
Oxygenation	**Non Invasive mechanical ventilation**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
Special Populations				
Cyanotic Heart Disease	Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. [3]			
Chronic Lung Disease	Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above.[3]			
Left Ventricular dysfunction	Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction.			

Figure 2.5.1 Paediatric Acute Respiratory Distress Syndrome (PARDS) classification. Used with permission from Khemani et al. (2015). CPAP – continuous positive pressure ventilation, PF – partial pressure of oxygen to fraction of inspired oxygen ratio, SF – oxygen saturation to fraction of inspired oxygen ratio, OI – oxygen index, OSI – oxygen saturation index.

Patients with ARDS frequently require mechanical ventilation for respiratory failure. Whilst mechanical ventilation is essential in the presence of ARDS to maintain adequate oxygenation, there is also the risk of causing further injury to the lungs. This is due the heterogeneity of lung mechanics that accompanies ARDS, resulting in increased stress and strain on lung tissue (Gattinoni, Carlesso & Caironi, 2012). Early studies using computed tomography (CT) scanning revealed that ARDS results in areas of relatively normal lung tissue and areas of lung tissue (predominately in the dependent regions) that are poorly or not aerated (Gattinoni et al., 1987). This disparity in aeration in the lungs is the result of a greater increase in the transpulmonary pressure down the vertical gradient in the ARDS lung compared to normal (Pelosi et al., 1994). A progressive deflation of gas is seen down the vertical gradient of the lung, with much lower gas to tissue ratios in the dependent lung regions. This is postulated to be the result of altered lung and chest wall compliance, but more importantly as a result of significantly increased superimposed hydrostatic pressures due to the heavier, oedematous lungs. Subsequently, there is partial or total collapse in the dependent lung regions whilst the non-dependent regions remain relatively inflated (Pelosi et al., 2001; Pelosi, Brazzi & Gattinoni, 2002). With conventional ventilation strategies, there is

the risk of over-distension of the non-dependent lung regions and cyclic opening and closing of the dependent lung regions exposing the lung to increased stress and strain and consequently further injury (Gattinoni, Carlesso & Caironi, 2012). Several methods have been employed to minimise the risk of further lung injury while still maintaining oxygenation, which include “lung protective” ventilation strategies and prone positioning.

2.5.2 Prone positioning

Prone positioning as a therapeutic modality was first suggested by Bryan (1974) in paralysed and mechanically ventilated patients. This suggestion was made as the supine position results in greater airway closure in the dependent lung regions, which may be exacerbated in the presence of pathology. The use of prone positioning in ARDS was first described in 1976 where improved oxygenation was observed in patients in the prone position (Piehl & Brown, 1976). Although numerous studies reported improvement in oxygenation in patients, it should also be noted that variability in individuals’ response to the prone position has also been reported (Pelosi et al., 1998). There have since been numerous studies examining the effects of prone positioning in ARDS in adult and, to a lesser extent, paediatric patients. Benefits of the prone position in ARDS include improved oxygenation, improved clearance of carbon dioxide, and a reduction in regional lung stress and strain and therefore a potential delay in ventilator induced lung injury (Pelosi et al., 1998; Gattinoni et al., 2003; Valenza et al., 2005).

2.5.2.1 Mechanism by which prone positioning may work

There are several mechanisms by which prone positioning may improve oxygenation. It is thought to improve secretion clearance; recruit the collapsed dorsal lung regions; improve FRC/EELV; improve ventilation-perfusion matching and result in a more homogenous gas to tissue ratio throughout the lung (Lamm, Graham & Albert, 1994; Pelosi, Brazzi & Gattinoni, 2002; Santini et al., 2015).

There is a more homogenous gradient of transpulmonary pressure in the prone position (Mutoh et al., 1992), which in turn results in more even alveolar inflation. There are several mechanisms which may affect the more uniform transpulmonary pressures observed in the prone position. Firstly, alterations in hydrostatic pressures (as a result of the heavy, oedematous lungs) may account for some of the change (Gattinoni et al., 1991). The superimposed hydrostatic pressures are greatest in the dependent lung regions, in the supine position this would be in the dorsal lung regions. When moving into the prone position, this superimposed pressure gradient is reversed with greater pressures now in the ventral lung regions (Gattinoni et al., 2001; Gattinoni, Pesenti & Carlesso, 2013). In the prone position, collapse of the dependent lung regions is expected given the shifts in hydrostatic pressure, however due to the triangular shape of the lung in the ventral to dorsal direction, there is a greater proportion of aerated or recruitable lung in the prone position

compared to the supine position (Mutoh et al., 1992; Gattinoni, Pesenti & Carlesso, 2013). Secondly, the mass of the heart has also been reported to be increased in ARDS (Malbouisson et al., 2000). This is postulated to be the result of right ventricle dilatation due to pulmonary hypertension, myocardial oedema, and a hyperkinetic state as a result of systemic inflammation (Malbouisson et al., 2000). Consequently, in the supine position, the heavier heart results in more positive pleural pressures in the dependent lung regions, further aggravating collapse. In the prone position, the majority of the heart rests on the sternum with little lung underneath it and therefore, the heart has less of an effect on pleural and transpulmonary pressures (Albert & Hubmayr, 2000). Another factor which may result in improved homogeneity of aeration is the reduction in chest wall compliance and improved lung compliance which occurs in the prone position (Pelosi et al., 1998). This coupled with mechanical ventilation may facilitate ventilation to the dependent lung regions. Since children have a more compliant chest wall, the assumed reduction of chest wall compliance in the prone position, may contribute substantially to the improvements seen in oxygenation (Kornecki et al., 2001). Alterations in abdominal hydrostatic pressure in the prone position may also facilitate better inflation of the dorsal lung regions. The abdominal hydrostatic pressure is reduced in the dorsal regions in the prone position, and this theoretically results in an increase in transpulmonary pressure which may improve FRC and prevent airway closure (Numa, Hammer & Newth, 1997). There is some disparity in the literature regarding the improvement of FRC in the prone position and the subsequent impact on oxygenation. Although FRC increased when moving from the supine to prone position (22.2 ± 1.4ml/kg to 23.4 ± 1.5ml/kg) in 30 mechanically ventilated infants and young children (age 3 - 7.6 years) with obstructive respiratory disease, restrictive respiratory disease or no respiratory disease, this change did not reach statistical significance (Numa, Hammer & Newth, 1997). Furthermore, EELV was not associated with the increase in oxygenation observed ($r=0.225$, $p=0.23$), however it must be noted that PaO_2 values were not obtained in all children and this was a small heterogeneous group of children who were not specifically diagnosed with ARDS, therefore these results may not be applicable to infants and children with ARDS.

Based on studies using radioactive isotopes it is widely accepted that perfusion is gravity dependent and increases down the vertical height of the lung (West, 1962; West, 1978). A study examining the effect of prone positioning in 12 adults with ARDS on oxygenation and V/Q matching suggested that the improvement in oxygenation occurs as a result of improved ventilation in atelectactic lung regions thereby improving the number of lung units with a normal V/Q rather than the redistribution of perfusion in the prone position (Albert et al., 1987; Pappert et al., 1994). Authors reported that in patients who responded to prone position (increase in PaO_2 of ≥10mmHg) the shunting, as a result of hypoxic pulmonary vasoconstriction, decreased by 11% and there was an increase in blood flow to areas with normal V/Q, whereas the patients who did not respond showed no difference in the shunt in

the prone position. Based on experimental studies in dogs, some authors suggest that gravity has little effect on the distribution of perfusion, since variability in blood flow was as large within iso-gravitational planes as it was across gravitational planes (Gattinoni et al., 1991; Glenny et al., 1991; Glenny, 2009). Several studies using imaging tools with higher spatial resolution, such as single-photon emission computerized tomography (SPECT), EBCT and magnetic resonance imaging (MRI), have demonstrated that in humans, the height up the lung had little effect on perfusion distribution in the horizontal postures compared to the upright position, accounting for 4 - 41% of the perfusion distribution (Hopkins et al., 2007; Petersson et al., 2007). In an experimental study in pigs using microspheres during parabolic flights, multiple stepwise linear regression analysis showed that the vertical height up the lung only accounted for 1 - 4% of the perfusion distribution (Glenny et al., 2000). The effect of the vertical height on perfusion within the lung is likely to be greater in the upright posture. If gravity and horizontal postures have little effect on the distribution of perfusion, improvements in oxygenation in the horizontal postures are likely to occur as a result of improved V/Q matching from changes in ventilation distribution (Petersson et al., 2007).

While these mechanisms have been extensively studied in the adult population, there are very few studies in the paediatric population. Whether prone turning results in improved homogeneity of ventilation or recruitment of dorsal lungs in children with ARDS, as is observed with CT images in adults, has not been studied.

2.5.2.2 Impact of prone positioning on clinical outcomes

Despite the improvements in oxygenation that occur with prone positioning, the impact on other clinically meaningful outcomes such as duration of ventilation, length of stay and mortality is yet to be consistently observed. Rather, it is proposed that improved survival is more likely to occur due to reduced ventilator induced lung injury as a result of improved ventilation homogeneity in the prone position (Albert et al., 2014; Guerin, 2014). Clinically meaningful benefits may be associated with other factors, one of which is the reduction in dead space as was observed by improved carbon dioxide clearance in the prone position (Gattinoni et al., 2003). This reduction in dead space was subsequently associated with an improved 28-day survival. Based on this, it has been suggested that the definition of a responder (to prone positioning) should extend beyond simply an improvement in oxygenation (Kavanagh, 2005).

Numerous adult studies have failed to show benefits of prone positioning on outcomes such as mortality (Gattinoni et al., 2001; Mancebo et al., 2003; Guerin et al., 2004; Mancebo et al., 2006; Taccone et al., 2009). However, a recent randomised controlled trial has shown significant improvements in 28 and 90-day mortality, ventilator-free days and successful extubation in adult patients with ARDS who were managed in the prone position with lung

protective ventilation (Guérin et al., 2013). Several meta-analyses have now shown the beneficial effects of prone positioning in adult ARDS on mortality, particularly in more severe disease and when ventilated with lower tidal volumes (Beitler et al., 2014; Lee et al., 2014; Sud et al., 2014). The results of these meta-analyses highlight that it may be the reduction in lung stress and strain that occurs in the prone position, which would be augmented by longer periods in the prone position and reduced tidal volumes, which contributes to improved survival (Henderson et al., 2014). Based on these findings, prone position is recommended in the early stages of ARDS and in severe ARDS (Guérin et al., 2013; Albert et al., 2014)

One of the first studies on prone positioning in the paediatric population was a small case series in seven children (Murdoch & Storman, 1994). Authors demonstrated significantly improved oxygenation despite children only spending 30 minutes in the prone position.

Curley, Thompson & Arnold (2000) performed a prospective case series (n=25, age range 2 months to 17 years) looking at the effect of prone positioning in children with ARDS which was defined by a PF ratio of <300mmHg. Children spent 20 hours per day in the prone position until their PF ratio was >300mmHg or they were nearing extubation. Their abdomens were unrestrained in the prone position. Responders to prone positioning were defined as those either showing an increase in the PF ratio of ≥ 20mmHg or a decrease of ≥10% in the OI. Response was further categorised as immediate (within one hour of being in the prone position), cumulative (over 19 hours of being in the prone position) and persistent (improvement was maintained after returning to the supine position after 20 hours in the prone position). Measurements of oxygenation, ventilatory parameters, and lung mechanics were taken at baseline (supine position), after one hour and 19 hours in the prone position and one hour after returning to the supine position. Eleven (44%) of the children were immediate responders, demonstrating a significant improvement in PF ratio after one hour in the prone position (134 ± 11 to 213 ± 21 mmHg, p=0.003). The increase in PF ratio persisted up to 19 hours (22 ± 25mmHg, p=0.02) and a persistent response was seen after returning to the supine position with a PF ratio of 170 ± 12mmHg (p=0.02 compared to baseline). In those that did not respond immediately (n=14, 56%), a cumulative response was seen after 19 hours with PF ratios improving from 152 ± 16mmHg (baseline) to 173 ± 15mmHg (19 hours, p=0.02), however this improvement did not persist once they returned to the supine position. Children with lower PF ratios at baseline compared to study enrolment and those that were positioned sooner after the start of mechanical ventilation had a persistent response to prone positioning. Improvements in oxygenation occurred in the majority (84%) of children during the course of the study period (i.e. these children had a greater number of response days than non-response days).

Similar improvements in oxygenation were observed in a small randomised cross-over trial (n=10, mean age 5 ± 3.6 years) (Kornecki et al., 2001). Children with an OI of ≥12 with FiO_2 ≥0.5 for at least 12 hours were included in the study. Children were randomised to one of two groups. The first group were placed in the supine position and then the prone position; the second group was first placed in the prone position and then the supine position. The abdomen was unrestrained in the prone position and each position was maintained for 12 hours. Measurements of oxygenation and respiratory mechanics were recorded in each position and an improvement of 20% in OI was considered clinically significant. OI was significantly better in the prone position compared to the supine position (p=0.0016), with improvements seen after 30 minutes and continuing up to two hours, with improved OI sustained for 12 hours. OI improved by 34 ± 17% (p=0.002) in 9 of 10 patients in the prone position. Interestingly, fluid balance was significantly less positive in the prone position (6.6 ± 15mL/kg/12hr vs 18 ± 13.6mL/kg/12hr, p=0.041). No changes in ventilatory parameters, haemodynamics, respiratory system and lung compliance were found (Kornecki et al., 2001). Children in both groups had severe ARDS with a mean OI of 21.3 ± 7.9 and 22.7 ± 9.9 respectively, which may explain the marked improvement observed in response to prone positioning. This is a small sample and therefore results may not be applicable to the whole population. Whether the improvements in OI and prone positioning resulted in improved outcomes such as a reduction in the duration of mechanical ventilation, shorter ICU stay and improved mortality was not examined.

Casado-Flores et al. (2002) performed an observational study investigating the effect of prone positioning in children (n=23, age range 0.5-129 months) with severe ARDS (PF ratio ≤200). Children were positioned in the prone position for eight hours, after which they were returned to the supine position, this was repeated until they were ready for weaning or their condition deteriorated in the prone position. The PF ratio before and after each position change was calculated. Children who demonstrated an increase of ≥15% were classified as responders and those who showed a decrease of ≤15% in their PF ratio were classified as non-responders. Position changes accounted for 36% of the ventilator time, and overall PF ratio increased from 92 ± 35 to 110 ± 46 (p<0.001) when in the prone position. Eighteen (76%) of the children were responders, whilst five (24%) were non-responders. Responses within the responders were also variable with a third of responders only showing an improvement after successive position changes. In this study, mortality rates were lower in the responders; however, this failed to reach statistical significance which is likely due to the small sample size. Complications reported included facial oedema and the development of scars/pressure ulcers (n=3).

A multi-centre, randomised control trial by Curley et al. (2005) examined the effects of prone positioning in children with ARDS on the number of ventilator free days after 28 days.

Children between the ages of 2 weeks to 18 years with a PF ratio of ≤300, bilateral infiltrates, and no left arterial hypertension were eligible for inclusion. Children were randomised into either the control group, which was standard care in supine position (n=51, median age 2.1 (0.3-11.0) years) or intervention group in which participants were placed in the prone position within 4 hours of randomisation and remained prone for 20 hours per day (n=51, median age 2.0 (0.3-8.2) years). Children in the intervention group had blood gases taken prior to and after an hour each position change. The number of days where an increase of ≥20% in PF ratio or a reduction of ≥10% in OI was observed was counted as responder days. Overall response was determined by whether the child had a greater number of response or non-response days. The primary outcome was the number of ventilator free days over 28 days, secondary outcomes included 28-day mortality, time to recovery of lung injury, number of organ-failure free days, and functional health. Unfortunately, the study was terminated early due to futility. After adjusting for confounders, there was no significant difference in the number of ventilator free days between the two groups (mean difference 0.3, 95% CI -3.0 – 3.5, p=0.87). Mortality was similar between groups (risk ratio 0.93, 95% CI 0.78 – 1.11, p=0.45) and there were no significant differences between other secondary outcomes. Overall 90% of those in the intervention group were responders; however, this did not impact on the number of ventilator free days compared to non-responders. The most frequent complications associated with position change were accidental extubation (n=9), transient desaturation (n=11), and pressure ulcers (n=26). One of the strengths of this study was that prone positioning was implemented early (median time from inclusion 28 (18-39) hours) and was sustained for prolonged periods of time (mean of 18 ± 4 hours per day), both of which are factors which have subsequently been associated with improved mortality in adults (Guérin et al., 2013; Henderson et al., 2014). The lack of clinically meaningful outcomes found by Curley et al. (2005) may be due to the inclusion of children with less severe ARDS, which at the time was appropriate based on the available definition for ARDS, and therefore these findings may not be applicable to those with severe ARDS (PF ratio ≤100 or OI ≥16). The lack of meaningful outcomes may reflect a Type II error as a result of stopping the study early. Although improvements in oxygenation were observed in those that were in the prone position, these did not translate into clinically meaningful outcomes such as fewer days on mechanical ventilation and therefore authors suggested that prone positioning in children should not be routinely used.

Prone positioning is not without complications. These include haemodynamic instability, desaturation, endotracheal tube extubation or occlusion, removal of vascular lines or catheters, enteral feeding intolerance and pressure ulcers (Curley, 1999). However, studies in the paediatric population report minimal adverse effects of prone positioning (Curley, Thompson & Arnold, 2000; Kornecki et al., 2001). In a sub-analysis of a multicentre randomised controlled trial of 102 children, there were no significant complications

associated with prone turning and no serious adverse events observed (Fineman et al., 2006). Authors have concluded that prone turning is safe and feasible in the paediatric population.

2.6 Conclusions

Despite the lack of evidence for positioning in the older paediatric population, it remains an important component of the management of children with respiratory disease and those who are critically ill. In order to correctly understand and implement positioning effectively in this population an understanding of ventilation distribution and possible factors affecting it is imperative.

Given the emerging evidence from neonatal studies, which indicate that the distribution of ventilation may not be as straightforward as previously thought, and the paucity of studies in older infants and children, the understanding of ventilation distribution in the older paediatric population is clearly limited. Due to obvious anatomical and physiological differences, results from neonatal and adult studies cannot be applied to older infants and children. The findings of the previous studies which have guided clinical practice until recently, are based on small paediatric populations and are not applicable to the general population. Furthermore, the lack of standardisation of testing procedures; relatively heterogeneous populations and the differences in which ventilation distribution is analysed among all the available studies makes it difficult to compare study findings and derive a clear understanding of ventilation distribution in the paediatric population. Further research, in larger, more homogenous groups and using standardised methodology, is clearly warranted to improve our understanding of ventilation distribution and possible determinants in the paediatric population.

The use of prone positioning has been extensively studied and is relatively well understood in the adult population. Despite little supporting evidence, it is a common belief that prone positioning recruits collapsed dorsal lung regions (Pelosi, Brazzi & Gattinoni, 2002). An alternative mechanism by which prone positioning improves oxygenation in the adult population, with ARDS, is through more homogenous alveolar inflation throughout the lung. This is achieved by recruiting the dorsal lung regions and improving the transpulmonary pressure gradients down the lung. Whether the recruitment of the dorsal lung regions is merely by improved resting volumes and/or greater ventilation in these regions is not clear in the literature. The beneficial effects of prone positioning on oxygenation have been examined in several paediatric studies; however, whether alterations in ventilation distribution and regional recruitment can account for these improvements remains unclear and requires further investigation.

2.7 Hypothesis, aim and objectives

The general aim and objectives are listed below. More detailed aims and objectives will be presented at the beginning of the relevant sections.

2.7.1 Hypotheses

1. Ventilation will be variably distributed in infants and children and will depend on a number of factors in both health and disease.
2. In the presence of ARDS, prone positioning results in recruitment of the dorsal lung regions in positive responders.

2.7.2 Aim

The general aim of this thesis is to describe the distribution of ventilation in older infants and children under different conditions.

2.7.3 Objectives

- To determine the distribution of ventilation in healthy, spontaneously breathing infants and children
- To determine the distribution of ventilation in mechanically ventilated infants and children
- To describe the distribution of ventilation in infants and children with neuromuscular disease
- To describe the distribution of ventilation in infants and children with respiratory disease
- To determine the effect of prone turning in hypoxic children with ARDS on the distribution of ventilation

Chapter 3 Outcome measures

In the past, ventilation distribution and respiratory muscle activity have been assessed by a limited number of techniques, such as ventilation scintigraphy, multiple breath washouts and transoesophageal electromyography, some of which are invasive or have the potential to alter normal respiratory mechanics. In recent years, however, non-invasive means, such as EIT and surface EMG, have become more readily available, and are therefore particularly appealing for use in the paediatric population.

The short-term effectiveness of clinical interventions such as mechanical ventilation and prone positioning, aimed at improving gaseous exchange is often monitored using measures such as changes in the partial pressure of oxygen, oxygenation index, partial pressure of oxygen to fraction of inspired oxygen ratio (PF ratio) and reductions in dead-space.

The various methods for monitoring ventilation distribution and respiratory muscle activity will be discussed in this Chapter. In addition, the possible measures to determine whether prone positioning in children with ARDS is successful or not, in terms of oxygenation, will be discussed in this Chapter.

3.1 Measurements of ventilation distribution

Traditionally, ventilation distribution in the paediatric population has been examined using ventilation scintigraphy or multiple breath washout (MBW) techniques. These techniques, however, often require specialised equipment, may require repeated radiation exposure, and since they cannot be performed at the bedside, impose risks associated with transporting ill children out of the ward or PICU (Frerichs et al., 2003). The emergence of EIT provides a possible alternative method of measuring ventilation distribution without some of the challenges inherent in the other techniques.

3.1.1 Ventilation scintigraphy

Radionuclide imaging of the lung can provide information on both ventilation and perfusion within the lungs. It can provide information about global and regional changes in ventilation distribution at lower radiation doses than computed tomography and chest radiography. This has proven to be a useful technique for measuring ventilation distribution and providing further information not obvious on clinical examination and in chest radiographs (Gordon, Helms & Fazio, 1981). Ventilation scintigraphy makes use of inhaled radioactive isotopes, and a gamma camera then detects the ionising radiation emitted by the isotopes. Isotopes which can be used for ventilation scanning in children are Technetium-99m (^{99m}Tc) labelled diethylenetriamine penta-acetic acid (DTPA), ^{99m}Tc-Technegas, Xenon-133 (^{133}Xe) and krypton-81m (^{81m}Kr). DPTA is eliminated rapidly via the kidneys thereby reducing radiation exposure. DPTA can be absorbed into the mucosa and therefore can also provide

information of mucociliary clearance, however if swallowed visualisation of the left lower lobe may be obscured due to a high gastric signal (Ciofetta et al., 2007). Since DPTA can remain in the airways for extended periods of time, dynamic imaging is not possible (Grant & Treves, 2011). ^{99m}Tc-Technegas penetrates well into distal airways due to its hydrophobic properties; however, it too can be swallowed resulting in a high gastric signal. Both DPTA and ^{99m}Tc-Technegas have low radiation doses with effective dose equivalents of approximately 0.02mSv/MBq and ± 0.047mSv/MBq respectively (Ciofetta et al., 2007). ^{133}Xe is also suitable for use in children as it requires little co-operation and has a relatively low radiation dose (effective dose equivalent 0.0027mSv/MBq) (Ciofetta et al., 2007). One advantage of ^{133}Xe is that dynamic ventilation images can be obtained and regional ventilation and lung volume can be differentiated (Grant & Treves, 2011). The use of ^{133}Xe requires an appropriate room where exhaled gas can be captured and removed (Grant & Treves, 2011; Parker et al., 2012). The half-life of ^{133}Xe is also considerably longer (5.2 days) than that of the other gases suitable for use in children (Parker et al., 1996). ^{81m}Kr is also suitable for use in the paediatric population and has been used in several studies describing ventilation distribution in the paediatric population (Heaf et al., 1983; Heaf et al., 1983; Davies et al., 1985; Davies, Helms & Gordon, 1992). The gas is delivered via an oxygen mask during tidal breathing making it suitable for patients with limited co-operation. Due to its very short half-life (13 seconds), the radiation dose is negligible (effective dose equivalent ± 0.004 - 0.01mSv/MBq) (Ciofetta et al., 2007). ^{81m}Kr is generated from 81m-Rubidium which also has a relatively short half-life of only 4.6 hours, making availability a challenge. Furthermore, the generators are costly and not widely available (Ciofetta et al., 2007). Due to the short half-life, the accuracy of ^{81m}Kr scanning to detect pure ventilation changes has been questioned, particularly in infants and young children where higher respiratory rates are common (Ciofetta et al., 2007). Rather, it is suggested that the scans are more likely to be representative of both ventilation and volume (Lythgoe et al., 1992; Ciofetta et al., 2007). Dynamic lung imaging could allow for the differentiation of ventilation versus volume changes detected. In an experimental model, Lythgoe et al. (1992), demonstrated a strong positive correlation between tidally exchanged ^{81m}Kr and ventilation distribution (R^2=0.95, p<0.001), while total ^{81m}Kr activity had a weaker positive correlation with ventilation distribution (R^2=0.63, p=0.001). A close linear relationship was demonstrated between tidal and total ^{81m}Kr in a group of adults and children (R^2=0.82, p<0.001). However, the authors noted that the use of steady-state images (i.e. total ^{81m}Kr) in conditions where there may be discrepancies between volume and ventilation may result in inaccurate estimations of regional ventilation, as was seen in a child with a hyperinflated (but poorly ventilated) left upper lobe (Lythgoe et al., 1992).

In summary, ventilation scintigraphy can measure ventilation distribution, the accuracy of which may depend on the nature of the gas used and whether steady-state or dynamic

images are analysed. Depending on the isotope used, the co-operation needed is minimal. There are, however, several limitations which may affect the feasibility of ventilation scintigraphy in the clinical setting. The equipment required and the gases can be costly, and are not readily available. Although, the short half-life of ^{81m}Kr makes it suitable for use in patients, it also means that it cannot be stored for long periods of time (Odenstedt et al., 2005), limiting its availability. Furthermore, this technique cannot be performed at the bedside, in some cases a specialised environment is required, and it requires the transport of patients out of their wards which has associated risks, particularly for critically ill patients.

3.1.2 Multiple breath washouts

Multiple-breath washouts (MBW) provide information about ventilation homogeneity and FRC. Furthermore, the function of the small airways, which is often overlooked in other lung function tests, can be determined with MBW (Vogt et al., 2014). This technique may assist in the early detection of airway abnormality as a result of obstruction when spirometry results may be normal and symptoms minimal (Aurora et al., 2004; Pillow, Frerichs & Stocks, 2006). Although MBW only provides information about global inhomogeneity, the technique can differentiate abnormalities of conductive and non-conductive airways (Pillow, Frerichs & Stocks, 2006; Robinson, Latzin & Gustafsson, 2010). It is recommended that ventilation inhomogeneity results are interpreted with other measures of lung volume, as MBW are only able to measure areas in communication with conducting airways resulting in underestimation of ventilation inhomogeneity (e.g. in the presence of lobar atelectasis) (Pillow, Frerichs & Stocks, 2006). MBW are an attractive technique for the young paediatric population where co-operation is limited, as measurements are taken during tidal breathing. It has been found to be feasible in a number of studies in infants and young children (during deep sleep or sedation), pre-school children and school-going children (Aurora et al., 2005; Aurora, Kozlowska & Stocks, 2005; Hülskamp et al., 2006; Lum et al., 2007; Robinson, Latzin & Gustafsson, 2010).

The wash-in and wash-out volumes of inert gases such as 4% sulphur hexafluoride (SF_6), methane (CH_4), helium (He), and argon (Ar) or the wash-out of nitrogen (N_2) using 100% oxygen are recorded during tidal breathing. The gas volumes are determined by the continuous monitoring of gas concentrations during the wash-in and/or wash-out periods. Measurements are taken either at normal tidal volume (commonly used in infants and young children) or at fixed tidal volumes, usually 1L (commonly used in adults) (Robinson et al., 2013). Both He and SF_6 are suitable for use in the paediatric population. Sulphur hexafluoride, although more expensive, is the preferred gas since the accuracy of He is compromised by its high diffusivity (low molecular mass) particularly in the presence of air-trapping and endotracheal tubes (Pillow, Frerichs & Stocks, 2006; Fuchs & Gappa, 2011). Although, SF_6 is perhaps the most suitable gas to use, it may not be readily available in all

countries due to its potential greenhouse effect (Fuchs & Gappa, 2011). Nitrogen, which is already present in the lungs, is an alternative; however, the washout is performed via the inhalation of 100% oxygen. While the use of 100% oxygen is advantageous since it is readily available and inexpensive, it is also problematic as it may induce atelectasis; potentially alter respiratory rate and pattern; expose the child to high concentrations of oxygen; and is not feasible in infants/children requiring a high inspired oxygen fraction index (F_iO_2) (Pillow, Frerichs & Stocks, 2006; Robinson et al., 2013). Since N_2 is also found in other body tissues, diffusion of N_2 from the blood into the alveoli may result in a prolonged wash-out period, affecting the accuracy of the results and FRC calculation (Robinson et al., 2013).

There are several types of equipment which can be used to measure the volumes of gas during the wash-in and wash-out periods. Mass spectrometry has been frequently used in the paediatric population. Briefly, it measures the concentrations of the gases by separating them based on their molecular mass. Concurrent flow measurements are taken with pneumotachography. The disadvantage of using mass spectrometry is that the equipment is expensive and is custom built and therefore not always readily available. Alternatively, measurements can be taken using an ultrasonic flow meter (USFM). This allows for simultaneous measurements of flow and gas density (molar mass), which are determined by the difference in transit time of the ultrasonic sound waves transmitted between two transducers a set distance apart (Fuchs & Gappa, 2011; Robinson et al., 2013). A disadvantage of this technique is that molar mass is significantly affected by the temperature and humidity of the expired gas, and molar mass includes other expired gases. Other USFMs have addressed the issues of temperature and humidity by including a side stream transducer where a relatively constant environment is created for the measurement of molar mass, while flow is still measured in the mainstream. Furthermore, the use of an infrared CO_2 analyser accounts for the contribution of CO_2 to the calculated molar mass.

Ventilation homogeneity is determined using various indices, such as the lung clearance index (LCI), over a series of breaths. LCI is the number of turnovers required to reduce the concentration of the inert gas to given proportion (2.5%) of the initial concentration at the beginning of the wash-out-period (Robinson et al., 2013). A lung turnover is determined by calculating the ratio of cumulative expired gas volume and FRC (Vogt et al., 2014). Indices used for the calculation of ventilation inhomogeneity are therefore dependent on accurate measures of FRC and a stable FRC during measurement. This may be difficult to achieve, particularly in infants where variations in respiratory rate and pattern are common (Robinson, Latzin & Gustafsson, 2010). It is, therefore recommended that measurements take place during non-rapid eye movement sleep and/or under sedation in infants and young children (Fuchs & Gappa, 2011; Robinson et al., 2013). Normative LCI values in healthy infants and

children are available (Fuchs et al., 2009; Fuchs et al., 2011). Variability of LCI is low, with a group of 44 healthy children and adolescents (5.3 – 20.3 years) demonstrating a within test co-efficient of variation (CV) of 5.1%. In the same population, reproducibility of LCI after one hour was 4.2% (mean difference −0.13; 95% CI −0.350 - 0.087) and after 6-15 months was 5.1%, (mean difference 0.017; 95% CI −0.016 - 0.348) (Fuchs et al., 2009). In infants (mean postmenstrual age ± SD, 36.5 (1.4) weeks) within test repeatability of LCI was found to be within acceptable limits with a CV of 9% (95% limits of agreement -26.6 – 23.1) and between test reproducibility of LCI was 10.3% (95% limits of agreement -31.7 – 36.1) (Sinhal et al., 2010). A large between subject variability in LCI index was found (intra-class correlation coefficient of 67%). It is likely that this high, although acceptable, variability was due to variations in respiratory rate and pattern and differences in the growth and development of the respiratory system (Sinhal et al., 2010).

MBW is a suitable technique for determining small airway disease and global ventilation homogeneity; however, it is not able to provide information regarding regional ventilation distribution. In addition, the accuracy of measurements may be comprised in conditions such as lobar atelectasis. Although several gases are readily available (namely He, N_2 and O_2), each of these has the potential to affect the accuracy of the results. MBW may not be suitable for use in mechanically ventilated children, particularly those with high FiO_2 requirements; however, several studies in relatively small samples have shown that MBW are feasible in mechanically ventilated children (Schibler & Henning, 2002; Bikker et al., 2009). The absence of radiation exposure, low co-operation requirements and the availability of normative data make MBW an attractive tool for measuring global ventilation homogeneity in the paediatric population.

3.1.3 Electrical impedance tomography (EIT)

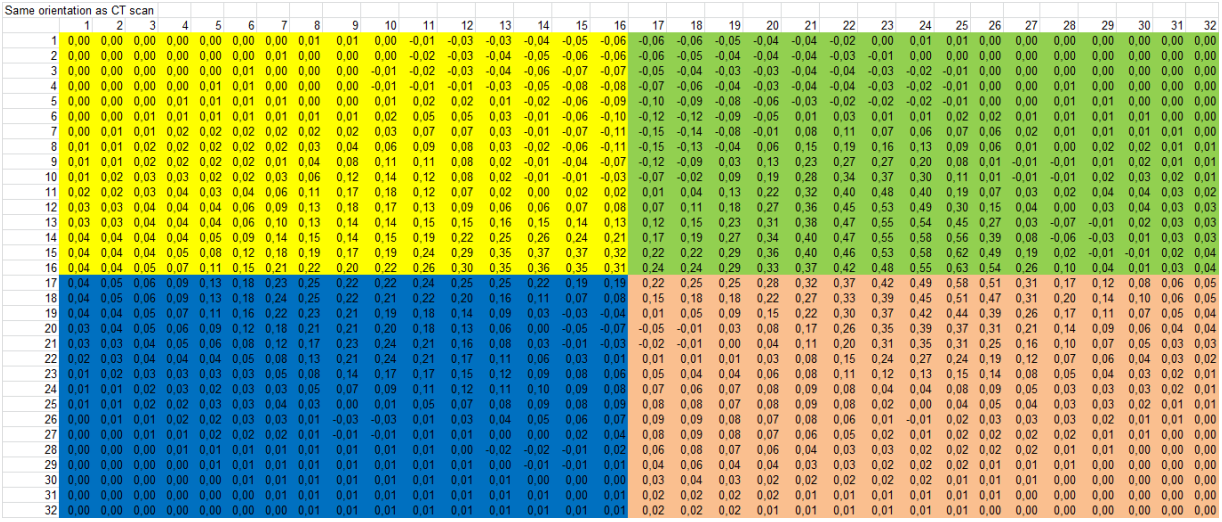
Biological tissues have electrical (capacitive and resistive) properties which depend on the state of the tissue (e.g. fat and water content, extracellular fluid and electrolyte concentrations) (Brown, 2003; Bodenstein, David & Markstaller, 2009). Bio-impedance refers to the resistivity of a circuit (i.e. tissue) to the flow of alternating current. EIT makes use of this bio-impedance, and since different tissues have different electrical impedance, changes in the tissue can be detected by EIT (Geddes & Baker, 1967; Barber & Brown, 1984; Brown, Barber & Seagar, 1985). In the thorax bio-impedance is influenced by two dynamic factors namely ventilation and perfusion. Perfusion changes are said to account for approximately 3% of the impedance change (Bodenstein, David & Markstaller, 2009). The lung has approximately five times higher impedance than other tissues in the thorax and this impedance has shown to vary between inspiration and expiration (Geddes & Baker, 1967; Brown, 2003). During inspiration, as the air content increases in the lung and the alveolar walls are stretched (become thinner) resistivity also increases; conversely, resistivity

decreases during expiration as the volume of air decreases (Brown, 2003; Calzia, Hahn & Hellige, 2005; Wolf & Arnold, 2005; Moerer, Hahn & Quintel, 2011). Impedance changes in the lungs have been shown to be closely related to tidal volume (Hahn et al., 1995; Frerichs et al., 2002b; Roth et al., 2015). Due to the high temporal resolution of EIT (20 - 50Hz compared to the 0.3 - 1Hz of CT), as a result of the rapid scan rates, not only is it able to monitor changes in regional tidal volume and resting volumes, but is also able to detect changes in regional filling and emptying (Frerichs et al., 2003), thus providing dynamic information regarding lung function.

EIT is proving to be a promising imaging technique which allows for real-time, bedside monitoring of lung function, global and regional ventilation distribution. EIT was first developed in the 1980's by Barber, Brown (1984) and since then, with advances in technology, there has been a marked improvement in the technical aspects of EIT. There is an ever-growing interest in the use of EIT, with most clinical studies taking place in the intensive care setting. EIT is relatively inexpensive, non-invasive, portable (can be used at the bedside), has high temporal resolution, can acquire data rapidly, can be used for extended periods of time, has no known harmful effects and is radiation free all of which make it an attractive tool for imaging and monitoring lung function in both adults and children (Brown, 2003; Pulletz et al., 2006).

3.1.3.1 Data acquisition and analysis

EIT data is obtained by the application of electrodes (16 or 32) around the thorax, usually placed at the nipple line (4^{th}-5^{th} intercostal space) (Bodenstein, David & Markstaller, 2009). A small alternating current (AC) of 5mA is then passed between adjacent pairs of electrodes whilst the remaining electrodes measure the resulting potential differences. Current injections can occur at frequencies varying from 50kHz to 1MHz. Sampling frequencies can vary from 0.8 - 50cycles.sec^{-1}, where one cycle is completed when the AC has passed through all pairs of electrodes. The resulting potential differences are then reconstructed via a weighted back-projection algorithm (Barber, 1989) and a 32 x 32 pixel matrix is produced which represents a cross-sectional image of the thorax, where each pixel is representative of the local relative impedance change in relation to a reference local impedance (Figure 3.1.1). Although the cross-sectional slices are not representative of the entire lung, they represent a slice that is approximately ~5cm in the cephalad and caudal directions in thickness depending on the circumference of the chest (Adler et al., 1997; Blue, Isaacson & Newell, 2000; Bodenstein, David & Markstaller, 2009). In smaller infants, it is likely that this slice would then represent the majority of the lung regions, however in older children with larger chest circumferences EIT image would only represent a portion of the lungs. In order to obtain information from specific lobes the position of the electrodes could be altered.



Same orientation as CT scan																																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,01	0,00	-0,01	-0,03	-0,03	-0,04	-0,05	-0,06	-0,06	-0,06	-0,05	-0,04	-0,04	-0,02	0,00	0,01	0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,00	0,00	0,00	-0,02	-0,03	-0,04	-0,05	-0,06	-0,06	-0,06	-0,05	-0,04	-0,04	-0,04	-0,03	-0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3	0,00	0,00	0,00	0,00	0,00	0,01	0,00	0,00	0,00	-0,01	-0,02	-0,03	-0,04	-0,06	-0,07	-0,07	-0,05	-0,04	-0,03	-0,03	-0,04	-0,04	-0,03	-0,02	-0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00
4	0,00	0,00	0,00	0,00	0,01	0,01	0,00	0,00	0,00	-0,01	-0,01	-0,01	-0,03	-0,05	-0,08	-0,08	-0,07	-0,06	-0,04	-0,03	-0,04	-0,04	-0,03	-0,02	-0,01	0,00	0,00	0,01	0,00	0,00	0,00	0,00
5	0,00	0,00	0,00	0,01	0,01	0,01	0,01	0,00	0,00	0,01	0,02	0,02	0,01	-0,02	-0,06	-0,09	-0,10	-0,09	-0,08	-0,06	-0,03	-0,02	-0,02	-0,02	-0,01	0,00	0,00	0,01	0,01	0,00	0,00	0,00
6	0,00	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,05	0,05	0,03	-0,01	-0,06	-0,10	-0,12	-0,12	-0,09	-0,05	0,01	0,03	0,01	0,01	0,02	0,02	0,01	0,01	0,01	0,01	0,00	0,00
7	0,00	0,01	0,01	0,02	0,02	0,02	0,02	0,02	0,02	0,03	0,07	0,07	0,03	-0,01	-0,07	-0,11	-0,15	-0,14	-0,08	-0,01	0,08	0,11	0,07	0,06	0,07	0,06	0,02	0,01	0,01	0,01	0,01	0,00
8	0,01	0,01	0,02	0,02	0,02	0,02	0,02	0,03	0,04	0,06	0,09	0,08	0,03	-0,02	-0,06	-0,11	-0,15	-0,13	-0,04	0,06	0,15	0,19	0,16	0,13	0,09	0,06	0,01	0,00	0,02	0,02	0,01	0,01
9	0,01	0,01	0,02	0,02	0,02	0,02	0,01	0,04	0,08	0,11	0,11	0,08	0,02	-0,01	-0,04	-0,07	-0,12	-0,09	0,03	0,13	0,23	0,27	0,27	0,20	0,08	0,01	-0,01	-0,01	0,01	0,02	0,01	0,01
10	0,01	0,02	0,03	0,03	0,02	0,02	0,03	0,06	0,12	0,14	0,12	0,08	0,02	-0,01	-0,01	-0,03	-0,07	-0,02	0,09	0,19	0,28	0,34	0,37	0,30	0,11	0,01	-0,01	-0,01	0,02	0,03	0,02	0,01
11	0,02	0,02	0,03	0,04	0,03	0,04	0,06	0,11	0,17	0,18	0,12	0,07	0,02	0,00	0,02	0,02	0,01	0,04	0,13	0,22	0,32	0,40	0,48	0,40	0,19	0,07	0,03	0,02	0,04	0,04	0,03	0,02
12	0,03	0,03	0,04	0,04	0,04	0,06	0,09	0,13	0,18	0,17	0,13	0,09	0,06	0,06	0,07	0,08	0,07	0,11	0,18	0,27	0,36	0,45	0,53	0,49	0,30	0,15	0,04	0,00	0,03	0,04	0,03	0,03
13	0,03	0,03	0,04	0,04	0,04	0,06	0,10	0,13	0,14	0,14	0,15	0,15	0,16	0,15	0,14	0,13	0,12	0,15	0,23	0,31	0,38	0,47	0,55	0,54	0,45	0,27	0,03	-0,07	-0,01	0,02	0,03	0,03
14	0,04	0,04	0,04	0,04	0,05	0,09	0,14	0,15	0,14	0,15	0,19	0,22	0,25	0,26	0,24	0,21	0,17	0,19	0,27	0,34	0,40	0,47	0,55	0,58	0,56	0,39	0,08	-0,06	-0,03	0,01	0,03	0,03
15	0,04	0,04	0,04	0,05	0,08	0,12	0,18	0,19	0,17	0,19	0,24	0,29	0,35	0,37	0,37	0,32	0,22	0,22	0,29	0,36	0,40	0,46	0,53	0,58	0,62	0,49	0,19	0,02	-0,01	-0,01	0,02	0,04
16	0,04	0,04	0,05	0,07	0,11	0,15	0,21	0,22	0,20	0,22	0,26	0,30	0,35	0,36	0,35	0,31	0,24	0,24	0,29	0,33	0,37	0,42	0,48	0,55	0,63	0,54	0,26	0,10	0,04	0,01	0,03	0,04
17	0,04	0,05	0,06	0,09	0,13	0,18	0,23	0,25	0,22	0,22	0,24	0,25	0,25	0,22	0,19	0,19	0,22	0,25	0,25	0,28	0,32	0,37	0,42	0,49	0,58	0,51	0,31	0,17	0,12	0,08	0,06	0,05
18	0,04	0,05	0,06	0,09	0,13	0,18	0,24	0,25	0,22	0,21	0,22	0,20	0,16	0,11	0,07	0,08	0,15	0,18	0,18	0,22	0,27	0,33	0,39	0,45	0,51	0,47	0,31	0,20	0,14	0,10	0,06	0,05
19	0,04	0,04	0,05	0,07	0,11	0,16	0,22	0,23	0,21	0,19	0,18	0,14	0,09	0,03	-0,03	-0,04	0,01	0,05	0,09	0,15	0,22	0,30	0,37	0,42	0,44	0,39	0,26	0,17	0,11	0,07	0,05	0,04
20	0,03	0,04	0,05	0,06	0,09	0,12	0,18	0,21	0,21	0,20	0,18	0,13	0,06	0,00	-0,05	-0,07	-0,05	-0,01	0,03	0,08	0,17	0,26	0,35	0,39	0,37	0,31	0,21	0,14	0,09	0,06	0,04	0,04
21	0,03	0,03	0,04	0,05	0,06	0,08	0,12	0,17	0,23	0,24	0,21	0,16	0,08	0,03	-0,01	-0,03	-0,02	-0,01	0,00	0,04	0,11	0,20	0,31	0,35	0,31	0,25	0,16	0,10	0,07	0,05	0,03	0,03
22	0,02	0,03	0,04	0,04	0,04	0,05	0,08	0,13	0,21	0,24	0,21	0,17	0,11	0,06	0,03	0,01	0,01	0,01	0,01	0,03	0,08	0,15	0,24	0,27	0,24	0,19	0,12	0,07	0,06	0,04	0,03	0,02
23	0,01	0,02	0,03	0,03	0,03	0,03	0,05	0,08	0,14	0,17	0,17	0,15	0,12	0,09	0,08	0,06	0,05	0,04	0,04	0,06	0,08	0,11	0,12	0,13	0,15	0,14	0,08	0,05	0,04	0,03	0,02	0,01
24	0,01	0,01	0,02	0,03	0,02	0,03	0,03	0,05	0,07	0,09	0,11	0,12	0,11	0,10	0,09	0,08	0,07	0,06	0,07	0,08	0,09	0,08	0,04	0,04	0,08	0,09	0,05	0,03	0,03	0,03	0,02	0,01
25	0,01	0,01	0,02	0,02	0,03	0,03	0,04	0,03	0,00	0,01	0,05	0,07	0,08	0,09	0,08	0,09	0,08	0,08	0,07	0,08	0,09	0,08	0,02	0,00	0,04	0,05	0,04	0,03	0,03	0,02	0,01	0,01
26	0,00	0,01	0,01	0,02	0,02	0,03	0,03	0,01	-0,03	-0,03	0,01	0,03	0,04	0,05	0,06	0,07	0,09	0,09	0,08	0,07	0,08	0,06	0,01	-0,01	0,02	0,03	0,03	0,03	0,02	0,01	0,01	0,00
27	0,00	0,00	0,01	0,01	0,02	0,02	0,02	0,01	-0,01	-0,01	0,01	0,01	0,00	0,00	0,02	0,04	0,08	0,09	0,08	0,07	0,06	0,05	0,02	0,01	0,02	0,02	0,02	0,02	0,01	0,01	0,00	0,00
28	0,00	0,00	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,00	-0,02	-0,02	-0,01	0,02	0,06	0,08	0,07	0,06	0,04	0,03	0,03	0,02	0,02	0,02	0,02	0,01	0,01	0,00	0,00	0,00
29	0,00	0,00	0,00	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,00	-0,01	-0,01	0,01	0,04	0,06	0,04	0,04	0,03	0,03	0,02	0,02	0,02	0,01	0,01	0,01	0,00	0,00	0,00	0,00
30	0,00	0,00	0,00	0,00	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,00	0,00	0,00	0,03	0,04	0,03	0,02	0,02	0,02	0,02	0,02	0,01	0,01	0,01	0,00	0,00	0,00	0,00	0,00
31	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,00	0,01	0,02	0,02	0,02	0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,00	0,00	0,00	0,00	0,00	0,00
32	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,02	0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,00

Figure 3.1.1 The 32x32 pixel matrix generated by EIT. Where each pixel represents the local relative impedance change. The orientation is similar to that of a CT scan. The yellow region is the right ventral region, green is the left ventral region, blue is the right dorsal region and the pink is the right dorsal region.

Through off-line analysis, functional EIT (fEIT) images can be generated (Figure 3.1.2). These represent the impedance variation over time which, in the lungs, depicts the ventilatory function (Hahn et al., 1995). In the fEIT images, each pixel is representative of local tidal volume change, the amplitude of which is depicted by different colour. Red indicates areas of high tidal volume change and blue indicates areas of low tidal volume change (Figure 3.1.1). Analysis can be performed for the entire thoracic region or specified regions of interest (ROI). These ROI include entire right and left lungs; dorsal and ventral lungs; and the four quadrants: right and left upper and lower. Two methods can be employed to define ROI, namely arbitrary ROI (Victorino et al., 2004; Odenstedt et al., 2005) or functional ROI (Frerichs, Hahn & Hellige, 1996; Frerichs, Hahn & Hellige, 1999). Arbitrary regions could be defined as quadrants or slices through the image. Functional regions are determined by delineating the edge of the “lung” region as a predefined percentage of either the maximum standard deviation or linear regression co-efficient of the impedance values. Using the functional method, other structures are excluded because of the low variation in impedance change compared to that of the lungs (Frerichs, Hahn & Hellige, 1996; Frerichs, Hahn & Hellige, 1999), as well as areas close to the surface which may be influenced by movement artefacts (Adler et al., 1997). However, a disadvantage of this method of determining ROIs is that only functional regions are defined, therefore areas of lung in which ventilation is not taking place (e.g. atelectasis) may not be included (Pulletz et al., 2006). A study comparing the standard deviation and linear regression co-efficient to define ROI report similar results between the methods (Pulletz et al., 2006). Authors of this study recommend using a cut-off between 20-35% to define the ROI. Furthermore, they recommend that using the linear regression co-efficient may be more suitable in electrically noisy environments. In the presence of pathology, where there may be areas of lung which

are not ventilated, a combination of functional and arbitrary methods to define ROI would ensure that all lung regions are evaluated (Pulletz et al., 2006).

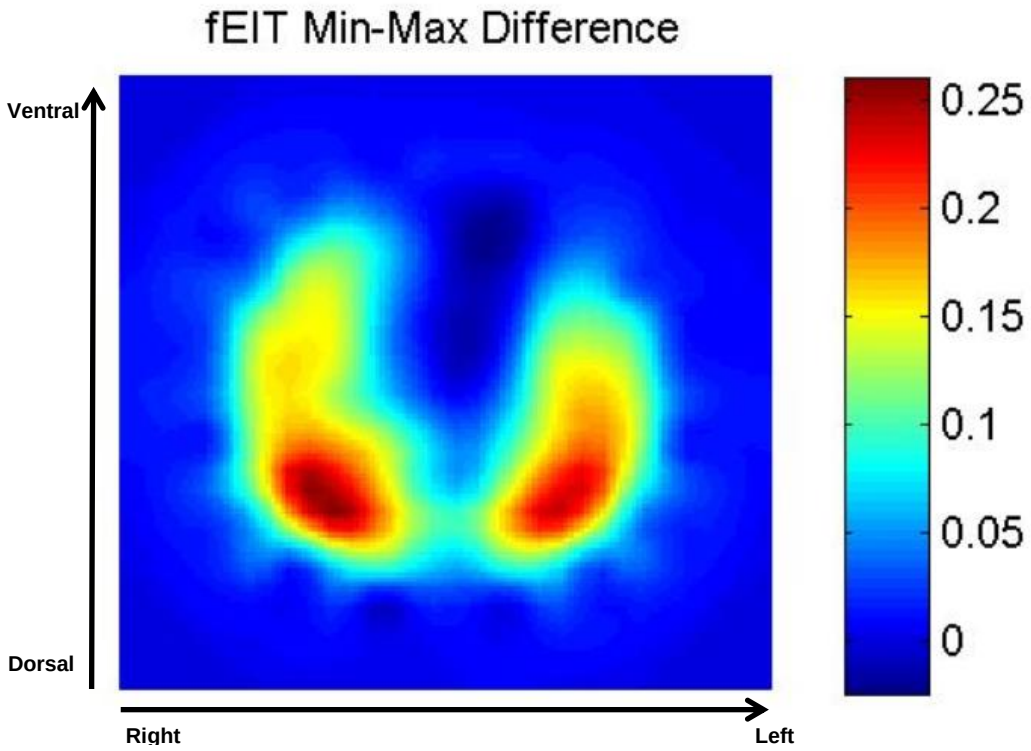


Figure 3.1.2 An example of a fEIT image. Red areas indicate regions of high impedance change (tidal volume change) and blue areas indicated lower impedance change (tidal volume change).

Differentiation of ventilation versus perfusion impedance changes can be achieved by calculating the frequency analysis using Fast Fourier Transformation and applying a band pass filter (Bodenstein, David & Markstaller, 2009). Subsequent fEIT images generated from the filtered data represent either ventilation or perfusion related impedance changes.

3.1.3.2 Validity

EIT has been well validated in a number of animal and human studies against other imaging tools, such as computed tomography scanning.

3.1.3.2.1 Experimental Studies

Hahn et al. (1995) performed a study on both heathy adult volunteers and ventilated pigs in which they compared EIT measurements to spirometry in the humans and to radiographic and staining methods in the animals. Although the authors were not able to demonstrate a quantitative correlation between spirometry and EIT results in humans, there was a clear qualitative correlation. In the animal studies, a strong correlation (intra-individual correlation coefficient range of 0.986-0.99) between changes in the air content of the lung and regional impedance measurements was found. Changes in ventilation following a selective blockade of lung regions in the animal study determined by EIT measurements also showed strong

correlation (R^2=0.973) in the left to right direction when compared to radiography and staining.

Adler et al. (1997) examined the ability of EIT to detect changes of air or fluid volumes in the lungs of anaesthetised dogs. In their first protocol, known air volumes were introduced via a calibrated syringe. EIT measurements were taken at each known volume and compared to the EIT measurements taken at FRC. EIT could accurately detect the volume change with an error of 27 ± 6mL. In their second protocol, four different tidal volumes were delivered by the mechanical ventilator and EIT measurements obtained at the end of inspiration and the end of expiration were compared. Volumes determined by EIT were within 90 ± 43 mL of the tidal volumes set. The larger error noted between the ventilator delivered volumes compared to the syringe delivered volumes was postulated to be as a result of operator delay in clamping the tube at end-inspiration and end-expiration and/or ventilator errors in the estimate of the tidal volume delivered. Lastly, known volumes of saline containing bovine albumin and Evan's blue dye were inserted into the right lower lobe. EIT could determine the fluid volumes within 10 ± 10mL of the volume injected. The errors in volumes measured with EIT were within the acceptable range of <5% or <100mL as recommended by the ATS/ERS for spirometry (Miller et al., 2005).

An experimental study carried out by Odenstedt et al. (2005) on 14 anaesthetised pigs examining the effects of three different recruitment strategies in acute lung injury, found a good correlation between EELV determined by EIT and those determined by a modified nitrogen washout technique (R^2>0.95) both before and after the lavage.

In an experimental study, using six intubated and mechanically ventilated pigs, Frerichs et al. (2002a) compared changes in air content in response to changes in tidal volumes and PEEP levels detected by EIT and electron beam computed tomography (EBCT). Six regions of interest were compared, namely left and right ventral, left and right middle, and left and right dorsal regions. Strong correlations in air content change detect by EIT and EBCT were found in all lung regions. The correlation was greatest in the dorsal lung regions (left r=0.92; right r=0.93), the middle lung regions showed correlation co-efficients of r=0.89 on the right and r=0.85 on the left, and the ventral lung regions showed correlation co-efficients of r=0.87 (right) and r=0.75 (left). The poorer co-efficients in the ventral lung regions were likely the result of movement artefacts from the ventral chest wall and heart in the EBCT images.

Wrigge et al. (2008) compared EIT to CT scanning in experimental lung injury. A total of 16 pigs (6 controls, 6 with direct ALI, and 4 with indirect ALI) were studied during a recruitment manoeuvre (slow inflation). Direct ALI may result from direct insult to the lung parenchyma (e.g. aspiration) and indirect ALI may result from an insult which is transmitted to the lung parenchyma via the vascular endothelium (Wrigge et al., 2008). To describe regional

ventilation, four quadrants (left ventral, right ventral, left dorsal and right dorsal) were used in both fEIT and CT images. Recruitment was measured by three methods with EIT. Briefly, the first was by determining the ratio of the area under the actual impedance vs time curve and the theoretical area under the impedance vs time curve (assuming a linear curve); the second by determining the slope of the impedance vs time curve; and thirdly, by determining the regional ventilation delay (RVD) which was the time delay from the start of the inspiration until the slope reached a certain threshold. RVD was standardised to take into account the global flow rate. Recruitment was determined using CT scanning by calculating the relative change in voxels in atelectactic or consolidated regions compared to the change in the entire ROI. Ventilation measured through the entire slice showed a mean bias of 6 ± 10% (2SD 14 ± 5%). There was good agreement between EIT and CT scans when measuring gas content in each of the four quadrants for both direct and indirect ALI (Table 3.1.1), with the best agreement occurring in the dependent lung regions. When measuring recruitment during the slow inflation in the dorsal lung regions, RVD was best correlated with the degree of recruitment detected by CT (R^2=0.63) while the AUC and slope methods showed poor correlation (R^2=0.08 and R^2<0.01 respectively). The RVD correlation was greater in the control group following a slow inflation after closed suctioning (R^2=0.71) and in the indirect lung injury group (R^2=0.79). These results suggest that RVD determined by EIT may best describe regional recruitment during a slow inflation recruitment manoeuvre. It is unclear whether this good correlation persists with other forms of recruitment manoeuvres.

Table 3.1.1 Summary of agreement between EIT and CT scans in different types of acute lung injury, adapted from Wrigge et al. (2008)

Lung region	Type of ALI	R^2	Limits of agreement
Left ventral	Direct	0.68	1% ± 12%
	Indirect	0.85	
Right ventral	Direct	0.63	1% ± 14%
	Indirect	0.69	
Left dorsal	Direct	0.86	2% ± 6%
	Indirect	0.87	
Right dorsal	Direct	0.83	4% ± 10%
	Indirect	0.88	

Changes in global and regional lung ventilation and volume during different ventilatory settings have been compared between EIT and positron emission tomography (PET) in experimental studies (Richard et al., 2009). Six anaesthetised pigs (three with induced ALI) underwent two experimental procedures, the first being random changes to tidal volume (6,

8 and 15ml/kg with zero PEEP) during which EIT and PET measurements were taken and the second being incremental 5cmH_2O changes in PEEP from 5cmH_2O to a maximum of 15cmH_2O. In three of the animals, acute lung injury was induced and the same experimental procedures were performed. Both EIT and PET measurements were taken in the mid thoracic plane. Investigators assessing EIT and PET data were blinded to the experimental procedures. Changes in ventilation determined by EIT and PET under different conditions were comparable in both normal lungs and those with ALI (Table 3.1.2). Better correlation was found when comparing global ventilation as opposed to regional ventilation. The authors postulate that the poorer regional correlations in ventilation may have been the result of the use of zero PEEP which will inevitably results in greater ventilation heterogeneity. Furthermore, the study had a very small sample size. A strength of this study is that EIT and PET measurements were taken simultaneously, whereas in other EIT validation studies using, for example CT scanning this was not possible due to interference.

Table 3.1.2 Summary of results comparing regional ventilation determined by EIT and PET, adapted from Richard et al. (2009)

		Normal		**Acute lung injury**	
		Global	Regional	Global	Regional
Ventilation*	R^2	0.95	0.63	0.91	0.73
	Bias	5.77	1.47	16.59	0.91
	LOA	-24.49 to 36.03	-29.71 to 32.66	-55.26 to 22.09	-27.94 to 29.76
Lung volumes**	R^2	0.96	0.76	0.94	0.54
	Bias	0.28	0.21	0.62	-2.54
	LOA	-30.17 to 29.61	-26.71 to 26.58	-51.53 to 52.78	-41.88 to 36.80

*change in tidal volume; **change in PEEP; LOA – limits of agreement

3.1.3.2.2 Human studies

End-expiratory lung volumes (EELV) determined by EIT were validated against those determined by a validated spirometry technique in 12 mechanically ventilated adults during changes in PEEP levels (Grivans et al., 2011). A good within subject correlation coefficient of 0.92 was shown from a total of 233 measurements. Authors report acceptable bias and limits of agreement (50mL and -31mL to 131mL) between EELV determined by spirometry and EIT at different PEEP levels.

Hinz et al. (2003) examined the effects of different PEEP levels on EELV and compared EIT measures of EELV to those determined by a modified nitrogen washout technique in ten mechanically ventilated adults. EELV determined by nitrogen washout was compared to the end-expiratory lung impedance change (measurements were taken simultaneously). An excellent linear correlation was found between the two measures (R^2=0.95), this strong

correlation persisted after normalising the data to account for the EIT reference value taken at zero PEEP.

Differences in ventilation and perfusion distribution between left and right lung regions detected by EIT, showed good agreement with ventilation scintigraphy in 14 adult patients undergoing pulmonary function testing pre-operatively (Kunst et al., 1998). Scintigraphy was performed using ^{81m}Kr for ventilation and ^{99m}Tc-macro aggregated albumin (MAA) for perfusion, and EIT measurements were taken at the third and sixth intercostal spaces. The proportion of ventilation and perfusion occurring in the left lung was compared between the two techniques. An excellent correlation (r=0.95) was found between scintigraphy measurement of perfusion and the perfusion induced impedance change in the posterior regions (measured at the third intercostal space). Ventilation induced impedance change at the third intercostal space was closely correlated to ventilation determined by scintigraphy (r=0.96). This correlation improved to r=0.98 by combining the EIT measurements taken at the third and sixth intercostal spaces. The authors demonstrated good reproducibility of EIT in both ventilation (r=0.95) and perfusion (r=0.93) measurements. EIT (combined third and sixth intercostal spaces) tended to underestimate ventilation in the left lung when compared to scintigraphy (-3.93 ± 5.51%, $p<0.05$), however the reliability co-efficient for determining left-right division was 0.94. Whether this significant difference was present at each independent level was not reported.

Victorino et al. (2004) examined the reproducibility of EIT and the agreement between EIT and CT data in ten mechanically ventilated adults. Sequential EIT measurements were taken (at the same thoracic plane – fifth intercostal space) during a slow inflation manoeuvre in the supine position. In addition, they tested two different methods of electrode placement. The first was the standard method whereby electrodes are placed equidistant around the thorax with the first electrode on the sternum, the fifth in the left mid-axillary line, the ninth over the spinous process and the thirteenth in the right mid-axillary line. The second arrangement was called the test position, whereby the fifth and thirteenth electrodes were placed more anteriorly, resulting in smaller spaces between the anterior electrodes and larger spaces between the posterior electrodes. The agreement between EIT and CT with regards to estimation of tidal volume distribution was within a priori established boundaries (bias of ± 2SD with boundaries of ± 25% for slices, or boundaries of ± 50% for large lung regions such as left or right), and was deemed to be “acceptable”. Specific values were not presented in the paper or online supplement. Agreement with CT scans was worse with the standard placement of the EIT electrodes (bias of +9.4% and limits of agreement of -6.4% - 25%). Tidal ventilation distribution in the left to right direction was similar between EIT and CT measurements (bias of 0% and limits of agreement of -10% - 10%). Similar results were also found in the ventral to dorsal direction; however, it was found that standard EIT

electrode placement tended to overestimate ventilation in the ventral region. Impedance changes were best correlated with changes in air content determined by CT (R^2=0.93); correlations were poorer with comparison to the gas to tissue ratio (R^2=0.56) and changes in mean density (R^2=0.57). The differences between these correlations and those found by Frerichs et al. (2002a) in experimental studies may be explained by the differences in chest shape between pigs (circular) and humans (oval), differing methods of ROI selection and EIT analysis. Reproducibly of EIT measurement was also performed (Victorino et al. 2004). There was a within-subject SD of 4.9% when electrodes were left in place and a within-subject SD of 7.4% when electrodes were re-applied (7.0% for standard and 7.7% for test positioning). These were within the acceptable limit of 9%, which was determined a priori. Slightly different methods for EIT analysis were used in this study (integral pixel values vs the commonly used average pixel values). It is therefore unclear whether similar reproducibility and agreement would be found with different methods of EIT analysis. Furthermore, this study only examined relatively large ROI, and it is therefore unclear whether the reproducibility and validity are as good within smaller ROI.

EIT was compared to high resolution computed tomography (HRCT) in a small group (n=5, mean age 38 ± 11 years) of patients with cystic fibrosis (CF) in a study by Zhao et al. (2013). 'Brody scores', which quantify the changes in lung morphology in CF were compared to the ratio of maximum expiratory flow (MEF) rates a 25% and 75% of the forced vital capacity (MEF_{25}/MEF_{75}) derived from the EIT measurements. A strong correlation was observed between the weighted Brody scores and median MEF_{25}/MEF_{75} (r^2=0.83, $p<0.05$). A lower median regional MEF_{25}/MEF_{75} was associated with a higher Brody score. Despite the small sample, authors concluded that EIT could reliably detect regional airway obstruction.

The global inhomogeneity (GI) index describes tidal ventilation distribution within the lung regions (Zhao et al., 2009; Zhao et al., 2014). Zhao et al. (2009) examined the difference between the GI index in healthy lungs and diseased lungs, as well as whether imbalances in ventilation could be detected using the GI index. Ten mechanically ventilated adults without lung disease served as the control group and 37 adults ventilated through a double lumen tube who had known lung disease were studied in the supine position as the test group. EIT measurements were taken once in the control group (both lungs ventilated) and twice in the test group, while both lungs were ventilated and when only one lung was ventilated. GI index was calculated in two ways from the measurements obtained during single lung ventilation: firstly using only the ventilated lung and secondly using both the ventilated and non-ventilated lung. The mean ± SD GI index in the control group was 0.52 ± 0.01; this was significantly different (p=0.025) to the test group during two lung ventilation (0.60 ± 0.11). GI index was able to detect ventilation inhomogeneity in the test group as was evident from the significantly higher GI index ($p<0.002$) during single lung ventilation (calculated using both

the ventilated and non-ventilated lung) compared to the GI index during two lung ventilation. Although homogeneity detected by GI index was not directly compared to another imaging tool, such as CT, the differences observed between healthy and diseased lungs and when known inhomogeneity exist (one lung ventilation in this case) suggest that GI index can reliably detect differences in ventilation homogeneity. Some limitations of the GI index are that it is currently only able to report on global inhomogeneity, whether it is able to reliably detect regional inhomogeneity still needs to be established. GI index is also sensitive to the type of method employed to determine the regions of interest, particularly when using the threshold method (as discussed in 3.1.3.1) where diseased lung may be excluded; therefore when using the threshold method, the same threshold should be consistently used if the GI index is to be used.

GI index was shown to correlate strongly with lung opening in patients with ARDS during a low flow manoeuvre (Zhao et al., 2014). Eighteen patients with ARDS and eight patients with heathy lungs who were sedated, paralysed and mechanically ventilated were included. EIT measures were taken during a low flow manoeuvre, whereby a constant flow of 4L/min was applied from zero PEEP until a tidal volume of 2L or maximum airway pressure of 35cmH_2O was reached. A lung region was defined as open (recruited) when the pixel amplitude exceeded 10% of the maximum pixel amplitude during the course of the manoeuvre (Pulletz et al., 2012; Zhao et al., 2014). The percentage of 'open' lung was compared to the GI index at the corresponding time points. Authors reported a linear relationship between the GI index and percentage of recruitable lung, with the GI index decreasing as the proportion of open lung increased. The median GI index was significantly lower in patients with healthy lungs compared to those with ARDS (healthy lung 0.41 ± 0.04 ARDS lung 0.52 ± 0.21, $p<0.05$). Strong correlations were found in both the heathy (n=6, $r^2=0.84 \pm 0.13$, $p<0.01$) and ARDS (n=16, $r^2=0.84 \pm 0.07$, $p<0.01$) patient groups between the two measures. This study confirms that GI index can identify ventilation inhomogeneity between health and disease states. While the GI index can demonstrate lung recruitment from zero PEEP, whether the same can be detected from differing levels of PEEP (as is seen in clinical practice) requires further investigation. There are several limitations to this study. Firstly, lung recruitment was determined by EIT and not by the gold standard of CT which would have strengthened the validity of both EIT and the GI index. Secondly, since the threshold method was used, it is possible that regions of lung where no ventilation was occurring may have been excluded from the fEIT images and subsequent GI index. Lastly, it is possible that the threshold of 10%, used to describe 'open' lung regions may underestimate actual open lung regions, although shown to be reliable (Wrigge et al., 2008). From this study (Zhao et al., 2014) and the previous study by Zhao et al. (2009), the GI index can detect differences in homogeneity between heathy and diseased lung and shows promise for real time monitoring at the bedside.

3.1.3.3 Repeatability and reliability

Excellent reproducibility was found in relative impedance change in 64 different ROI during repeated measures at two different PEEP levels in mechanically ventilated pigs (Frerichs et al., 2007). At zero PEEP, there was only one region out of 64 ROI with a significant difference between repeated measures. The mean difference (%) and SD on the right was 2.2 ± 2.2 and on the left, was -1.4 ± 2.8. At the second PEEP level (10cmH_2O), five out of 64 regions had significant difference between repeated measures, with the mean difference (%) and SD of -2.0 ± 2.6 on the right and -1.0 ± 3.3 on the left. This study demonstrates that EIT measurements are reproducible in small ROI, however it must be noted that these measurements were taken under relatively controlled conditions and in animals with healthy lungs.

Inter-investigator and intra-investigator reproducibility was examined by Smit et al. (2003) during measures of perfusion by two investigators. Adult volunteers with no pulmonary disease (n=24) and pulmonary disease (n=6) were studied. EIT measurements were taken in duplicate by one investigator, this was followed by removal of the electrodes and subsequent measurement by a second investigator after 45 minutes; a third set of measurements was then performed by the first investigator after 45 minutes and required re-application of the electrodes. Intra-investigator reproducibility was very good (r = 0.97 and a mean difference of -1.44×10^{-2}). Inter-investigator reproducibility was also very good (r=0.96 and a mean difference of 5.46×10^{-2}). Very good reproducibility (intra- and inter-investigator) was also demonstrated in the three different ROI used with coefficients of reproducibility ranging from 0.89 – 0.97.

Reifferscheid et al. (2011) tested the reproducibility of EIT measurements taken on two separate occasions (mean of eight days apart) in 10 healthy adults. Electrodes were removed and reapplied at each measurement. Two levels of electrode placement were used, namely at the fourth intercostal space and at the seventh intercostal space. Measurements were taken during tidal breathing and during an expiratory vital capacity manoeuvre in three different postures (supine, sitting and right side lying). The authors reported good reproducibility of EIT measurements taken on the different days (Table 3.1.3). Furthermore, they also concluded that inevitable, but small, differences in electrode placement did not affect the reproducibility of the EIT measurements.

Table 3.1.3 Summary of Pearson's correlation co-efficients for EIT measurements taken at two different levels on different days, adapted from Reifferscheid et al. (2011)

	Tidal Breaths		Expiratory Vital Capacity	
	4th intercostal space	7th intercostal space	4th intercostal space	7th intercostal space
Sitting	0.91	0.91	0.94	0.93
Supine	0.84	0.87	0.89	0.93
Right side lying	0.91	0.87	0.93	0.94

EIT measurements were found to be highly repeatable in a cohort of preterm and term infants (Riedel et al., 2009). Two measurements, with a mean of 75 minutes between measurements, were taken in 30 infants. A mean (SD) co-efficient of variation of 3.60% (2.26%) was found. Standard care, such as position change and feeding, was permitted between measures; however, this did not result in significant differences between the measurements. It is unclear whether electrodes were replaced between the two measurements.

3.1.3.4 Clinical applications

There are numerous animal and human studies which demonstrate the feasibility of using EIT to determine changes in ventilation distribution, as well as regional filling and emptying characteristics under different mechanical ventilation settings, during recruitment manoeuvres and during PEEP titration (Kunst et al., 1999; van Genderingen, van Vught & Jansen, 2003; Barbas et al., 2005; Hinz et al., 2005; Wolf et al., 2010). EIT can also be used to monitor the effects of common procedures, such as suctioning (Lindgren et al., 2007; Wolf et al., 2007) and surfactant administration (Frerichs et al., 2006), on regional ventilation. EIT may also able to show potentially recruitable or overinflated lung regions, which may be particularly useful in guiding mechanical ventilation settings and potentially avoiding ventilator induced lung injury. This was demonstrated by who developed an algorithm that takes into account changes in regional compliance (in relation to driving pressure) compared to the "best compliance" for that pixel value. In their case report (n=2) over-distension determined by EIT was closely correlated to that determined by CT scans (R^2=0.85 and 0.95 respectively).

In addition, EIT can detect pneumothoraces and pleural effusions in both experimental and clinical scenarios (Hahn et al., 2006; Beraldo, Costa & Gomes, 2007; Costa et al., 2008). Costa et al. (2008) developed a novel algorithm which identified areas of increased aeration and decreased ventilation. This method of detecting new pneumothoraces as a result of recruitment manoeuvres or incorrect ventilation settings showed 100% sensitivity for detecting pneumothoraces of ≥20mL. Hahn et al. (2006) showed that different forms of EIT

image analysis were able to observe new pneumothoraces and pleural effusions by calculating changes in ventilation and changes in electrical and tissue resistivity (increased with air, decreased with fluid). In addition, the detection of already present pneumothoraces and pleural effusions detected by EIT (using the methods above) showed "good agreement" (values not reported) with CT scan images. It also shows potential for determining ventilation-perfusion ratios (Costa et al., 2009).

3.1.3.5 Limitations

Despite the high temporal resolution of EIT, it has relatively low spatial resolution, 32x32 pixels, compared to the 512x512 of CT, making it unsuitable for anatomical imaging (Zhao et al., 2014). The solution to improving the low spatial resolution remains unclear (Bodenstein, David & Markstaller, 2009). Owing to differences in individual morphology, only intra-individual observations can be reliably made using EIT. Inter-individual comparisons may be made using indices such as the global inhomogeneity (GI) index (Zhao et al., 2009) or using normalised data. EIT is still in the experimental stages and therefore the methods of data analysis and information acquisition are still too complex for full integration of EIT into clinical practice. However, much work is being done to improve the user interface of EIT to make the information obtained easier to access and interpret (some of which are seen in the commercially available EIT devices such as the Pulmovista500 (Dräger, Lübeck, Germany) and Elisa 800VT (Salvia Medical, Kronberg, Germany). Nursing care may be made more challenging with the large number of electrodes and cables attached to the patient. The newer commercially available EIT devices have developed specialised belts to overcome this problem; however, these belts are presently only suitable for patients >40 kg body weight.

3.2 Respiratory muscle activity

Over the last two decades, techniques for monitoring of respiratory muscle activity have improved, allowing for non-invasive, bedside monitoring. Information gathered can be used to diagnose neuromuscular disease and muscle dysfunction, provide additional information about the muscles' contractile function, provide information on the pattern of activity, and provide greater insight into the control of breathing when diaphragm activity is measured (American Thoracic Society/European Respiratory Society, 2002; Hutten et al., 2010). Several methods may be employed to measure respiratory muscle activity; these are depicted in Table 3.2.1. Given the non-invasive nature of sEMG, it was used in the studies in this thesis.

Table 3.2.1 Electromyography methods of monitoring respiratory muscle activity. Adapted from American Thoracic Society/European Respiratory Society (2002)

Type	Electrode placement	Advantages	Disadvantages
Transcutaneous EMG (sEMG)	Electrodes placed on skin	Non-invasive Detect a large number of motor neuron potentials	Subject to crosstalk Lack of standardisation of placements Influenced by body habitus
Transoesophageal EMG(te-EMG)	Catheter with electrodes passed into the oesophagus	Less crosstalk Less affect by habitus	Invasive Discomfort Aspiration Vagal stimulation
Intramuscular EMG (im-EMG)	Electrodes place directly into muscle	Allow for single motor unit sampling Less crosstalk	Invasive Risk of pneumothorax Difficult to place

EMG records the electrical activity (action potentials) occurring in the motor units of the muscle. Values obtained are the sum of action potentials from many motor units. This provides information regarding the contractile function or potential of a muscle under different conditions. The diaphragm and intercostal muscles are the most common respiratory muscles assessed.

3.2.1 sEMG data acquisition and analysis

Guidelines with regards to respiratory muscle testing have been laid out by the American Thoracic Society and European Respiratory Society (American Thoracic Society/European Respiratory Society, 2002).

Data is obtained by the application of seven electrodes to the thorax. A reference electrode is placed on the sternum. To measure diaphragm activity, electrodes are placed at the costal margin anteriorly on the left and right and in line with the nipple. Two electrodes are placed posteriorly at the same level on the left and right. Intercostal activity is measured by the application of two electrodes, on the left and right respectively, in the second intercostal space and in the midclavicular line (Hutten, van Eykern & van Aalderen, 2010). The activity of the intercostals, left, right, ventral and dorsal portions of the diaphragm are then recorded (Figure 3.2.1).

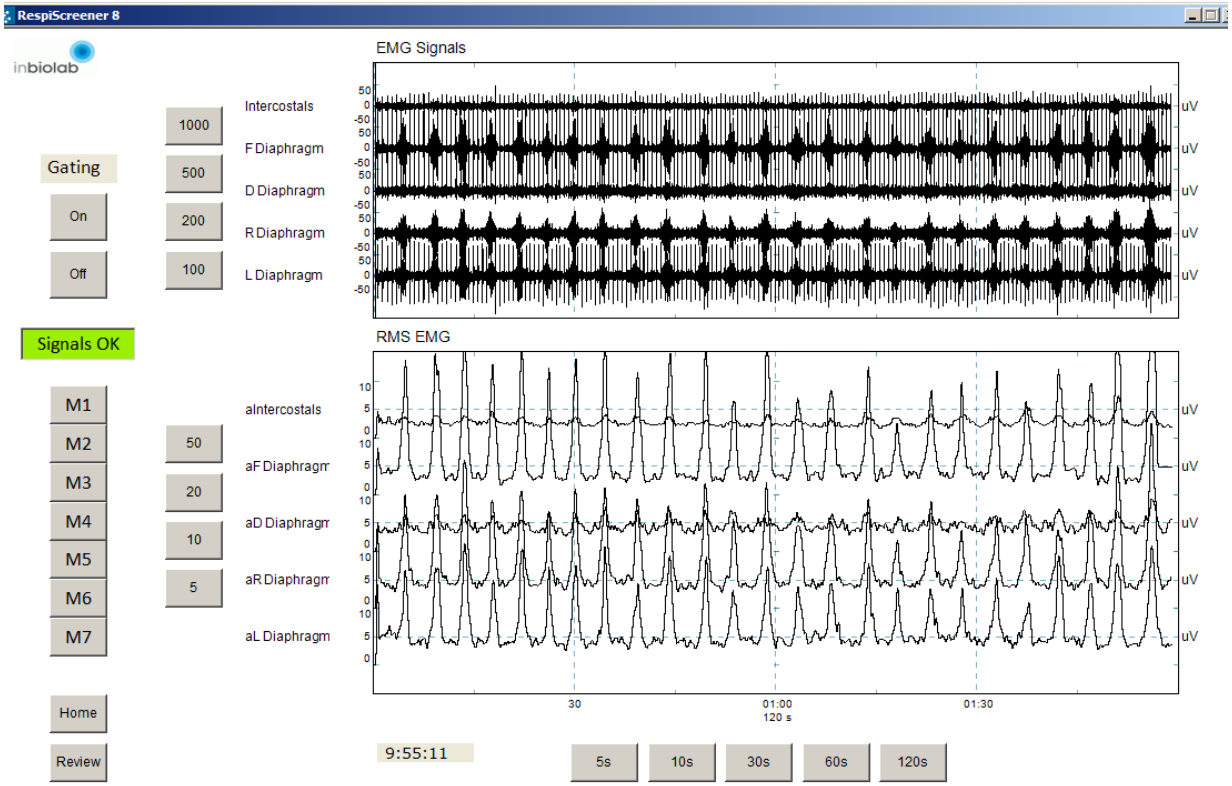


Figure 3.2.1 An example of the interface whilst collecting data. Activity of the intercostals as well as the left, right, ventral and dorsal hemi-diaphragms is collected. This data is then exported into MS Excel for further analysis.

It is recommended that a differential amplifier is used as this eliminates signals, such as from power lines, in the paired inputs which influence both the outputs. This is also known as common mode rejection. In order to optimise voltage readings between electrode pairs, high input impedances are used. Both a high pass filter, to eliminate background noise, and a low pass filter to avoid the effects of under-sampling are applied. Specific filter setting will depend on the type of electrodes (American Thoracic Society/European Respiratory Society, 2002). During data acquisition, signals are gated, whereby the QRS complex is removed and replaced with a running average (Maarsingh et al., 2000). Cables should be shielded to prevent mains interference and this can be further reduced by applying low impedance current through the shielded cables, in a technique is known as guarding (American Thoracic Society/European Respiratory Society, 2002; Hutten et al., 2010). The sEMG device used in these studies complies with the above recommendations and specific details can be found in Chapter 2.3 Data obtained (Figure 3.2.1) is then exported for further off-line analysis.

3.2.2 Validity, reproducibility and repeatability

To the best of my knowledge, there are no validity studies comparing sEMG to other means of measuring respiratory muscle activity (such as trans-oesophageal EMG). Several studies have reported sEMG to be a feasible tool with good repeatability for measuring diaphragm

activity and its relation to various measures of lung function in the neonatal and paediatric populations (Maarsingh et al., 2002; Maarsingh et al., 2006; Hutten et al., 2008).

Hutten et al. (2008) examined the feasibility and repeatability of sEMG, well as the impact of respiratory muscle activity on flow rates (n=20) and end expiratory lung volume determined by a SF_6 washout technique (n=12). Twenty pre-term healthy infants were studied during quiet sleep. Three consecutive measurements of flow rates and respiratory muscle activity were taken. Both measurements were found to be repeatable, with the only significant difference occurring in the time to peak tidal expiratory flow across the three measurements. Good agreement was found between the time indices for ultrasonic measures of flow and respiratory muscle activity with a mean difference of -16.4msec and limits of agreement of -99 to 131.8msec for inspiration and a mean difference of 9.7msec and limits of agreement of -94.7 to 114.1msec for expiration. No relation was found between peak muscle activity and ventilatory measures of respiratory drive (such as tidal volume). A weak correlation ($r=0.523$, $r^2=0.273$, $p<0.01$) was found between FRC and the ratio of the time between the onset of the averaged activity and flow and the time between two successive peak muscle activities. This poor correlation may be the result of using the combined activity of diaphragm and intercostal muscles, since diaphragmatic activity showed greater breath-by-breath variability compared to intercostal muscle activity. The relatively small sample (n=12) may also contribute to the poor correlation. Authors found sEMG to be a feasible measuring technique in the neonatal population. In a separate, but similar study, Hutten et al. (2010) examined the relationship between respiratory muscle activity and FRC in infants with chronic lung disease (CLD) and age-matched healthy infants. They found weak, but significant, correlations in both infants with CLD ($r=-0.33$, $p<0.001$) and healthy infants ($r=0.39$, $p<0.001$).

A more recent study examined the feasibility and repeatability of sEMG for cardio-respiratory monitoring in neonates (Kraaijenga et al., 2015). Respiratory rate, using the averaged ventral diaphragm activity, and heart rate determined by sEMG were compared to the conventional method of cardio-respiratory monitoring (chest impedance) in 31 neonates. Measurements were taken simultaneously for one hour on day one, three and seven post birth. Only 16 neonates had complete measurements on all three days. A good correlation was found between RR determined by sEMG and chest impedance ($r=0.85$, $p<0.001$) with a mean difference of -2.3breaths/min and limits of agreement of -17.3 to 12.7breaths/min. This correlation was improved ($r = 0.92$) when only stable time intervals were examined. An excellent correlation ($r=0.98$, $p<0.001$; mean difference -0.3 beats/min and limits of agreement of -5.3 to 4.7) was also found when comparing heart rate determined by sEMG and chest impedance. The correlations did not differ significantly over three measurement days. Repeatability was only properly tested in 16 neonates. Although the correlation co-

efficients are not reported for these neonates, authors comment that they were no different to the overall group.

A study examining respiratory muscle activity in healthy young adults (n=11), healthy primary school children (n=20); primary school children with asthma (n=19) and healthy preschool children (n=16) found good repeatability and reproducibility of sEMG (Maarsingh et al., 2000). In the healthy adults, two measurements were taken three weeks apart and in the primary and preschool children three measurements were taken with intervals of one hour and 24 hours between the second and third measurements. In the adults, excellent correlations were found between the two measurements for average intercostal activity (r=0.98), average ventral diaphragm activity (r=0.93) and the average dorsal diaphragm activity (r=0.98). The correlation co-efficients for the school and pre-school children are shown in Table 3.2.2 . Poor correlations were found in the school children, particularly the healthy ones. Compared to the acceptable level of agreement defined by the ATS for spirometry of less than 5% variation (Miller et al., 2005), the sEMG measurements were acceptable.

Table 3.2.2 Summary of correlation co-efficients between two measurements for the study performed by Maarsingh et al. (2000)

	Healthy school children		**Asthmatic School children**		**Pre-school children**	
	1 hour	24 hours	1 hour	24 hours	1 hour	24 hours
Anterior diaphragm	0.75	0.90	0.91	0.48	0.84	0.89
Dorsal diaphragm	0.59	0.41	0.90	0.79	0.93	0.97
Intercostals	0.53	0.65	0.65	0.57	0.98	0.99

In repeated measures (24 hours apart) in 15 children with mild to moderate asthma a fair agreement was found between measures with intra-class correlation coefficients of 0.64, 0.81, 0.74 for the ventral diaphragm, dorsal diaphragm and intercostal muscles respectively (Maarsingh et al., 2000).

In a study on diaphragm activity in seven healthy adults and seven adults with chronic obstructive disease (COPD) sEMG measurements were taken on two different days, with the time between days ranging from one week to four weeks (Duiverman et al., 2004). A fair correlation was found between the two measurements in both healthy adults (r=0.77) and those with COPD (r=0.73). Authors report that increased diaphragm activity was noted in both patient groups on the second day. This may be attributed to a learning effect and/or

alterations in breathing pattern (which was recorded) and therefore account for the correlations found.

3.2.3 Clinical applications

There are limited studies examining the possible clinical utility of sEMG in the paediatric population. Studies that have been done suggest that sEMG may be able to provide additional diagnostic and monitoring information, but whether this improves clinical management and outcomes is still unclear.

In healthy spontaneously breathing neonates and those with bronchopulmonary dysplasia, respiratory muscle activity has been shown to be closely related to flow rates and significantly associated with FRC and EELV (Hutten, van Eykern & Latzin, 2008; Hutten et al., 2008). In a population where lung function testing is challenging, sEMG may be able to provide additional information regarding lung function, disease progress and coping mechanisms that may not be obvious in conventional monitoring of lung volumes.

In 25 infants with recurrent wheeze, it was found that there was a significantly shorter period of time between respiratory muscle activity and the start of flow after the delivery of a bronchodilator (Hutten, 2009). Furthermore, greater variation in the contribution of the diaphragm to total respiratory muscle activity was higher after the administration of a bronchodilator, which may suggest an adaptive response. No association between sEMG activity and FRC was found and a weak negative correlation was found between tidal volume and sEMG activity before ($r=0.67$, $p<0.05$) and after ($r=0.55$, $p<0.05$) bronchodilator administration. Whether the response to the bronchodilator was positive or negative, whether the same response occurred in all children and the consequent effects on sEMG measurements are unclear. The authors suggested that monitoring of respiratory muscle activity may give an indication of bronchodilator responsiveness in infants with recurrent wheeze (Hutten, 2009).

In a histamine challenge in asthmatic pre-school children, sEMG showed a linear relationship with the histamine dose and increased respiratory muscle activity was associated with clinical symptoms, such as wheeze, cough or prolonged expiration (Maarsingh et al., 2004). Measures of lung function such as forced expiratory volume in one second (FEV_1) were not taken in this study, the addition of which may have strengthened the case for the clinical utility of sEMG in respiratory monitoring. In a similar study performed in older children and where FEV_1 measures in addition to sEMG measurements were taken, an increase in sEMG readings were associated with a fall in FEV_1 (Maarsingh et al., 2002; Maarsingh et al., 2004). These studies suggest that sEMG may have a role in monitoring lung function in children with asthma, where standard lung function tests may be

challenging. Whether the addition of sEMG monitoring of children with asthma translates into improved clinical management and improved clinical outcomes needs to be investigated.

Recently sEMG monitoring, described in 3.2.2, of the diaphragm has been shown to be feasible for monitoring heart and respiratory rates in neonates (Kraaijenga et al., 2015).

3.2.4 Limitations

Due to the proximity of the respiratory muscles and the heart, interference from the heart in the EMG readings obtained is inevitable (Schweitzer et al., 1979; O'Brien, Van Eykern & Prechtl, 1983). Two methods have been developed to try and minimise this. The first is via gating, whereby the QRS complex is removed from the EMG reading and replaced by a running average (Schweitzer et al., 1979; Sprikkelman et al., 1998; Maarsingh et al., 2000). This however, becomes problematic with high heart rates where a substantial portion of the EMG reading may be "lost", in addition valuable EMG readings may be lost if contaminated by the QRS complex (Hutten et al., 2010). The second method is the subtraction method, whereby an ECG template is subtracted from the EMG reading each time it occurs; this however may not be a suitable method with a fluctuating ECG signal (Bartolo et al., 1996). Measurements obtained may contain movement artefacts, however most of these would be excluded by applying high-pass filters (American Thoracic Society/European Respiratory Society, 2002). sEMG signals may be contaminated by crosstalk from muscles in the vicinity (such as the abdominals) (Stegeman et al., 2000), however a subsequent case report found no crosstalk from the abdominals (Hutten et al., 2007).

3.3 Monitoring oxygenation

The oxygen content of blood provides information regarding gaseous exchange and is commonly used to measure the response to interventions such as prone positioning in ARDS, in children with respiratory disease and critical illness. There are several invasive and non-invasive methods which can be used which will be discussed specifically around monitoring in paediatric ARDS.

3.3.1 Arterial Blood Gas (Invasive)

Arterial blood gas (ABG) analysis is one of the most frequently performed tests in the intensive care unit, and provides vital information to guide the management of critically ill patients and those with respiratory failure. It is considered the gold standard for measuring gaseous exchange (Collins et al., 2015), and is a commonly used outcome measure in studies examining the effects of various interventions on gaseous exchange and oxygenation.

This technique requires a sample of arterial blood obtained from either direct puncture or via an indwelling line. Common sites used are the radial or femoral arteries. From this sample, the partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), as well as blood pH, are

determined. These are used to guide the need for and settings of mechanical ventilation in patients. Although it provides invaluable information, it is invasive and is not without complications which include pain, blood loss and haematoma formation (Wilkins, 2009). The use of in dwelling arterial lines may help reduce discomfort, but these lines are also associated with complications, such as infection (Scheer, Perel & Pfeiffer, 2002).

Although the information obtained from an ABG, namely PaO_2, can provide information regarding oxygenation it does not account for the amount of oxygen the patient is receiving or individual respiratory mechanics. The ratio of the partial pressure of oxygen to the fraction of inspired oxygen (FiO_2) (PF ratio) or the oxygenation index (OI) are measures which take these factors into account.

3.3.1.1 PF ratio

The PF ratio is currently used to classify ARDS severity in the adult population (Force, 2012). One disadvantage of the PF ratio is that respiratory mechanics and ventilator settings (other than FiO_2) are not accounted for. In the paediatric population, this may be problematic as the amount of PEEP and FiO_2 used is highly variable among clinicians and centres as was seen in a large international multicentre observational study in which 3823 children were screened and 165 children with ARDS were included (Santschi et al., 2010). Despite this limitation, PF ratio may predict mortality in children with ARDS (odds ratio (OR) 1.21 (95% CI 1.05 to 1.39), p=0.01) (Ghuman, Newth & Khemani, 2012).

3.3.1.2 Oxygenation index

Oxygenation index takes into account both the FiO_2 and the mean airway pressure (MAP) and is calculated as shown in Equation 3.3.1:

$$OI = \frac{FiO_2 \; x \; Mean \; airway \; pressure \; x \; 100}{PaO_2}$$

Equation 3.3.1 Calculation of oxygenation index

Given the variability in ventilator settings among paediatric intensivists and the frequent use of high frequency oscillatory ventilation (HFOV), OI is recommended for the monitoring of oxygenation in children where ABG's are available (Khemani et al., 2015). Furthermore, OI has been shown to predict outcomes, specifically mortality, in several paediatric studies. In a prospective study of 131 children, OI was found to be an independent predictor of mortality (91% reliability in bootstrapping after square transformation, $p<0.001$), particularly 12 hours after intubation, and a higher peak OI was associated with a longer duration of mechanical ventilation (Trachsel et al., 2005). Ghuman, Newth & Khemani (2012) in a retrospective review in children with ARDS found that the OI was associated with mortality with an OR of

1.06 (95% CI 1.02 to 1.10, p=0.04). OI may also better predict mortality risk (determined by the area under the receiver operated curve (ROC)) than PF ratio based on both the initial (OI 0.723 (95% CI 0.668 – 0.766) vs PF 0.707 (95% CI 0.652 – 0.761)) and worst measurement in three days (OI 0.747 (95% CI 0.697 – 0.797) vs PF 0.715 (95% CI 0.662 – 0.769)) (Khemani et al., 2015).

3.3.2 Pulse oximetry (Non-invasive)

This is a non-invasive measure of oxygen bound haemoglobin (oxyhaemoglobin) in the blood. It is based on the principle that oxyhaemoglobin and haemoglobin absorb light at different wavelengths. By passing light at two different wavelengths through the tissues, it can determine the proportion of oxygen bound haemoglobin in arterial blood. Probes are often placed on the fingers, ears or feet of infants and children.

Pulse oximetry is very useful for continuous monitoring due its non-invasive nature, immediate readings and minimal complications. It does, however, have several limitations. Readings can be affected by movement artefacts, ambient light, peripheral perfusion and abnormal haemoglobin (Poets & Southall, 1994; Khemani, Bart & Newth, 2007). With the increasing use of non-invasive monitoring of oxygenation in PICU, the use of measures not requiring PaO_2 has been investigated in both adult and paediatric populations.

3.3.2.1 Pulse oximetric saturation/fraction of inspired oxygen (SF ratio)

The SF ratio has been considered as an alternative to the PF ratio, as this may allow for earlier identification of children with respiratory failure. Khemani et al. (2009b) examined whether the SF ratio could be a surrogate for PF ratio in children through a retrospective review. Using linear regression equations and ROC it was found that a cut-off of SF ratio of 263 could discriminate ALI (ROC AUC=0.848) with a sensitivity of 0.93 and specificity of 0.43 compared to PF ratio. Similarly, a SF ratio cut-off of 201 could discriminate ARDS (ROC AUC=0.898) with a sensitivity of 0.84 and specificity of 0.78. Similar results were found in two prospective studies in paediatric patients. Firstly, Thomas et al. (2010), reported that a SF ratio of 253 showed good discriminatory ability for ALI (ROC AUC=0.87) and a SF ratio of 212 for ARDS (ROC AUC=0.88). Secondly, Khemani et al. (2012) reported that a SF ratio of 264 (95% 259 – 269) had sensitivity of 91% and a specificity of 53% for detecting cases of ALI, while a SF ratio of 221 (95% CI 215 -269) had a sensitivity of 88% and specificity of 78% for detecting ARDS. The relationship between PaO_2 and SpO_2 is linear when SpO_2 is between 88-97% given the shape of the oxyhaemoglobin curve (Khemani et al., 2015). Therefore, the accuracy of the SF ratio when SpO_2 exceeds 97% is reduced and consequently when using the SF ratio, FiO_2 should be titrated to achieve SpO_2 between 88-97% (Khemani et al., 2012). In a retrospective review of children with ARDS the SF ratio could predict mortality with an OR of 1.21 (95% CI 1.02 to 1.43, p=0.29) (Ghuman,

Newth & Khemani, 2012). In the absence of invasive monitoring, the SF ratio is a reliable surrogate for monitoring oxygenation in critically ill children.

3.3.2.2 Oxygen saturation index (OSI)

Similarly to OI, OSI takes into account airway pressure and can be calculated as shown in Equation 3.3.2.

$$OSI = \frac{FiO_2 \; x \; Mean \; airway \; pressure \; x \; 100}{SpO_2}$$

Equation 3.3.2 Calculation of oxygen saturation index. FiO_2 – fraction of inspired oxygen; SpO2 – pulse oximetric oxygenation

Khemani et al. (2012) identified four cut-off values for OSI (6, 9.9, 13.7 and 24.7) based on a regression equation and clinically meaningful OI cut-offs (6, 13, 20 and 40). The derived OSI values showed an excellent linear relationship with OI values and each of the four cut-off values had positive likelihood ratios of >7 and negative likelihood ratios of <0.2. Furthermore, OSI had excellent ability to discriminate the clinical meaningful OI cut-offs, with the area under the ROC being > 0.95 for all four values (Khemani et al., 2012). In addition to the close relationship with OI, OSI is also able to identify mortality risk (1.09 (95% CI 1.04 to 1.16) p=0 .001) (Ghuman, Newth & Khemani, 2012). In light of the excellent linear relationship with OI, OSI can be used as surrogate for OI when ABG is not available (Khemani et al., 2015).

3.4 Summary

EIT was chosen as the outcome measure for ventilation distribution, given that is non-invasive, does not require specialised equipment (other than the device which was available) and has been well validated in numerous studies. Furthermore, EIT can provide information on both regional and global ventilation and ventilation homogeneity. sEMG was used to monitor respiratory muscle activity, given the invasive nature of other methods. To monitor oxygenation and response to prone positioning, OI was used since it is more suited for use in the paediatric population than PF ratio and can predict clinically meaningful outcomes such as ventilator free days and mortality. The SF ratio and OSI were considered, however at the time of data collection it was not guaranteed that the FiO_2 was titrated to achieve SpO_2 of 88-97%, therefore these measures may not have been accurate.

3.4.1 Primary outcome measure

The distribution of ventilation as determined by EIT was used as the primary outcome measure in all studies.

3.4.2 Secondary outcome measures

Respiratory muscle activity as determined by sEMG was used as a secondary outcome measure in Study 1 - 4.

To measure oxygenation and response to prone positioning, OI was used as a secondary outcome measure in Study 5.

Chapter 4 Methodology for positioning studies

4.1 Introduction

Four studies were performed to investigate the effects of body position on the distribution of regional ventilation and respiratory muscle activity. Each study was performed in a cohort of infants and children with different respiratory/disease statuses:

- Study One examined spontaneously breathing, healthy infants and children, with no acute or chronic respiratory conditions.
- Study Two examined infants and children who were receiving invasive mechanical ventilation for respiratory failure.
- Study Three was a pilot study examining infants and children with neuromuscular disease.
- Study Four was a pilot study examining infants and children with either acute or chronic respiratory disease.

Considering the methodologies were similar for each of the above positioning studies; an overview of the methodology is presented in this chapter, with specific methodological considerations highlighted in individual chapters.

4.2 Study design

All four positioning studies were prospective cross sectional observational studies.

4.3 Participants

A sample of convenience was used. Infants and children attending various out-patient clinics or admitted to the wards at Red Cross Children's War Memorial Hospital (RCWMCH), Cape Town, South Africa, were screened and the parents approached for consent to participate, if they met the inclusion criteria listed below. This method of selection may have created a degree of selection bias, particularly in the out-patient setting where some mothers and children were difficult to approach (due to the seating arrangement) and therefore were not screened. In the wards, however, all patients were screened and included if they met the criteria, which should have minimised the selection bias. For the healthy children, it is unlikely that selection bias would have affected the results, and this method of screening was chosen for pragmatic reasons.

4.3.1 Inclusion and exclusion criteria

These were applied to obtain similar groups of infants and children within each study. Inclusion criteria differed between the studies; however, exclusion criteria were similar in all studies.

4.3.1.1 Inclusion Criteria

Infants and children aged between six months and nine years were considered eligible for the specific studies if they met the following criteria listed below. This age range was selected as there is currently no recent (<30 years old) data on ventilation distribution in children beyond six months of age and the upper age limit was selected as it is likely that at this age most respiratory development is complete.

- Study One
    - Spontaneously breathing with no acute or chronic respiratory conditions.
- Study Two
    - Receiving mechanical ventilation through either an endotracheal tube or tracheostomy
- Study Three (Pilot study)
    - With a known neuromuscular disease without ventilatory assistance
- Study Four (Pilot Study)
    - With a known acute or chronic respiratory disease

4.3.1.2 Exclusion Criteria

These were the same across all positioning studies. Infants and children were excluded if they met any of the following criteria:

- haemodynamic instability (changes in mean arterial blood pressure, oxygen saturation and heart rate >20%) over the preceding 12 hours
- underlying cardiac defect or disease
- thoracic or abdominal surgery in the preceding three months
- general anaesthetic in the preceding six weeks
- dressings over the thoracic region, which would hinder the correct application of the electrodes (including intercostal drains)
- fragile/broken skin
- raised intracranial pressure, or the potential for raised intracranial pressure (e.g. traumatic head injury, meningitis)
- any other contraindication to changing position as specified by the overseeing doctor

4.3.2 Recruitment

After obtaining ethical and institutional approval (Appendix 1 & Appendix 2), infants and children were screened in the wards or in the waiting areas of the out-patient clinics by the primary investigator (ALS). If the child met the inclusion criteria, their parent or legal guardian was approached. Parents were provided with information about the relevant study and any questions were answered. Once written informed consent was obtained the infant or child was included into the study. Where age appropriate, the study was explained to the

child and verbal or written assent was obtained (Appendix 3). If the parents or legal guardian did not speak English, the study procedure was explained to them in their preferred language either by the investigator (in the case of Afrikaans speaking parents) or by a medical staff member fluent in the preferred language.

4.3.3 Sample size

At the initiation of the studies there was no data available from a similar cohort upon which a sample size calculation could be based. Based on the sample sizes in the available neonatal studies and after an *a priori* interim analysis after enrolling 10 participants, it was estimated that 40 children (10 in each of the four age groups) would be required to detect a mean difference of four and a standard deviation (SD) of 3.5 (alpha 0.05; power 80%) in large lung regions.

Based on the preliminary data (n=56) obtained from Study One, a sample size of 22 was subsequently calculated as being required to detect a mean difference in relative impedance change (ΔZ) of 4.2, in large lung regions, and a standard deviation of 6 (alpha 0.05; power 90%) in the remaining positioning studies.

4.4 Intervention-positioning

Positions examined were left and right side lying positions; supine position with the head in the midline and turned to the left and right; and prone position with the head turned to the left and right (Table 4.5.1). The order of positions was that of patient preference for the spontaneously breathing infants and children in Studies 1, 3 and 4. In the mechanically ventilated children, the order of positions was one of convenience to minimise patient handling and discomfort. Each position was maintained for approximately five minutes. In the infants and children where both EIT and sEMG measurements were taken each position was maintained for approximately 10 minutes. The time in a position was determined by how long it took the infant/child to settle and achieve a regular/stable breathing pattern. Multimedia was used to assist in settling the child and obtaining a stable breathing pattern. The user interface of the EIT software shows tracings of global impedance change; this tracing was used to determine whether an adequate series of breaths (at least five consecutive breaths of similar amplitude, without inspiratory or expiratory pauses) had been obtained in each position. Each EIT measurement was recorded for approximately one minute. sEMG measurements were recorded for approximately two minutes. The total time from the application of the electrodes to the end of the measurement period was approximately 90 minutes when only EIT measurements were taken and approximately 120 minutes when EIT and sEMG measurements were taken.

4.5 Outcome measures

The primary outcome measure used in all positioning studies was regional ventilation distribution, determined by EIT (Chapter 3.1.3).

Respiratory muscle activity was a secondary outcome measure, measured using sEMG (Chapter 3.2.1) The sEMG device was only acquired after data collection had commenced in Studies One and Five, therefore sEMG measurements were only performed in a subset of Study One (n=22), and Studies Two, Three and Four.

Table 4.5.1 Description of positions used

Position	Description	
Supine	Infant/child positioned on their back, with arms relaxed at the sides and the legs extended in neutral position. The neck was in neutral (i.e. no pillow) and measurements were taken with the head was in midline and turned to the left and right.	
Prone	Infant/child positioned on stomach, with arms relaxed at sides. No pillows were used under the head or abdomen. Head was rotated to left and right.	
Side lying (left and right)	The infant/child was positioned on the side, with the dependent shoulder flexed to approximately 90^0. The hips and knees were flexed to approximately 45^0. A pillow was placed under the head to ensure the neck was in a neutral position.	

Images used with permission.

4.5.1 EIT

A Goettingen Goe-MF II EIT System (Viasys/ Carefusion, Hochberg, Germany) was used for EIT data acquisition. Sixteen neonatal sized electrodes (Blue Sensor BR-50-K, Ambu, Denmark) were placed circumferentially at the 4th intercostal space (or nipple line). In this study, this level was chosen to reduce the effect of the heart in the EIT images. Furthermore, measurements at this level could allow for comparison with neonatal studies and adults studies (where the same level was used) and to determine differences and similarities in ventilation distribution (Frerichs et al., 2017). Electrodes were placed equidistant from each other (Figure 4.5.1). One reference electrode was placed on the abdomen. The EIT system passes a small alternating current of $5mA_{(rms)}$ at a frequency of 50kHz between adjacent electrodes in a rotational pattern, whilst the remaining electrodes measure the resulting potential difference (Figure 4.5.1) (Hahn et al., 2002). The rate of data acquisition was 13 cycles/second (Heinrich et al., 2006; Frerichs et al., 2017). The data was processed via a back-projection algorithm which calculates the ΔZ using the following formula $\frac{Zinst - Zref}{Zref}$, where Z_{inst} is the instantaneous local reference impedance, determined from each cycle of current injections and voltage measurements at each image pixel (Barber, 1989). The ΔZ values are depicted in a 32x32 pixel matrix, where each pixel is representative of the relative impedance change within the chest (Frerichs et al., 2001).

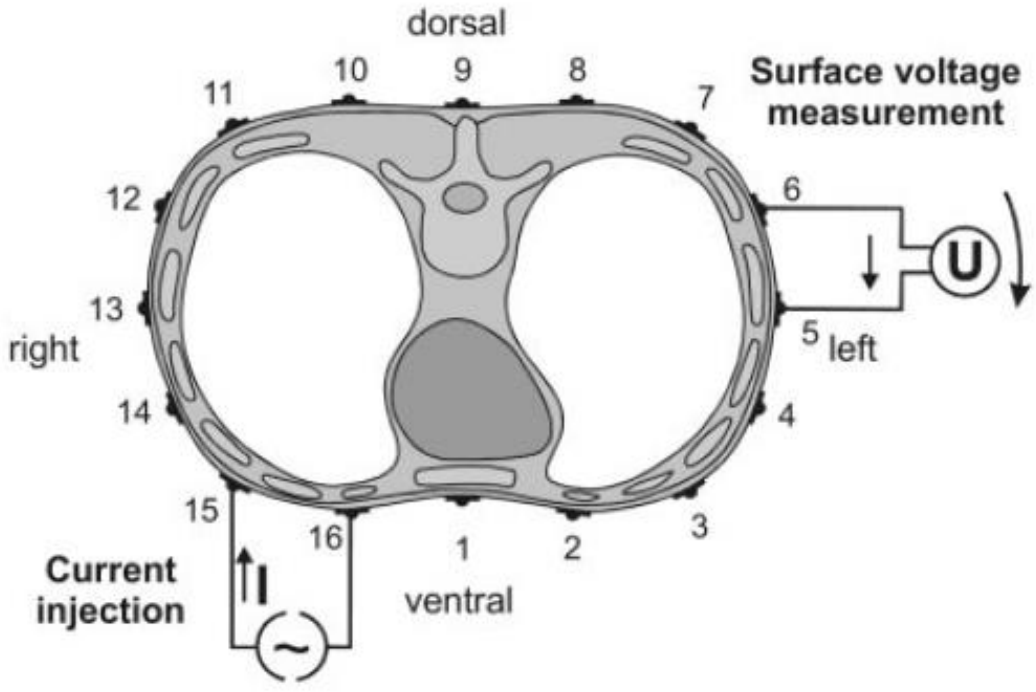


Figure 4.5.1 Placement of EIT electrodes. A current (~) is passed between adjacent pairs of electrodes, whilst the remaining measure the resulting potential difference (U) (Used with permission from Frerichs et al. (2001))

4.5.1.1 Data processing

Data was processed and stored on a laptop computer connected to the EIT system. A reference EIT measurement of 30 seconds was taken prior to commencing study measurements, for each child. In the first 56 children of Study One, only one reference measurement was taken, usually in sitting. For all subsequent children and studies a reference measurement was taken prior to each EIT measurement (i.e. in each position). Study measurements were taken for one minute or until a series of at least five reproducible breaths had been obtained.

Off-line analysis was performed using Auspex v1.6 software (Viasys Healthcare, Amsterdam, Netherlands). Based on the frequency of EIT spectra generated during measurement, data were filtered to a frequency to exclude biological noise such as heartbeat (Figure 4.5.2). A series of five reproducible breaths were then selected for further analysis (Figure 4.5.3). Breaths were considered reproducible if they met the following criteria:

1. Regular respiratory rate
2. Breaths were of similar amplitude and the end-expiratory volumes were similar
3. No inspiratory or expiratory pauses were present (Frerichs et al., 2003; Heinrich et al., 2006).

Once the five consecutive breaths were selected, the end-expiratory and end-inspiratory points were identified. A breath-by-breath difference between these two points was then used to generate new EIT images (Figure 4.5.4), known as “functional EIT” (fEIT) images, where each pixel in the matrix represents the local mean end-expiratory to end-inspiratory relative impedance change, indicative of local tidal ventilation (Figure 4.5.5) (Hahn et al., 1996; Frerichs et al., 2003).

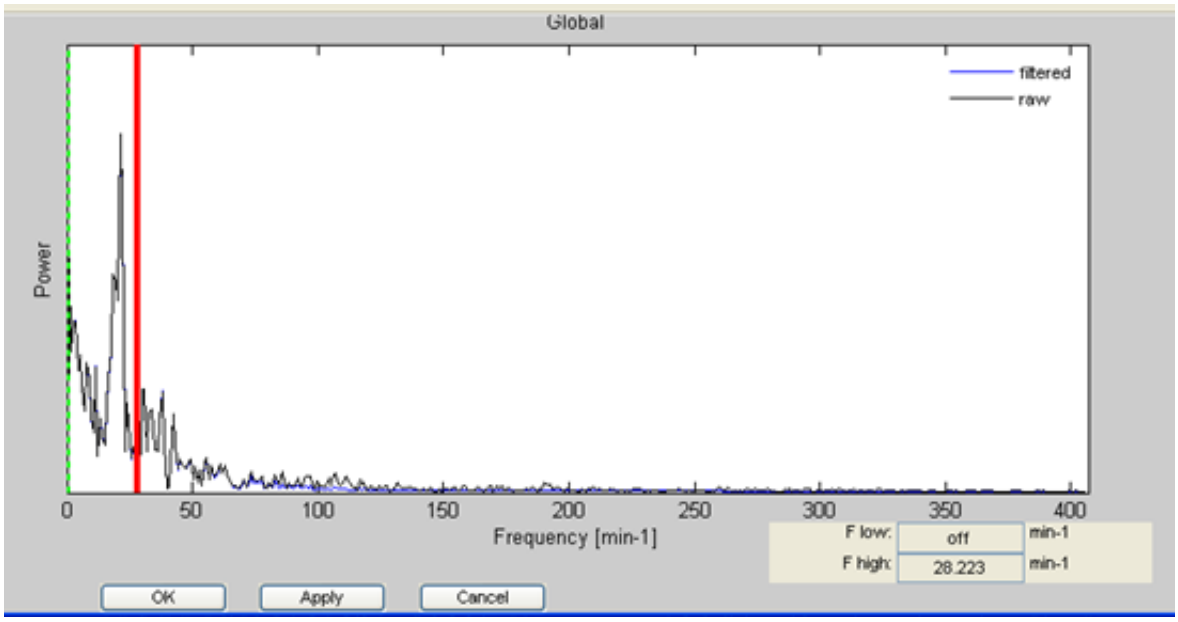


Figure 4.5.2 Filtering of the EIT signal to the respiratory domain. The black signal represents the raw signal and the blue signal represents the filtered signal.

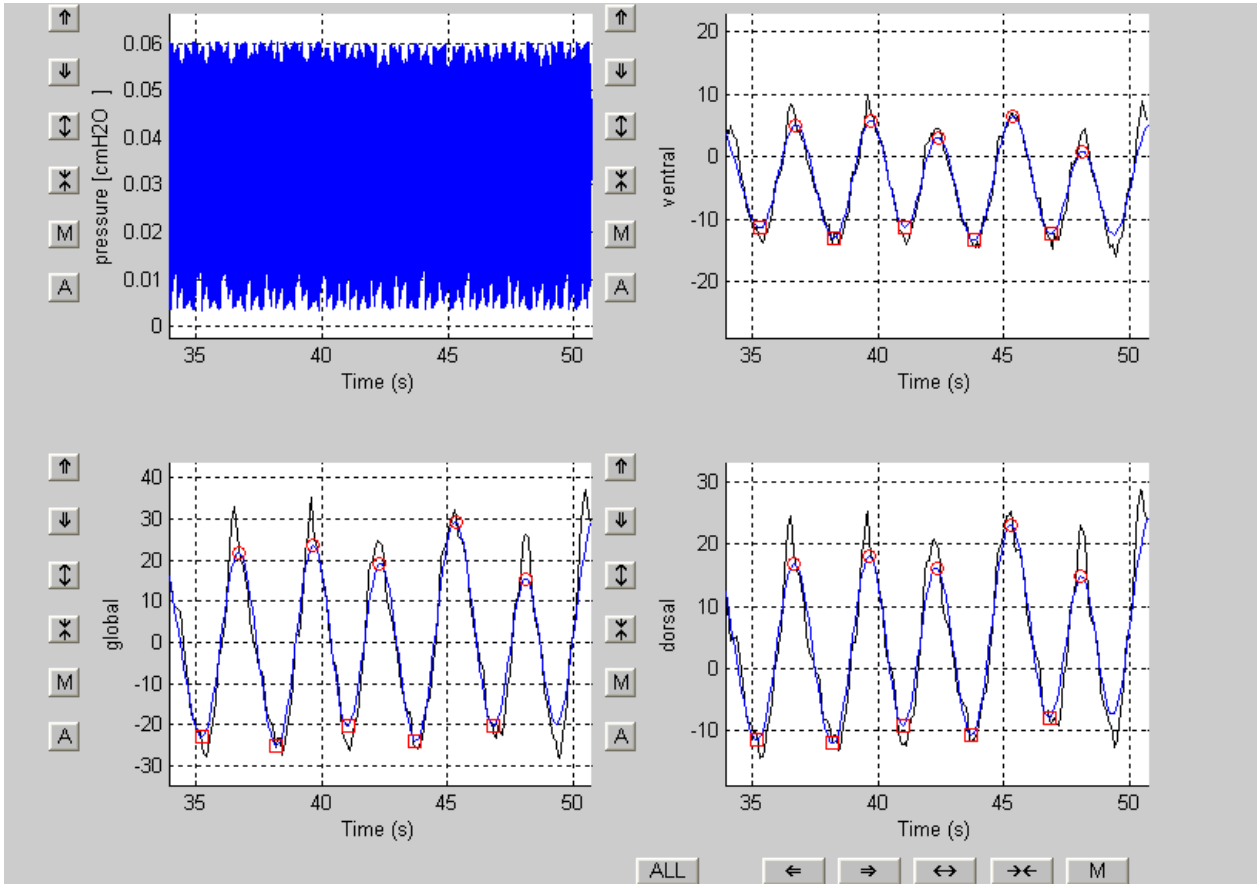


Figure 4.5.3 The identification of five reproducible breaths including end-expiratory (o) and end-inspiratory (□) points. The black signal represents the raw signal and the blue signal represents the filtered signal.

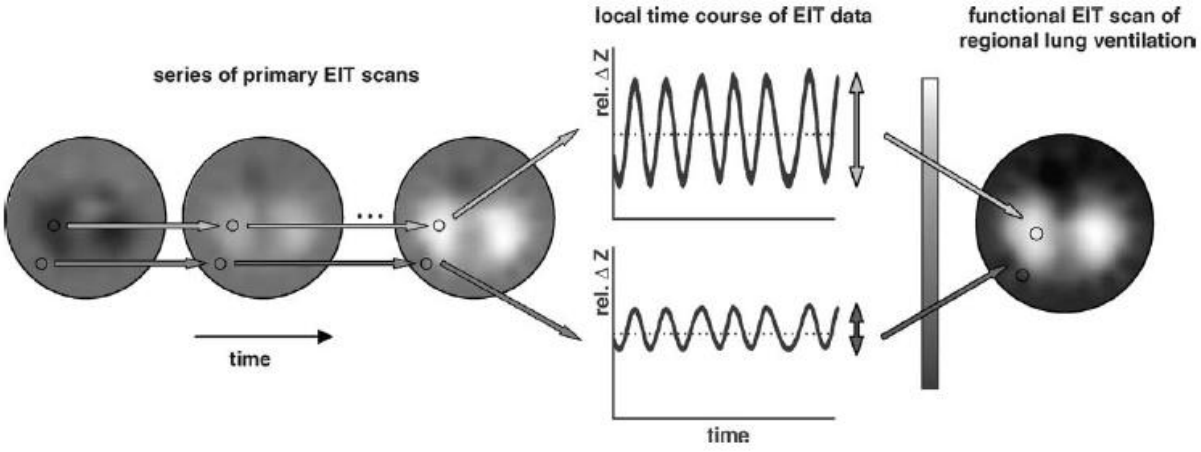


Figure 4.5.4 The generation of fEIT images from original EIT scans. Used from Frerichs et al. (2004) with permission.

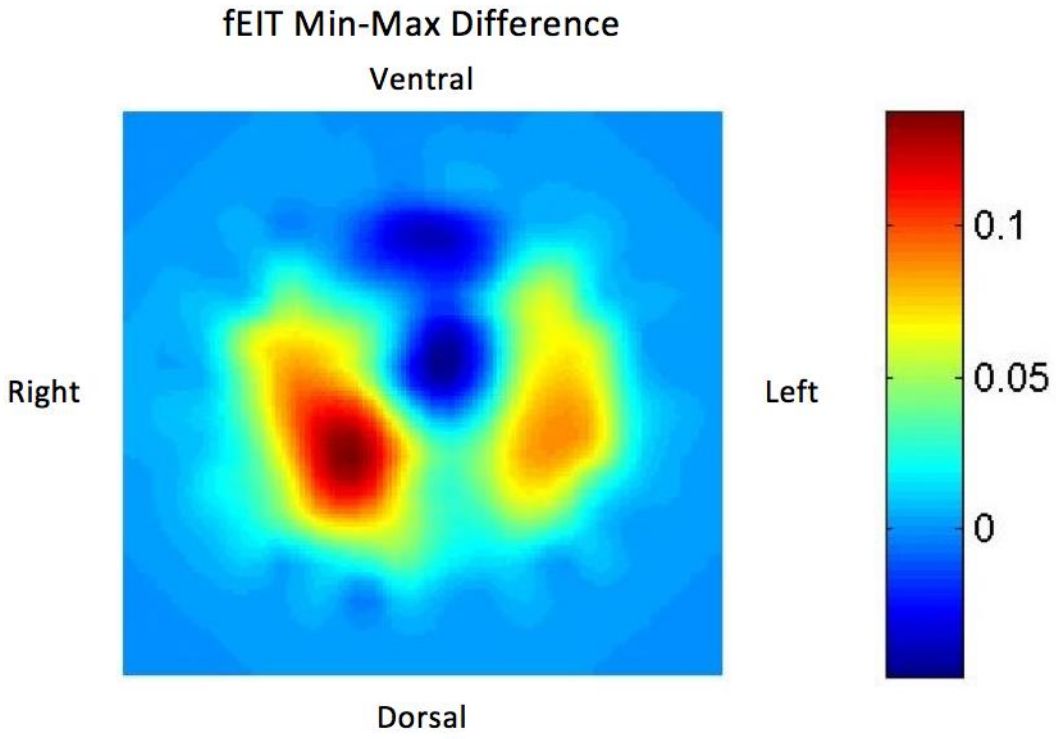


Figure 4.5.5 The fEIT image generated from a healthy boy (1.29 years old) in the supine position (head midline). The orientation is similar to that of a CT scan. Red areas indicate regions of high relative impedance change and blue areas indicate regions of low relative impedance change.

4.5.1.1.1 Mean relative impedance change

The pixel values generated from the fEIT images were then imported as text into Microsoft (MS) Excel spreadsheets for further analysis. Calculations were performed using the sum of all pixel values within a specified region of interest (ROI). Arbitrary ROI were used in order

ensure all lung regions were studied. These were defined on the 32x32 pixel matrix (and can be seen in Figure 3.1.1) as follows:

- Left lung (columns 17-32)
- Right lung (columns 1-16)
- Ventral lung (rows 1-16)
- Dorsal lung (rows 17-32)
- Global (the entire 32x32 pixel matrix)

For analysis of regional ventilation, comparison was made between lung regions in a position, within lung regions between positions, between lung regions when each region was in non-dependent position, and lastly between lung regions when each region was in the dependent position (Table 4.5.2).

Table 4.5.2 Description of methods used of analysis of mean relative impedance change and filling indices in the positioning studies.

Side lying positions	**Supine and prone positions**	**Head positions**
Left vs right lung region	Ventral vs dorsal lung regions	Left vs right lung
Dependent lung regions [a]	Dependent lung regions [c]	
Non-dependent lung regions [b]	Non-dependent lung regions [d]	

[a] i.e. left lung in left side lying vs right lung in right side lying; [b] left lung in right side lying vs right lung in left side lying; [c] ventral lung in prone position vs dorsal lung in supine position; [d] ventral lung in supine position vs dorsal lung region in prone position

4.5.1.1.2 Proportion of ventilation

To account for age-related differences in tidal volumes and hence relative impedance change, the proportion of ventilation for each region relative to global ventilation was calculated to allow for comparison between participants (Equation 4.5.1).

$$Proportion\ of\ ventilation = \left(\frac{Mean\ regional\ relative\ impedance\ change}{Mean\ global\ relative\ impedance\ change}\right) x100$$

Equation 4.5.1 Calculation for the proportion of ventilation

4.5.1.1.2.1 Pattern followed

The proportion of ventilation occurring in specified ROI relative to global ventilation was calculated to determine the pattern of ventilation followed in each position.

A greater proportion of ventilation (i.e. >50%) occurring in the dependent (lower) lung region is described as the “adult pattern” and a greater proportion of ventilation occurring in the non-dependent (upper) lung region is described as the “paediatric pattern”, throughout this thesis. To determine the overall pattern of ventilation consistently followed in the side lying

positions or supine and prone positions, the pattern followed in each position was determined. Infants and children either followed the same pattern (i.e. either paediatric or adult) or a "different" pattern in both positions. If it was found that the infant or child followed a "different" pattern, it was then determined whether they demonstrated consistently greater ventilation in either the left or right lung region in the side lying positions (Figure 4.5.6), or ventral or dorsal lung regions in the supine and prone positions (Figure 4.5.7).

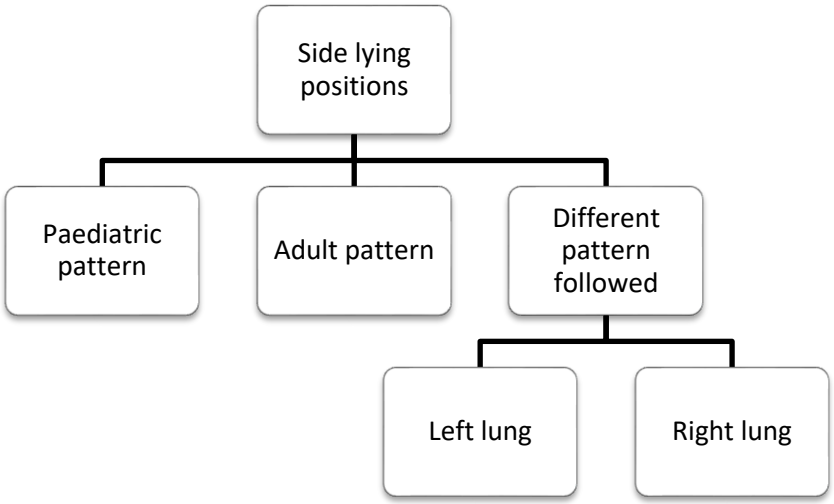


Figure 4.5.6 Types of pattern of ventilation consistently seen in side lying positions.

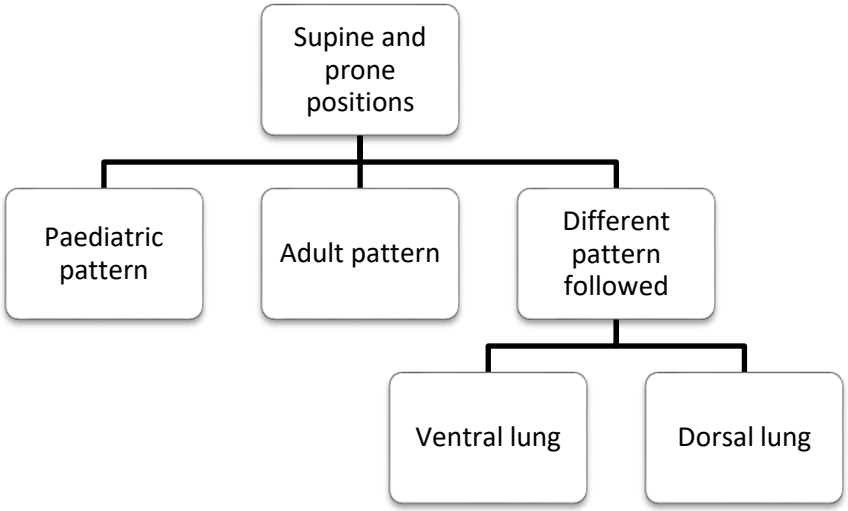


Figure 4.5.7 Types of pattern of ventilation consistently seen in supine and prone positions.

4.5.1.1.3 Regional filling indices

Regional filling and emptying of the lung regions can be described using the filling index (FI) and is also referred to as filling capacity. The FI describes the curve of the plot of a ROI's rate of filling and emptying (i.e. tidal volume) versus the global rate of filling and emptying (tidal volume) (Hahn et al., 2010; Moerer, Hahn & Quintel, 2011). Where the rate of filling and emptying of a ROI is equal to the global rate of filling and emptying, a linear relationship

is seen and the FI=1 (Figure 4.5.8). Where a ROI shows an initially slow rate of filling and emptying which becomes greater than the global rate towards the end of the breath, a FI>1 is observed. Where a ROI shows a rate of filling and emptying which is initially greater than the global rate but slows to less than the global rate towards the end of the breath, a FI<1 is observed (Grant et al., 2009; Humphreys et al., 2011; Moerer, Hahn & Quintel, 2011).

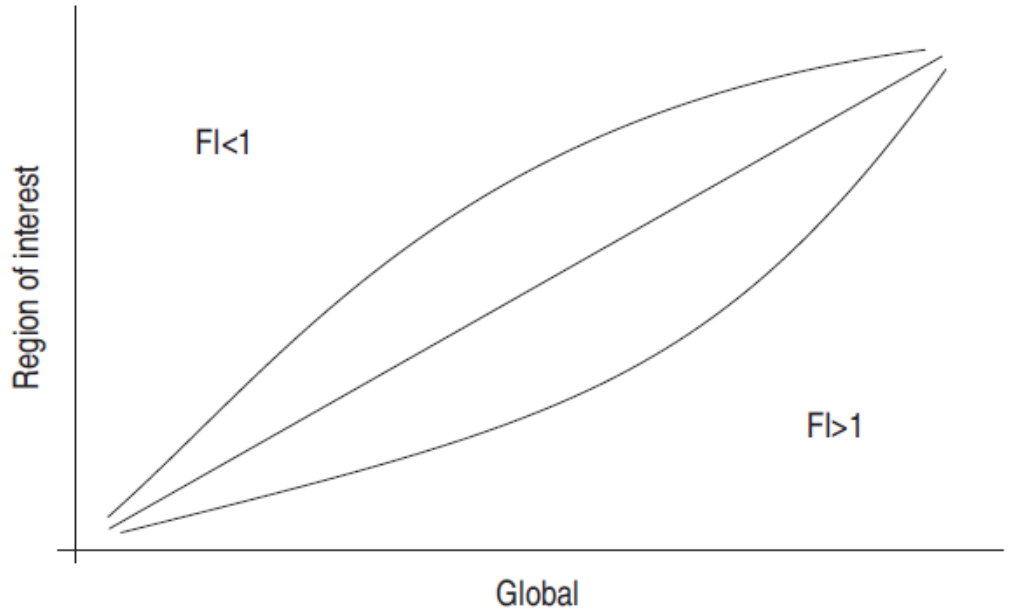


Figure 4.5.8 Plot depicting different filling indices. A FI=1 represents uniform rates of filling between the ROI and global filling, a FI>1 indicates regional filling that is initially slow but speeds up during inspiration relative to global; A FI<1 indicates fast initial filling of the ROI which slows during inspiration relative to global filling. Figure used with permission from Schibler (2010)

4.5.1.1.4 Global inhomogeneity index

To calculate the GI index, the median value of all pixels within in the 32x32 pixel matrix was calculated. The sum of the absolute difference between the median value and each pixel value was calculated. This value was then normalised to the sum of the impedance values within the lung regions. The equation used to calculate the GI index is shown in Equation 4.5.2 (Gattinoni et al., 1993). The higher the GI index the more inhomogenously tidal ventilation is distributed within the lung region (Zhao et al., 2009; Humphreys et al., 2011).

$$GI = \frac{\sum_{x,y \in lung} \left| DI_{xy} - Median\left(DI_{lung}\right) \right|}{\sum_{x,y \in lung} DI_{xy}}$$

Equation 4.5.2 Calculation of GI index. DI_{xy} - differential impedance of ROI; DI_{lung} – differential impedance of the entire lung field; Sigma (∑) denotes the sum; x,y∈lung represent the range and 'x,y' values are members of the 'lung' set (Zhao et al., 2009)

4.5.2 sEMG

Respiratory muscle activity, specifically the diaphragm and intercostal muscles, was measured using a Dipha® amplifier (Inbiolab BV, Groningen, Netherlands). Three pairs of standard single self-adhesive electrodes (Bluetrode™, ElectroSpyres, South Africa) were placed on the thorax and a control electrode was placed on the sternum (Figure 4.5.9). To measure the activity of intercostal muscles two electrodes were placed anteriorly in the second intercostal space at the midclavicular line on the left and right respectively. Diaphragm activity was measured by two electrodes placed bilaterally on the anterior costal margins in the midclavicular line and another two placed posteriorly at the same height (Hutten et al., 2008).

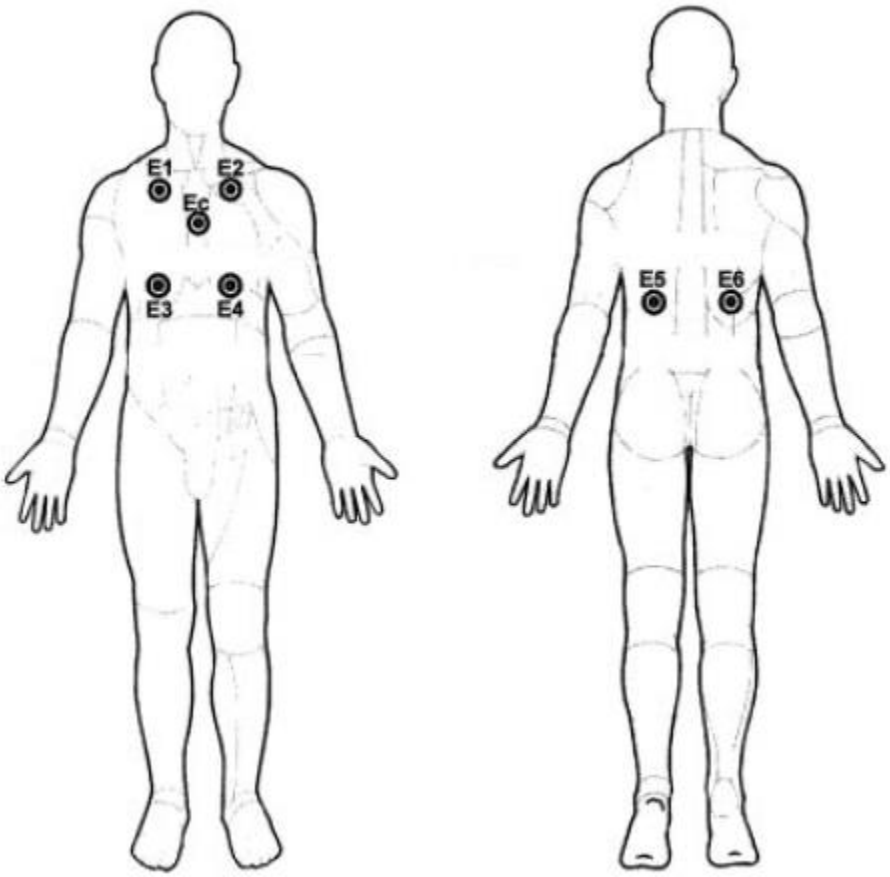


Figure 4.5.9 The placement of the EMG electrodes. Used with permission (Hutten et al., 2008).

The Dipha® amplifier uses high input impedances (>2GΩ) and low input noise currents (<1.2µVpp at 0.1-10Hz). The voltage range was 4V, the signal range was 400mV and the common mode rejection ratio (CMRR) was >100dB at 50-60Hz. The use of shielded cables and signal guarding minimise interference from the mains, as well as cable movements.

4.5.2.1 Data processing

During acquisition, data was managed by a Digital Signal Processor (DSP). Errors resulting from crosstalk and phase errors were reduced by oversampling and skew, phase and gain error correction algorithms. Thereafter, data was converted from digital to analog. Resolution of the digital data was enhanced via decimation filtering. Samples with a resolution of 24 bits were produced following sub-sampling at a frequency of 500Hz, these were then time stamped and transmitted in high frequency (2.5GHz) bursts to the study laptop. The electrical activity of the heart was removed from the data via gating in real time during acquisition (O'Brien, Van Eykern & Prechtl, 1983).

Off-line processing was performed using Polybench (Inbiolab BV, Groningen, Netherlands). Ten consecutive breaths were selected for analysis and processed per the "Hutten" method (Hutten et al., 2008); this was performed automatically by the Polybench software. Data was then exported into MS Excel spreadsheets where the total muscle activity for each muscle as depicted by the mean area under the curve (AUC) was calculated over 10 breaths for the following muscle groups:

- Intercostals
- Anterior diaphragm
- Posterior diaphragm
- Left diaphragm
- Right diaphragm
- Total diaphragm (sum of left and right hemi-diaphragm values)

Data acquisition complied with the guidelines set out by the American Thoracic Society and European Respiratory Society (American Thoracic Society/European Respiratory Society, 2002).

4.5.3 Physiological parameters

Respiratory rate (RR) was recorded by the investigator prior to the commencement of study measurements. If the infant or child was on non-invasive monitoring (Studies Three and Four), heart rate (HR), RR and oxygen saturation were documented at the start and end of study measurements. In addition, they were monitored throughout the study period.

In Study Two, physiological parameters (HR, RR, blood pressure (BP), and oxygen saturation) were documented at the start and end of study measurements. They were also closely monitored throughout the duration of measurement. Ventilator settings which included: mode of ventilation, peak inspiratory pressure (PIP), mean airway pressure (MAP), PEEP; FiO_2, and respiratory rate (both preset and spontaneous) were manually recorded at the start of measurement.

4.6 Statistical analysis

Data were tested for normality by means of the Shapiro- Wilks W test. Differences in mean relative impedance change between a) EIT measurements of selected ROI and b) mean muscle activity of specific respiratory muscles, respectively, in different body positions were determined using repeated measures analysis of variance (ANOVA), after ensuring residuals were normally distributed. Post-hoc t-tests or Mann-Whitney U tests were performed according to distribution to determine where any significant differences may have occurred. To determine the differences in the proportion of ventilation (pattern followed) between groups of infants and children, two-sided difference tests (Z test) were performed. Analysis was performed using Statistica12 (StatSoft, Tulsa, USA). To determine whether age (grouped by those younger and older than 12 months) or disease state determined the pattern of ventilation (grouped by paediatric, adult or different) a multinomial logistic regression model was applied to the data using SPSS 23 (SPSS Inc., Chicago, IL).

Reliability of both EIT and sEMG measurements was determined by calculating the intra-class correlation co-efficients between the first and second measurements taken. SPSS 23 (SPSS Inc., Chicago, IL) was used for this analysis.

To determine a possible association between regional ventilation distribution and muscle activity, a linear mixed-effects regression model was applied to the data. For the proportion of ventilation (relative to global ventilation) occurring in each of the left, right, ventral and dorsal lung regions respectively, the fixed effects of the respective portion of diaphragm and intercostals were applied using SPSS 23 (SPSS Inc., Chicago, IL). For all analyses a significance level of $p=0.05$ was used. Bonferroni corrections for multiple comparisons were made where appropriate.

4.7 Study procedure

Ethical and institutional approval was first obtained (Appendix 1 & 2). Once consent was obtained from the parent/legal guardian and assent (Appendix 3) was obtained from the child, where possible and appropriate, participants were enrolled in the study for the duration of recording (approximately 1.5 - 2 hours). EIT and sEMG electrodes were placed on the thorax as previously described.

In the subgroup of Study One where sEMG readings were not taken, the infant/child lay in their initial position of choice. A reference EIT reading was taken in this position (usually supine or sitting), after which EIT measurements began. The order of positioning was one of convenience or patient choice. EIT measurements were taken in all positions. Infants and children were kept entertained with media on a mobile device to ensure they lay relatively still. Only a minority (approximately 10) of the younger infants (<18 months) needed to be

held in place, this was done in a manner that did not upset the infant or interfere with the recording electrodes.

In the remaining studies, where both EIT and sEMG measurements were taken, the order of positioning was again one of infant/child preference or convenience to minimise handling. An EIT measurement was taken, followed by a sEMG measurement (as described in Section 4.4). This was then followed by a second EIT and sEMG measure to test reliability of the readings (electrodes were not removed between measurements). EIT and sEMG measurements had to be taken separately owing to unavoidable interference from the EIT with the sEMG recording. This was repeated for each position. In studies using both EIT and sEMG, *a priori* analysis of reliability was conducted after five children had been enrolled to ensure the reliability of the measures.

In Studies One, Three and Four, infants/children were awake and not receiving any sedation. In Study Two, however, if the infant/child was receiving sedation at enrollment, this was continued throughout the study procedure.

4.8 Ethical considerations

All studies were approved by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (Appendix 1 & 2). These studies complied with the principles described in the Declaration of Helsinki (2013).

4.8.1 Vulnerable population

This is a vulnerable population group. To correctly and appropriately guide and optimise clinical practice, a thorough understanding of ventilation distribution in infants and children is needed. There is currently insufficient evidence known about the effect of positioning on the distribution of ventilation in the paediatric population. It is not possible or appropriate to apply the findings of neonatal or adult studies to this population, given the discrepancies found in studies examining ventilation distribution and body positioning in neonates and younger infants and children and the differences observed in the adult population. In addition, one of the objectives is to determine whether ventilation distribution in infants and children is different to adults under different conditions. This can only be done by studying this population group.

4.8.2 Consent

The nature of the respective study was explained to the parent/legal guardian and when appropriate to the child by the investigator in their preferred language. Once any concerns or questions were addressed, written informed consent was obtained from the parent/legal guardian and where age appropriate, verbal or written assent was obtained for the child (Appendix 3). Consent forms were available in English, Afrikaans and isiXhosa. It was reiterated to parents that should they not provide consent to their child taking part in study, it

would not affect the care their child received in any way. It was made clear to the parent that they may withdrawal their child from the study at any time and that this would not affect the care their child received.

4.8.3 Risk

These studies are deemed to be of minimal risk. Position changes and positioning occur frequently for care procedures as part of standard care in the various wards for infants and children who are unable to change position for themselves, and as part of therapeutic procedures such as cardiorespiratory physiotherapy. Infants and children on continuous monitoring were monitored throughout the measurement period. Any deterioration was noted and reported to the sister or doctor overseeing the care of the child and measurements were stopped if necessary. Feedback on any clinically relevant information learnt during the measurements or when requested by the overseeing doctor was given to members of the multidisciplinary team involved in patient care. Two such examples included cases where respiratory muscle dysfunction was suspected and the overseeing clinician requested feedback on the respiratory muscle activity.

Both EIT and sEMG are non-invasive and carry minimal risk and they do not interfere with routine care procedures. There have not been any adverse events reported with either EIT or sEMG (Pillow, Frerichs & Stocks, 2006).

4.8.4 Confidentiality

All personal/demographic information obtained has been stored anonymously. No identifiers will be used in any output arising from these studies. Information has been stored in locked filing cabinets and data has been stored on password protected laptops used for study purposes.

Chapter 5 The effect of body position on regional ventilation distribution under different conditions

5.1 Introduction

Changing body position is often used by various members of the medical team to improve oxygenation, aid in mobilising secretions and re-expand collapsed lung regions (Stiller, 2000). Some of these objectives may be achieved by altering the distribution of ventilation and enhancing ventilation-perfusion matching (Dean, 1985). To correctly guide clinical practice and optimise clinical management, a thorough understanding of ventilation distribution is imperative. The distribution of ventilation is well established in the adult population under a variety of different conditions. However, practice in the paediatric population has been based on studies performed in the 1980's on heterogeneous population groups, most of whom had lung disease, using radionuclide ventilation scanning (Heaf et al., 1983; Davies et al., 1985). The results of these studies were then applied to the general paediatric population without further validation. Results of more recent studies have refuted the "one-size-fits-all" pattern of ventilation distribution in the neonatal population, with distribution reported to be dissimilar to the previously described pattern (Frerichs et al., 2003); similar to that of adults (Schibler et al., 2009); and unaffected by gravity (Hough et al., 2012). In addition, the distribution of ventilation did not change during the first six months of life (Pham et al., 2011) and was affected by head position (Heinrich et al., 2006). Respiratory disease, neuromuscular disease and mechanical ventilation alter respiratory mechanics and therefore may affect ventilation distribution. Varying respiratory patterns, commonly seen in clinical practice, and body position may also affect respiratory muscle activity, which in turn may affect ventilation distribution.

5.2 Study One – The effect of body position on regional ventilation distribution and respiratory muscle activity in healthy, spontaneously breathing infants and children

5.2.1 Introduction

To understand the effects of disease and medical interventions on the distribution of ventilation, an understanding of what occurs under normal conditions is essential. Respiratory disease, neuromuscular disease and mechanical ventilation all alter lung and chest wall mechanics to some extent, therefore results from studies of participants with these conditions cannot be extrapolated to the general population.

5.2.2 Aim

To describe the pattern of regional ventilation distribution in a cohort of heathy, spontaneously breathing infants and children.

5.2.3 Objectives

- To determine the distribution of ventilation in different body positions in healthy infants and children.
- To determine whether there are age-related differences in regional ventilation distribution.
- To determine whether head position affects regional ventilation distribution in supine and prone positions.
- To determine whether patterns of respiratory muscle activity are associated with the observed patterns of regional ventilation.

5.2.4 Methods

Study One was comprised of two sub-studies. The first examined only regional ventilation distribution in 56 children. Based on the results of an interim analysis of this data, where variable patterns of ventilation distribution were observed, the second sub-study (22 children) included measures of respiratory muscle activity as well as regional ventilation distribution, in an attempt to identify whether respiratory muscle activity influenced the patterns seen. Regional ventilation distribution results are the cumulative results of both sub-studies (i.e. 78 children).

This was a prospective observational study. Healthy infants and children were recruited from the day surgery ward (where they were seen pre-operatively, before any medication was given) and from non-respiratory out-patient clinics at Red Cross War Memorial Children's Hospital, Cape Town, South Africa. The surgeries included corrective eye surgery, plastic surgery, minor orthopaedic surgery, tonsillectomies and adenoidectomies (with no signs of severe acute or chronic airway obstruction). If there were signs or a history

of upper airway obstruction, such as snoring or stridor, these children were excluded. The primary reasons for children attending the out-patient clinics were for dressing changes and orthopaedic follow-up. Details regarding inclusion and exclusion criteria, detailed study procedure and study instruments can be found in Chapter 4. Once enrolled into the study, EIT and sEMG electrodes were applied as detailed in Chapter 4. Measurements were taken in the following body positions, the order of which was one of patient preference:

- Left side lying
- Right side lying
- Supine position with the head
    - in the midline
    - turned to the left
    - turned to the right
- Prone position with the head
    - turned to the left
    - turned to the right.

Due to unavoidable interference between the EIT and sEMG devices, simultaneous measurements were not possible. Therefore, EIT readings were taken first, followed by sEMG readings in each of the above-mentioned positions (in the sub-study). These measurements were repeated twice in each position to ensure repeatability of the measurements. Each measurement period lasted for approximately one minute. Specific information regarding the measuring tools (Chapter 3) and data acquisition and analysis (Chapter 4) have been previously explained. Demographic information and respiratory rates were recorded prior to the commencement of the measurements (Appendix 4.1).

Demographic data, regional ventilation and respiratory muscle activity data were tested for normality and not all data was found to be normally distributed, therefore, data are presented as median and interquartile range (IQR) or means ± 95% confidence interval (CI) for ANOVA. Residuals were normally distributed allowing for analysis by ANOVA (Appendix 5.1). To account for multiple comparisons when analysing the effect of head position, a Bonferroni correction was applied. Data for left and right side lying positions are presented, followed by the data for supine and prone positions. The pattern of ventilation; regional distribution of ventilation; filling indices; age-related differences; respiratory muscle activity; and, lastly, the association between respiratory muscle activity and regional distribution of ventilation, are presented for the different positions. A plain language summary is presented at the beginning of the results section.

5.2.5 Results

5.2.5.1 Plain language summary of results

Seventy-eight healthy spontaneously breathing infants and children were studied. Varying patterns of ventilation were found with the majority showing consistently greater ventilation of the right lung in the side lying positions, and the dorsal lung in supine and prone positions. Global ventilation was unaffected by position change. Overall, the right and dorsal lungs showed greater ventilation than the left and ventral lungs respectively. Differences between the left and right lung regions were only significant in the left side lying position. The right lung showed faster later filling while the left lung showed faster initial filling. This difference in regional filling was only significant in right side lying. The dorsal lung showed faster later filling while the ventral lung showed faster initial filling. This difference in regional filling was significant in both supine and prone positions. Infants tended to show greater ventilation of the non-dependent lung regions in side lying positions, while no age-related differences were found in the supine and prone positions. Head position did not affect ventilation distribution. Respiratory muscle activity was unaffected by position in the side lying and supine positions; greater activity was seen in the dorsal diaphragm compared with the ventral diaphragm in the prone position. Intercostal and dorsal diaphragm activity were associated with changes in regional ventilation.

5.2.5.2 Demographics

Seventy-eight (44 male) infants and children, between the ages of six months and nine years, were recruited into the study between March 2012 and October 2014. The flow chart of participants through the study is presented in Figure 5.2.1. Consent was not obtained in six cases, with given reasons of a) it was not their child, b) they did not want to lose their place in the queue (out-patients) and c) that the intervention would take too long. Four children did not want to partake in the study. Poor data (n=5) was defined as data not meeting the requirements of five reproducible breaths (as described in Chapter 4.5.1.1), this occurred due to children crying or movement artefacts. Incomplete measurements (n=2) were when measurements were taken in fewer than two positions, this was as a result of children being taken to theatre earlier than scheduled. Population characteristics are shown in Table 5.2.1.

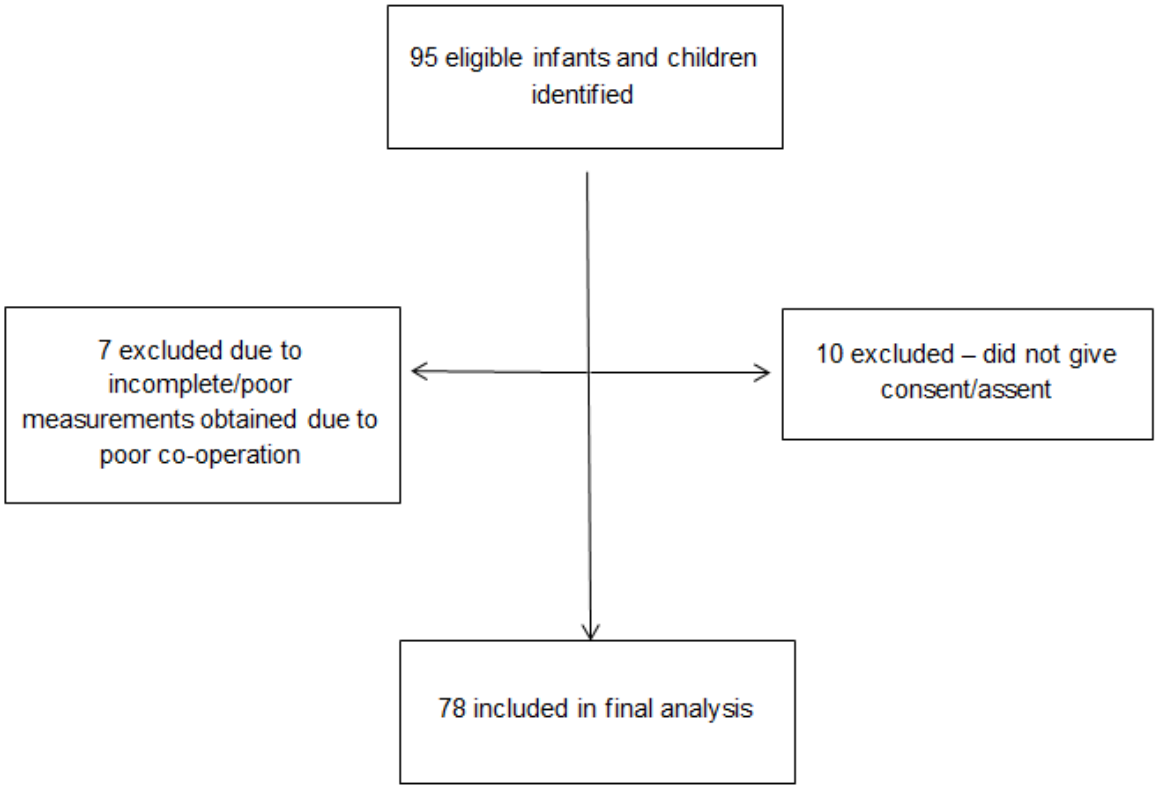


Figure 5.2.1 Flow of participants through the study.

Table 5.2.1 Population characteristics

Age (years) (n=78)	4.66 (2.22 – 6.38)
Gender (n=78):	
Male	44 (56%)
Female	34 (44%)
Respiratory rate (breaths per minute)	24.00 (21.00 – 28.00)

5.2.5.3 Side lying positions

Complete measurements were obtained in 76 of the 78 infants and children in left and right side lying positions.

5.2.5.3.1 Pattern followed

Of the 76 infants and children examined in the side lying positions, 20 (26%) demonstrated consistently greater ventilation in the non-dependent lung regions, referred to as the "paediatric pattern". Seventeen (22%) infants and children consistently demonstrated greater ventilation in the dependent lung regions, referred to as the "adult pattern". The majority (39, 52%) of the infants and children did not demonstrate a consistent "paediatric" or

"adult" pattern, but rather consistently demonstrated greater ventilation in either the left lung (6, 8%) or right lung region (35, 46%) (Figure 5.2.2)

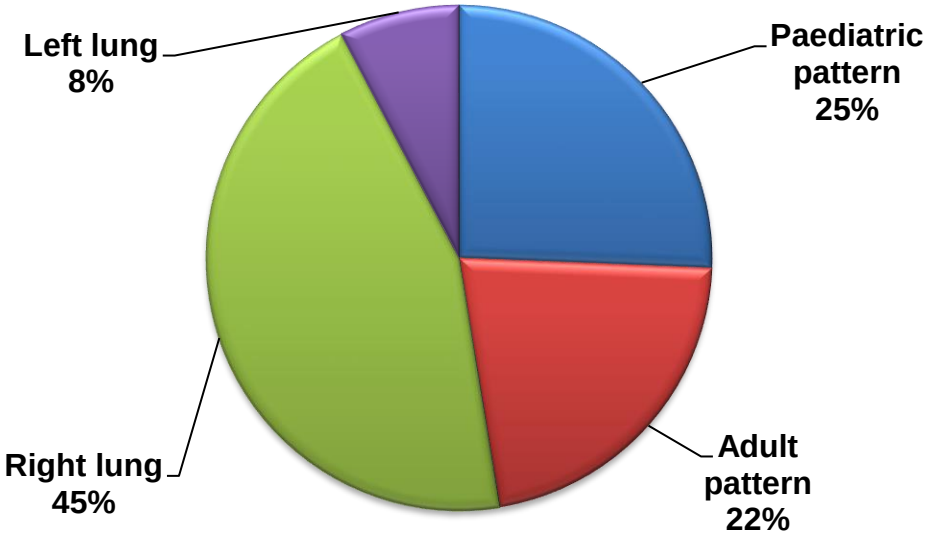


Figure 5.2.2 Proportion of infants and children demonstrating consistently greater ventilation in the non-dependent lung ("paediatric pattern"), dependent lung ("adult pattern"), right lung region, and left lung region in the side lying positions.

5.2.5.3.2 Regional Ventilation Distribution

Mean relative impedance change values are depicted in Table 5.2.2. Global ventilation was unaffected by position (p=0.22). The right lung had greater ventilation than the left lung in both positions, however this was only significant in the left side lying position. Ventilation within the left (p=0.58) and right (p=0.08) lung regions did not differ significantly between the left and right side lying positions (Table 5.2.2).

Table 5.2.2 Mean relative impedance change and filling indices in the side lying positions presented as medians and IQR.

	Left side lying (n=77)		**Right side lying (n=77)**	
Left lung				
ΔZ	16.55	(10.45 – 20.18) *	14.80	(11.03 – 17.97)
Filling index	0.79	(0.67 – 0.89) †	0.82	(0.72 – 0.99) ‡
Right lung				
ΔZ	18.79	(14.58 – 23.33)	17.05	(12.79 – 20.33)
Filling index	0.99	(0.89 – 1.11)	0.96	(0.79 – 1.06)
Global ΔZ	33.70	(29.30 – 41.31)	32.18	(25.23 – 38.09)

*p=0.007 between left and right lung regions in left side lying; †p<0.001 between left and right lung regions in left side lying position; ‡p=0.003 between left and right lung regions in right side lying.

The right lung region was significantly better ventilated ($p<0.01$) than the left lung region when each lung was in the non-dependent position. There was no significant difference in ventilation between left and right lung regions when each lung was in the dependent position ($p=0.27$). The interaction between the effect of lung regions (left and right) and whether the lung region was dependent or non-dependent on the mean relative impedance change in side lying positions was not significant (Figure 5.2.3).

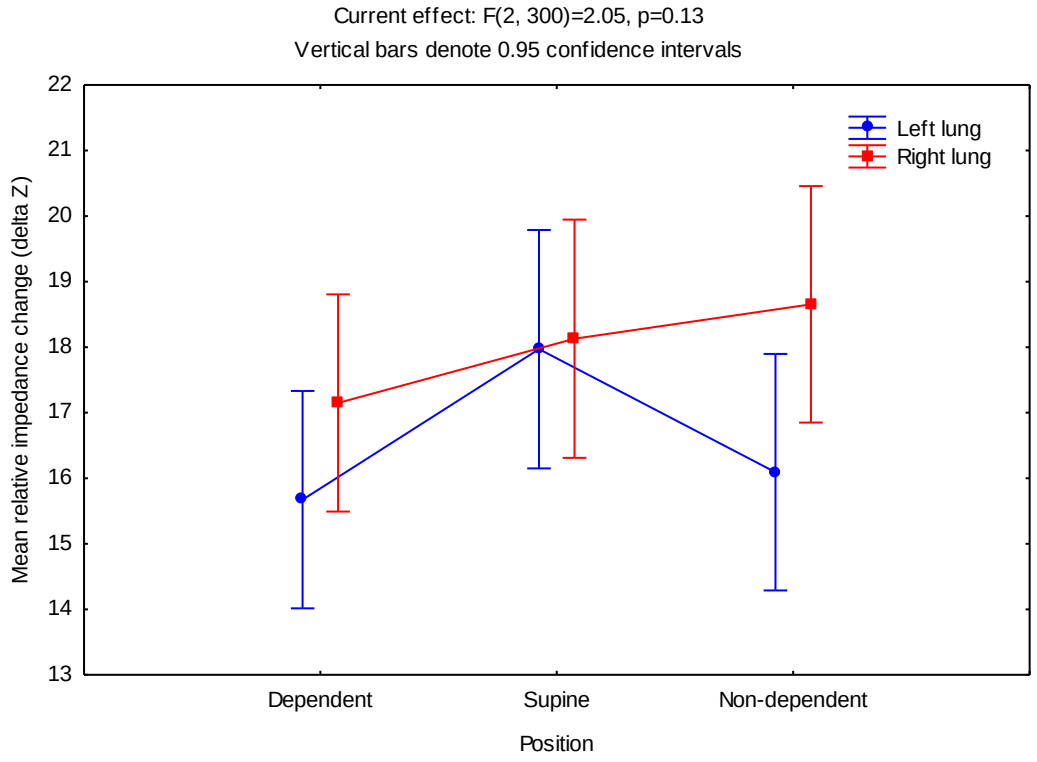


Figure 5.2.3 Ventilation (mean relative impedance change) in the left and right lung regions when in the dependent, non-dependent or supine (neutral) positions.

5.2.5.3.3 Regional filling

The right lung region had a significantly higher filling index compared to the left lung region in both left and right side lying positions, demonstrating an almost linear relationship with global filling and emptying (Table 5.2.2). When comparing the left and right lung regions when each lung was either in the dependent and non-dependent position, the right lung had a significant higher filling index than the left lung ($p<0.001$) in both positions (Figure 5.2.4).

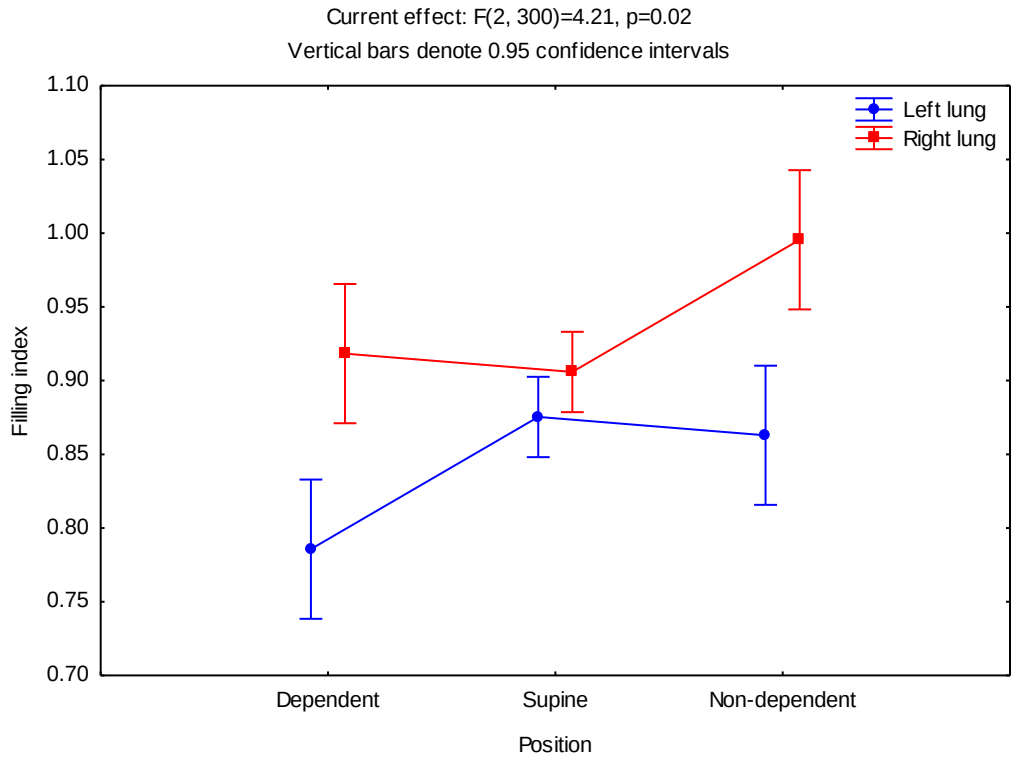


Figure 5.2.4 Filling indices in left and right lung regions when in either the dependent or non-dependent position.

5.2.5.3.4 Age-related differences

The “paediatric pattern” of ventilation was seen in the majority of infants, whilst children mainly demonstrated greater ventilation in the right lung in both left and right side lying positions (Table 5.2.3). Infants were more likely to follow a paediatric pattern than a “different” pattern (i.e. consistently greater ventilation of either the left or right lung) compared to children (p=0.05, Table 5.2.4). Although the data suggests that infants may be more likely to follow the paediatric pattern than the adult pattern compared to children, this difference did not reach statistical significance (p=0.16). The interaction between the effects of age group and lung region (dependent or non-dependent) on distribution of ventilation (ΔZ) was not significant (p=0.77) (Figure 5.2.5).

Table 5.2.3 Pattern of ventilation consistently followed in side lying positions in the different age groups.

Age Group	Overall pattern			
	Paediatric	Adult	Left	Right
6-12 months (n=10)	6 (60%)	1 (10%)	0 (0%)	3 (30%)
1-3 years (n=23)	3 (13%)	6 (26%)	3 (13%)	11 (48%)
4-6 years (n=29)	6 (21%)	9 (31%)	2 (7%)	12 (41%)
7-9 years (n=14)	5 (36%)	1 (7%)	1 (7%)	7 (50%)

Paediatric – greater ventilation of the non-dependent lung region in both positions; Adult – greater ventilation of the dependent lung region in both positions; Left – greater ventilation of the left lung region in both positions; Right – greater ventilation of the right lung region in both positions

Table 5.2.4 Association between age (younger 12 months) and the pattern followed in side lying positions

Pattern [a]	Odds Ratio	Std. error	p-value
Adult	-1.82	1.16	0.12
Different [b]	-1.58	0.80	0.05

[a] Paediatric is the reference category. [b] Includes those that consistently followed a left or right pattern

In the left side lying position, the right lung had greater ventilation than the left in all age groups, however this difference became less with increasing age and was not statistically significant (Figure 5.2.6).

In the right side lying position, similarly to left side lying, the right lung had greater ventilation than the left in children and this difference became progressively less with increasing age. Infants, however, showed greater ventilation in the left lung, with significant differences in proportion of ventilation within the left and right lung regions, respectively, occurring between those aged 6-12 months and the 1-3 years and 4-6 years age groups respectively (Figure 5.2.7). No difference was found between the 6-12 months and 7-9 years age groups with the left (p=0.23) and (p=0.23) right lungs respectively.

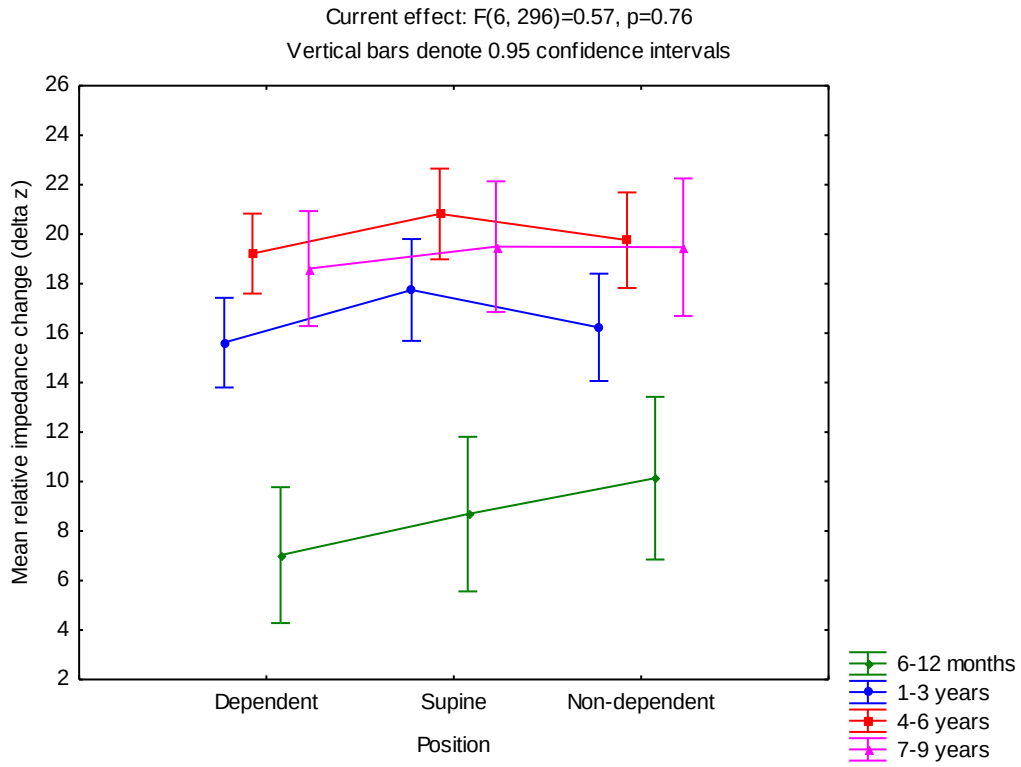


Figure 5.2.5 Mean relative impedance change in the dependent and non-dependent lung regions in the side lying positions between different age groups.

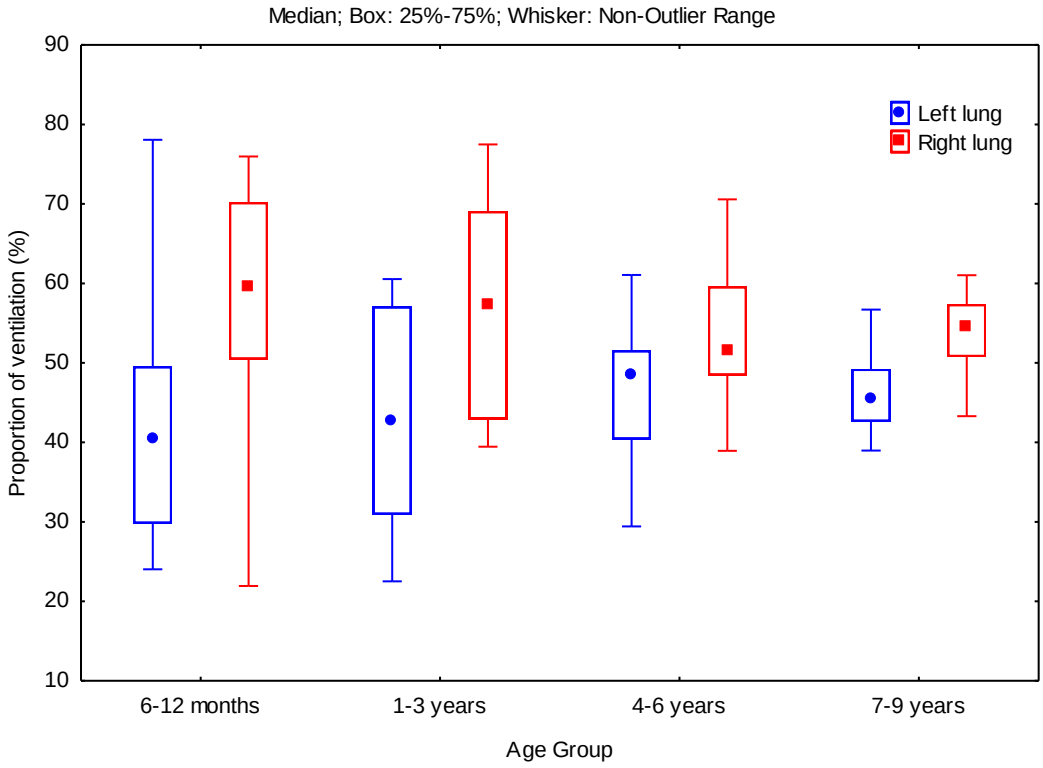


Figure 5.2.6 Proportion of ventilation in the left and right lung regions in the left side lying position between age groups.

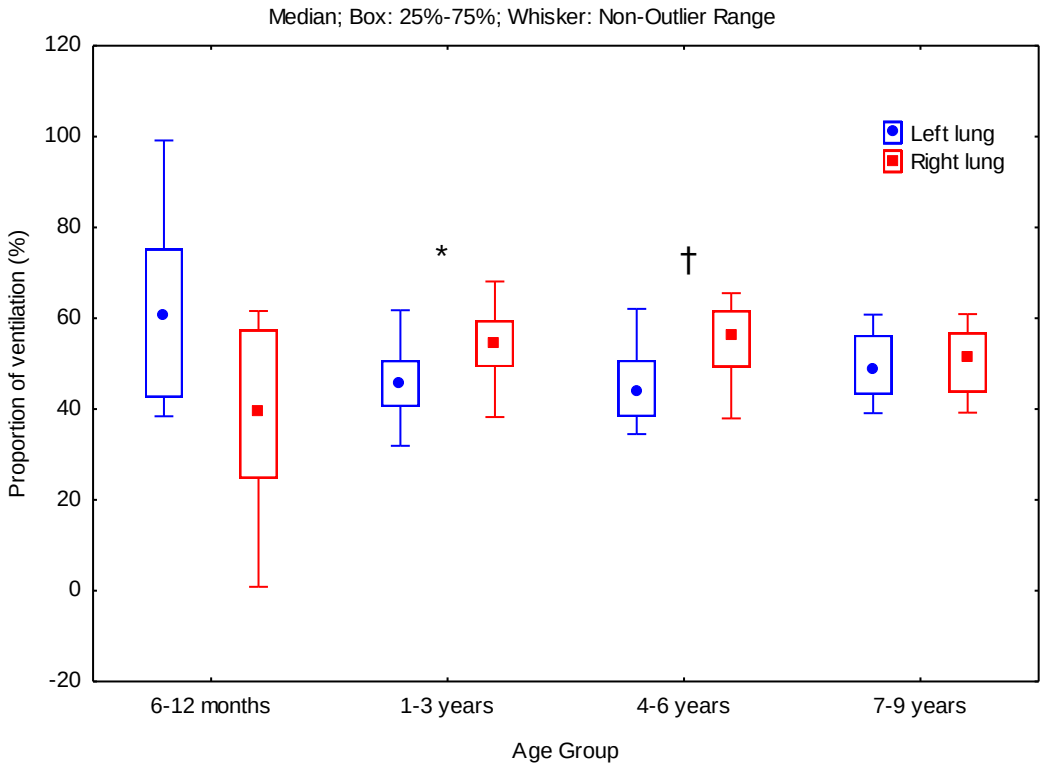


Figure 5.2.7 Proportion of ventilation in the left and right lung regions in the right side lying position between age groups. *p=0.04 within left and right lung regions respectively between the 6-12 month and 1-3 years age groups. †p=0.02 within the left and right lung regions respectively between the 6-12 month and 4-6 years age groups

No difference was found in regional filling between dependent and non-dependent lung regions in children, however, in infants the non-dependent lung regions had a significantly higher filling index than the dependent lung regions ($p<0.001$, Figure 5.2.8). The difference between age groups was only significant in the non-dependent position ($p=0.04$) (Figure 5.2.8)

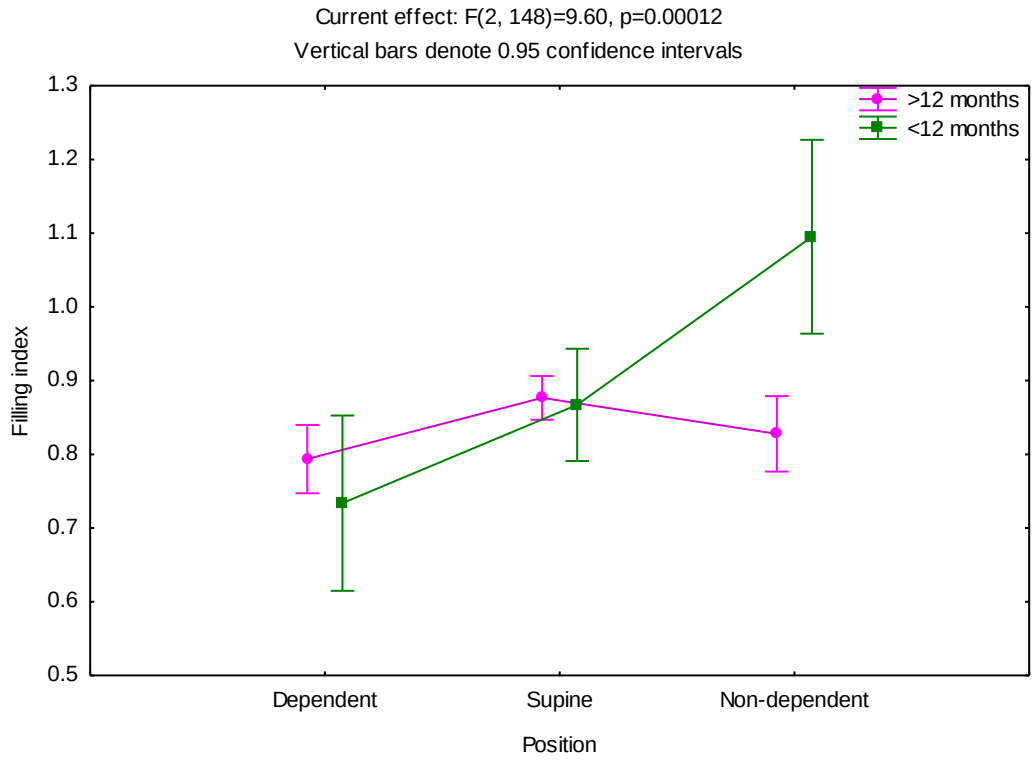


Figure 5.2.8 Filling indices in the dependent or non-dependent lung regions in infants and children.

5.2.5.4 Supine and prone positions

Complete measurements were obtained in 71 infants and children in the supine (SR) and prone (PR) positions.

5.2.5.4.1 Pattern followed

In supine and prone positions, nine (13%) infants and children consistently demonstrated greater ventilation in the non-dependent lung regions, referred to as the “paediatric pattern”; while three (4%) consistently demonstrated greater ventilation in the dependent lung regions, referred to as the “adult pattern”. The majority (55, 79%) of the infants and children consistently demonstrated greater ventilation of the dorsal lung region in both supine and prone positions. Greater ventilation was consistently seen in the ventral lung region in three (4%) of the infants and children (Figure 5.2.9).

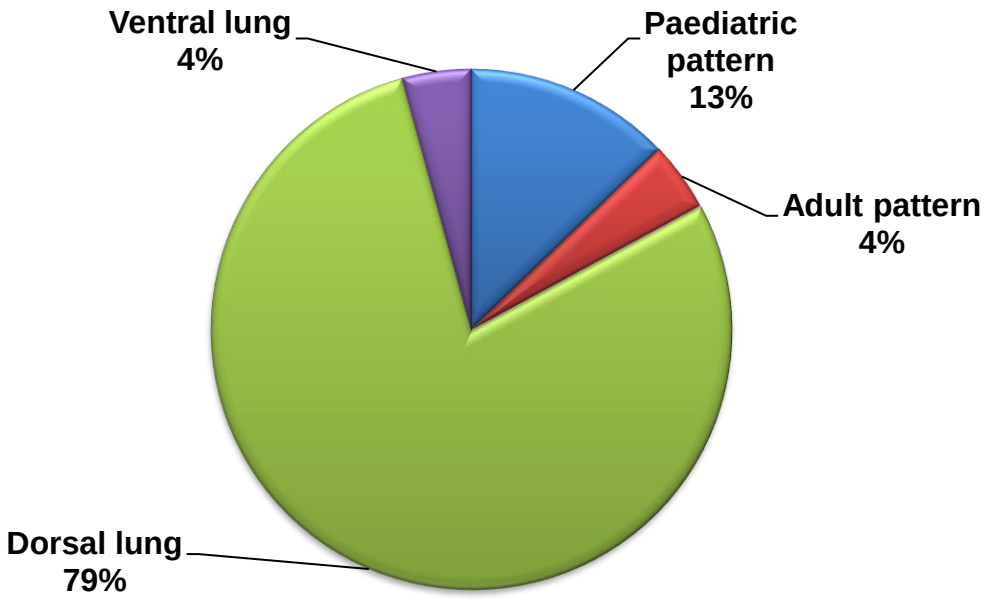


Figure 5.2.9 Proportion of infants and children demonstrating consistently greater ventilation in the non-dependent lung ("paediatric pattern"), dependent lung ("adult pattern"), right lung region, and left lung region in the supine and prone positions.

5.2.5.4.2 Regional ventilation distribution

Global ventilation was unaffected by position ($p=0.43$) (Table 5.2.5). The dorsal lung region showed significantly greater ventilation ($p<0.001$) than the ventral lung region in both the supine and prone positions. Ventilation distribution did not change significantly within the ventral ($p=0.74$) and dorsal ($p=0.11$) lung regions between the supine and prone positions. Although the dorsal lung region was significantly better ventilated than the ventral lung region in both dependent and non-dependent positions ($p<0.001$), there was no significant interaction between the effects of lung region and whether the region was dependent or non-dependent on ventilation distribution ($p=0.34$) (Figure 5.2.10).

Table 5.2.5 Mean relative impedance change in the ventral and dorsal lung regions in the supine and prone positions presented as medians and IQR.

	Supine position		Prone position	
Ventral lung				
ΔZ	14.64	(9.13 – 18.84) *	14.02	(10.61 – 18.09) *
Filling index	0.79	(0.71 – 0.88) †‡	0.71	(0.62 – 0.84) ‡
Dorsal lung				
ΔZ	19.49	(14.97 – 25.28)	20.91	(16.74 – 26.58)
Filling index	0.99	(0.90 – 1.07) §	1.07	(0.94 – 1.17)
Global ΔZ	34.54	(22.72 – 42.70)	36.32	(28.63 – 44.71)

* p<0.001 between ΔZ in ventral and dorsal lung regions in supine and prone positions; †p=0.004 within the ventral lung region between supine and prone positions; ‡p<0.001 between ventral and dorsal lung regions in both supine and prone positions; §p=0.009 within the dorsal lung region between supine and prone positions

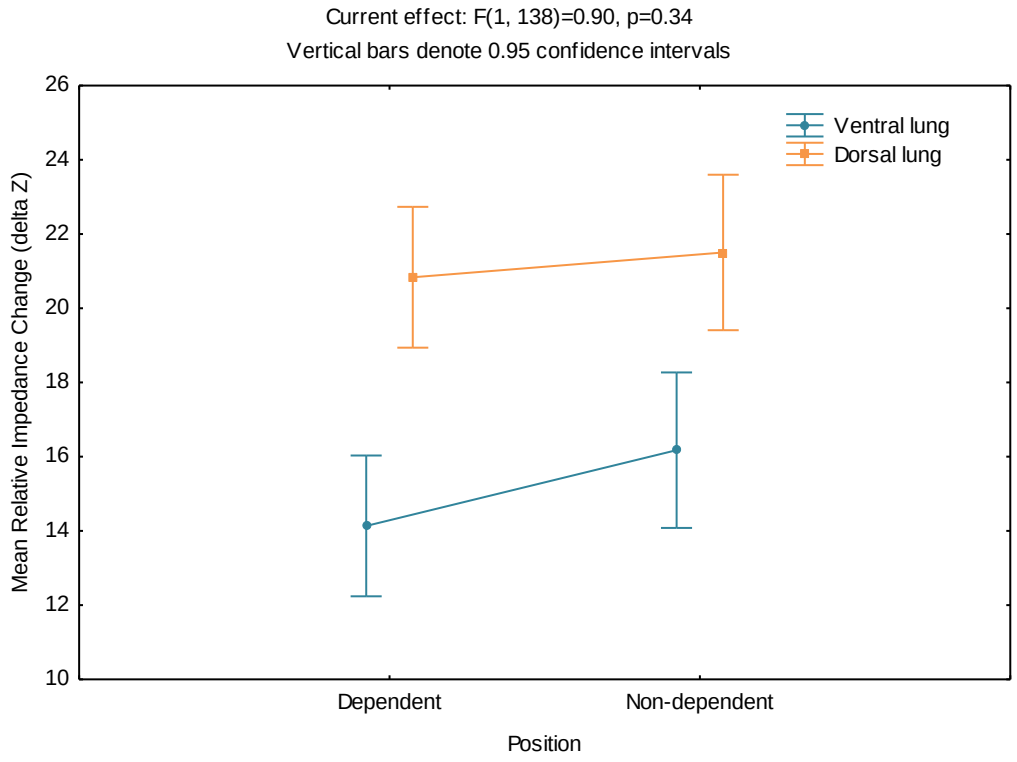


Figure 5.2.10 Ventilation (mean relative impedance change) in the ventral and dorsal lung regions when the dependent and non-dependent positions.

5.2.5.4.3 Regional filling

The dorsal lung region showed significantly higher filling indices than the ventral lung region in both the supine and prone positions. Both the ventral and dorsal lung regions showed significantly higher filling indices when each lung was in the non-dependent position compared to when each lung was in the dependent position (Table 5.2.5).

5.2.5.4.4 Age-related differences

The majority of participants in all age groups showed consistently greater ventilation of the dorsal lung in both the supine and prone positions (Table 5.2.6). Age (younger or older than 12 months) did not predict which pattern would be followed by the child (Table 5.2.7). There were no significant interactions between the effect of age and dependent and non-dependent lung regions and the distribution of ventilation in the supine and prone positions (p=0.95) (Figure 5.2.11).

Table 5.2.6 Pattern of ventilation consistently followed in supine and prone positions in different the age groups.

Age Groups	**Overall pattern**			
	Paediatric	Adult	Ventral	Dorsal
6-12 months (n=7)	1 (14%)	1 (14%)	0 (0%)	5 (71%)
1-3 years (n=21)	5 (24%)	0 (0%)	1 (5%)	15 (71%)
4-6 years (n=28)	2 (7%)	2 (7%)	0 (0%)	24 (86%)
7-9 years (n=14)	1 (7%)	0 (0%)	2 (14%)	11 (79%)

Paediatric – greater ventilation of the non-dependent lung region in both positions; Adult – greater ventilation of the dependent lung region in both positions; Ventral – greater ventilation of the ventral lung region in both positions; Dorsal – greater ventilation of the dorsal lung region

Table 5.2.7 Association between age (younger 12 months) and the pattern followed in supine and prone positions.

Pattern [a]	**Odds Ratio**	**Std. error**	**p-value**
Adult	1.37	1.62	0.39
Different [b]	-0.26	1.16	0.82

[a] Paediatric is the reference category. [b] Includes both ventral and dorsal patterns

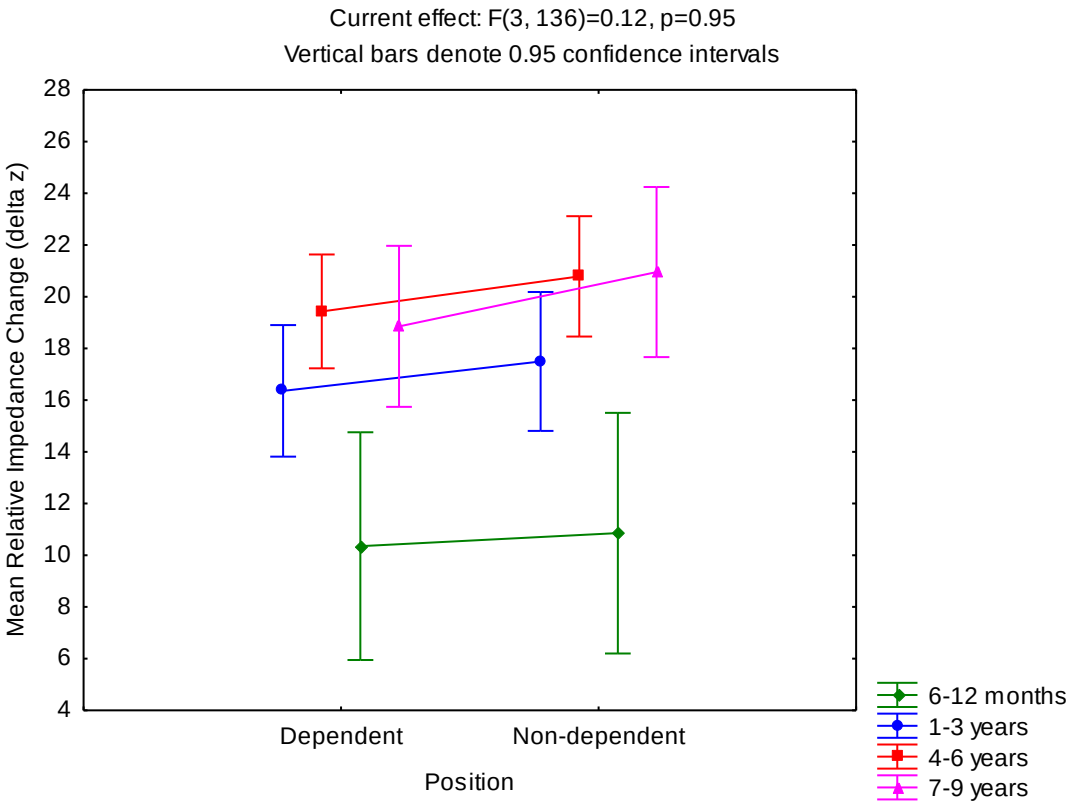


Figure 5.2.11 Mean relative impedance change (ΔZ) in the dependent and non-dependent lung regions in supine and prone positions between different age groups

Ventilation distribution and regional filling was similar amongst all age groups in the supine and prone positions (Figure 5.2.13, Figure 5.2.14 & Figure 5.2.15).

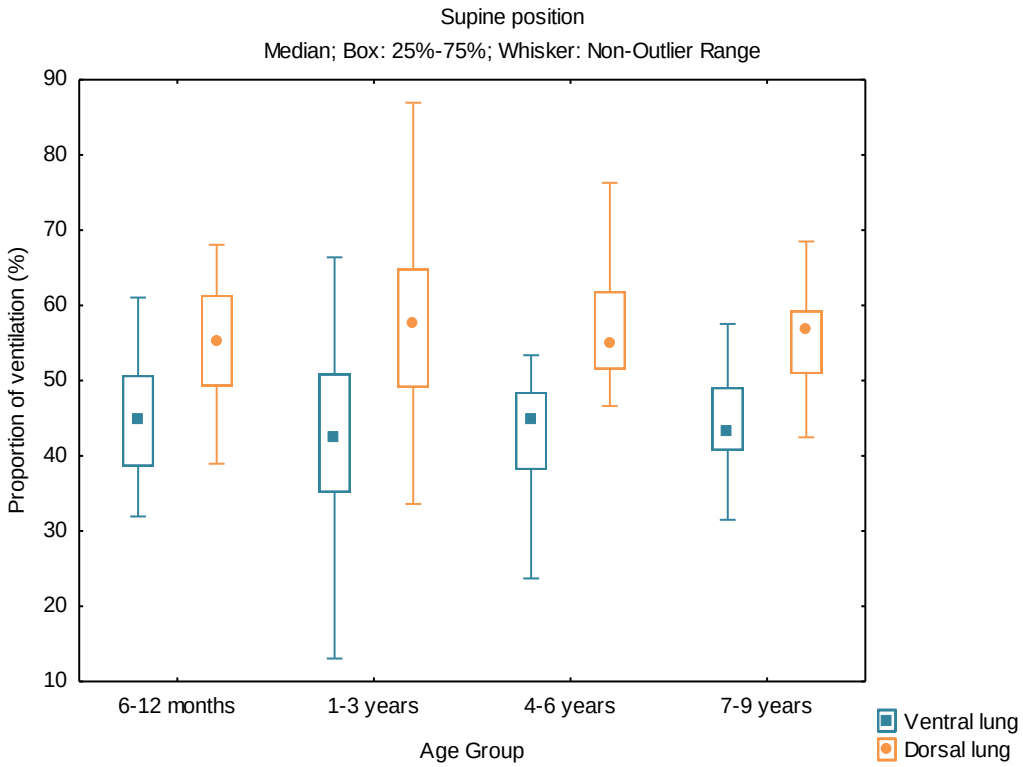


Figure 5.2.12 Proportion of ventilation in the ventral and dorsal lung regions in the supine position among age groups.

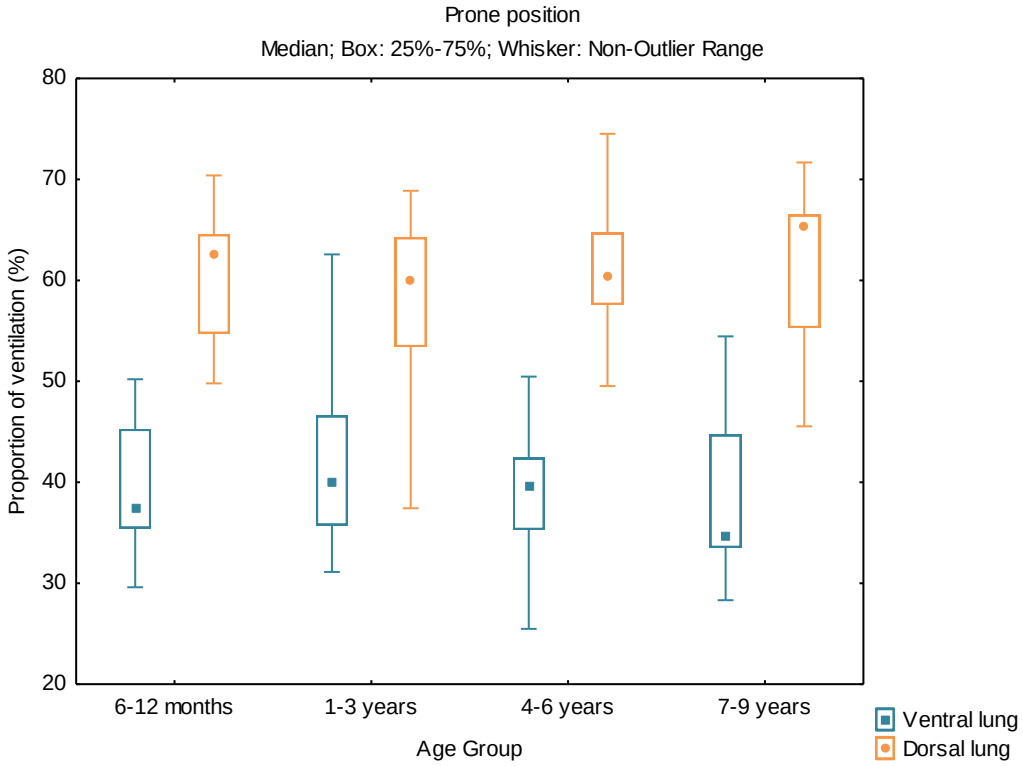


Figure 5.2.13 Proportion of ventilation in the ventral and dorsal lung regions in the prone position among age groups.

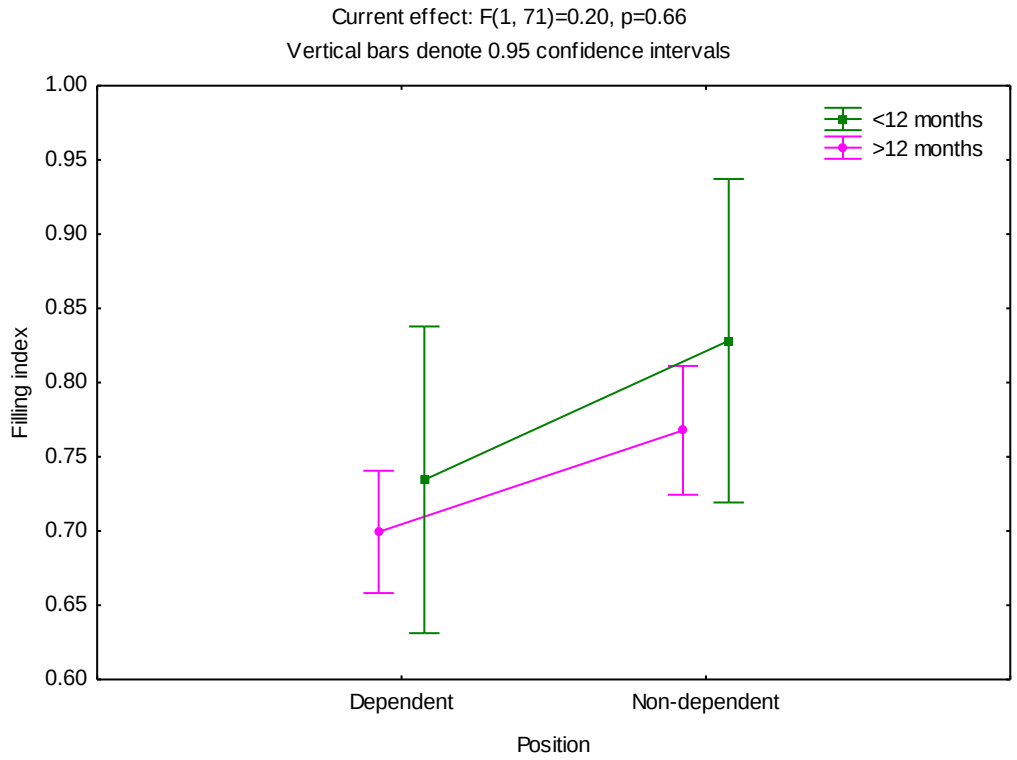


Figure 5.2.14 Filling indices in the dependent and non-dependent position in infants and children.

5.2.5.4.5 Head position

Head position had no significant effect on global and regional ventilation in the supine and prone positions (Table 5.2.8).

Table 5.2.8 Mean relative impedance change in the different lung regions with different head positions in the supine and prone positions.

	Left lung	Right lung	P-value
SM	16.6 (12.8 – 22.1)	18.3 (12.8 – 22.9)	0.64
SL	15.8 (11.4 – 21.1)	19.2 (15.3 – 22.7)	0.02
SR	17.0 (12.3 – 21.9)	17.1 (12.3 - 21.9)	0.99
PL	16.7 (11.7 – 20.7)	18.4 (14.1 – 22.8)	0.12
PR	17.3 (12.6 – 21.8)	18.0 (14.0 – 22.6)	0.48

SM – supine position with head midline; SL – supine position with head to left; SR – supine position with head to right; PL – prone position with head to left; PR – prone position with head to right. After applying a Bonferroni correction p=0.01 was considered significant.

5.2.5.5 Regional ventilation distribution and respiratory muscle activity

In a subset of 22 participants, measures of respiratory muscle activity were taken in addition to regional ventilation. Population characteristics are displayed in Table 5.2.9.

Table 5.2.9 Population characteristics

Age (years) (n=22)	5.60	(3.60 – 6.33)
Gender (n=22):		
Male	13	(59%)
Female	9	(41%)
Respiratory rate (breaths per minute)	24.00	(20.00 – 26.00)

5.2.5.5.1 Side lying positions

5.2.5.5.1.1 Regional ventilation distribution

Complete measurements were obtained in 21 of the infants and children in the side lying positions.

In this subgroup of children, two (10%) demonstrated consistently greater ventilation of the non-dependent lung region (paediatric pattern), nine (43%) demonstrated consistently greater ventilation of the dependent lung region (adult pattern), three (14%) consistently showed greater ventilation in the left lung region, and six (29%) showed consistently greater ventilation in the right lung in side lying positions.

Regional ventilation and filling, shown in Table 5.2.10, in this cohort was similar to the large cohort of children studied.

Table 5.2.10 Mean relative impedance change in the left and right lung regions in the side lying positions presented as medians and IQR

	Left side lying		**Right side lying**	
Left lung				
ΔZ	17.78	(16.31 – 21.38)	16.40	(14.73 – 21.43)
Filling index	0.89	(0.80 – 1.02)	0.79	(0.73 – 0.90) *
Right lung				
ΔZ	18.61	(15.14 – 22.05)	20.05	(16.65 - 21.32)
Filling index	0.89	(0.77 – 0.98)	0.99	(0.89 – 1.06)
Global ΔZ	35.74	(30.94 – 42.06)	36.66	(32.49 – 39.23)

* p=0.002 between left and right lung regions in right side lying

5.2.5.5.1.2 Repeatability of EIT measurements

No significant difference was found in the interaction of the effects of measurement and body position on mean relative impedance change within the left lung (p=0.95) (Figure 5.2.15) and right lung regions (p=0.45) (Figure 5.2.16) respectively. Good agreement was found

between measurements one and two in the left, right and global lung regions in the side lying positions (Table 5.2.11).

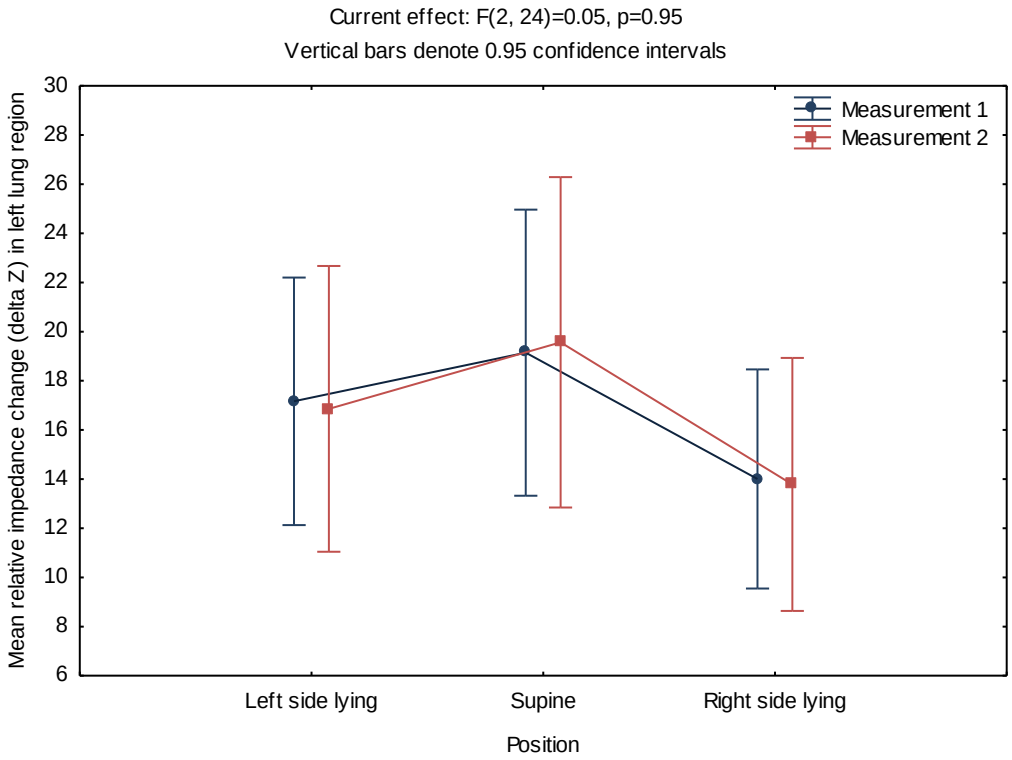


Figure 5.2.15 Mean relative impedance change in the left lung region in side lying positions between measurements one and two.

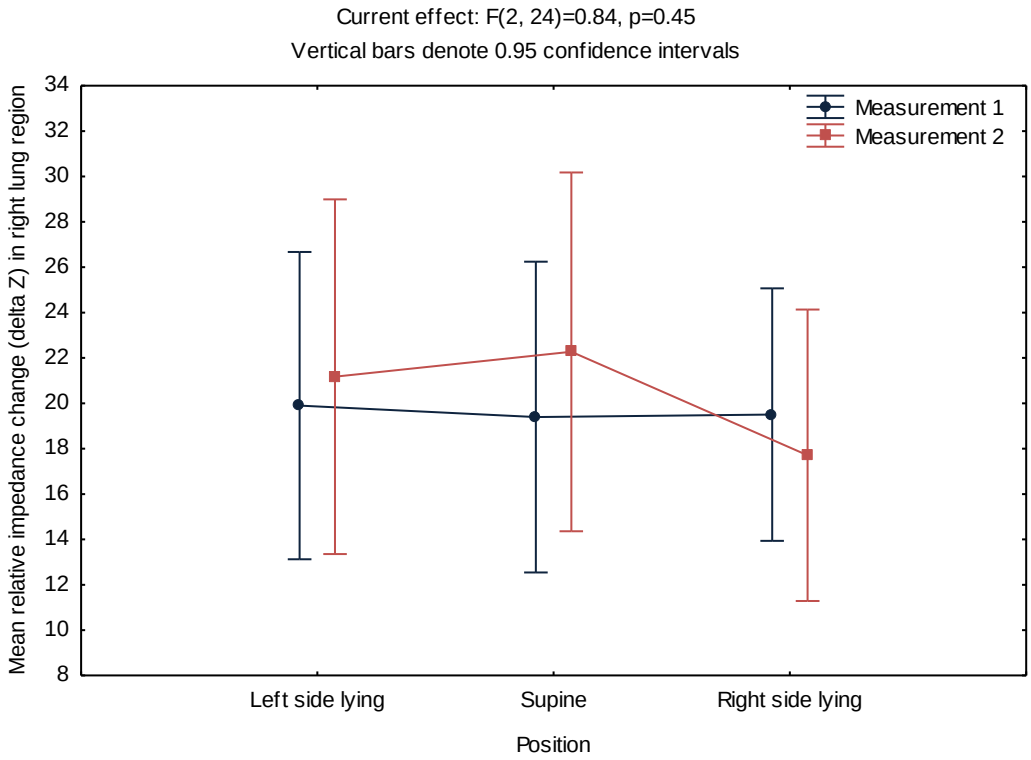


Figure 5.2.16 Mean relative impedance change in the right lung region in side lying positions between measurements one and two.

Table 5.2.11 Intra-class correlation co-efficients (ICC), mean difference and limits of agreement between EIT measurement one and measurement two in the side lying positions

Position	Lung region	ICC	95% CI	p-value	Mean difference	Limits of agreement
Left side lying	Left	0.87	-0.12 – 0.98	0.03	0.09	-10.15 – 10.33
	Right	0.88	0.04 – 0.98	0.02	0.34	-12.13 – 12.80
	Global	0.87	-0.14 – 0.98	0.03	0.44	-22.07 – 22.92
Right side lying	Left	0.86	0.12 – 0.98	0.02	0.24	-8.07 – 8.54
	Right	0.94	0.07 – 0.99	<0.01	3.16	-1.16 – 7.47
	Global	0.92	0.56 – 0.99	<0.01	3.40	-8.00 – 14.80

5.2.5.5.1.3 Respiratory muscle activity

Differences in respiratory muscle activity in the left and right hemi-diaphragm, as well as the intercostals were not statistically significant in the side lying positions (Table 5.2.12). No significant interaction between the effects of hemi-diaphragm (left or right) and position (dependent (p=0.13) or non-dependent (p=0.37)) on mean muscle activity was found (Figure 5.2.17).

Table 5.2.12 Mean muscle activity (μV) in side lying positions presented as medians and IQR.

	Left side lying	Right side lying	p-value [a]
Left hemi-diaphragm	8.82 (6.53 – 11.95)	7.98 (6.04 – 11.44)	0.50
Right hemi-diaphragm	9.41 (6.74 – 12.07)	12.16 (5.19 – 18. 66)	0.23
Intercostals	3.02 (2.06 – 10.08)	4.63 (2.20 – 13.14)	0.36

[a] Between left and right side lying positions. p=0.80 between left and right hemi-diaphragms in left side lying; p=0.10 between left and right hemi-diaphragms in right side lying; p=0.36 for intercostal activity between left and right side lying positions.

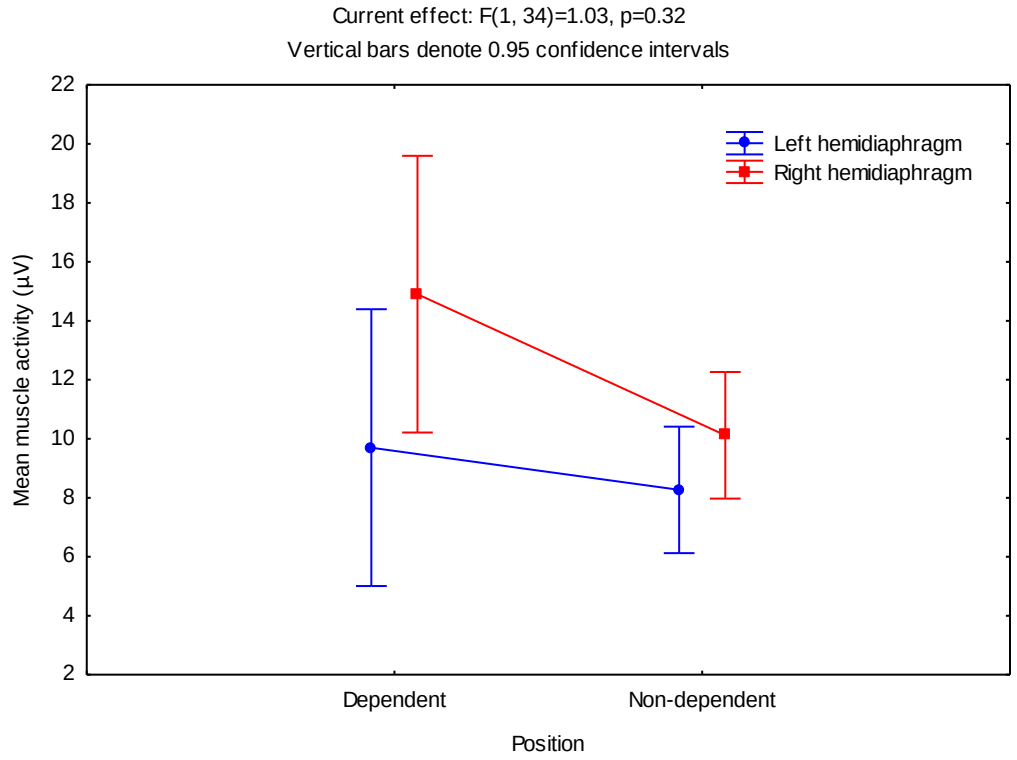


Figure 5.2.17 Mean activity of the left and right hemi-diaphragms in when dependent and non-dependent in the side lying positions.

5.2.5.5.1.4 Repeatability of sEMG measurements

No significant interaction was found between the effects of measurement number and body position on the left hemi-diaphragm activity; however, the pattern of activity differed between measurements (Figure 5.2.18). Poor agreement was found between measurements for the intercostals and left and right hemi-diaphragms in the left side lying position (Table 5.2.13). There was no significant interaction between the effects of measurement number and body position on the activity of the right hemi-diaphragm (Figure 5.2.19) and good agreement was found between the two measurements (Table 5.2.13).

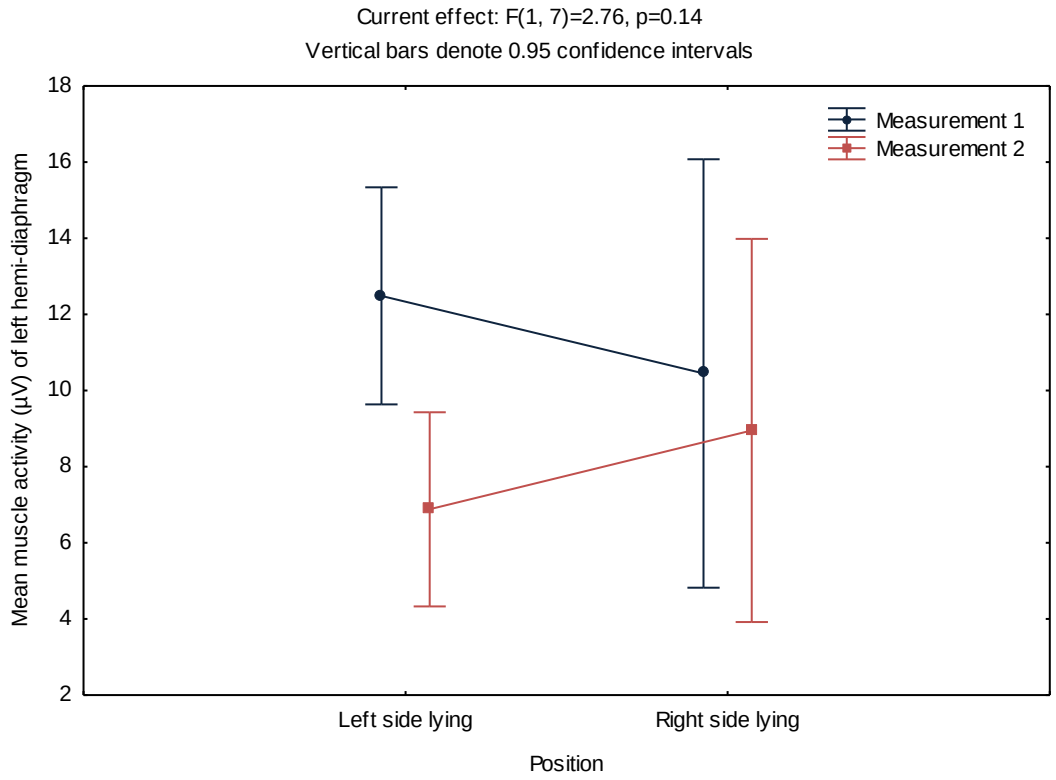


Figure 5.2.18 The interaction between the effects of the measurement number and body position on activity of the left hemi-diaphragm.

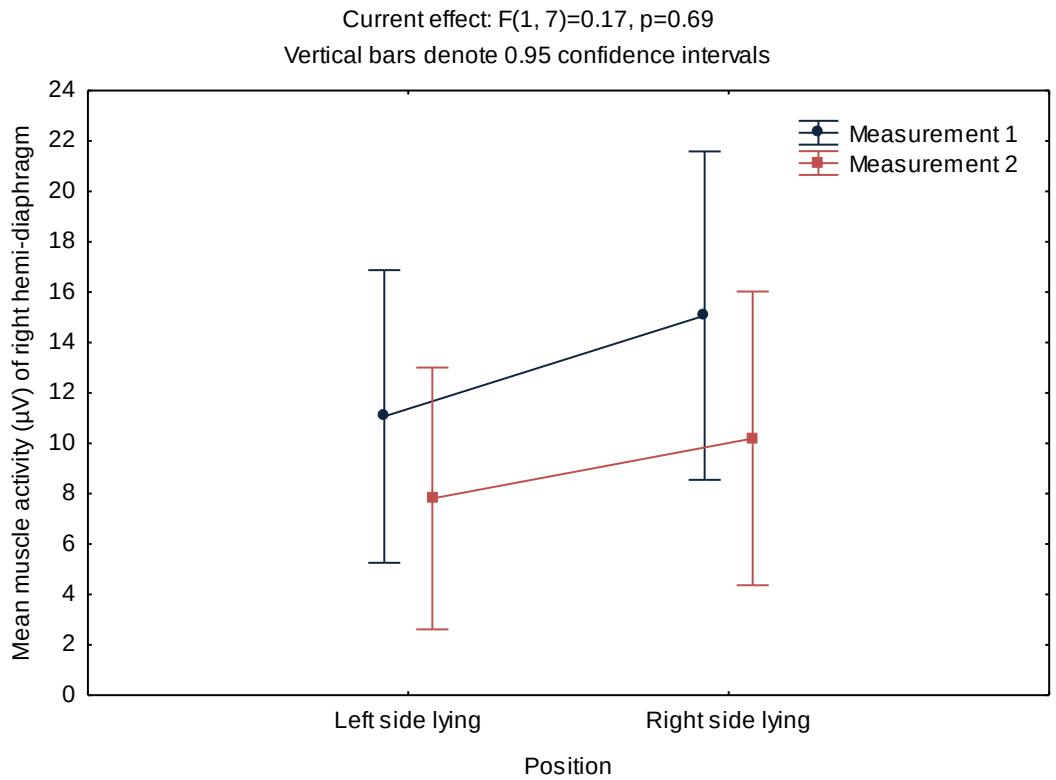


Figure 5.2.19 The interaction between the effects of the measurement number and body position on activity of the right hemi-diaphragm.

Table 5.2.13 Intra-class correlation co-efficients (ICC), mean differences and limits of agreement between sEMG measurement one and measurement two for muscle activity in the side lying positions

Position	Muscle	ICC	95% CI	p-value	Mean difference	Limits of agreement
Left side lying	Intercostals	0.01	-16.95 – 0.94	0.50	-1.51	-7.57 – 4.54
	Left Hemi-diaphragm	-0.49	-0.78 – 0.65	0.86	3.80	-2.55 – 10.14
	Right Hemi-diaphragm	0.24	16.04 – 0.96	0.42	-0.01	-13.69 – 13.67
Right side lying	Intercostals	0.67	-7.64 – 0.97	0.19	0.37	-5.82 – 6.56
	Left Hemi-diaphragm	0.94	0.44 – 0.99	0.01	0.06	-3.92 – 4.03
	Right Hemi-diaphragm	0.90	0.26 – 0.99	0.02	1.37	-3.96 – 6.69

5.2.5.5.1.5 Interaction between regional ventilation distribution and respiratory muscle activity

No significant interaction was found between proportion of ventilation in the left lung region and left hemi-diaphragm and intercostal activity (Table 5.2.14). Activity of the right hemi-diaphragm did not affect the proportion of ventilation in the right lung region. A significant association was, however, found between intercostal activity and the proportion of ventilation in the right lung region (Table 5.2.15, p=0.04).

Table 5.2.14 Interaction between intercostal and left hemi-diaphragm activity and the proportion of ventilation in the left lung region in side lying positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	45.27	36.95	53.62	0<01
Intercostals	0.25	-0.27	0.77	0.34
Left Hemi-diaphragm	0.09	-0.72	0.90	0.82

Table 5.2.15 Interaction between intercostal and right hemi-diaphragm activity and the proportion of ventilation in the right lung region in side lying positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	54.35	48.76	59.94	0<01
Intercostals	-0.51	-1.00	-0.03	0.04
Right Hemi-diaphragm	0.13	-0.18	0.43	0.41

5.2.5.5.2 Supine and prone positions

5.2.5.5.2.1 Regional ventilation distribution

Complete measurements were obtained in 19 infants and children.

In four (21%) infants and children, the non-dependent lung had consistently greater ventilation (paediatric pattern) and two infants/children (11%) had consistently greater ventilation in the dependent lung (adult pattern). Most (12, 63%) of the infants and children demonstrated consistently better ventilation in the dorsal lung region, while only one (5%) had consistently greater ventilation in the ventral lung region.

Regional ventilation and filling, shown in Table 5.2.16, was similar to the large cohort of children studied.

Table 5.2.16 Mean relative impedance change and filling indices in supine and prone positions presented as medians and IQR

	Supine position	**Prone position**
Ventral lung		
∆Z	17.30 (13.66 - 23.39)	16.0 (15.22 – 21.24)
Filling index	0.88 (0.80 – 0.91) *	0.76 (0.71 – 0.89) †
Dorsal lung		
∆Z	19.25 (15.65 - 26.76)	22.84 (19.56 -22.26)
Filling index	0.91 (0.88 – 0.99)	1.02 (0.89 – 1.07)
Global ∆Z	37.23 (29.64 – 47.76)	39.93 (33.10 – 45.54)

*p=0.04 between ventral and dorsal lung regions; † p<0.001 between ventral and dorsal lung regions

5.2.5.5.2.2 Repeatability of EIT measurements

Ventilation was similar in both ventral (p=0.85) (Figure 5.2.20) and dorsal (p=0.58) (Figure 5.2.21) lung regions with no significant interaction between effects of the first and second measurements and supine and prone positions. Good agreement was found between the two EIT measurements in the ventral, dorsal and global lung regions in both supine and prone positions (Table 5.2.17).

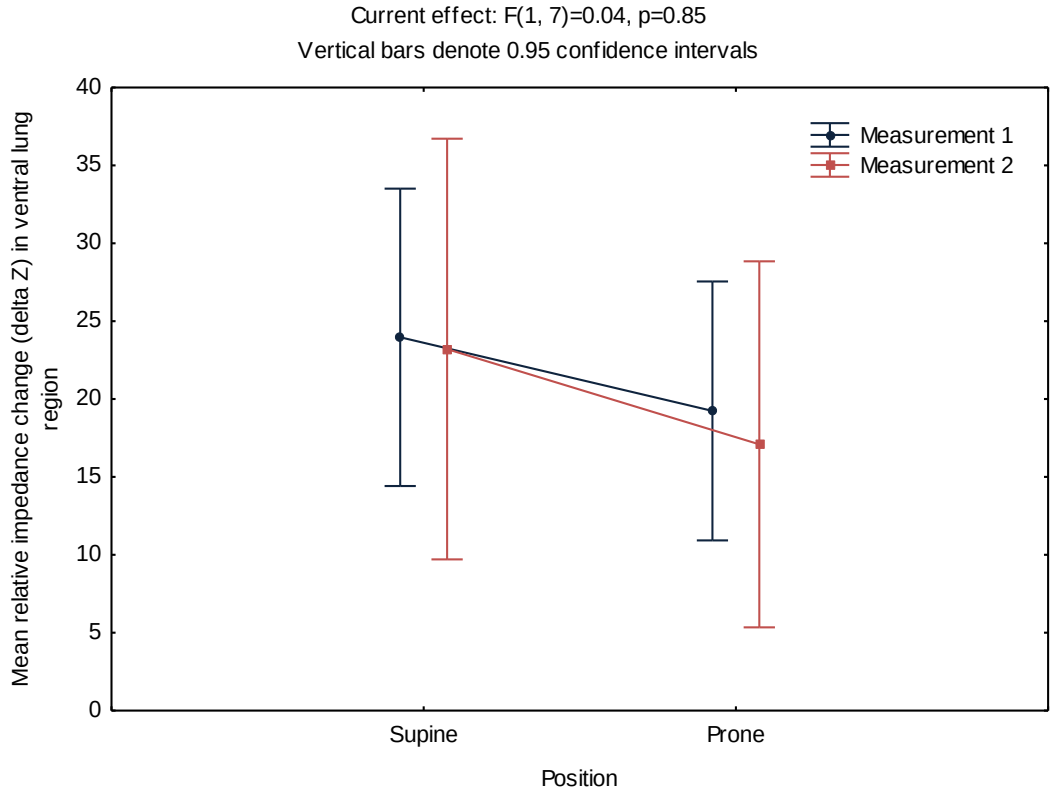


Figure 5.2.20 Mean relative impedance change in the ventral lung region in the supine and prone positions between measurements one and two.

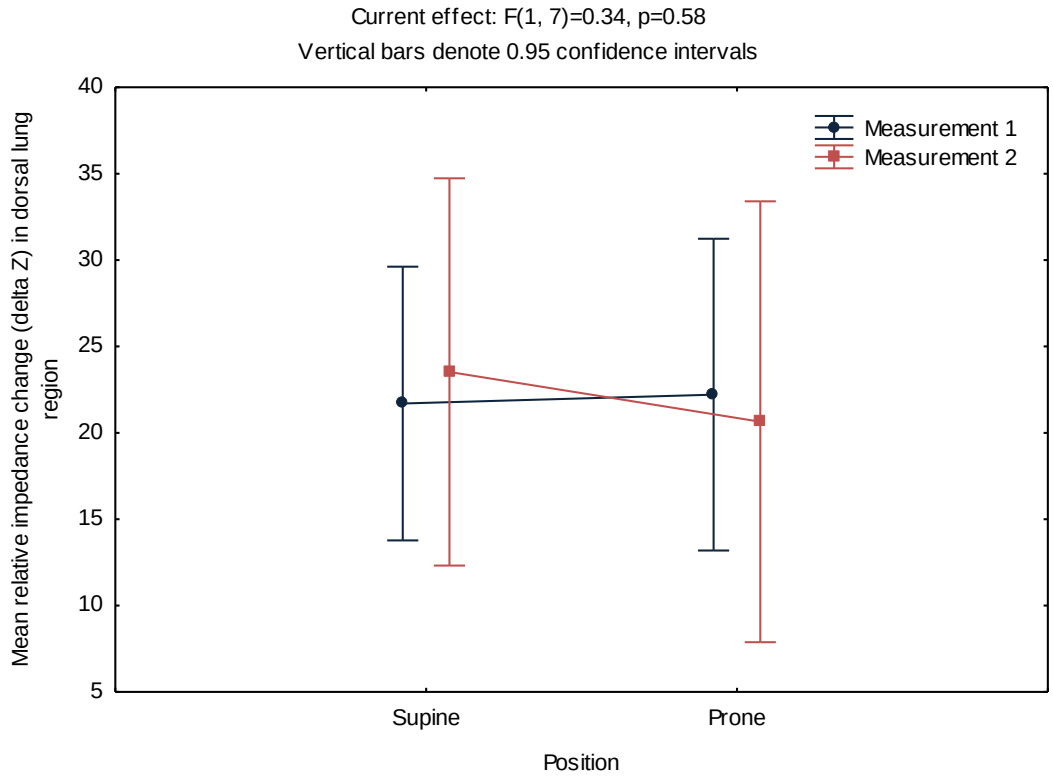


Figure 5.2.21 Mean relative impedance change in the dorsal lung region in the supine and prone positions between measurements one and two.

Table 5.2.17 The intra-class correlation co-efficients (ICC), mean differences and limits of agreement in the ventral, dorsal and global lung regions in supine and prone positions between the first and second EIT measurements.

Position	Lung region	ICC	95% CI	p-value	Mean difference	Limits of agreement
Supine	Ventral	0.86	0.19 - 0.98	0.02	3.60	-9.72 – 16.91
	Dorsal	0.86	-0.81 – 0.97	0.06	-0.08	-13.26 – 13.10
	Global	0.88	0.21 – 0.98	0.02	3.52	-19.40 – 26.44
Prone	Ventral	0.93	0.23 – 1.00	0.02	3.01	-4.04 – 10.06
	Dorsal	0.80	-0.73 – 0.99	0.10	3.99	-9.27 – 17.24
	Global	0.87	-0.12 – 0.99	0.05	7.00	-12.64 – 26.64

5.2.5.5.2.3 Respiratory muscle activity

In the prone position, the dorsal diaphragm showed significantly greater activity compared to the ventral diaphragm (p=0.007). Ventral diaphragm activity was unaffected by position, while the dorsal diaphragm had greater activity in the prone position (p=0.05). No significant difference (p=0.73) was found in intercostal muscle activity between the supine and prone positions (Table 5.2.18).

The pattern of activity in the ventral and dorsal hemi-diaphragm when in the dependent and non-dependent positions was similar (Figure 5.2.22). There was no difference in activity between the ventral and dorsal diaphragm when in the dependent position (p=0.36). The ventral diaphragm showed significantly greater activity in the non-dependent position compared to the dorsal diaphragm when non-dependent (p=0.01).

Table 5.2.18 Muscle activity (µV) in the supine and prone positions presented as medians and IQR.

	Supine		Prone		p-value [a]
Ventral diaphragm	7.04	(4.13 – 11.23)	3.58	(2.79 – 5. 69)*	0.86
Dorsal diaphragm	6.84	(3.93 – 7.60)	7.27	(5.29 – 10.49)	0.05
Intercostals	6.49	(3.00 – 13.12)	8.69	(3.24 – 12.25)	0.73

[a] between supine and prone positions. *p=0.007 between ventral and dorsal diaphragms in the prone position p=0.45 between ventral and dorsal diaphragms in the supine position.

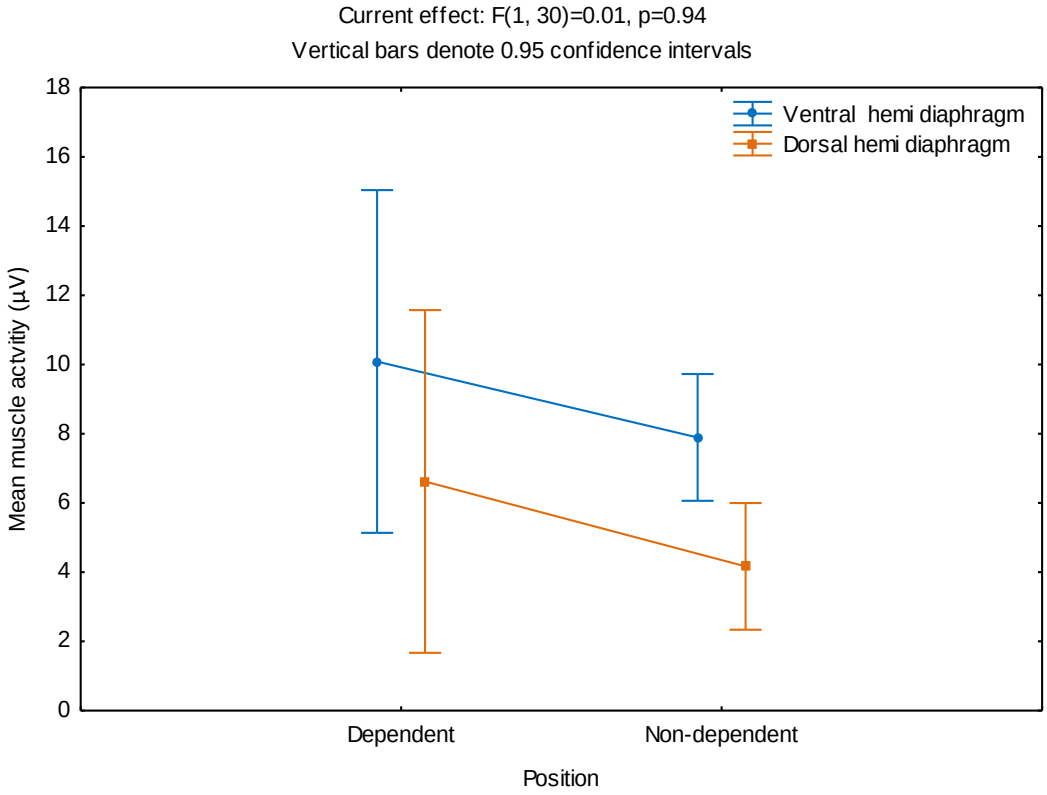


Figure 5.2.22 Mean muscle activity of ventral and dorsal hemi-diaphragms when in the dependent and non-dependent position.

5.2.5.5.2.4 Repeatability of sEMG measurements

There was no significant interaction between the effects of measurement one or two and body position for the ventral hemi-diaphragm ($F_{(1, 5)}$=0.01, p=0.94) and dorsal hemi-diaphragm ($F_{(1, 5)}$=0.32, p=0.60) respectively. Agreement was very good between measures, with high intra-class correlation co-efficients found for intercostal muscles, ventral and dorsal hemi-diaphragms in supine and prone positions (Table 5.2.19).

Table 5.2.19 The intra-class correlation co-efficients, mean differences and limits of agreement for respiratory muscle activity in the supine and prone positions between measurements one and two.

Position	Muscle	ICC	95% CI	p-value	Mean difference	Limits of agreement
	Intercostals	0.91	0.12 – 0.99	0.03	-1.42	-4.99 – 2.16
Supine	Ventral Hemi-diaphragm	0.99	0.92 – 1.00	<0.01	0.66	-1.52 – 2.84
	Dorsal Hemi-diaphragm	0.88	-0.47 – 0.99	0.07	0.85	-3.20 – 4.90
	Intercostals	0.95	0.02 – 1.00	<0.01	2.41	-0.93 – 5.74
Prone	Ventral Hemi-diaphragm	0.98	0.67 – 1.00	<0.01	0.77	-0.72 – 2.25
	Dorsal Hemi-diaphragm	0.93	0.33 – 1.00	0.03	1.05	-2.63 – 4.73

5.2.5.5.2.5 Interaction between regional ventilation distribution and respiratory muscle activity

Activity of the ventral hemi-diaphragm and intercostal muscles was not associated with changes in the proportion of ventilation occurring in the ventral lung region (Table 5.2.20).

Table 5.2.20 Interaction between intercostal and ventral hemi-diaphragm activity and the proportion of ventilation in the ventral lung region in supine and prone positions

	Coefficient	95% Confidence interval		p-value
	Estimate	Lower	Upper	
Intercept	49.80	45.44	54.16	0<01
Intercostals	-0.11	-0.37	0.17	0.45
Ventral Hemi-diaphragm	-0.08	-0.33	0.30	0.91

A significant interaction was found between dorsal hemi-diaphragm activity and proportion of ventilation occurring in the dorsal lung region (p=0.04). It was found that an increase in dorsal hemi-diaphragm activity was associated with a decrease in the proportion of ventilation in the dorsal lung region (Table 5.2.21). Intercostal muscle activity was not associated with changes in ventilation in the dorsal lung region.

Table 5.2.21 Interaction between intercostal and dorsal hemi-diaphragm activity and proportion of ventilation in the dorsal lung region in supine and prone positions

	Coefficient	95% Confidence interval		p-value
	Estimate	Lower	Upper	
Intercept	58.83	54.61	63.06	0<01
Intercostals	0.01	-0.18	0.20	0.92
Dorsal Hemi-diaphragm	-0.82	-1.36	-0.29	0.04

5.2.6 Discussion

This study examined the effects of body and head position, age and respiratory muscle activity on regional ventilation distribution in healthy, spontaneously breathing infants and children. These novel findings indicate that regional ventilation distribution is not as straight-forward as previously thought and the “paediatric” pattern cannot be uniformly applied to the entire paediatric population. To the best of my knowledge, this is the first study to examine regional ventilation distribution, and possible determinants, in healthy children.

5.2.6.1 Ventilation distribution

Based on previous studies, it was postulated that ventilation would be distributed to the non-dependent lung (“paediatric” pattern) in infants and children in the side lying positions

irrespective of whether the radiological appearance was normal or not (Heaf et al., 1983; Davies et al., 1985; Davies, Helms & Gordon, 1992). The results of this study do not support this consistent "paediatric" pattern of ventilation, with only a quarter of children consistently following this pattern in side lying positions. To the best of my knowledge, no studies have reported the effect of side lying, supine and prone positions on the pattern of ventilation beyond the neonatal age. The "paediatric" pattern cannot be applied to all infants and children in the supine and prone positions with just over 10% consistently following it in the supine and prone positions. Rather, the pattern of regional ventilation distribution was highly variable amongst infants and children studied.

5.2.6.1.1 Regional ventilation distribution

The discrepancies between these results and those performed in the 1980's may be due to differences in population characteristics and study methodology. Children in previous studies (Heaf et al., 1983; Davies et al., 1985) had conditions such as acute or chronic respiratory disease, neuromuscular disease, diaphragmatic hernia, exomphalos, hypoplastic lungs and atelectasis, all of which may have affected local lung mechanics and thereby ventilation distribution. Infants and children included in these studies were young, with the eldest being 27 months. The young age and the consequent differences in respiratory mechanics (as discussed in Section 2.1) together with the medical conditions the infants presented with, may have predisposed these infants to small airway collapse and reduced volumes in the dependent lung regions resulting in the pattern of ventilation described. Furthermore, it is suggested that unless dynamic images are taken, krypton 81m scanning may reflect both resting volume and tidal volume change (Lythgoe et al., 1992). It is therefore possible that, in the previous studies, non-dependent lung regions had higher volume but not necessarily greater ventilation (tidal volume change); although it is possible that ventilation in these lung regions was in fact greater. Furthermore, previous methods would have required the use of facemasks and possibly sedation, both of which alter breathing pattern and respiratory mechanics (Frerichs et al., 2003; Hutten et al., 2008; Hutten et al., 2010). Therefore, the results of previous studies are not applicable to all infants and children, including those with unimpeded, spontaneous breathing.

Of the more recent studies, this is the first to report the regional ventilation distribution in both side lying positions. Additionally, previous studies report cumulative findings (i.e. the mean proportion of ventilation or mean relative impedance change for all infants/children in a position) and do not report inter-individual differences in ventilation distribution (as described by our analysis of pattern followed), making direct comparison with our results difficult.

Our findings of greater ventilation in the dorsal lung region in both supine and prone positions are in keeping with those of Hough et al. (2012 & 2013), who also reported greater ventilation in the dorsal lung regions in both supine and prone positions in neonates who

were breathing spontaneously or receiving ventilatory support. Pham et al. (2011) also reported greater ventilation in the dorsal lung region in the supine position in infants less than six months of age; however, whether this also occurred in the prone position was not investigated.

Our finding of greater ventilation in the right lung, which occurred irrespective of position, has been reported in previous EIT studies in neonates (Frerichs et al., 2003; Heinrich et al., 2006; Hough et al., 2012). In the present study ventilation of the right lung was significantly greater than the left lung in left side lying and this occurred across all age groups. This finding may be attributed to the larger size of the right lung compared to the left, resulting in a greater number of pixels in the fEIT images used for analysis (Heinrich et al., 2006). In addition, in the left side lying position shift of the mediastinal structures in response to gravity may limit the space available for the left lung to expand and therefore impact on ventilation, whereas in right side lying the heart may shift more centrally creating more space for the left lung to expand. Since this is a finding consistently seen in EIT studies, it could be related to methodological aspects of EIT imaging. This requires further investigation.

The lack of a distinct pattern of ventilation distribution as is seen in the adult population is difficult to fully explain. Since ventilation distribution is determined by the interaction of several factors, such as respiratory pattern, tidal volumes, resting lung volumes and chest wall mechanics, individual variances in these may have played a role. It is also possible that the short amount of time spent in each position and the order of the positions may account for some of the variability found.

5.2.6.1.2 The effect of age

Despite only studying 10 children younger than 12 months of age, our results suggested that infants younger than 12 months are more likely to follow the paediatric pattern of ventilation distribution in side lying positions compared to those older than 12 months. This is supported by the greater proportion of ventilation, albeit non-significant, and higher filing indices seen in the non-dependent lung regions in side lying positions in infants. This may be attributed to the differences in respiratory mechanics and respiratory system maturity. At the younger age, infants may not be spending as much time in an upright, anti-gravity posture and chest wall and respiratory mechanics (Chapter 2.1) may predispose to airway closure in the dependent lung regions resulting in greater ventilation of the non-dependent lung. This finding in the younger population is in keeping with previous ventilation scintigraphy studies (Heaf et al., 1983; Davies et al., 1985); however, the variability still present in this age group was not reported in previous studies. In side lying positions, there were no overall differences in ventilation distribution between all age groups. Regional ventilation distribution became more equal between dependent and non-dependent lungs with increasing age in both left and right side lying positions. The significant difference

between those younger than 12 months and the 1-3 year and 4-6 year age groups may be explained by differences in development of the respiratory system (as previously discussed). We did not find the expected difference between those younger than 12 months and those in the 7-9 year age groups, which may be related to the relatively small number of infants/children in each of these groups. Age did not appear to affect the distribution of ventilation in the supine and prone positions with the majority of children, irrespective of age, showing greater ventilation in the dorsal lung region. The absence of age related differences in the supine position is in keeping with those of Pham et al. (2011), who showed no difference in ventilation distribution in infants up to six months of age, but rather a change in the amplitude of relative impedance change, which would be expected with growth.

5.2.6.1.3 The effect of head position

Head position did not affect significantly ventilation distribution in either the left or right lung regions in the supine and prone positions. These findings are different to those of Heinrich et al. (2006), who reported that head position significantly affected ventilation distribution, particularly in the left lung region, in both spontaneously breathing and mechanically ventilated new-born infants. They speculated that changes in ventilation may have been attributable to tractional forces within the mediastinum as well as the larger angle of divergence of the left main bronchus which may limit flow to the left main bronchus.

5.2.6.2 Regional filling characteristics

In the side lying positions, the right lung showed significantly higher filling indices compared to the left lung. Earlier lung models showed that as volumes increase so the amount of gas delivered to the upper lung regions decreases, while the amount of gas delivered to the lower lung regions increases (Koler, Young & Martin, 1959; Milic-Emili et al., 1966). This indicates faster initial filling in the non-dependent lung regions which slows as inspiration progresses and faster filling in the dependent lung regions towards the end of inspiration. This is due to the fact that the dependent lung regions are placed on the steeper portion of the pressure-volume curve.

Our findings of higher filling indices in the right lung when dependent are in keeping with this lung model. It would be expected that a similar rate of filling would be seen in the left lung when in the dependent position; however, this was not observed in this study. This observation may be explained by the larger angle of divergence of the left main bronchus, resulting in greater air flow via the right main bronchus (Fewell, Arrington & Seibert, 1979). Another possible explanation is a greater degree of airway closure in the left lung region when dependent due to compression by the heart and mediastinal structures, resulting in the slower filling rates observed.

Studies in younger infants and older children have reported greater filling indices in the non-dependent lung in the supine position during spontaneous breathing (Humphreys et al., 2011; Pham et al., 2011; Hough et al., 2013), indicating the dependent (dorsal) lung regions had faster rates of filling at the beginning of inspiration which slowed towards end inspiration. This is contrary to our findings, where the dorsal lung regions demonstrated slow initial filling which became faster as inspiration progressed in both supine and prone positions. The filling characteristics, of the dorsal lung region in the supine position found in the present study are in keeping with patterns of filling shown by Milic-Emili et al. (1966). The persistence of this pattern in the dorsal lung in the prone position may be explained by the more uniform distribution of ventilation and pleural pressures which occur in the prone position (Mutoh et al., 1992). Furthermore, expansion of the anterior (more mobile) chest wall is limited in the prone position and the heart occupies a greater portion of the anterior compartment, both of which may limit expansion of the ventral lung region.

The significant difference in filling characteristics between infants and children supports the differing patterns of ventilation observed between the two groups and may be attributed to differences in respiratory mechanics. Infants may have greater airway closure in the dependent lung regions, resulting in the faster initial filling in the non-dependent lung regions as demonstrated by these results. Faster respiratory rates in infants may result in faster inspiratory flow rates and consequently faster filling of the non-dependent lung regions (Chang, 1999). Although the present findings with regards to regional filling are in keeping with those reported by Milic-Emili et al. (1966) and support the distribution of ventilation findings, it must be noted that although FI has been reported in a number of recent studies, to date it has not been well validated against other methods of determining regional filling. If this method is to be used in clinical practice to guide management, it is recommended that it first be validated.

5.2.6.3 Repeatability and feasibility of EIT measurements

In both side lying and supine and prone positions EIT showed very good repeatability with intra-class correlation co-efficients greater than 0.80. These findings are in keeping with adult (Smit et al., 2003) and neonatal (Riedel et al., 2009) studies, who demonstrated excellent reproducibility of EIT with repeated measures.

EIT was well tolerated by the children in this study. Most of the set-up time was spent numbering the electrodes and placing them on the thorax, which took approximately 15 minutes. This time could be minimised by using electrode belts (not currently available for people <40kg). Electrodes were relatively cheap (~ZAR180 per child) and are readily available. While EIT may be expensive to purchase (~GBP50 000), the maintenance costs are less than other imaging tools such as computed tomography. Although EIT can provide real time information, analysis still needs to be done off line for better data interpretation.

Internationally, work is being done to develop a user-friendly interface where off-line analysis is not necessary.

5.2.6.4 Respiratory muscle activity and regional ventilation distribution

This is the first study to report respiratory muscle activity in different body positions in healthy infants and children. Due to the paucity of similar studies, drawing comparisons is difficult. Following the observation of variable patterns of ventilation distribution in the interim analysis after 56 children, along with the findings of Hutten et al. (2008) who reported that respiratory muscle activity in neonates varied on a breath by breath basis, it was postulated that the variability observed in the distribution of ventilation in the present study, may be accounted for by varying respiratory muscle activity.

Respiratory muscle was also affected by different body positions. In the horizontal and lateral positions, there is cephalad displacement of the dependent diaphragm (Froese & Bryan, 1974) and greater movement and better contraction of the dependent diaphragm have been reported. This was said to occur as a result of the smaller radius of curvature, which according to LaPlace's Law results in greater pressure generated for a given tension (Froese & Bryan, 1974). Furthermore, the force of contraction is augmented by increased resting length (Pengelly, Alderson & Milic-Emili, 1971). It is likely that in addition to the smaller radius, the resting length of the dependent diaphragm is greater due to compression by the abdominal contents. Whether this greater movement or improved contraction may be associated with greater muscle activity is unclear.

Greater activity was seen in the dependent hemi-diaphragms, although this was not statistically significant, this should be confirmed in larger samples. Since sEMG activity more accurately provides information regarding the innervation and electrical activity of the muscles, additional measures of diaphragmatic strength and function, using measures such as ultrasound and maximal inspiratory pressure should also be included in future studies. The association of intercostal muscle activity in right side lying on the proportion of ventilation in the right lung region is difficult to explain and requires further investigation. Given the location of the electrode placement, measurement of intercostal activity may be susceptible to crosstalk particularly from the pectoralis muscles. It is possible, therefore, that this finding may be the result of inaccurate measurements or chance.

The findings in the supine and prone positions were contradictory to the side lying results, where the non-dependent diaphragm showed greater activity, although this was only significant in the prone position. Possible explanations for this observation may be related to chest wall mechanics and abdominal hydrostatic pressures. In the supine position, higher abdominal hydrostatic pressures place increased tension on the dorsal diaphragm and increase the resting length, thereby optimising contraction. Thus, less electrical activity may

be required for effective contraction. In the prone position, the abdominal hydrostatic pressure has less of an effect on the dorsal diaphragm and therefore the resting length may be shorter. Consequently, greater activity may be required to generate the contraction. The finding that dorsal diaphragm activity was associated with a small but significant reduction in the proportion of ventilation in the dorsal lung region is perplexing and difficult to explain. Again, these findings need to be validated in a larger sample, in conjunction with other measures of diaphragm strength and function. Simultaneous measures of diaphragm motion or strength may have value in determining whether respiratory muscle activity and function may account for some of the variability in ventilation distribution.

5.2.6.5 Repeatability and feasibility of sEMG measurements

Repeatability of sEMG measurements in the left side lying position was very poor. The poor repeatability may be partly attributed to the method of filtering cardiac activity. Owing to the proximity of the heart to the electrodes measuring left hemi-diaphragm activity it is possible that a portion of the diaphragmatic muscle activity is also removed during the gating process. Individual differences in respiratory rate and pattern may have also affected repeatability; however, the good repeatability of the right hemi-diaphragm activity, which should have also been affected by breath-by-breath variability, suggests that this is not the case. Very good repeatability was found between all muscle groups in the supine and prone positions with high intra-class correlation co-efficients and relatively small differences and limits of agreement.

sEMG required minimal time to set up and apply the electrodes which are readily available and cheap (~ZAR30 per child). sEMG measurements were well tolerated by the children, however testing during NREM or sedation may help minimise the effect of crosstalk. Similarly, to EIT, data analysis is performed off-line and not readily available at the bedside. In addition, the software used in this study is complex and requires thorough training or good technical support. sEMG is therefore currently not suitable for clinical use at the bedside.

5.2.7 Limitations

There are a number of limitations to this study. Given that this study was performed on awake, spontaneously breathing infants and children, positioning was not absolutely standardised (for example by using wedges and straps to keep the infant/child in an exact, repeatable position), it was however reproducible (Table 4.5.1) between participants. Another major limitation to this study is that the position sequence was not randomised and order effects were not examined. Given that there were seven different positions examined, and children were awake and active, it was felt that an order of convenience would best achieve maximal co-operation and ensure the measurements were completed as quickly as possible. Although the order of position was recorded, the number of different position orders made it difficult to examine the effect of sequence. We did not investigate the effect

of time in a position and this may have influenced the results. It has been suggested that at least 15 minutes is needed to allow the ventilation distribution to "settle" (Caruana et al., 2015). Although in the subgroup of children studied, ventilation distribution was similar between the two measurements taken approximately five minutes apart, whether longer periods of time in the position affect ventilation distribution remains unclear and requires further investigation. The effect of time and order of positions should be examined in future studies, perhaps in separate studies examining side lying positions and supine and prone positions.

The classification of pattern based on the 50% cut-off may have resulted in the overestimation of some patterns, for example if the proportion of ventilation to the dependent lung was 52% that would have been classified as an "adult" pattern for that position. Since there is limited data available in the older paediatric population and that these were healthy children, it was felt that this threshold was appropriate for providing baseline data describing ventilation distribution. Whether there is a clinically meaningful difference in the proportion of ventilation between lung regions will need to be determined in children where ventilation to specific regions and V/Q matching may be compromised.

Differing tidal volumes, EELV and flow rates may provide some explanation for the variability found in this study (Schnidrig et al., 2013). Although, for each position breaths analysed were selected based on similar volumes without pauses, exact reproduction of these breaths was not possible between positions and individuals. Measures of tidal volumes and EELV would have strengthened this study. Despite the standardised criteria for breath selection, this was performed by a single investigator thereby potentially introducing an element of selection bias. Future studies could address this limitation by having two individuals selecting the breaths used for analysis.

Despite being well validated by numerous other methods, EIT only provides information on ventilation distribution for a cross sectional slice of the thorax. This slice covers a thickness of approximately 5cm, which in smaller infants and children would represent a large portion of the lung and when taken at the nipple line is likely to represent the majority of the lung (Bodenstein, David & Markstaller, 2009). A study by Marquis et al. (2006) examined the effect of body habitus on EIT measurement of tidal volume in healthy adult studies. They found that thoracic circumference did not affect the correlation of EIT measurement and lung volume determined by spirometry. Whether chest circumference affects EIT measurements in infants and children has not been examined. Measurement of chest circumference and the effect on ventilation distribution were not examined in this study, and may account for some of the variability found.

The unavoidable interaction between the EIT and sEMG devices did not allow for simultaneous measurement of ventilation distribution and respiratory muscle activity. Although the two measures of EIT and sEMG, taken separately, were repeatable; results describing the interaction between respiratory muscle activity and ventilation distribution need to be interpreted with caution. The gating technique used in the sEMG analysis to remove the activity of the heart, may also affect the quality of the measures obtained, especially in infants and children with higher heart rates, as during the removal of the QRS complex, portions of muscle activity may also be lost. This needs to be addressed in the future development and refinement of sEMG monitoring. Furthermore, sEMG is a measure of excitement and may more accurately represent respiratory drive, rather than strength and function, and results should be interpreted accordingly. Both EIT and sEMG results may have been strengthened by taking readings on a separate day to ensure test-retest reliability, however given the setting of the study and that these were healthy children, having them return on another day was not feasible.

5.2.8 Clinical implications and future research

It is clear from this data that ventilation distribution in older infants and children is variable. When using positioning as a therapeutic modality, position should not be chosen based on the notion that ventilation will always be greatest in the non-dependent lung. In side lying positions, infants may be more likely to follow the paediatric pattern of ventilation. Consistently greater ventilation of the right lung was the predominant pattern observed in side lying positions, with the overall finding showing that the right lung was better ventilated, particularly in left side lying. Differences between ventilation in the left and right lung regions in the side lying positions were most notable in left side lying position across all ages, whereas in right side lying, there was a relatively even distribution in children. This should be considered when using side lying positions to improve ventilation to specific lung regions. Since there appears to be no consistent pattern of ventilation followed, in the absence of EIT measurements at the bedside, position should be chosen based on individual response. This response could be measured by observation of respiratory rate and pattern, work of breathing, auscultation, and monitoring of vital signs. However, the association of these factors with improvements in regional ventilation needs to be examined in future studies.

While contributing to a better understanding of ventilation distribution, this study also highlights important areas for further research. Given the variability observed, these findings should be confirmed in a larger sample. The effect of time in a position and the consequent effect on ventilation distribution should also be examined as well as the effects of respiratory disease and mechanical ventilation in older infants and children.

5.2.9 Conclusions

The novel results of this study indicate that ventilation distribution in healthy, spontaneously breathing infants and children is far more complex than previously thought. These results do not support the premise that all children preferentially ventilate the non-dependent lung regions; rather ventilation distribution is variable amongst infants and children. These results also suggest that ventilation distribution is not significantly affected by head position. Age does not affect ventilation distribution in children, whereas infants tended to show greater ventilation in the non-dependent lung region.

Analysis of regional filling characteristics revealed that the dorsal lung region (in supine and prone positions) and right lung region (in side lying positions) both showed slower initial filling which became faster towards the end of inspiration, indicating possible recruitability, in the respective body positions. While this finding is in keeping with the changes observed in mean relative impedance change, it is contrary to the well-established principle that regional filling is also gravity dependent. These results require further validation.

Respiratory muscle activity appears to have a minimal effect on ventilation distribution; however, these results require further investigation.

This is the first study to report the distribution of ventilation in healthy, spontaneously breathing infants and children of different ages. This data provides a guide for the distribution of ventilation under normal conditions to which future studies in different disease states can be compared. This study also highlights the feasibility and potential utility of EIT in the clinical setting.

5.3 Study Two - The effect of body position on regional ventilation distribution and respiratory muscle activity in mechanically ventilated infants and children

5.3.1 Introduction

It is well established that ventilation is not homogenously distributed during mechanical ventilation. Factors such as the underlying condition(s), the use of paralysis or sedatives, and ventilator settings have the potential to alter the distribution. Literature has consistently shown that where no spontaneous breathing is permitted, ventilation is greatest in the non-dependent lung, whereas where spontaneous breathing or effort is permitted ventilation is greatest in the dependent lung region in adults (Frerichs et al., 1998; Neumann et al., 2005; Riedel, Richards & Schibler, 2005; Humphreys et al., 2011). The latter has not yet been confirmed in children. Recent studies in neonates receiving either IPPV or CPAP have found that distribution of ventilation was no different to spontaneously breathing neonates in the supine and prone positions, with greater ventilation occurring in the dorsal lung regions (Hough et al., 2012; Hough et al., 2013).

In mechanically ventilated infants and children, positioning is an important component of their medical and physiotherapeutic management. Positioning can improve oxygenation with minimal adverse effects, primarily through improved ventilation perfusion matching (Dean, 1985; Gillies, Wells & Bhandari, 2012). Furthermore, changing body position can aid in the mobilisation and clearance of secretions and pressure care. For appropriate positioning to be used in clinical practice, an understanding of how ventilation distribution is affected by position in mechanically ventilated infants and children is important.

5.3.2 Aim

To describe the distribution of ventilation in response to different head and body positions in infants and children receiving invasive mechanical ventilation.

5.3.3 Objectives

- To determine the effect of body position on the regional distribution of ventilation in mechanically ventilated infants and children.
- To determine whether there are age-related differences in regional ventilation distribution.
- To determine whether head position affects regional ventilation distribution in supine and prone positions.
- To determine whether patterns of respiratory muscle activity are associated with the observed patterns of regional ventilation.

5.3.4 Methods

A prospective observational study was conducted in the paediatric intensive care unit (PICU) at RCWMCH, Cape Town, South Africa. Details regarding inclusion and exclusion criteria, study procedure and instruments can be found in Chapter 4.3.1. EIT measurements were taken in all eligible infants/children. Due to only acquiring the sEMG equipment halfway through data collection, sEMG readings were only obtained in the last 10 infants/children. As with the previous study, due to interaction between EIT and sEMG devices, simultaneous measures could not be obtained, therefore EIT measurements were taken first followed by the sEMG measurements. These measurements were repeated twice in each position to ensure reproducibility of the data. Measurements were taken in the following positions:

- Left side lying
- Right side lying
- Supine position with the head
    - in the midline
    - turned to the left
    - turned to the right
- Prone position with the head
    - turned to the left
    - turned to the right.

Additional information recorded at the beginning of the study and monitored throughout included vital signs and ventilatory settings (Appendix 4.1).

Demographic data, regional ventilation and respiratory muscle activity data were tested for normality and not all data was found to be normally distributed, therefore, data are presented as median and interquartile range (IQR) or means ± 95% confidence interval (CI) for ANOVA. Residuals were normally distributed allowing for analysis by ANOVA (Appendix 5.2). Data for left and right side lying positions are presented, followed by the data for supine and prone positions.

The pattern of ventilation; regional distribution of ventilation; the effect of lung disease; global homogeneity indices; filling indices; respiratory muscle activity; and, lastly, the association between respiratory muscle activity and regional distribution of ventilation, are presented for the different positions. Lastly, the comparison with spontaneously breathing healthy infants and children is presented. A plain language summary is presented at the beginning of the results section.

5.3.5 Results

5.3.5.1 Plain language summary of results

Twenty-one mechanically ventilated children were studied. Varying patterns of ventilation were found, with the majority showing consistently greater ventilation of the right lung region in side lying positions and the dorsal lung region ion supine and prone positions. Global ventilation was unaffected by position. Overall, the right lung showed greater ventilation than the left and this was unaffected by position. In supine and prone positions, the non-dependent lung showed greater ventilation in each position, however this was not significant. The right lung showed faster later filling when compared to the left lung, however this was not significant. In the supine and prone positions, the dorsal lung showed faster later filling compared to the ventral lung, this was only significant in the prone position. In mechanically ventilated infants and children, head position and age did not affect ventilation distribution. The global inhomogeneity index was not affected by position in mechanically ventilated infants and children. Respiratory muscle activity was not affect by position in side lying; however, in the supine and prone positions, the ventral diaphragm showed greater activity compared to the dorsal diaphragm. Activity of the left hemi-diaphragm was associated with an increase in ventilation in the left lung, and activity of the dorsal diaphragm was associated with an increase in ventilation in the dorsal lung regions.

5.3.5.2 Demographics

Twenty-one (11 male) infants and children with a median age of 1.28 (0.95 – 2.59) years were studied (Figure 5.3.1 & Table 5.3.1). Most (19, 90%) were receiving pressure controlled synchronised intermittent mandatory ventilation (PC SIMV) and two (10%) were receiving continuous positive airway pressure (CPAP) ventilation via an endotracheal tube or tracheostomy. No children were receiving muscle paralysis during the study. Sixteen (76%) children were receiving some form of sedation at the lowest dose to keep the child comfortable; this resulted in full ventilatory support in only four children (Table 5.3.2). Spontaneous breathing over and above the ventilator breaths occurred in 17 (81%) infants/children, whilst four (19%) showed no spontaneous breathing. Detailed characteristics can be found in Table 5.3.2. As is evident from the ventilator settings children in this study had less severe lung disease and measurements were usually taken towards the end of their course of mechanical ventilation.

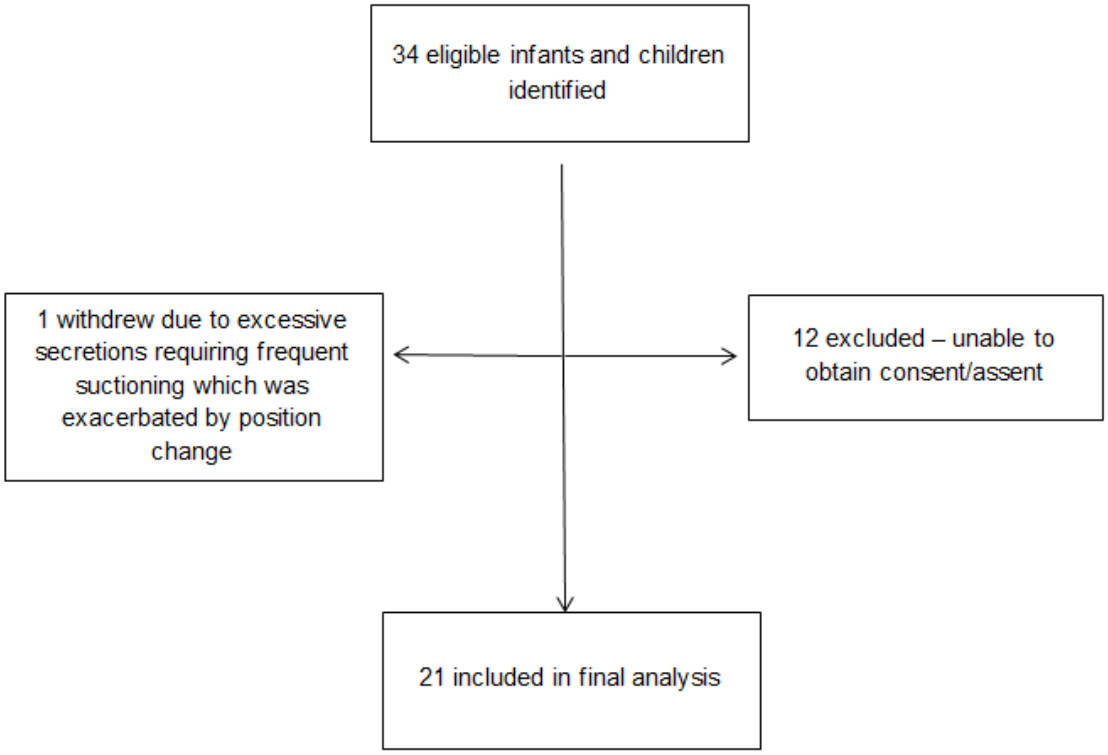


Figure 5.3.1 Flow of participants through study. The decision to withdraw the child was made by the primary investigator and nursing sister looking after the child.

Table 5.3.1 Population characteristics

Age (years)	1.28	(0.95 - 2.59)
Gender:		
Male	11	(52%)
Female	10	(48%)
Ventilator parameters		
Mode		
SIMV PC	19	(90%)
CPAP	2	(10%)
Respiratory rate (breaths per minute)		
Pre-set	25.0	(19.0 - 30.0)
Recorded	33.0	(28.0 - 38.0)
Spontaneous	7.5	(2.0 - 16.0)
MAP	10	(9.0 - 11.5)
PIP	17.0	(14.5 - 19.0)
PEEP	5.0	(5.0 - 6.0)
FiO_2	0.3	(0.3 - 0.35)
Vital signs		
Heart rate (beats per minute)	114.0	(102.0 - 132.0)
Mean arterial blood pressure (mmHg) (n=15)	78.0	(70.0 - 89.0)
Saturation (%)	100.0	(95.0 - 100)

Table 5.3.2 Detailed population characteristics

ID	Age (years)	Gender	Primary Diagnosis	Lung Disease	Mode of Ventilation	Spontaneously breathing	Sedation
1	0.63	female	Severe pneumonia	Bilateral	PC SIMV	Yes	Yes
2	1.14	female	Encephalitis	Bilateral	PC SIMV	No	Yes
3	1.17	female	Bronchiolitis	Unilateral (Right)	PC SIMV	Yes	Yes
4	1.58	female	Organophosphate poisoning	None	PC SIMV	Yes	No
5	0.77	female	Seizures	Bilateral	PC SIMV	No	Yes
6	2.59	male	Guillian-Barre Syndrome (GBS)	Bilateral	PC SIMV	Yes	No
7	1.28	female	Recurrent meningitis, hydrocephalus	Bilateral	PC SIMV	Yes	Yes
8	0.85	female	Severe pneumonia	Bilateral	PC SIMV	Yes	Yes
9	1.11	female	Severe pneumonia	Bilateral	PC SIMV	Yes	Yes
10	1.37	male	Bronchiolitis, reflux	Unilateral (Right)	PC SIMV	Yes	Yes
11	1.52	female	Multi-lobar pneumonia	Bilateral	PC SIMV	Yes	Yes
12	6.78	male	GBS	Unilateral (Left)	CPAP	Yes	No
13	0.63	male	Viral croup	None	PC SIMV	Yes	Yes
14	2.85	male	Bronchopneumonia	Bilateral	PC SIMV	Yes	Yes
15	1.87	female	Pneumonia	Unilateral (Right)	CPAP	Yes	Yes
16	0.50	male	Bronchiolitis	Bilateral	PC SIMV	Yes	Yes
17	5.52	male	Bronchopneumonia	Bilateral	PC SIMV	Yes	Yes
18	1.02	male	Severe pneumonia	Bilateral	PC SIMV	Yes	Yes
19	4.45	male	Myasthenia gravis, LRTI	Bilateral	PC SIMV	No	No
20	4.27	male	Leucoencephaly, LRTI	Bilateral	PC SIMV	No	No
21	0.95	male	ARDS	Bilateral	PC SIMV	Yes	Yes

LRTI – lower respiratory tract infection; PC SIMV – pressure controlled synchronised intermittent mandatory ventilation; CPAP continuous positive airway pressure

5.3.5.3 Side lying positions

Complete measurements were obtained in all 21 infants and children in left and right side lying positions.

5.3.5.3.1 Pattern followed

The “paediatric pattern”, of consistently greater ventilation in the non-dependent lung region, was observed in three (14%) of the infants and children. A similar number of infants and children (3, 14%) showed consistently greater ventilation of the dependent lung regions (“adult pattern”). The majority (11, 53%) of infants and children demonstrated consistently greater ventilation of the right lung in both left and right side lying positions, while the remaining four (19%) showed consistently greater ventilation of the left lung (Figure 5.3.2). The age of the child, grouped by those younger than 12 months and those older than 12 months, did not predict the pattern followed (Table 5.3.3).

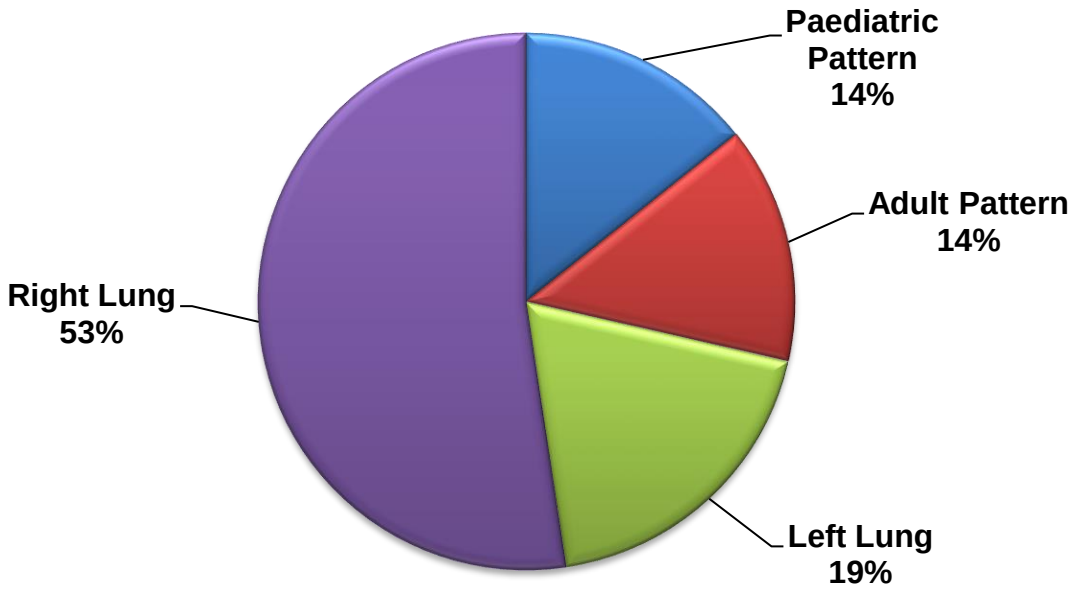


Figure 5.3.2 Proportion of infants and children demonstrating consistently greater ventilation in the non-dependent lung (“paediatric pattern”), dependent lung (“adult pattern”), right lung region, and left lung region in the side lying positions.

Table 5.3.3 Association between patterns followed and age in side lying positions

Pattern	Age	Odds Ratio	95% Confidence interval		p-value
			Lower	Upper	
Left	<12 months	2.67	0.25	28.44	0.42
Paediatric	<12 months	1.33	0.09	20.71	0.84

Right is reference category. No children (n=6) followed an adult pattern, therefore was removed from the model.

5.3.5.3.2 Regional Ventilation Distribution

Global ventilation was unaffected by position (p=0.55). Ventilation was unaffected by position change within and between left and right lung regions (Table 5.3.4). No significant interaction between the effects of lung region and position on mean relative impedance change was found (Figure 5.3.3).

Table 5.3.4 Mean relative impedance change, filling indices and global inhomogeneity indices in the side lying positions presented as medians and IQR

	Left side lying	Right side lying
Left lung region		
∆Z	10.92 (8.39 – 16.21)	9.25 (4.81 – 13.58)
Filling index	0.82 (0.77 – 1.12)	0.83 (0.66 – 0.88)
Right lung region		
∆Z	11.53 (9.00 – 20.48)	12.01 (9.19 – 19.85)
Filling index	0.96 (0.66 – 1.01)	0.96 (0.90 – 1.12)
Global ∆Z	24.35 (15.18 – 37.89)	21.76 (15.49 – 31.94)
GI	0.89 (0.86 – 1.06)	0.92 (0.83 – 1.06)

5.3.5.3.2.1 The effect of disease pattern on ventilation distribution

The majority of the infants/children had bilateral lung disease (15, 71%). No significant interaction was found between the effects of type of lung disease (unilateral, bilateral or none) and position (dependent or non-dependent) on the proportion of ventilation occurring in the left lung region ($F_{(2, 18)}$=1.81, p=0.19) and right lung region ($F_{(2, 18)}$=1.81, p=0.19) respectively.

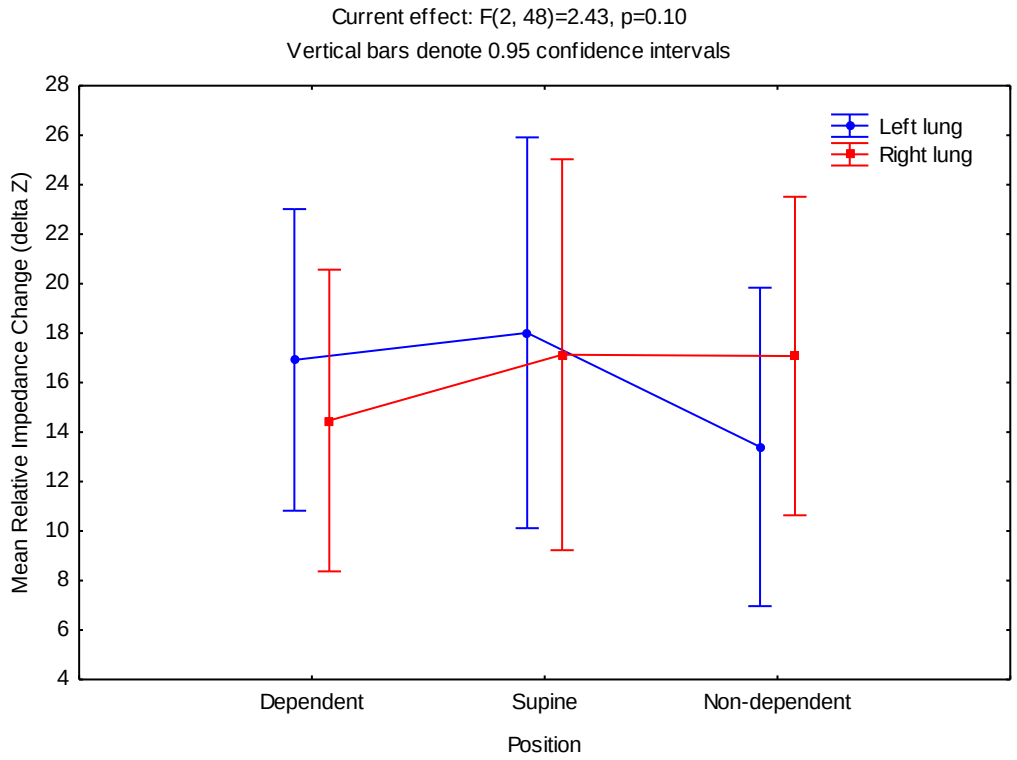


Figure 5.3.3 Ventilation (mean relative impedance change) in the left and right lung regions when dependent, non-dependent or supine (neutral) positions.

5.3.5.3.3 Global inhomogeneity index

The GI index was similar in left and right side lying positions (p=0.69) (Table 5.3.4).

5.3.5.3.4 Regional filling

Regional filling was unaffected by position change (Table 5.3.4). The interaction between the effects of lung region and position on filling index was not significant (p=1.00) (Figure 5.3.4). No differences were found in regional filling between left and right lung regions when each lung was in the dependent (p=0.08) and non-dependent (0.08) positions.

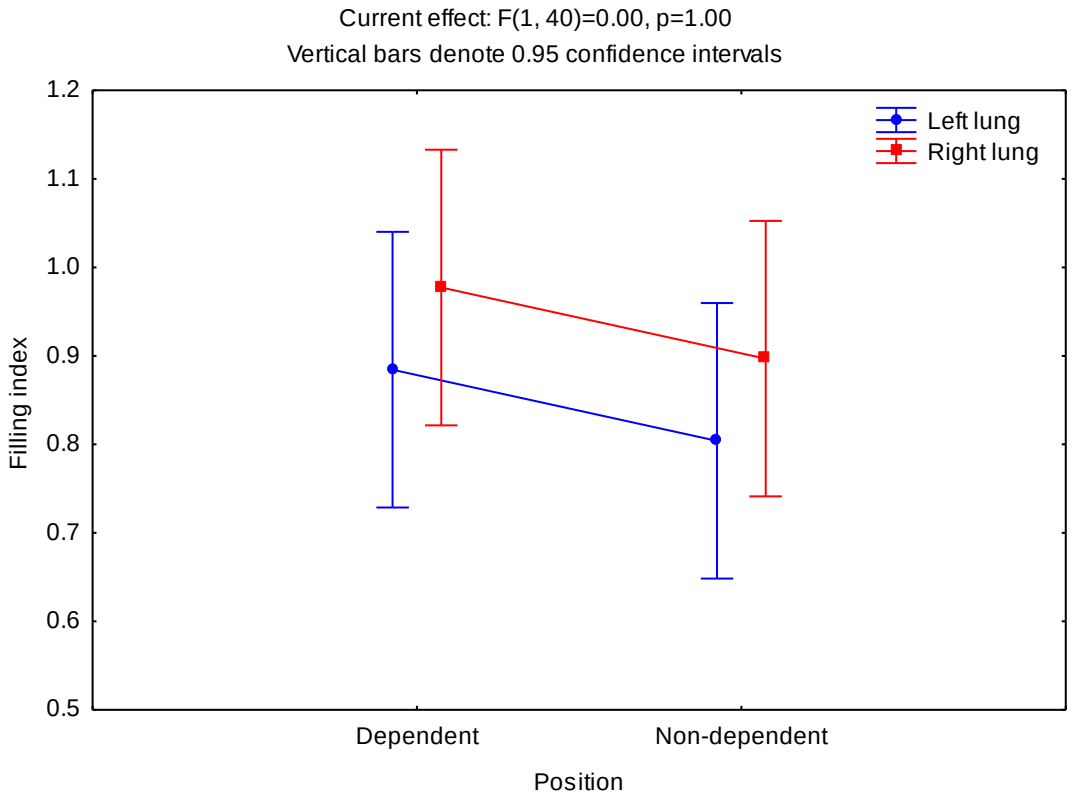


Figure 5.3.4 Filling indices in left and right lung regions when in either the dependent or non-dependent position.

5.3.5.3.5 Repeatability of EIT measurements

There were no significant interactions in either the left (p=0.39, Figure 5.3.5) or right (p=0.54, Figure 5.3.6) lung regions between the effects of measurement number and body position. Excellent agreement was found between the two measurements in the left, right and global lung regions in the side lying positions as shown by the high intra-class correlation co-efficients in Table 5.3.5.

Table 5.3.5 The intra-class correlation co-efficients (ICC), mean differences and limits of agreement between the two measurements in side lying positions.

Position	Lung region	ICC	95% CI	p-value	Mean difference	Limits of agreement
Left side lying	Left	0.98	0.92 - 0.99	<0.001	-1.77	-7.43 – 3.89
	Right	0.97	0.91 - 0.99	<0.001	-1.13	-8.10 – 5.83
	Global	0.98	0.92 - 0.99	<0.001	-2.90	-14.09 - 8.29
Right side lying	Left	0.96	0.88 - 0.99	<0.001	0.94	-6.76 – 8.64
	Right	0.97	0.92 - 0.99	<0.001	-1.08	-6.64 – 4.47
	Global	0.98	0.94 - 0.99	<0.001	-0.14	-9.76 – 9.47

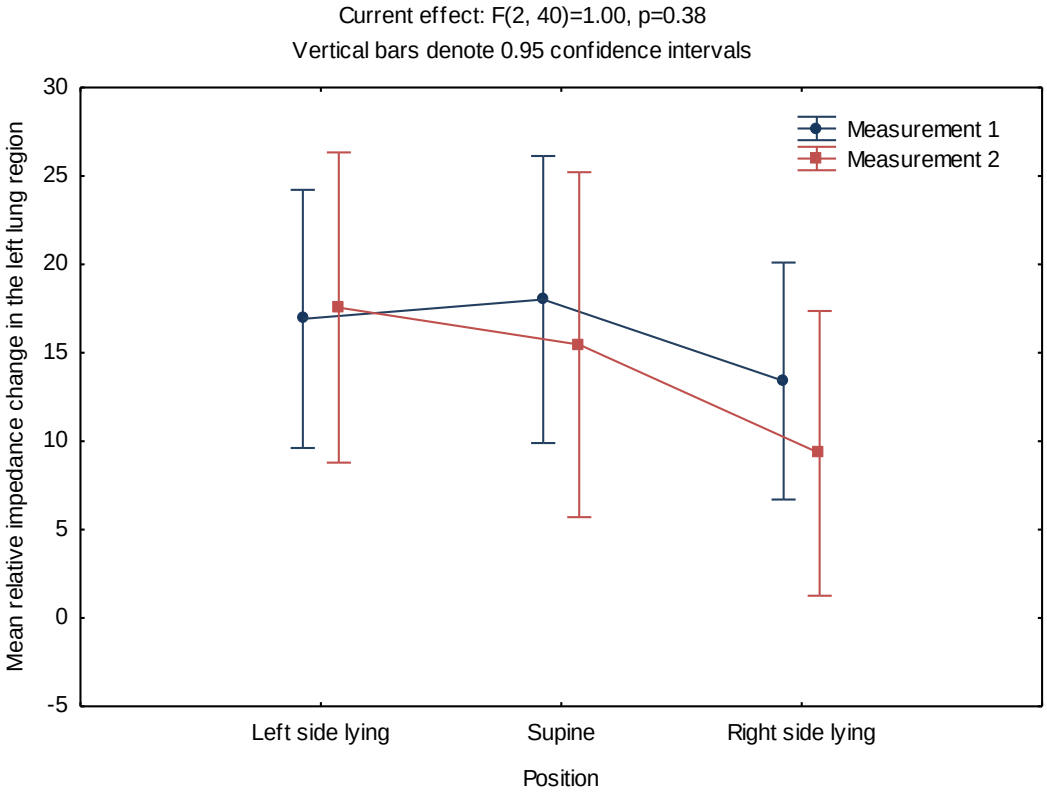


Figure 5.3.5 Mean relative impedance change in the left lung region in different positions between measurement one and two.

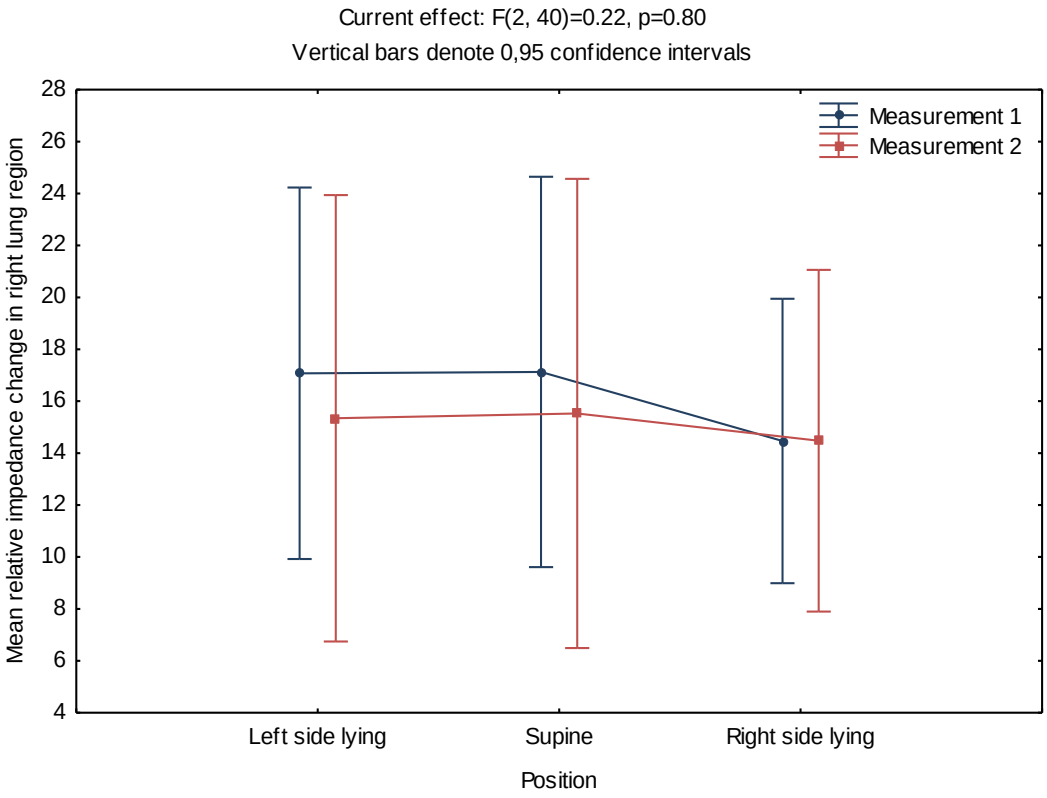


Figure 5.3.6 Mean relative impedance change in the right lung region in different positions between measurement one and two.

5.3.5.3.6 Regional ventilation and respiratory muscle activity

5.3.5.3.6.1 Respiratory muscle activity

Respiratory muscle activity was unaffected by position (Table 5.3.6). Muscle activity in both hemi-diaphragms was similar when each was in the dependent and non-dependent position (Figure 5.3.7).

Table 5.3.6 Mean muscle activity (μV) in side lying positions presented as medians and IQR

	Left side lying (n=10)	**Right side lying (n=10)**	**p-value [a]**
Left hemi-diaphragm	2.35 (1.49 – 3.09)	2.28 (1.82 – 3.28)	0.85
Right hemi-diaphragm	2.03 (1.54 – 3.36)	2.88 (1.91 – 3.49)	0.36
Intercostals	1.12 (0.00 – 4.69)	0.86 (0.00 – 3.45)	0.91

[a] between positions. p=0.91 between left and right hemi-diaphragms in left side lying. p=0.68 between left and right hemi-diaphragms in right side lying.

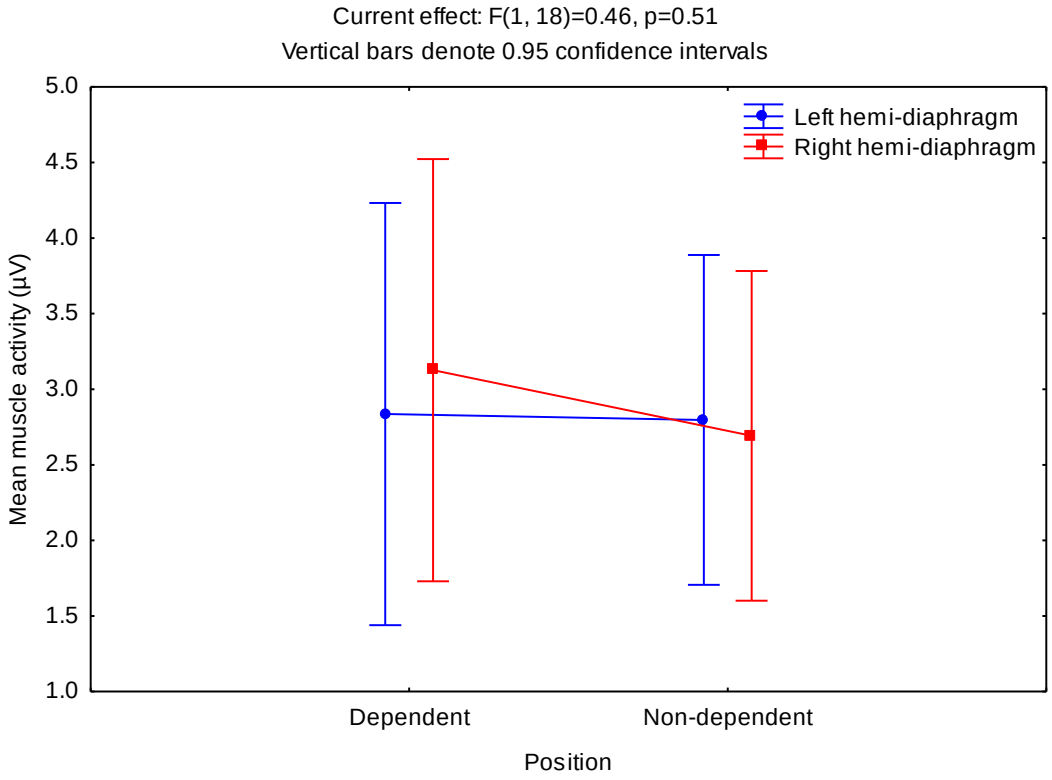


Figure 5.3.7 Mean activity of the left and right hemi-diaphragm when in the dependent or non-dependent in the side lying positions.

5.3.5.3.6.2 Repeatability of sEMG readings

No significant interactions were found between the effects of measurement number and body position on both left hemi-diaphragm activity ($F_{(1, 14)}$=2.62, p=0.13) and right hemi-

diaphragm activity ($F_{(1, 14)}$=0.33, p=0.57). Good agreement was found between measurement one and two for the intercostal muscles and left and right hemi-diaphragms as depicted in Table 5.3.7.

Table 5.3.7 The intra-class correlation co-efficients (ICC), mean differences and limits of agreement for respiratory muscle activity between the two measurements in side lying positions

Position	Muscle	ICC	95% CI	p-value	Mean difference	Limits of agreement
Left side lying	Intercostals	0.98	0.92 - 1.00	<0.01	2.26	-8.97 - 13.49
	Left Hemi-diaphragm	0.88	0.37 - 0.98	0.01	1.17	-4.42 - 6.75
	Right Hemi-diaphragm	0.84	0.28 - 0.97	0.01	1.01	-2.56 - 4.58
Right side lying	Intercostals	1.00	1.00 - 1.00	<0.01	0.69	-0.67 - 2.05
	Left Hemi-diaphragm	0.75	-0.41 - 0.96	0.07	0.28	-3.99 - 4.54
	Right Hemi-diaphragm	0.88	-0.41 - 0.97	0.01	1.43	-2.35 - 5.21

5.3.5.3.6.3 Interaction between regional ventilation distribution and respiratory muscle activity

Increased activity of the left hemi-diaphragm was associated with an increase in the proportion of ventilation in the left lung region (p<0.001) (Table 5.3.8). No association of muscle activity on the proportion of ventilation occurring in the right lung region was found (Table 5.3.9).

Table 5.3.8 Interaction between intercostals and left hemi-diaphragm activity and the proportion of ventilation in the left lung region in side lying positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	-7.29	-20.32	5.74	0.24
Intercostals	0.09	-0.22	0.40	0.55
Left Hemi-diaphragm	12.31	8.56	16.06	0<01

Table 5.3.9 Interaction between intercostals and right hemi-diaphragm activity and the proportion of ventilation in the right lung region in side lying positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	31.88	12.57	51.20	0<01
Intercostals	-0.06	-0.68	0.58	0.85
Right Hemi-diaphragm	0.52	-4.38	5.42	0.86

5.3.5.4 Supine-Prone positions

Complete measurements were obtained in both supine and prone positions in 13 infants and children. Incomplete measurements were either due to recently inserted tracheostomies (day 0 or 1 post insertion) or the child refusing to turn into the prone position.

5.3.5.4.1 Pattern followed

The "paediatric pattern" was consistently observed in two (16%) of the infants/children (Figure 5.3.8). Two (15%) infants/children consistently demonstrated the "adult pattern". Three (23%) infants/children showed consistently greater ventilation in the ventral lung region, while the majority (6, 46%) of infants/children showed greater ventilation of the dorsal lung region in both supine and prone positions. Owing to the small number of infants and children examined in the supine and prone position, we were not able to determine whether infants were more likely to follow a specific pattern.

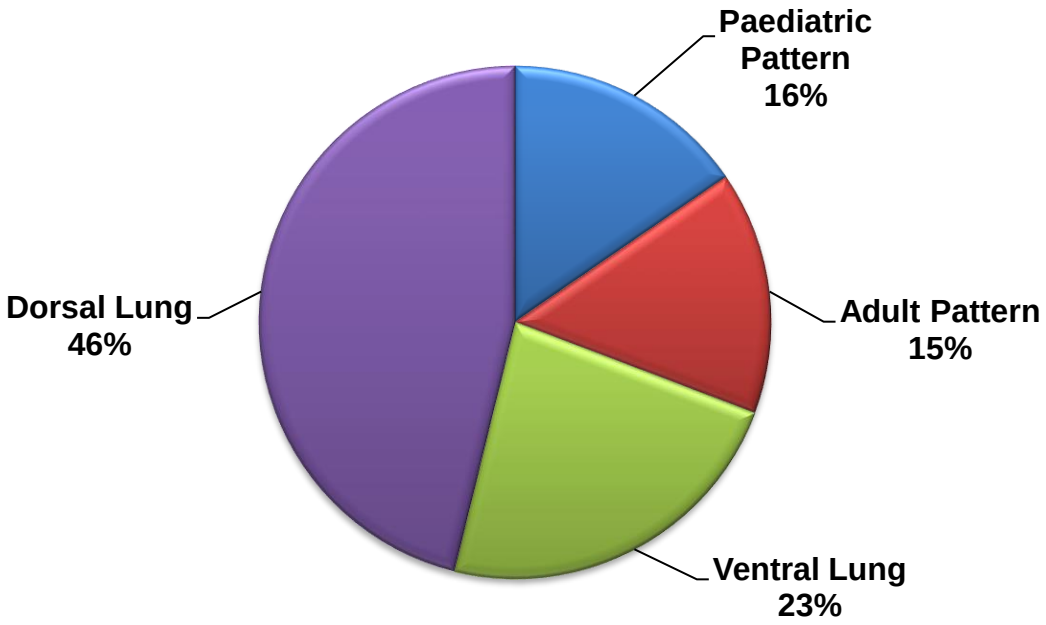


Figure 5.3.8 Proportion of infants and children demonstrating consistently greater ventilation in the non-dependent lung ("paediatric pattern"), dependent lung ("adult pattern"), ventral lung region, and dorsal lung region in the supine and prone positions.

5.3.5.4.2 Regional ventilation distribution

Global ventilation and regional ventilation was unaffected by position (p=0.44) (Table 5.3.10). Ventilation was similar within the ventral (p=0.28) and dorsal (p=0.86) lung regions in supine and prone positions. No significant differences were found between ventral and dorsal lung regions in the supine (p=0.86) or prone (p=0.19) positions. There was no significant interaction between the effects of lung region and position on mean relative impedance change in the supine and prone positions (Figure 5.3.9)

Table 5.3.10 Mean relative impedance change, filling indices and global inhomogeneity indices in supine and prone positions presented as medians and IQR

	Supine position	Prone position
Ventral lung		
ΔZ	16.44 (7.84 – 24.13)	9.79 (6.39 – 17.70)
Filling index	0.85 (0.76 – 1.01)	0.80 (0.66 – 0.93) *
Dorsal lung		
ΔZ	11.94 (10.53 – 19-47)	12.39 (10.19 – 18.85)
Filling index	0.93 (0.68 – 1.02)	0.98 (0.85 – 1.12)
Global ΔZ	27.90 (18.47 – 23.28)	21.81 (17.19 – 38.52)
GI	0.87 (0.85 – 1.04)	0.93 (0.82 – 0.94)

* p=0.007 between ventral and dorsal lung regions in the prone position. p=0.28 within the ventral lung region between positions; p=0.86 within the dorsal lung region between positions; p=0.86 between ventral and dorsal lung regions in the supine position; p=0.19 between ventral and dorsal lung regions in the prone position.

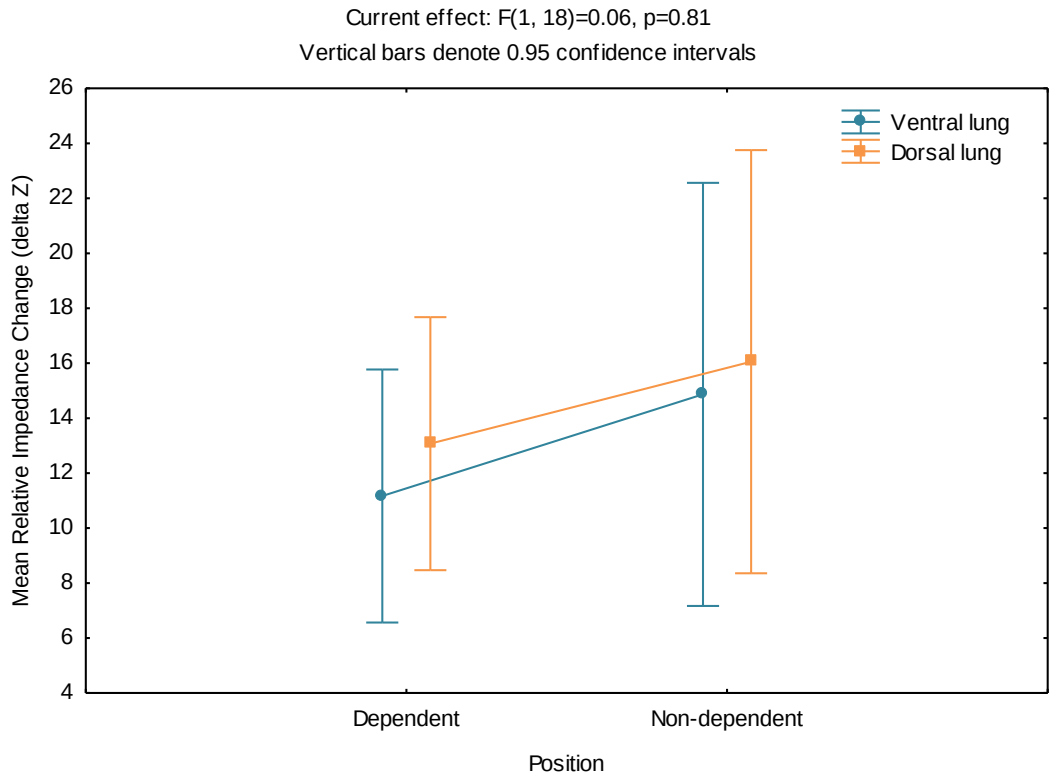


Figure 5.3.9 Ventilation (mean relative impedance change) in the ventral and dorsal lung regions when in the dependent and non-dependent positions.

5.3.5.4.2.1 The effect of disease pattern on regional ventilation distribution

The interaction between the effects of disease pattern seen on the chest radiograph and position and the proportion of ventilation in either the ventral ($F_{(1, 7)}$=0.01, p=0.99) or dorsal ($F_{(1, 7)}$=0.01, p=0.99) lung regions in the supine and prone positions was not significant.

5.3.5.4.3 Global inhomogeneity index

No significant difference in ventilation homogeneity was found between supine and prone positions (p=0.80) (Table 5.3.10).

5.3.5.4.4 Regional filling

Regional filling within the ventral (p=0.19) and dorsal (p=0.19) lung regions was unaffected by position (Table 5.3.10). Supine position did not affect regional filling, however in the prone position, the dorsal lung region had a significantly higher filling index than the ventral lung (p=0.007). The interaction between the effects of lung region and position (dependent and non-dependent) and filling index in the supine and prone positions was not significant (Figure 5.3.10).

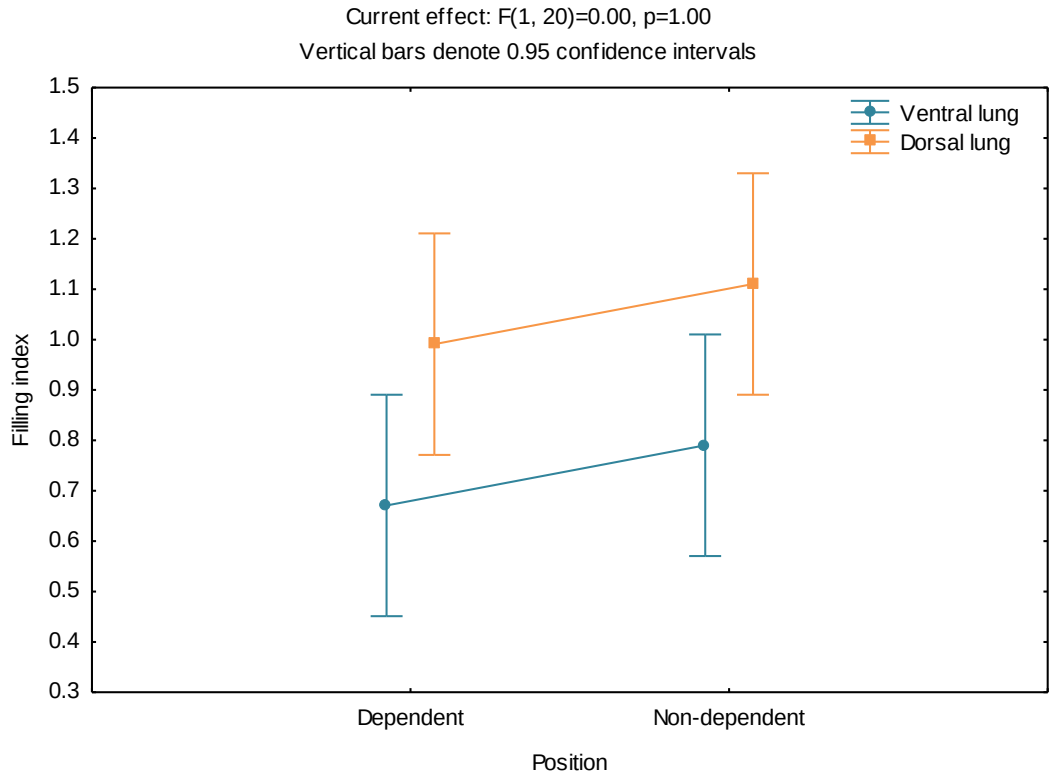


Figure 5.3.10 Filling indices in the ventral and dorsal lung regions in the dependent or non-dependent positions. The difference between ventral and dorsal lung regions was not significant in either position (p=0.12).

5.3.5.4.5 Head position

Head position had no effect on ventilation distribution in the supine and prone positions (Table 5.3.11).

Table 5.3.11 Mean relative impedance change in the left, right, ventral and dorsal lung regions with different head positions in supine and prone positions

	Left Lung	**Right Lung**	**p-value**
SM (n=13)	14.87 (5.78 – 23.43)	17.16 (5.30 – 25.49)	0.96
SL (n=17)	9.53 (6.73 – 18.89)	17.18 (12.09 – 21.18)	0.16
SR (n=19)	15.87 (7.33 – 21.32)	16.24 (8.97 – 25.88)	0.98
PL (n=6)	15.38 (10.85 – 16.98)	14.90 (9.07 – 23.37)	0.94
PR (n=11)	11.84 (6.40 – 19.58)	14.35 (9.68 – 18.37)	0.55

SM – supine head in midline; SL – supine head to left; SR – supine head to right; PL – prone head to left; PR – prone head to right.

5.3.5.4.6 Repeatability of EIT measurements

Ventilation was similar between measurements one and two. No significant interaction between the effects of measurement number and position on regional ventilation in the ventral (p=0.62) (Figure 5.3.11) and dorsal (p=0.12) (Figure 5.3.12) lung regions was found. Good agreement was found between the repeated measures in all lung regions in the supine position, and in the ventral and global lung regions in the prone position (Table 5.3.12). Acceptable agreement was found between the measurements for the dorsal lung region in the prone position (Table 5.3.12).

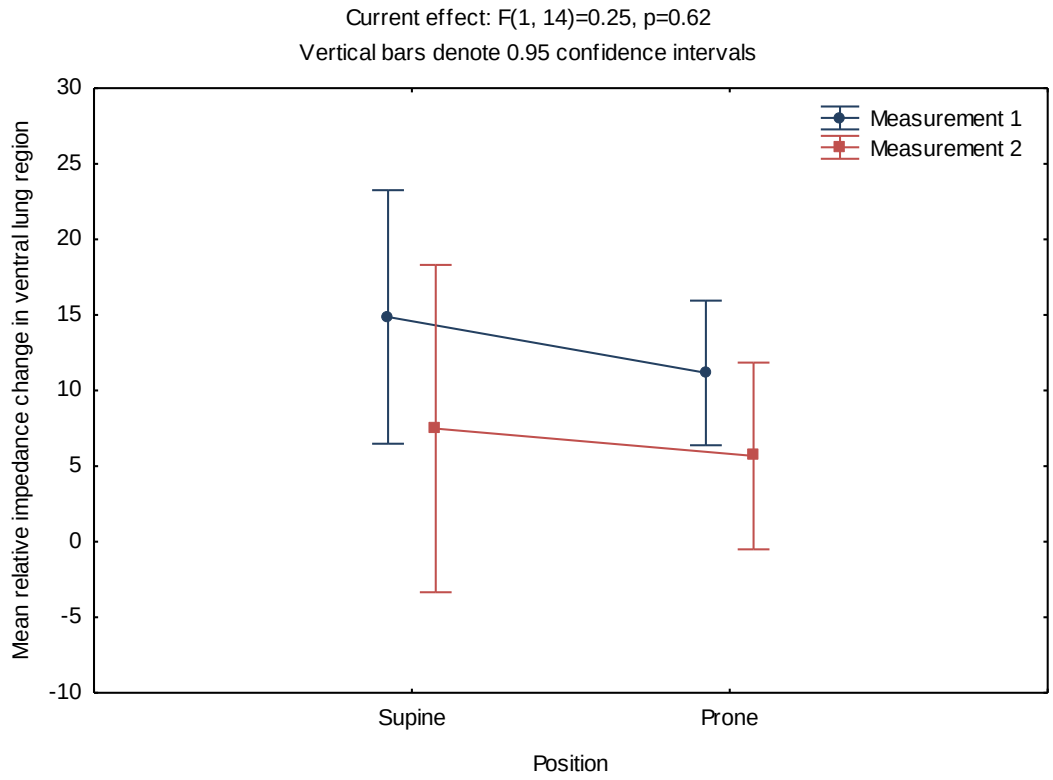


Figure 5.3.11 Mean relative impedance change in the ventral lung region between measurement one and two.

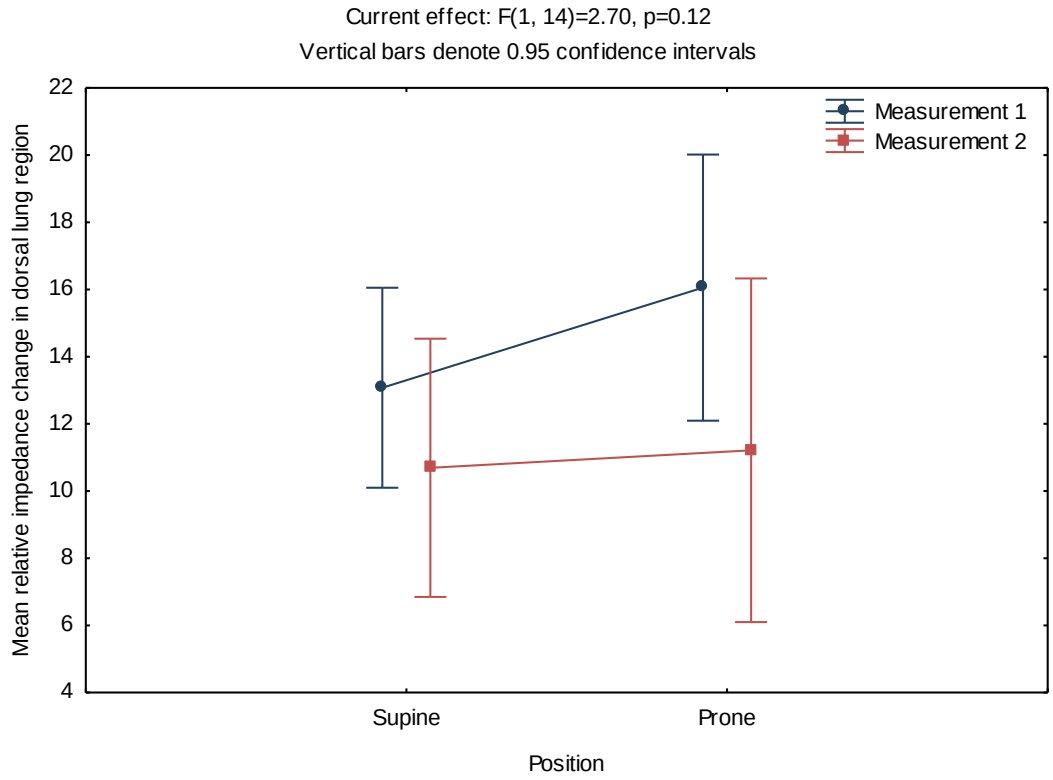


Figure 5.3.12 Mean relative impedance change in the dorsal lung regions between measurements one and two.

Table 5.3.12 The intra-class correlation co-efficients (ICC), mean differences and limits of agreement between the two EIT measurements in the supine and prone positions

Position	Lung region	ICC	95% CI	p-value	Mean difference	Limits of agreement
Supine	Ventral	0.98	0.95 - 1.00	<0.001	0.68	-13.23 - 14.95
	Dorsal	0.97	0.91 - 0.99	<0.001	2.28	-13.32 - 17.89
	Global	0.98	0.94 - 0.99	<0.001	2.96	-25.85 - 31.78
Prone	Ventral	0.99	0.94 - 1.00	<0.001	0.50	-1.40 - 2.41
	Dorsal	0.59	-1.55 - 0.94	0.19	0.24	-5.66 - 6.15
	Global	0.87	-0.12 - 0.99	0.05	0.75	-5.15 - 6.65

5.3.5.4.7 Regional ventilation distribution and respiratory muscle activity

5.3.5.4.7.1 Respiratory muscle activity

Significantly greater activity was found in the ventral hemi-diaphragm compared to the dorsal hemi-diaphragm in both supine and prone positions (p=0.04) (Table 5.3.13). No significant interaction between the effects of respiratory muscle (ventral or dorsal hemi-diaphragm) and body position on muscle activity was found (Figure 5.3.13).

Table 5.3.13 Mean muscle activity (μV) in the supine and prone positions presented as medians and IQR

	Supine position (n=7)	Prone position (n=5)	p-value [a]
Ventral hemi-diaphragm	2.71 (2.30 – 6.09) *	1.96 (1.88 – 2.66) *	0.26
Dorsal hemi-diaphragm	1.54 (0.69 – 2.20)	1.10 (0.70 – 1.59)	0.52
Intercostals	1.64 (0.00 – 19.21)	1.56 (0.00 – 1.95)	0.21

[a] between supine and prone positions. * p=0.04 between ventral and dorsal diaphragm in both supine and prone positions.

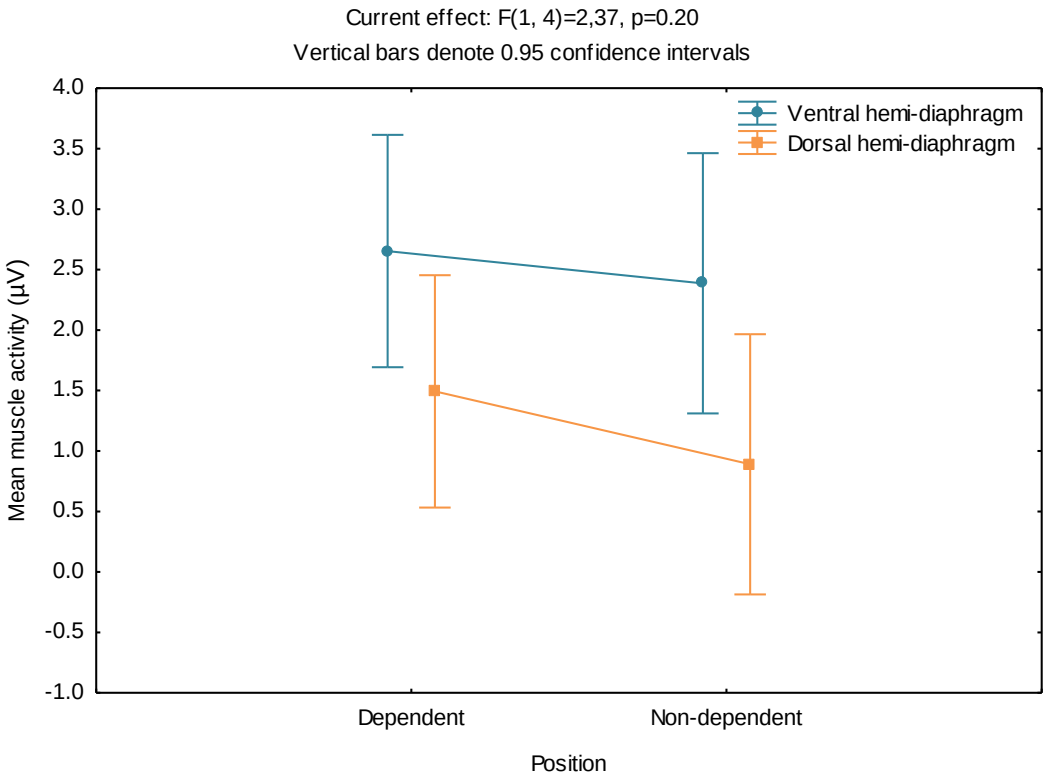


Figure 5.3.13 Mean muscle activity of ventral and dorsal hemi-diaphragms when in the dependent and non-dependent positions.

5.3.5.4.7.2 Repeatability of sEMG measurements

No significant interaction was found between the effects of measurement number and body position on activity of the ventral hemi-diaphragm ($F_{(1, 4)}$=0.29, p=0.62). A significant interaction was found between the effects of measurement number and body position on dorsal diaphragm activity ($F_{(1, 4)}$=10.55, p=0.03). Agreement between measurement one and two was very good for all muscles in the supine and prone positions as seen in Table 5.3.14.

Table 5.3.14 The intraclass correlation coefficients, mean difference and limits of agreement between the two sEMG measurements in the supine and prone positions

Position	Muscle	ICC	95% CI	p-value	Mean difference	Limits of agreement
Supine	Intercostals	1.00	0.97 - 1.00	<0.001	0.63	-7.75 - 9.02
	Ventral Hemi-diaphragm	1.00	0.99 - 1.00	<0.001	0.12	-1.19 - 1.43
	Dorsal Hemi-diaphragm	0.92	0.29 - 0.99	<0.01	0.35	-0.37 - 1.08
Prone	Intercostals	0.94	0.97 - 0.99	0.01	0.74	-4.31 - 5.79
	Ventral Hemi-diaphragm	0.97	0.75 - 1.00	<0.01	0.18	-0.33 - 0.69
	Dorsal Hemi-diaphragm	0.71	-0.52 - 0.97	0.09	0.43	-0.67 - 1.54

5.3.5.4.7.3 Interaction between regional ventilation distribution and respiratory muscle activity

Activity of the intercostals and ventral hemi-diaphragm was not associated with the proportion of ventilation occurring in the ventral lung region (Table 5.3.15). Dorsal hemi-diaphragm activity was associated with an increase in the proportion of ventilation in the dorsal lung region (p=0.04) (Table 5.3.16).

Table 5.3.15 Interaction between intercostal and ventral hemi-diaphragm activity and the proportion of ventilation in the ventral lung region in supine and prone positions

	Coefficient Estimate	**95% Confidence interval**		**p-value**
		Lower	Upper	
Intercept	30.33	-3.36	64.03	0.07
Intercostals	-0.01	-1.12	1.10	0.98
Ventral Hemi-diaphragm	1.16	-2.85	5.17	0.53

Table 5.3.16 Interaction between intercostal and dorsal hemi-diaphragm activity and proportion of ventilation in the dorsal lung region in supine and prone positions

	Coefficient Estimate	**95% Confidence interval**		**p-value**
		Lower	Upper	
Intercept	18.84	3.93	33.76	0.01
Intercostals	0.04	-0.47	0.56	0.86
Dorsal Hemi-diaphragm	8.51	0.61	16.41	0.04

5.3.5.5 Differences in regional ventilation compared to spontaneously breathing children

5.3.5.5.1 Side lying positions

The patterns consistently followed by infants differed between those who were spontaneously breathing and those who were mechanically ventilated. Although not significant, a greater number of spontaneously breathing infants followed the paediatric pattern, while the left and right patterns were predominantly followed by the mechanically ventilated infants (Figure 5.3.14). Patterns consistently followed by infants and children were similar between those who were spontaneously breathing and those receiving mechanical ventilation. Majority of infants and children in both groups demonstrated consistently greater ventilation of the right lung in both side lying positions (Figure 5.3.14).

5.3.5.5.1.1 Mean relative impedance change and regional filling characteristics

The interaction between the effects of ventilation type (spontaneous or mechanically ventilated) and body position on mean relative impedance change was not significant in either the left (Figure 5.3.15) or right (Figure 5.3.16) lung regions.

Regional filling was similar between mechanically ventilated and spontaneously breathing infants and children in the left (Figure 5.3.17) and right (Figure 5.3.18) lung regions, with higher filling indices in the dependent lung regions in side lying positions.

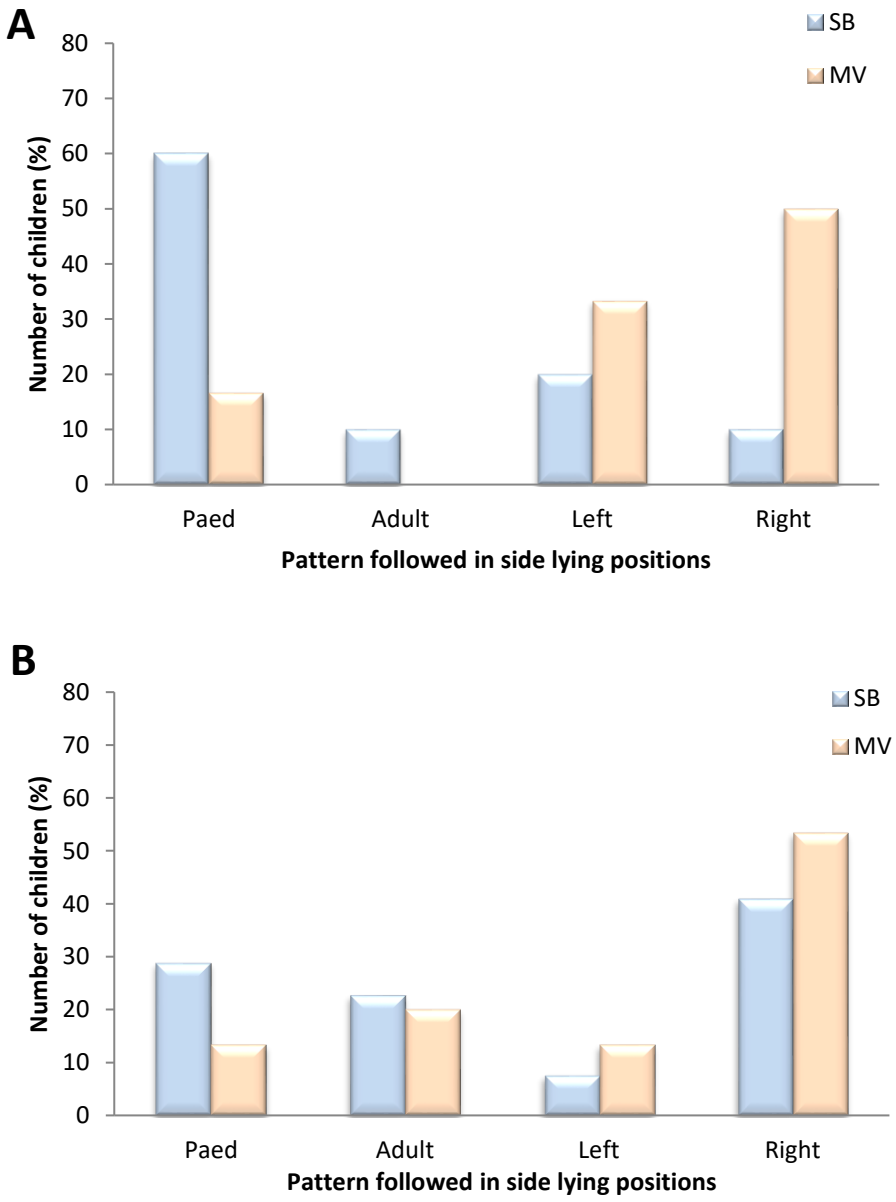


Figure 5.3.14 The pattern of ventilation followed in the side lying positions in spontaneously breathing (SB) and mechanically ventilated (MV) infants and children (A) infants and (B) children. No significant differences between SB and MV children in A: p=0.09 paediatric pattern, p=0.42 adult pattern, p=0.56 left pattern, p=0.07 right pattern; and B: p=0.20 paediatric pattern, p=0.80 adult pattern, p=0.54 left pattern, and p=0.40 right pattern.

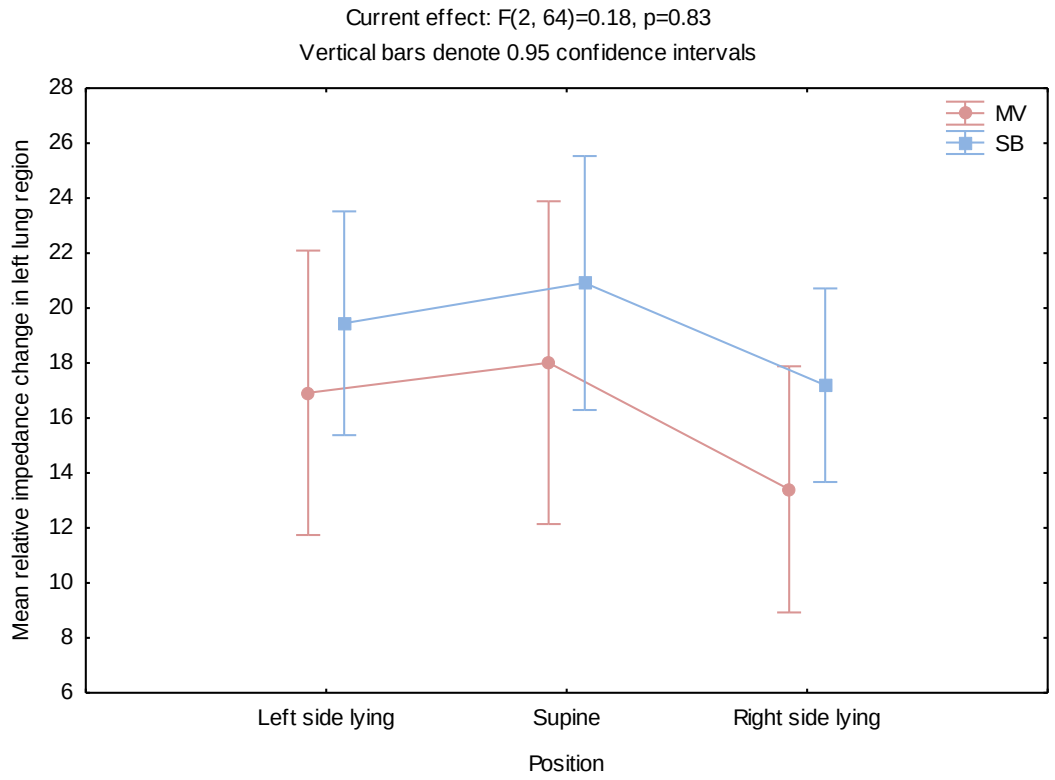


Figure 5.3.15 Mean relative impedance change in left lung in spontaneously breathing and mechanically ventilated infants and children in side lying positions.

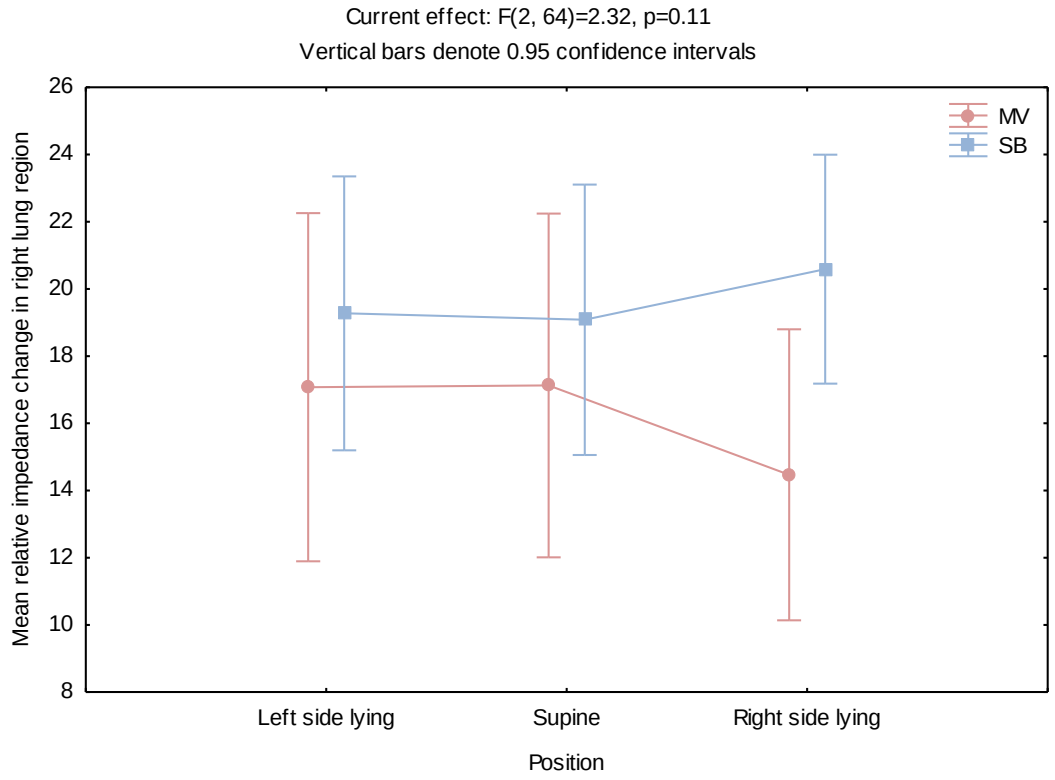


Figure 5.3.16 Mean relative impedance change in left lung in spontaneously breathing and mechanically ventilated infants and children in side lying positions.

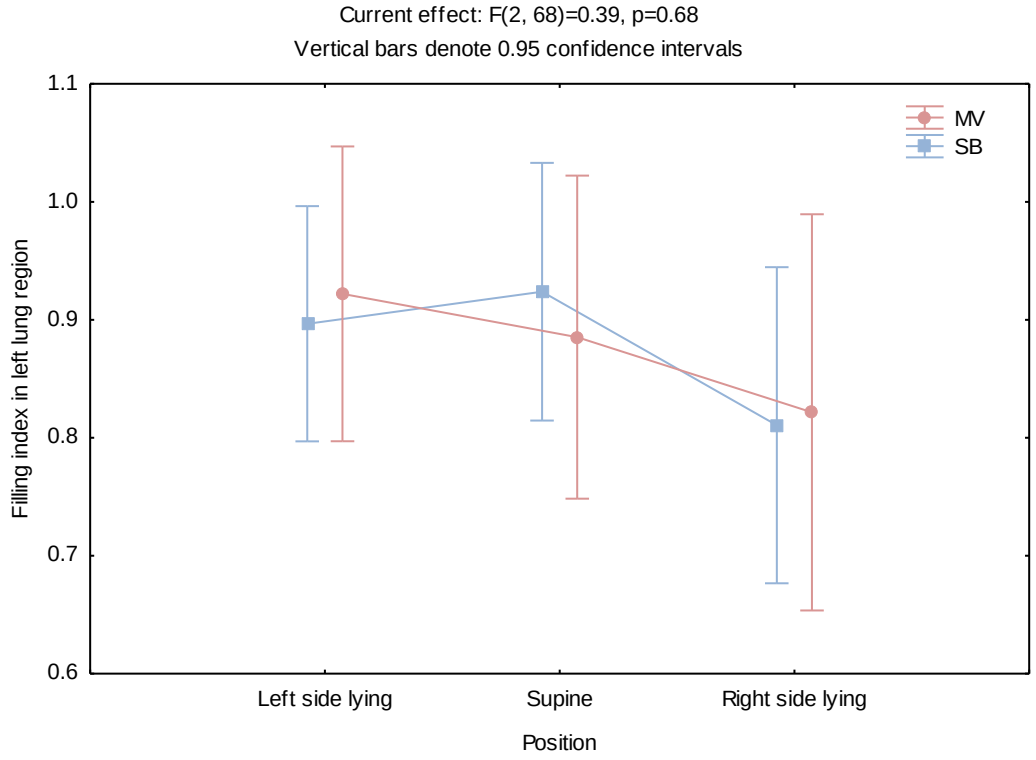


Figure 5.3.17 Filling indices in the left lung region in side lying positions in spontaneously breathing (SB) and mechanically ventilated (MV) infants/children.

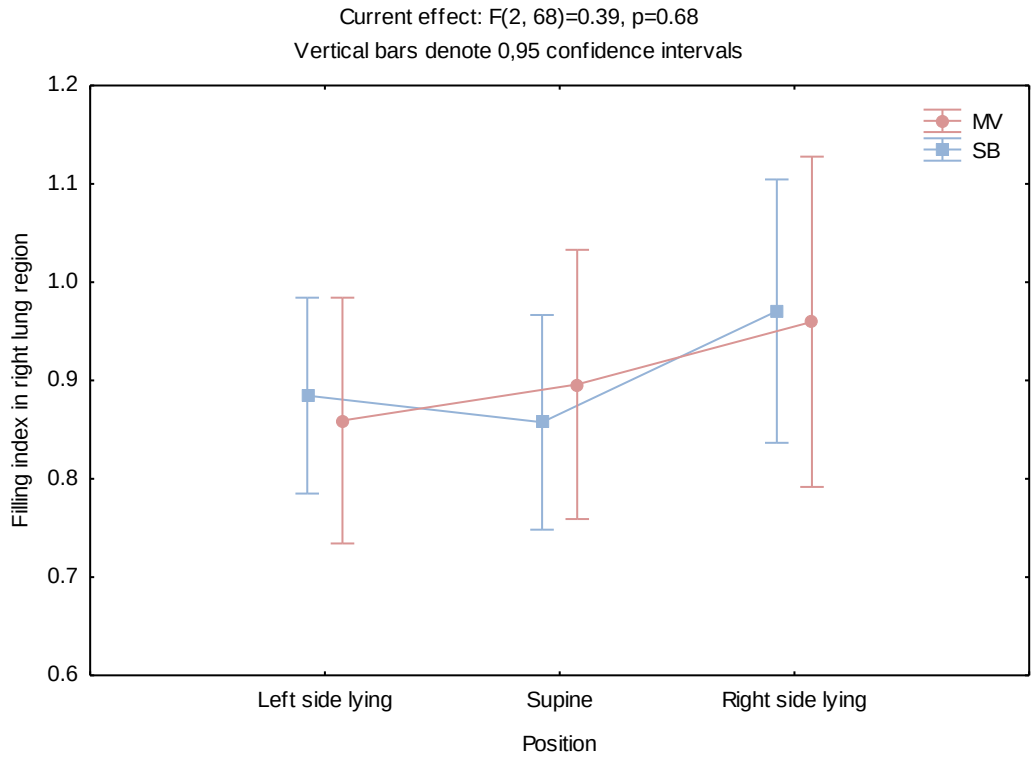


Figure 5.3.18 Filling indices in the right lung region in side lying positions in spontaneously breathing (SB) and mechanically ventilated (MV) infants/children.

5.3.5.5.2 Supine and prone positions

Consistently better ventilation of the dorsal lung region was the predominant pattern in both spontaneously breathing and mechanically ventilated infants and children (Figure 5.3.19). No paediatric or adult pattern of ventilation was consistently observed in infants who were mechanically ventilated. A relatively even distribution of patterns was followed by children who were mechanically ventilated, with significantly fewer following the dorsal pattern compared to those who were spontaneously breathing (p=0.01, Figure 5.3.19).

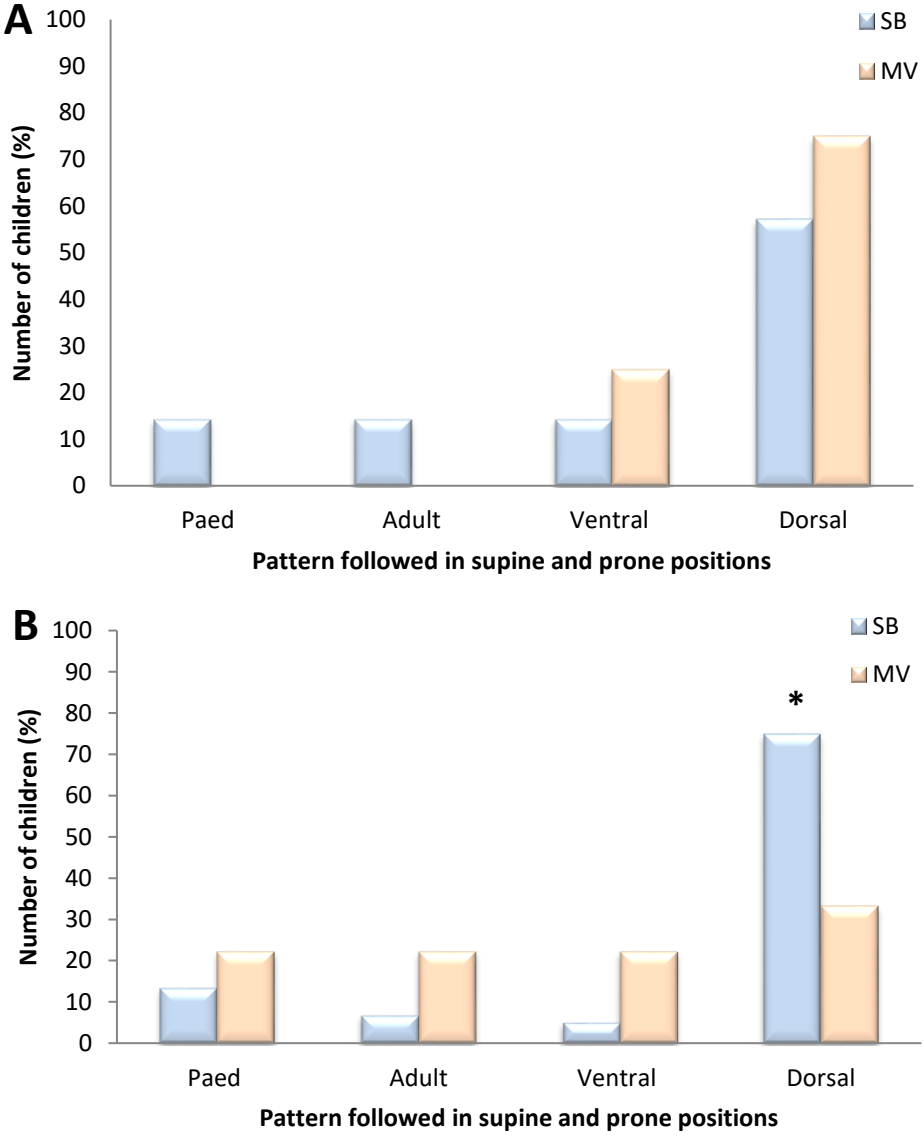


Figure 5.3.19 The pattern of ventilation followed in the supine and prone positions in spontaneously breathing (SB) and mechanically ventilated (MV) children (A) less than 12 months of age and (B) older than 12 months of age. * p=0.01 between SB and MV children. No other significant differences in A: p=0.43 paediatric and adult patterns respectively, p=0.65 ventral pattern, and p= 0.55 dorsal pattern; in B p=0.47 paediatric pattern, p=0.14 adult pattern, p=0.07 ventral pattern.

5.3.5.5.2.1 Mean relative impedance change and regional filling characteristics

No significant interaction was found between the effects of ventilation type (spontaneous or mechanically ventilated) and body position on regional ventilation in the ventral (Figure 5.3.20) and dorsal (Figure 5.3.21) lung regions respectively.

Regional filling in the ventral (Figure 5.3.22) and dorsal (Figure 5.3.23) lung regions was no different between mechanically ventilated and spontaneously breathing infants and children, with higher filling indices occurring in the non-dependent lung regions.

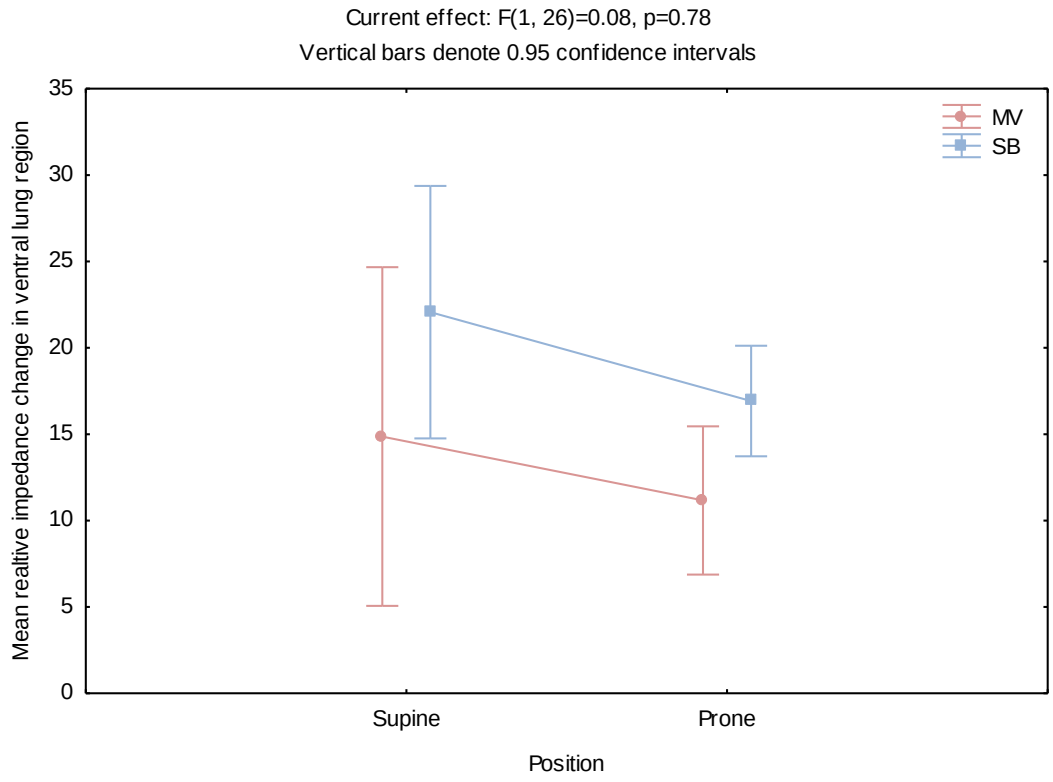


Figure 5.3.20 Mean relative impedance changing in ventral lung spontaneously breathing (SB) and mechanically ventilated (MV) infants and children in supine and prone positions.

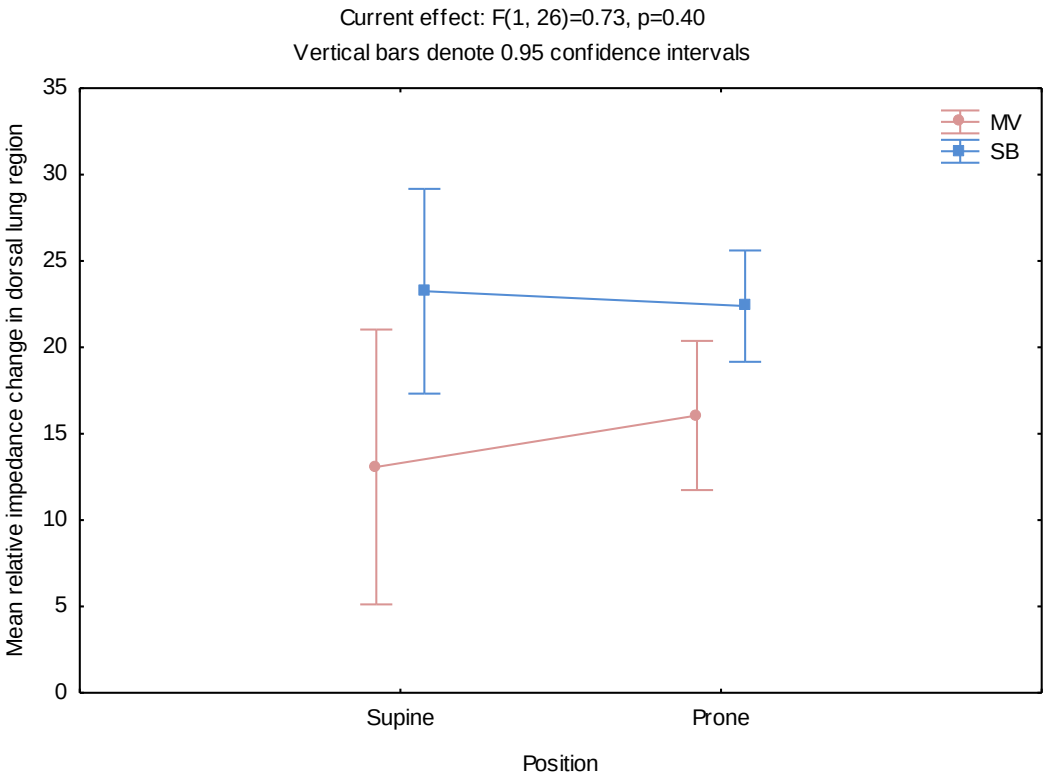


Figure 5.3.21 Mean relative impedance changing in dorsal lung spontaneously breathing (SB) and mechanically ventilated (MV) infants and children in supine and prone positions.

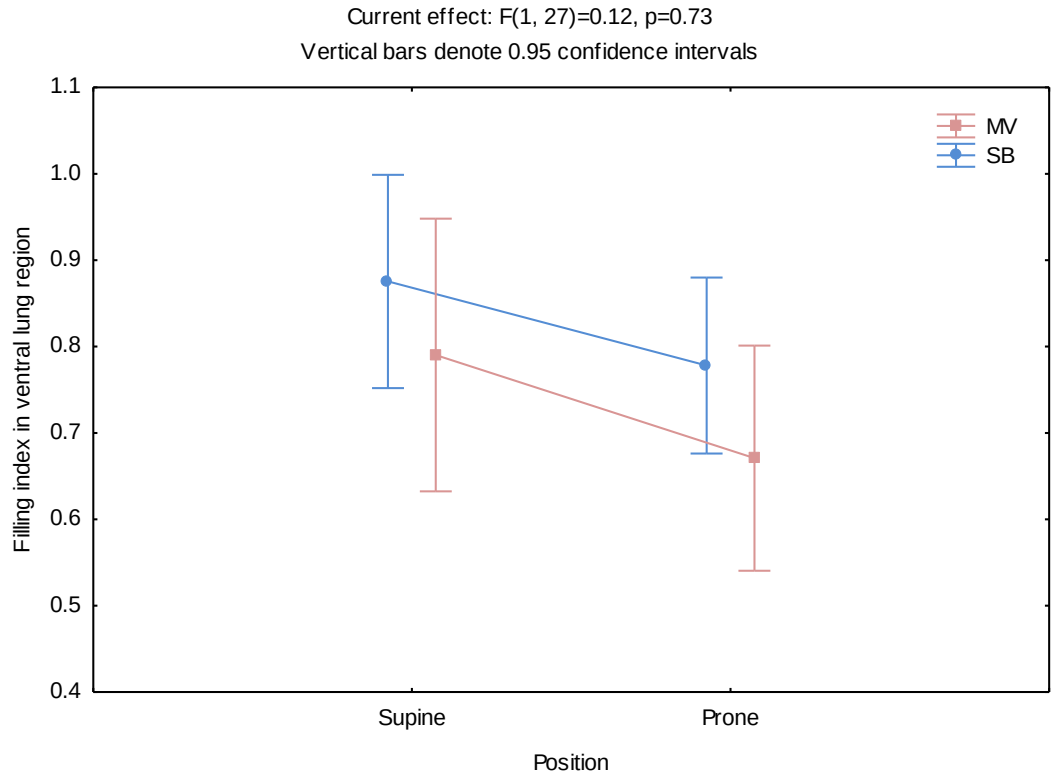


Figure 5.3.22 Filling indices in the ventral lung region in supine and prone positions in spontaneously breathing (SB) and mechanically ventilated (MV) infants/ children.

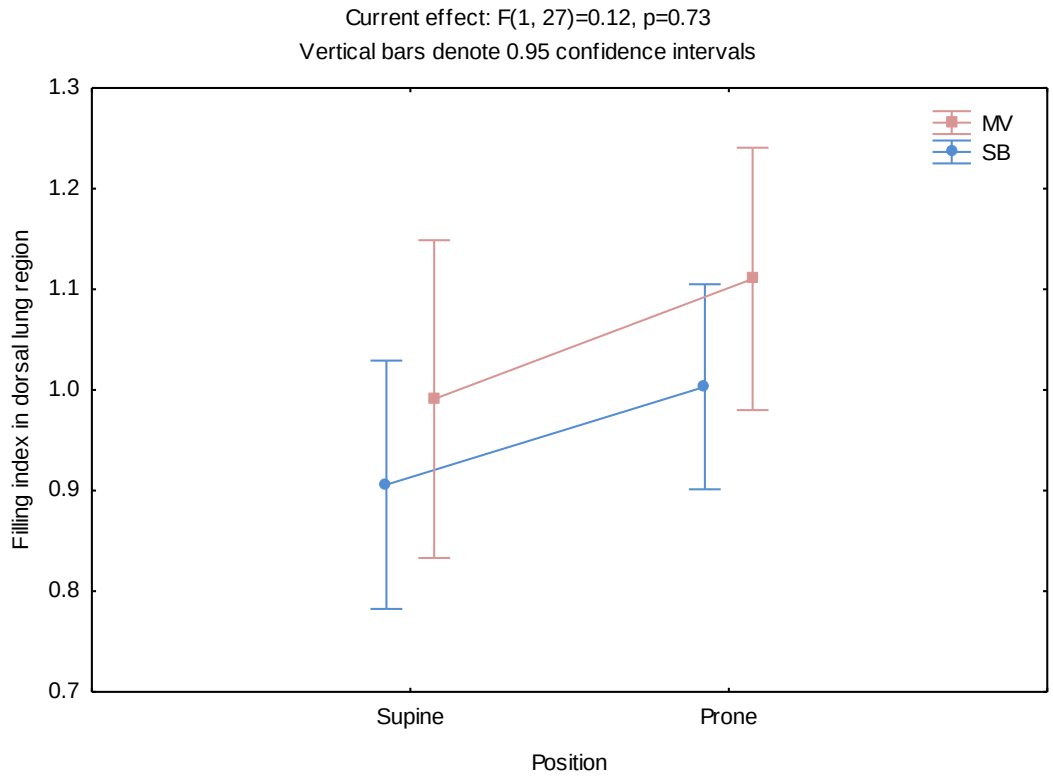


Figure 5.3.23 Filling indices in the dorsal lung region in supine and prone positions in spontaneously breathing (SB) and mechanically ventilated (MV) infants/children.

5.3.6 Discussion

This study examined the effect of body and head position on the distribution of ventilation in mechanically ventilated infants and children in the absence of anaesthesia/deep sedation or muscle paralysis. These findings do not support the generally accepted notion that all children preferentially ventilate the non-dependent lung regions, rather these results indicate that ventilation distribution in mechanically ventilated infants and children is variable, with no clear dependent/non-dependent pattern observed.

5.3.6.1 Ventilation distribution

As was found in the healthy spontaneously breathing infants and children, the distribution of ventilation was variable with majority of children demonstrating consistently better ventilation of their right lung in side lying positions, and of the dorsal lung in supine and prone positions. This is contrary to previously established and generally applied concept that preferential ventilation occurs in the non-dependent lung regions (Heaf et al., 1983; Davies et al., 1985).

5.3.6.1.1 Regional ventilation distribution

There are very limited studies investigating the effects of mechanical ventilation and different body positions on the distribution of ventilation in infants and children beyond the neonatal period. Of the available studies, Humphreys et al. (2011) reported that in infants and children who are mechanically ventilated and anesthetised, ventilation is greater in the non-

dependent lung in the supine position, which is in keeping with adult studies (Rehder, Sessler & Rodarte, 1977; Frerichs et al., 1998). Both these adult and paediatric studies examined patients who were sedated, paralysed and fully ventilated, making direct comparison with our population difficult.

Our findings of greater mean relative impedance change in the dependent lung regions in the side lying positions is in keeping with a number of adult studies who report that during mechanical ventilation, where spontaneous breathing is allowed, ventilation is greatest in the dependent lung regions (Frerichs et al., 1998; Bein et al., 2010; Riedel & Frerichs, 2010; van der Burg et al., 2016). This finding did not differ significantly from the distribution seen in spontaneously breathing infants and children. While a more heterogeneous distribution of ventilation may be expected during mechanical ventilation with underlying respiratory disease, the application of PEEP may help ameliorate this. The application of PEEP has shown to minimise collapse of dependent lung regions and therefore improve compliance and facilitate better ventilation of the dependent lung regions (Gattinoni et al., 1993; Hinz et al., 2005; Frerichs et al., 2007; Meier et al., 2008).

A different pattern was observed in the supine and prone positions, with greater ventilation in the non-dependent lung regions. A study in ventilated neonates found no difference in ventilation between the dependent and non-dependent lung regions in the supine and prone positions (Hough et al., 2013). Chest wall mechanics may be related to the pattern seen. Since children in the present study were relatively young (median age of 1.28 years), they may have had more compliant chest walls, which were unimpeded in the supine position. This effect may be augmented by reduced muscle tension as a result of sedatives (Emeriaud et al., 2014). The increased chest wall compliance, together with the positive pressure ventilation, may facilitate better ventilation to the non-dependent (ventral) lung region (Riedel, Richards & Schibler, 2005; Riedel & Frerichs, 2010). In the prone position, particularly where the anterior chest wall and abdomen are not kept free, movement of the anterior chest wall is impeded by the bed, whilst a reduction in the abdominal hydrostatic pressure in the dorsal regions, may facilitate improved diaphragm activity and lung compliance, resulting in greater ventilation in the non-dependent lung regions (Froese & Bryan, 1974; Pelosi et al., 1998; Hinz et al., 2005). Significantly fewer children receiving mechanical ventilation had consistently greater ventilation of the dorsal lung region compared to spontaneously breathing children. This may partly be related to the fewer children in the MV group or due to the application of PEEP which improves EELV (Frerichs et al., 2007) allowing for better ventilation of the dependent lung regions.

Age (younger or older than 12 months) did not predict the pattern followed in the side lying positions. The lack of age-related difference in this group, compared to Study One, may be related to the smaller number of children under the age of 12 months (n=6). Furthermore, if

age related differences can be accounted for by the differences in respiratory mechanics (Chapter 2.1) and the tendency of dependent lung regions to collapse, the application of PEEP (Frerichs et al., 2007) and the more regular flow rates, tidal volumes, and respiratory rates may help prevent airway closure in the dependent lung regions.

The radiographic presentation (unilateral, bilateral or normal) did not affect ventilation distribution, which is in keeping with the findings reported by Davies et al. (1985). It must be noted, however, that these chest radiographs were not all taken on the day of study inclusion and therefore the condition may have changed at the time of the study.

5.3.6.1.2 The effect of head position

Unlike the findings of Heinrich et al. (2006) who reported a significant effect of head position on regional ventilation between the left and right lung regions in the prone position, these results suggest that head position had no effect on ventilation distribution in mechanically ventilated, older infants and children. This may be due to differences in maturation of the respiratory system, whereby the cartilage and smooth muscle are more developed, making the trachea and larger airways less susceptible to tractional forces caused by different head positions. This was a relatively small sample and therefore this finding needs to be confirmed in a larger population.

5.3.6.1.3 Regional filling characteristics

In side lying positions regional filling indices were higher in the dependent lung regions, indicating slower initial but faster late filling in relation to global filling, in keeping with the principles put forward by Milic-Emili et al. (1966). While these values were higher, albeit non-significantly, than the non-dependent lung regions they were still less than one, which may be the result of higher EELV due to the application of PEEP (Gattinoni et al., 1995; Hinz et al., 2005; Andersson et al., 2011). Regional filling in ventilated children was no different to spontaneously breathing infants and children in the side lying positions.

The dorsal lung regions had higher filling indices in both supine and prone positions, although this only reached statistical significance in the prone position. This suggests a more “recruitable” dorsal lung in both positions. This finding is in keeping with the regional filling described in adults with ARDS, where the ventral lungs regions are relatively hyperinflated, whereas dorsal lung regions are more recruitable in the supine position (Hinz et al., 2007). Regional filling indices in the supine and prone positions in mechanically ventilated infants and children were similar to those observed in spontaneously breathing infants and children. The higher filling indices in the dorsal lung region may be attributed to the higher compliance in the supine position and stabilisation of the anterior rib cage and better excursion of the dorsal diaphragm in the prone positions.

5.3.6.1.4 Repeatability and feasibility of EIT measurements

EIT showed excellent repeatability between the two measurements in the side lying positions with high intra-class correlation co-efficients and relatively small limits of agreement. Repeatability was good in the supine and prone positions. The lower intra-class correlation co-efficient for the dorsal lung region, while still acceptable, is of concern. This lower value may be a result of breath by breath variability between measures and the smaller number of children in whom measurements were taken in the prone position. Despite the lower ICC value, the mean difference and limits of agreement for this lung region are still within the acceptable range.

With regards to the feasibility of EIT in the PICU environment, measurements were well tolerated by the infants/children. The time to set up was slightly longer (approx. 30 minutes) than for the healthy children, largely as a result of the additional lines, attachments, and positioning the child (with invasive devices and ECG electrodes already *in situ*) to accurately place the electrodes on the thorax. The number of electrode wires proved challenging to manage at times, however the development of electrode belts should remedy this. Issues regarding costs and information available at the bedside have been discussed in Chapter 5.2.6.3.

5.3.6.2 Respiratory muscle activity and ventilation distribution

This is the first study to investigate the effect of different body positions on respiratory muscle activity and the distribution of ventilation in mechanically ventilated infants and children.

No difference was seen in side lying positions between activity of the left and right hemi-diaphragms. However, a significant interaction was observed where left diaphragm activity was associated with an increase in the proportion of ventilation in the left lung region in side lying positions. Since the same was not observed on the right, this is difficult to fully explain and we can only speculate possible reasons for this observation. Greater movement, and therefore possibly activity, is observed in the dependent diaphragm when spontaneous breathing is permitted during mechanical ventilation (Froese & Bryan, 1974). In addition, the dependent diaphragm has a longer resting length and results in better force production (Pengelly, Alderson & Milic-Emili, 1971). In left side lying, it is likely that the heart compresses the lung tissue limiting the potential for expansion. More efficient diaphragm activity in this position may help overcome this, resulting in better ventilation of the left lung.

The ventral hemi-diaphragm showed significantly greater activity than the dorsal diaphragm in both supine and prone positions. Greater activity of the ventral diaphragm would be expected in the prone position, where it is dependent, based on the previously outlined principles. In the supine position, however, this is difficult to explain. Despite the lower

activity of the dorsal diaphragm relative to the ventral diaphragm, dorsal diaphragm activity was associated with an increase in the proportion of ventilation occurring in the dorsal lung region. Greater activity of the dorsal diaphragm during inspiration may help improve tidal volumes or, during expiration may help reduce airway closure in the dorsal lung regions, improving compliance and facilitating better ventilation in the dorsal lung region. Since there are no studies in a similar population to compare to, these results require confirmation in larger samples.

5.3.6.2.1 Repeatability and feasibility of sEMG measurements

sEMG measurements in all positions showed good agreement and repeatability in mechanically ventilated children. In contrast to the findings in healthy children, repeatability of left hemi-diaphragm measurements was very good in this population. This suggests that perhaps breath by breath differences in breathing pattern may account for the findings in Study One, since breathing parameters (such as volumes and flow rates) are more regulated in mechanically ventilated children.

sEMG is feasible in the ICU environment with regards to costs, setup time and patient tolerance of measurements. At times, placement of the electrodes for the intercostal measurements was challenging owing to the fact that this is the area where ECG electrodes are placed for monitoring, particularly in the smaller children. Although sEMG has shown to be a valid tool in measuring respiration (Kraaijenga et al., 2015), the impact of high heart rates on the accuracy of measurements requires further validation. The issues regarding the interface and whether sEMG is a user-friendly bedside tool has been discussed in Chapter 5.2.6.5.

5.3.7 Limitations

While this study provides novel insights into the distribution of ventilation in different body positions in mechanically ventilated infants and children, it is not without limitations. Although the sample size is comparable to similar studies in neonates (Frerichs et al., 2003; Heinrich et al., 2006; Hough et al., 2012; Hough et al., 2013) and was initially calculated to be adequately powered, final analysis indicated that it was underpowered (<80%). These results should therefore be confirmed in larger, adequately powered studies. As with Study One, positioning was not absolutely standardised, although it was reproducible between participants; this may have affected the results. Often with position change, secretions are mobilised and endotracheal suctioning is required. For obvious ethical reasons, endotracheal suctioning was permitted during the study. It is possible that this may have influenced ventilation distribution; the loss of PEEP during open endotracheal suction (due to disconnection from the ventilator) as well as the application of negative pressure may result in decruitment of lung regions (Morrow, Futter & Argent, 2006; Wolf et al., 2007; Hough et al., 2014). The effect of time in the position and order of positions were not examined, and

should be considered in future studies since ventilation distribution may change over time and there may be order effects (Caruana et al., 2015).

Limitations regarding the instruments are similar to those of Study One. Of note in this population though, is the higher heart rates which were commonly observed and may have influenced the quality of EMG readings. The QRS complex is removed from the sEMG signal and replaced by a running average through a technique called gating, therefore the higher the heart rate the greater the amount of signal that may be lost. Simultaneous measures of respiratory muscle function, such as ultrasonography of the diaphragm, together with sEMG may have strengthened these results. Additionally, analysis of the time sequence of respiratory muscle activity may have provided more information with regards to their contribution to ventilation distribution.

5.3.8 Clinical implications and future research

This study does not support the current clinical practice of choosing position on the basis of preferential ventilation to the non-dependent lung. Rather, the distribution of ventilation in mechanically ventilated infants and children is variable and at times significantly different. Therefore, position should be chosen on the basis of individual response. In the critical care setting, response could be determined by improvements in oxygenation, work of breathing, vital signs, auscultation, and ventilatory parameters (such as compliance and tidal volumes), however the association between these clinical factors and improved ventilation in a lung region requires validation and further investigation. Due to the small sample size, we were unable to determine whether factors such as age, amount of spontaneous breathing, and ventilator settings could be used to predict the "pattern" of ventilation distribution in different body positions. These results also highlight the potential clinical benefits of EIT as a tool to guide different therapies in the PICU.

Results of this study should be confirmed in larger samples. Future research should be directed at examining the effects of different disease states and time in a position on the distribution of ventilation. The effects of different ventilatory settings on the distribution of ventilation and regional filling should be investigated in the paediatric population. The feasibility and suitability of sEMG for monitoring in the critical care setting requires further investigation.

5.3.9 Conclusion

The principles previously guiding positioning in the paediatric population are not supported by this study. Rather this study indicates that ventilation distribution in mechanically ventilated infants and children, without anaesthesia or paralysis, is variable with the majority of children consistently showing greater ventilation of their right or dorsal lung. Ventilation distribution in side lying positions did not differ from that of spontaneously breathing infants

and children. Although mean relative impedance change was similar to spontaneously breathing children in supine and prone positions, significant differences were seen in the pattern of ventilation consistently followed. Significantly more mechanically ventilated children consistently showed greater ventilation in the ventral lung, whereas more spontaneously breathing children consistently showed greater ventilation of the dorsal lung region.

Unlike the studies in neonates, results of this study suggest that head position had no effect on the distribution of ventilation in the left, right, ventral or dorsal lung regions.

Regional filling in the left and right lung regions was not statistically different in the side lying positions. In the side lying positions, the dependent lung regions showed faster later filling when compared to the non-dependent lung regions. In supine and prone positions, the dorsal lung showed faster later filling in both positions, however this was only statistically significant in the prone position.

Left and right side lying positions did not affect respiratory muscle activity, but left diaphragm activity was associated with an increase in ventilation to the left lung region. In the supine and prone positions, activity of the ventral diaphragm was significantly greater; this however did not affect the distribution of ventilation. Dorsal diaphragm activity was associated with an increase in ventilation in the dorsal lung region.

This study provides new insight into the distribution of ventilation in mechanically ventilated infants and children. Furthermore, it provides some baseline data against which future studies can compare and highlights important areas for further research.

5.4 Study Three – A pilot study into the effect of body position on regional ventilation distribution and respiratory muscle activity in infants and children with neuromuscular disease

5.4.1 Introduction

Neuromuscular diseases have significant, but variable, effects on respiratory mechanics. The effect of neuromuscular disease (NMD) on the respiratory system depends on the time of onset and the extent of respiratory muscle weakness (Fauroux & Khirani, 2014). In early childhood, respiratory mechanics in infants and children with NMD may be similar to those of neonates and new-born infants (Papastamelos, Panitch & Allen, 1996). The more compliant chest wall leads to lower FRC and is susceptible to deformation during diaphragm contraction, resulting in reduced lung volumes. Depending on the degree of muscle weakness, flow rates and tidal volumes may be reduced, all of which are important factors in the determination of ventilation distribution. With aging and growth the chest wall stiffens, due to immobility and disuse, and postural deformities may occur, resulting in reduced chest wall compliance and a restrictive type respiratory pattern (Gibson et al., 1977; Estenne et al., 1983; Redding et al., 2008). Furthermore, these children are prone to frequent respiratory tract infections as a result of a poor cough, reduced expiratory flow rates and relative immobility, and consequently are prone to atelectasis and recurrent airway inflammation and obstruction.

Given the important differences in respiratory mechanics that occur with NMD, it is unclear whether the same principle of preferential ventilation to the non-dependent lung or the variability seen in our previous studies will occur in children with NMD.

5.4.2 Aim

To describe the pattern of regional ventilation distribution in a cohort of infants and children with neuromuscular disease.

5.4.3 Objectives

- To describe the effect of body position on regional ventilation distribution in infants and children with neuromuscular disease.
- To describe whether patterns of respiratory muscle activity are associated with the observed patterns of regional ventilation.
- To describe whether regional ventilation distribution in infants and children with NMD is different to that observed in healthy and mechanically ventilated infants and children.

5.4.4 Methods

A prospective observational study was conducted in the wards and out-patient clinics at RCWMCH, Cape Town, South Africa. Details regarding inclusion and exclusion criteria, study procedure and instruments can be found in Chapter 4.3.1. As with the previous studies, due to interaction between EIT and sEMG devices, simultaneous measures could not be obtained, therefore EIT measurements were taken first followed by the sEMG measurements. These measurements were repeated in twice in each position to ensure reproducibility of the data. Measurements were taken in the following positions:

- Left side lying
- Right side lying
- Supine position with the head in the midline
- Prone position

Additional information was recorded at the beginning of the study and if the child was on continuous monitoring this was also recorded (Appendix 4.1). The effect of head position and age-related differences were not studied in this cohort of infants and children owing to the small sample size.

Demographic data, regional ventilation and respiratory muscle activity data were tested for normality and not all data was found to be normally distributed, therefore, data are presented as median and interquartile range (IQR) or means ± 95% confidence interval (CI) for ANOVA. Residuals were normally distributed allowing for analysis by ANOVA (Appendix 5.3). Data for left and right side lying positions and supine and prone positions will be presented.

The pattern of ventilation; regional distribution of ventilation; global homogeneity indices; filling indices; respiratory muscle activity; and the association between respiratory muscle activity and regional distribution of ventilation, is presented for the different positions. Lastly, the comparison with spontaneously breathing, healthy and mechanically ventilated infants and children is presented. A plain language summary is presented at the beginning of the results section.

5.4.5 Results

5.4.5.1 Plain language summary of results

Six children were studied in this pilot study. Varying patterns of ventilation were found, with half of the children showing a paediatric pattern in side lying positions. Global ventilation was unaffected by position. The right lung had greater ventilation and faster later filling when compared to the left; however, these differences were not significant. Complete

measurements in supine and prone positions were obtained in two children. In supine and prone, there was greater ventilation and faster later filling of the ventral lung; however, this was not significant. Muscle activity was unaffected by position and was not associated with changes in regional ventilation.

5.4.5.2 Demographics

Six children (4 male) were recruited from the wards and out-patient clinics at RCWMCH, (Cape Town, South Africa) between March 2014 and October 2015 (Figure 5.4.1). Data collection was stopped early due to slow enrolment and termination of the loan of the EIT device. All infants/children were awake during study measurements. Complete measurements were obtained in all infants/children for the side lying positions. Due to postural deformities, relatively new tracheostomies, and refusal from the child, only two complete measurements were obtained in the both supine and prone positions. Population characteristics are shown in Table 5.4.1. Detailed characteristics are presented in Table 5.4.1.

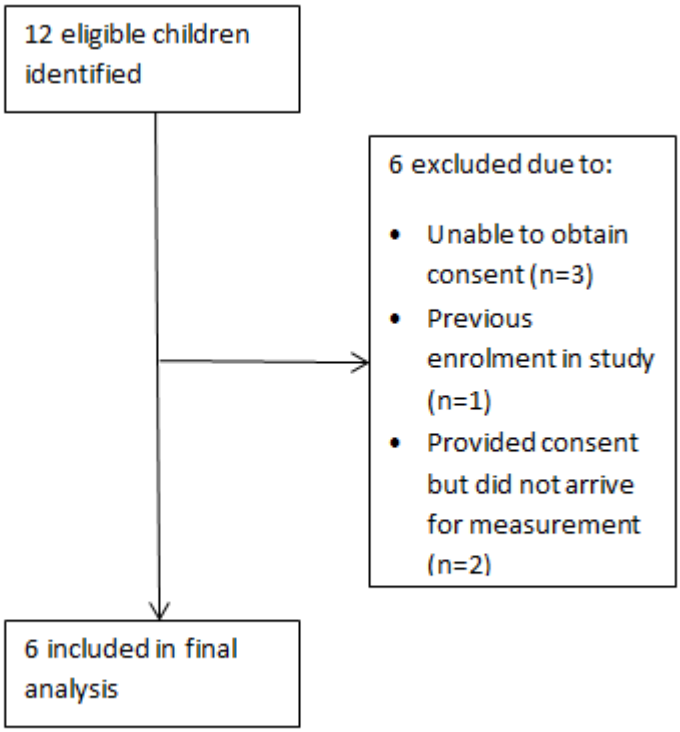


Figure 5.4.1 Flow of participants through study.

Table 5.4.1 Population characteristics

Age (years) (median, interquartile range)	5.05 (2.40 – 6.66)
Gender	
Male	4 (67%)
Female	2 (33%)
Respiration	
Artificial airway	
Tracheostomy	3 (50%)
None	3 (50%)
Development	
Normal	4 (67%)
Delayed	2 (33%)
Skeletal deformities	
Scoliosis	2 (33%)
Concave to right, with kyphosis	1 (50%)
Concave to right – undergoing correction with rods	1 (50%)
None	4 (67%)

Table 5.4.2 Detailed characteristics of the infants and children enrolled

ID	Age (years)	Gender	Primary diagnosis	Deformities	Artificial airway
1	6.66	male	Nemaline myopathy	Scoliosis (concave to right)	Tracheostomy
2	6.23	male	CMD	Kyphoscoliosis (concave to right)	None
3	3.86	male	GBS	None	Tracheostomy
4	1.48	female	Centronuclear myopathy	None	None
5	2.40	female	GBS	None	Tracheostomy
6	7.36	male	Myositis	None	None

CMD – congenital muscular dystrophy; GBS – Guillian Barré Syndrome

5.4.5.3 Regional ventilation distribution

5.4.5.3.1 Side lying positions

5.4.5.3.1.1 Pattern followed

Mixed patterns of ventilation were observed. Three infants/children consistently followed the paediatric pattern. Two children showed consistently greater ventilation of the dependent lung region (adult pattern) and one showed consistently better ventilation of the right lung

region. None of the children demonstrated consistently greater ventilation of the left lung region in side lying positions (Figure 5.4.2).

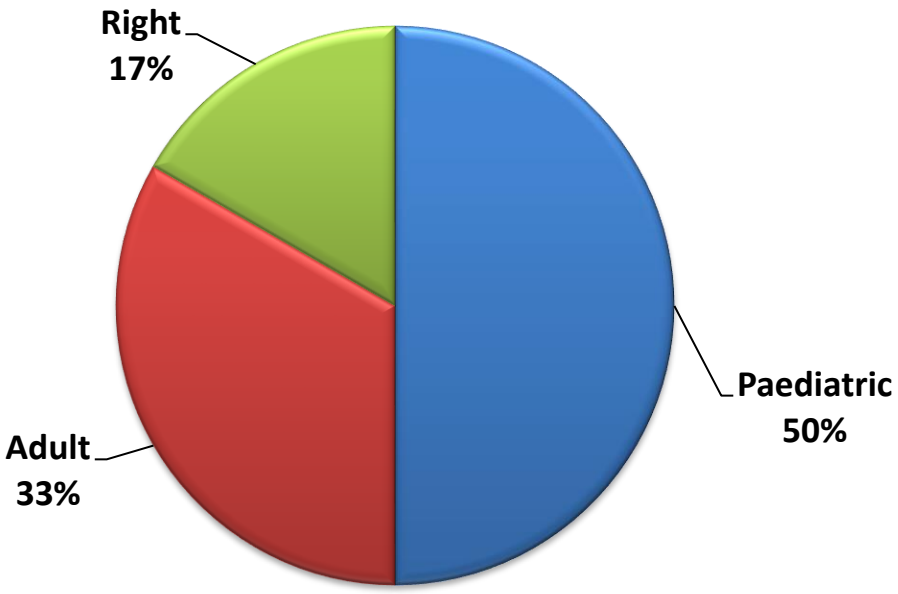


Figure 5.4.2 Proportion of infants and children demonstrating consistently greater ventilation in the non-dependent lung ("paediatric pattern"), dependent lung ("adult pattern"), and right lung region in the side lying positions.

5.4.5.3.1.2 Mean relative impedance change

Global ventilation was unaffected by position (p=0.38) (Table 5.4.3). No significant differences were found between left and right lung regions in left (p=0.38) and right (p=0.30) side lying positions. Ventilation was similar within the left (p=0.47) and right (p=0.58) lung regions between the side lying positions.

No significant interaction between the effects of lung region and position (dependent or non-dependent) and ventilation distribution was found (Figure 5.4.3). Ventilation was similar between left and right lung regions when in the dependent (p=0.69) and non-dependent (p=0.17) positions.

Table 5.4.3 Mean relative impedance change, regional filling indices and global inhomogeneity index in side lying positions, presented as medians and interquartile range

	Left side lying (n=9)	Right side lying (n=9)
Left lung		
ΔZ	14.08 (10.09 - 19.34)	11.63 (8.78 -16.26)
Filling index	0.77 (0.66 - 1.02)	0.85 (0.70 - 0.93)
Right lung		
ΔZ	17.14 (11.93 - 31.34)	15.77 (11.49 - 17.22)
Filling index	1.02 (0.77 - 1.12)	0.93 (0.85 - 1.08)
Global ΔZ	28.98 (24.85 - 31.65)	25.98 (19.59 - 31.10)
GI	0.91 (0.86 - 1.17)	0.87 (0.84 - 1.103)

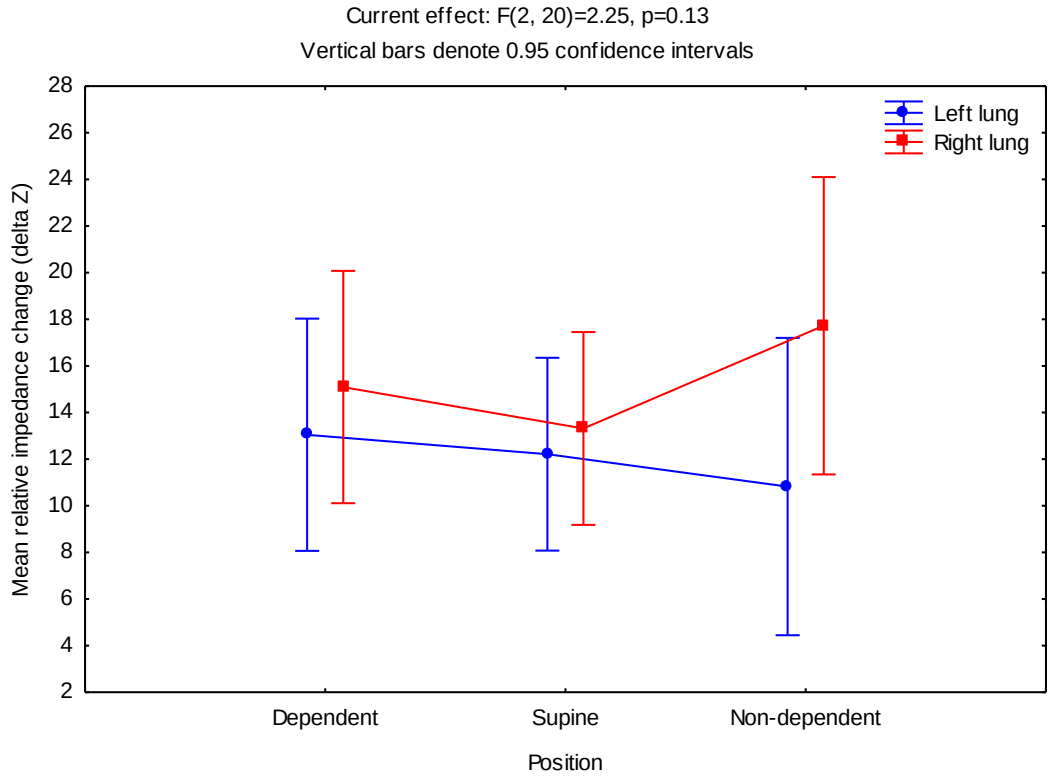


Figure 5.4.3 Ventilation (mean relative impedance change) in the left and right lung regions when dependent, non-dependent or supine (neutral) positions.

5.4.5.3.1.3 Regional filling

Although the right lung had higher filling indices than the left lung, these were not significant in either left side lying (p=0.13) or right side lying (p=0.17) (Table 5.4.3). No significant differences were found between lung regions when in the dependent position (p=0.13) or

non-dependent position (p=0.13). The interaction between the effects of lung region and position on the filling index was not significant (Figure 5.4.4).

5.4.5.3.1.4 Global inhomogeneity index

The GI was similar in left and right side lying positions (p=0.81) (Table 5.4.3).

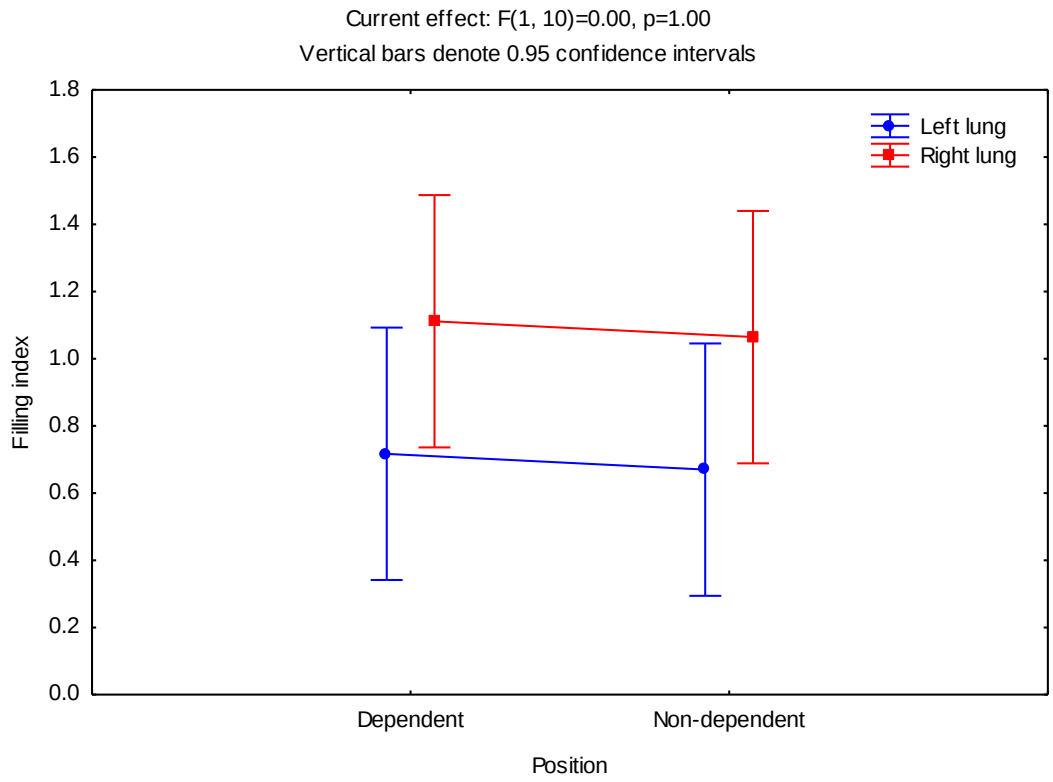


Figure 5.4.4 Filling indices in left and right lung regions when in either the dependent or non-dependent position.

5.4.5.3.1.5 Respiratory muscle activity

There were no significant differences in left and right hemi-diaphragm activity in the left and right side lying positions (p=1.00 respectively, Table 5.4.4). No difference was found within the left-hemi-diaphragm (p=0.17), right hemi-diaphragm (p=0.58), and intercostal (p=0.30) activity between side lying positions. Although the two hemi-diaphragms appear to behave differently no significant interaction between the effects of hemi-diaphragm (left or right) and position (dependent or non-dependent) on muscle activity were found (Figure 5.4.5).

Table 5.4.4 Mean muscle activity (µV) of respiratory muscles presented as medians and interquartile range.

	Left side lying	Right side lying	p-value [a]
Left hemi-diaphragm	3.16 (2.74 – 3.50)	2.50 (2.44 – 3.09)	0.17
Right hemi-diaphragm	3.09 (1.81 – 4.70)	2.74 (1.23 – 3.71)	0.50
Intercostals	2.08 (1.18 – 3.96)	1.00 (0.52 – 2.33)	0.37

[a] between left and right side lying. p=0.79 between left and right hemi-diaphragms in left side lying, p=0.67 between left and right hemi-diaphragms in right side lying

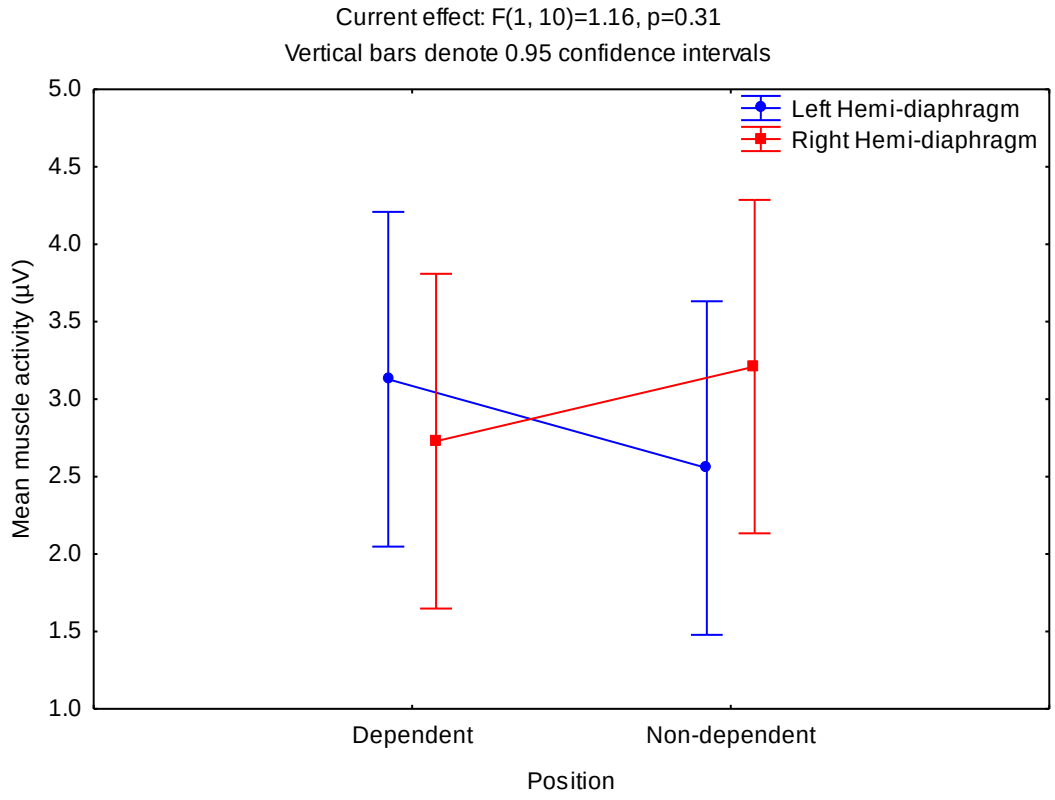


Figure 5.4.5 Mean activity (µV) of the left and right hemi-diaphragm when in the dependent or non-dependent in the side lying positions.

5.4.5.3.1.6 Interaction between respiratory muscle activity and regional ventilation

Respiratory muscle activity did not have a significant effect on the proportion of ventilation in either the left lung region (Table 5.4.5) or the right lung region (Table 5.4.6) in side lying positions.

Table 5.4.5 Interaction between intercostal and left hemi-diaphragm activity and the proportion of ventilation in the left lung region in side lying positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	23.22	-1.42	47.85	0.06
Intercostals	-0.52	-6.33	5.23	0.84
Left Hemi-diaphragm	4.56	-4.15	13.27	0.27

Table 5.4.6 Interaction between intercostal and right hemi-diaphragm activity and the proportion of ventilation in the right lung region in side lying positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	73.55	46.68	100.41	0.00
Intercostals	3.16	-4.85	11.17	0.41
Right Hemi-diaphragm	-5.41	-16.39	5.56	0.31

5.4.5.3.2 Supine and prone positions

5.4.5.3.2.1 Pattern followed

The paediatric pattern was consistently followed by both children in whom measurements were obtained in both supine and prone positions.

5.4.5.3.2.2 Mean relative impedance change and filling indices

There was no significant difference between mean relative impedance change between ventral and dorsal lung regions in the supine (p=0.38) or prone (p=0.70) position. Although mean relative impedance change was greater for both ventral and dorsal lung regions in the prone position compared to the supine position, this was not significant in either of the lung regions (p=0.15, respectively). Regional filling was similar between ventral and dorsal lung regions in the supine and prone positions (p=0.70, Table 5.4.7). The global inhomogeneity index was similar in the supine and prone positions (p=0.77).

Table 5.4.7 Mean relative impedance change and filling indices in the supine and prone positions, presented as median and interquartile range

	Supine position		Prone position	
Ventral lung				
∆Z	13.04	(12.21 – 17.39)	21.27	(20.03 – 22.23)
Filling index	1.10	(0.988 – 1.33)	0.90	(0.82 – 0.98)
Dorsal lung				
∆Z	8.30	(5.91 – 13.35)	18.57	(14.12 – 23.03)
Filling index	0.68	(0.45 – 0.90)	0.88	(0.80 – 0.96)
Global	23.31	(20.51 – 26.39)	39.84	(6.34 – 43.34)
GI	0.87	(0.83 – 1.18)	086	(0.85 – 0.86)

5.4.5.3.2.3 Respiratory muscle activity

Mean muscle activity of the intercostals, ventral and dorsal hemi-diaphragms is shown in Table 5.4.8. Activity of the ventral and dorsal hemi-diaphragms was similar in both the supine position (p=0. 38) and prone position (p=1.00).

Table 5.4.8 Mean muscle activity (μV) in the supine and prone positions, presented as median and interquartile range

	Supine position	Prone position
Ventral hemi-diaphragm	2.87 (2.67 – 3.12)	2.10 (2.08 – 2.12)
Dorsal hemi-diaphragm	2.18 (1.84 – 2.95)	1.19 (1.57 – 2.12)
Intercostals	1.94 (1.38 – 1.99)	1.07 (0.91 – 1.23)

5.4.5.4 Differences in regional ventilation compared to healthy, spontaneously breathing and mechanically ventilated children

The majority of children with NMD followed a paediatric pattern of ventilation in the side lying positions, whilst majority of those who were spontaneously breathing or mechanical ventilated showed greater ventilation of the right lung region (Figure 5.4.6).

As a result of only two children with NMD being measured in supine and prone positions, comparison to spontaneously breathing and mechanically ventilated children is not presented. More children with NMD demonstrated a consistent paediatic pattern than those who were mechanically ventilated (p=0.05), this was not significant compared to spontaneously breathing children (p=0.20).

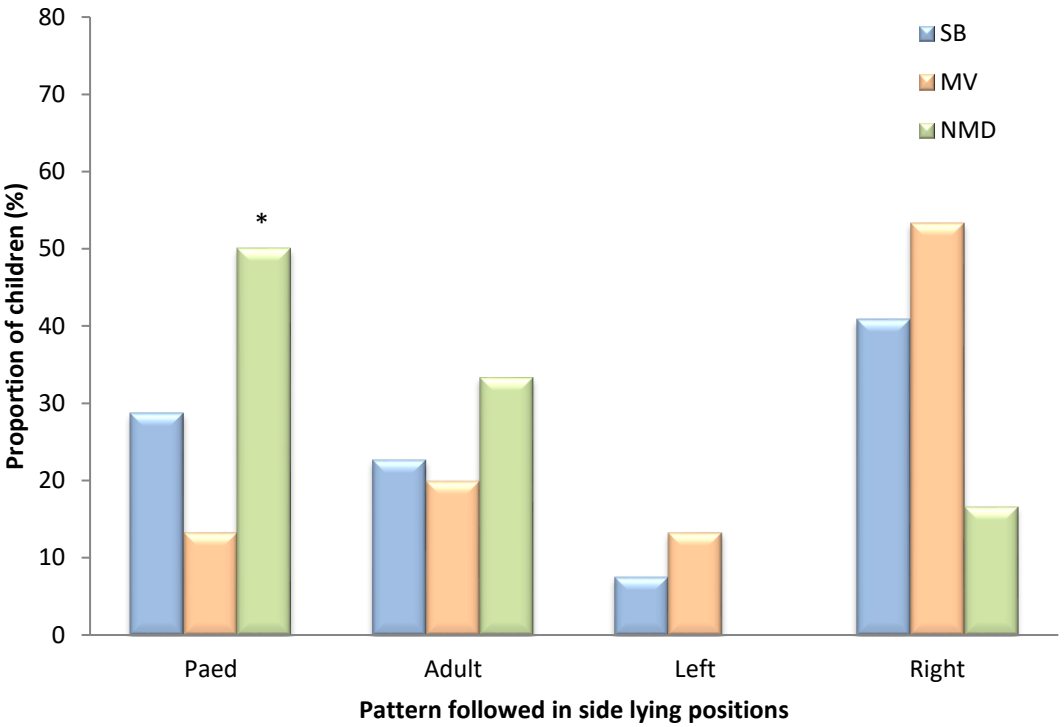


Figure 5.4.6 Pattern of ventilation consistently followed by healthy, spontaneously breathing (SB) infants and children and infants, mechanically ventilated (MV) children and children with neuromuscular disease (NMD) older than 12 months of age. * p=0.05 between MV and NMD children

5.4.6 Discussion

This is the first study to provide examine the distribution of ventilation in different body positions in children with NMD. Although limited by a small sample, the results suggest that children with NMD also have variable patterns of ventilation distribution.

5.4.6.1 Regional ventilation distribution

The pattern consistently followed by children with NMD varied, which is in keeping the results of Study One and Study Two. Of note in this population, however, is the predominance of the paediatric pattern of ventilation compared to the healthy and mechanically ventilated and NMD paediatric cohorts.

The distribution of ventilation between left and right lung regions was unaffected by body position. However, given the small sample size, this finding needs to be confirmed. The pattern of greater ventilation in the non-dependent lung may be explained, in part, by changes in respiratory mechanics as a result of muscle weakness. Although measures of respiratory muscle activity were taken, these may not correlate with respiratory muscle strength. If respiratory muscle weakness were present, this would result in lower chest wall compliance and consequently a lower FRC, as well as smaller tidal volumes which may predispose the child to collapse of the dependent lung regions (Schnidrig et al., 2013). As a result, greater opening pressures would be required to ventilate the dependent regions.

5.4.6.2 Respiratory muscle activity and ventilation distribution

These results suggest that respiratory muscle activity was unaffected by body position in children with NMD. Additionally, respiratory muscle activity did not appear to be associated with ventilation within the respective lung regions. To make any substantial conclusion, respiratory muscle activity needs to be examined in a larger sample. Since the mean activity may more accurately provide information about respiratory drive, rather than strength, analysis of the pattern of activation may provide more pertinent information, particularly in children with NMD where respiratory muscle weakness is to be expected. In addition, sleep studies in adults with NMD have shown alterations in the activity of accessory muscles which is associated with desaturations and sleep disordered breathing (Bye et al., 1990; White et al., 1995) and therefore measuring the activity of accessory muscle may also provide valuable insight in these children.

5.4.6.3 Limitations

Due to the small sample size, this study is underpowered, and therefore results presented here cannot be considered applicable to the greater NMD population until they are confirmed in a larger sample. Limitations with regards to the methodology and instruments are similar to those of Study One and Study Two. Due to postural deformities and reluctance to change position (due to discomfort) in some of the children, measurements were not obtained in all positions. This limits the conclusions we can draw on the effect of the horizontal postures on ventilation distribution. It is suggested that alternative positions, such a quarter-turn prone position, should be considered in future studies. Furthermore, the effect of marked postural deformities, such as scoliosis, as was the case in two children on the accuracy of EIT is, to the best of my knowledge, unknown. Owing to the small sample size we did not examine the effect of age or head position; these should be examined in future studies.

Although all children had some form of NMD, there was still a fair degree of heterogeneity in the population, for example, some had postural deformities, some had chronic NMD and others had acute or less severe forms of NMD. Children with an acute NMD are unlikely to present with many of the changes in respiratory mechanics that commonly occur with congenital/chronic NMD. Therefore, it is difficult to identify the factors most likely to account for the distribution of ventilation observed.

5.4.6.4 Clinical implications and future research

Despite the limitations of this study, it does support the previous findings that ventilation distribution in children with acute or chronic NMD is variable. Therefore, the choice of position in practice should be individualised and based on the clinical response of the child. Particularly in children with NMD, where certain positions may be poorly tolerated, alternative positions should be investigated. Whilst EIT provides valuable information regarding ventilation distribution, accompanying measures of lung function may assist in

gaining a better understanding of ventilation distribution and therefore more accurately guide clinical practice. In addition, the validation of EIT in the presence of marked postural deformity is required. Studying more homogenous groups of children with NMD may provide clearer insight into the possible factors influencing ventilation distribution in NMD. To more accurately determine the impact of the respiratory muscles on the distribution of ventilation, measurements of the pattern of muscle activity and the inclusion of accessory muscles should be included and as well as specific measures of respiratory muscle strength.

5.4.7 Conclusion

Although this study had limited power, it echoes the findings of Study One and Two that ventilation distribution is not as straightforward as previously thought. This is the first study to report the distribution of ventilation in children with NMD, and information gained from this study can help guide and develop future studies to improve our understanding.

Results of this study suggest that ventilation distribution in children with NMD is dissimilar to that of healthy, spontaneously breathing children in the side lying and supine positions, with more children following the paediatric pattern. Respiratory muscle activity was not affected by body position and did not influence ventilation distribution in this cohort of children with NMD.

This study provides some novel insights into ventilation distribution in children with NMD and highlights areas that can strengthen future studies.

5.5 Study Four – A pilot study into the effect of body position on regional ventilation distribution and respiratory muscle activity in infants and children with respiratory disease

5.5.1 Introduction

Positioning is most frequently used in infants and children with respiratory disease. The studies which have guided clinical practice until now were the first performed on infants and children with respiratory disease (Heaf et al., 1983; Davies et al., 1985). There have been no subsequent studies to confirm these findings. Respiratory disease can alter the compliance of the respiratory system and airway resistance, which can have significant effects on the distribution of ventilation (Chapter 2.2.1).

5.5.2 Aim

To describe the regional ventilation distribution in a cohort of infants and children with respiratory disease.

5.5.3 Objectives

- To describe the effect of body position on regional ventilation distribution in infants and children with respiratory disease.
- To describe the association of respiratory muscle activity and the observed patterns of regional ventilation.
- To compare regional ventilation distribution in infants and children with respiratory disease to that observed in healthy infants and children, mechanically ventilated infants and children with neuromuscular disease.

5.5.4 Methods

A prospective observational study was conducted in wards and out-patient clinics at RCWMCH, Cape Town, South Africa. Details regarding inclusion and exclusion criteria, study procedure and instruments can be found in Chapter 4.3.1. As with the previous studies, due to interaction between EIT and sEMG devices, simultaneous measures could not be obtained, therefore EIT measurements were taken first followed by the sEMG measurements. These measurements were repeated in twice in each position to ensure reproducibility of the data. Measurements were taken in the following positions:

- Left side lying
- Right side lying
- Supine position with the head in the midline
- Prone position

Additional information was recorded at the beginning of the study. If the infant or child was on continuous monitoring of their vital signs, these were monitored throughout the study period (Appendix 4.1). Owing to the small sample size, the effect of head position and age-related differences were not studied in this cohort of infants and children.

Demographic data, regional ventilation and respiratory muscle activity data were tested for normality and not all data was found to be normally distributed, therefore, data are presented as median and interquartile range (IQR) or means ± 95% confidence interval (CI) for ANOVA. Residuals were normally distributed allowing for analysis by ANOVA (Appendix 5.4). Data for left and right side lying and supine and prone positions will be presented.

The pattern of ventilation; regional distribution of ventilation; global homogeneity indices; filling indices; respiratory muscle activity; and, the association between respiratory muscle activity and regional distribution of ventilation, is presented for the different positions. Lastly, the comparison with spontaneously breathing healthy infants and children, mechanically ventilated infants and children and those with neuromuscular disease is presented. A plain language summary of the results is presented at the beginning of the results section.

5.5.5 Results

5.5.5.1 Plain language summary of results

Five children were studied in this pilot study. Varying patterns of ventilation were found in the side lying positions, while the majority of the infants/children showed consistently greater ventilation of the dorsal lung in the supine and prone positions. Global ventilation was unaffected by position. In the side lying positions, greater ventilation and faster later filling was seen in the dependent lungs, however no significant differences were found. In both supine and prone positions, greater ventilation was found in the dorsal lung region, however this was not significant. The dependent lung regions showed faster later filling than the non-dependent lung regions in the supine and prone positions, this was only significant in the supine position. Side lying positions did not affect muscle activity; however, in the supine position, significantly greater activity was found in the ventral hemi-diaphragm. Intercostal muscle activity was associated with change in the proportion of ventilation in the ventral and dorsal lung regions in the supine and prone positions.

5.5.5.2 Demographics

Five children (4 male), with a median age of 4.65 (2.67 – 6.86) years, were recruited from the wards and out-patient clinics at RCWMCH, (Cape Town, South Africa). Data collection was stopped early due to slow enrolment and termination of the loan of the EIT device. All infants/children were awake during study measurements. Measurements were obtained in side lying positions for all the children and complete measurements were obtained in four

children in the supine and prone positions. The type of respiratory disease is presented in Table 5.5.1.

Table 5.5.1 Type of respiratory disease seen in the infants and children enrolled

Condition	Number of children
Cystic fibrosis	1
Asthma	2
Acute lower respiratory tract infection	1
Lung fibrosis	1

5.5.5.3 Regional ventilation distribution

5.5.5.3.1 Side lying positions

5.5.5.3.1.1 Pattern followed

Mixed patterns of ventilation were observed (Figure 5.5.1). Two infants/children consistently followed the adult or paediatric patterns, respectively. The remaining child consistently showed a greater proportion of ventilation in the right lung region in both left and right side lying positions. None of the children demonstrated consistently greater ventilation of the left lung region in side lying positions.

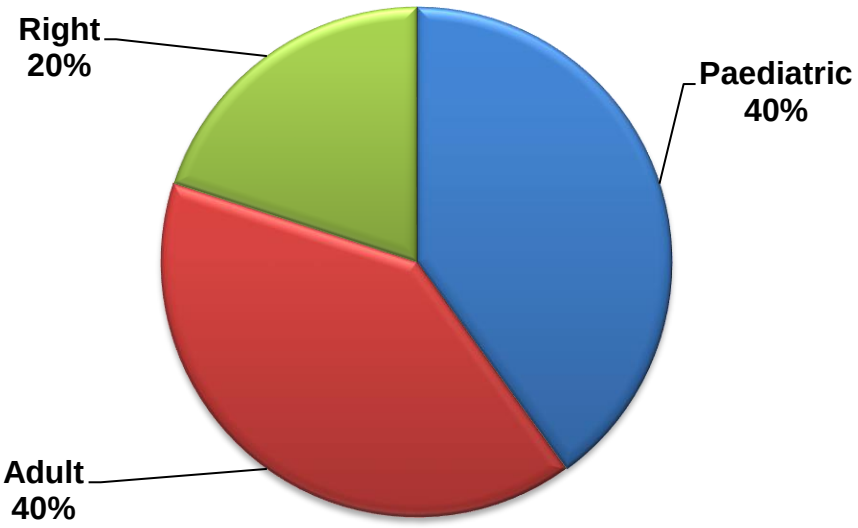


Figure 5.5.1 Proportion of infants and children demonstrating consistently greater ventilation in the non-dependent lung ("paediatric pattern"), dependent lung ("adult pattern") and right lung region in the side lying positions.

5.5.5.3.1.2 Mean relative impedance change

Global ventilation was unaffected by position (p=0.67) (Table 5.5.2). No significant differences were found between left and right lung regions in left (p=1.00) and right (p=0.84) side lying positions. Ventilation was similar within the left (p=0.67) and right (p=0.89) lung regions between the side lying positions.

No significant interaction between the effects of lung region and position on the pattern of ventilation was observed (Figure 5.5.2). Ventilation was similar between left and right lung regions when each lung was in the dependent (p=1.00) and non-dependent (p=0.68) positions.

Table 5.5.2 Mean relative impedance change, regional filling indices and global inhomogeneity index in side lying positions, presented as medians and IQR

	Left side lying (n=5)	**Right side lying (n=5)**
Left lung		
∆Z	14.37 (13.55 – 21.68)	14.50 (10.15 – 25.80)
Filling index	0.93 (0.89 – 1.18)	0.83 (0.81 – 1.10)
Right lung		
∆Z	8.79 (8.18 – 24.99)	16.72 (13.79 – 17.36)
Filling index	0.85 (0.60 – 0.89)	0.95 (0.68 – 0.98)
Global ∆Z	30.47 (22.55 – 41.55)	31.21 (19.08 – 43.29)
GI	0.88 (0.87 – 0.91)	0.91 (0.90 – 0.99)

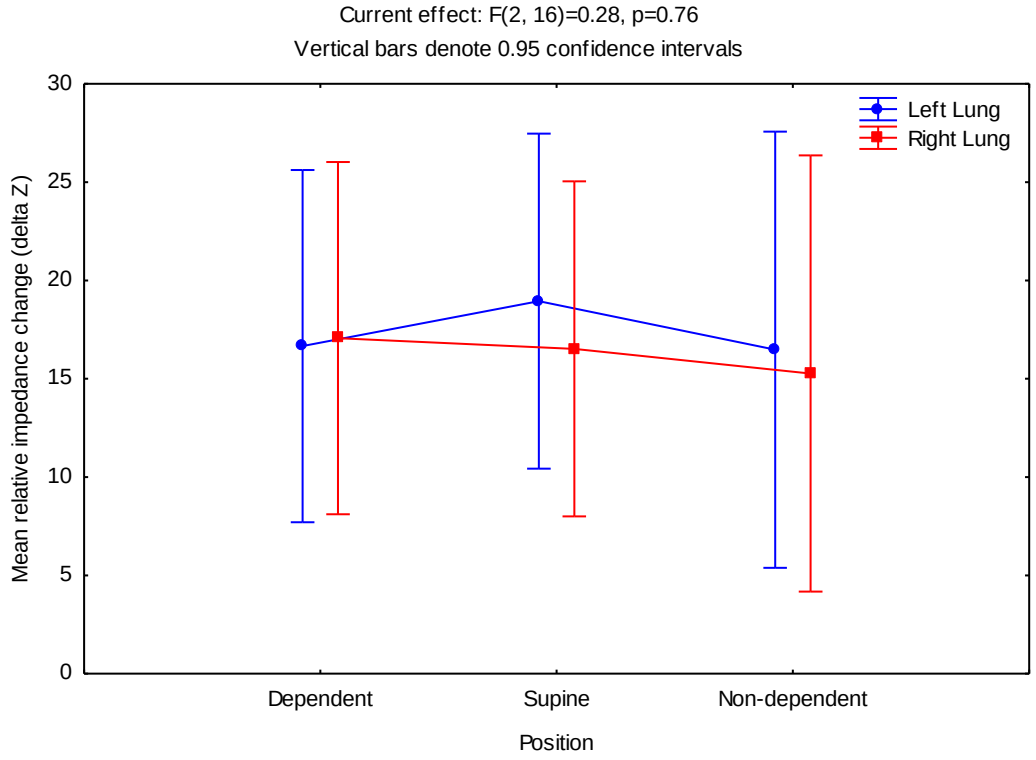


Figure 5.5.2 Ventilation (mean relative impedance change) in the left and right lung regions when dependent, non-dependent or supine (neutral) positions.

5.5.5.3.1.3 Regional filling

Regional filling was similar between left and right lung regions in left (p=0.29) and right (p=1.00) side lying positions. Filling characteristics were similar within the left (p=0.53) and right (p=0.53) lung regions in the side lying positions (Table 5.5.2). No difference in regional filling was observed between left and right lung regions when each lung was in the dependent (p=1.00) or non-dependent (p=1.00) position (Figure 5.5.3).

5.5.5.3.1.4 Global inhomogeneity index

The GI was similar in left and right side lying positions (p=0.67) (Table 5.5.2).

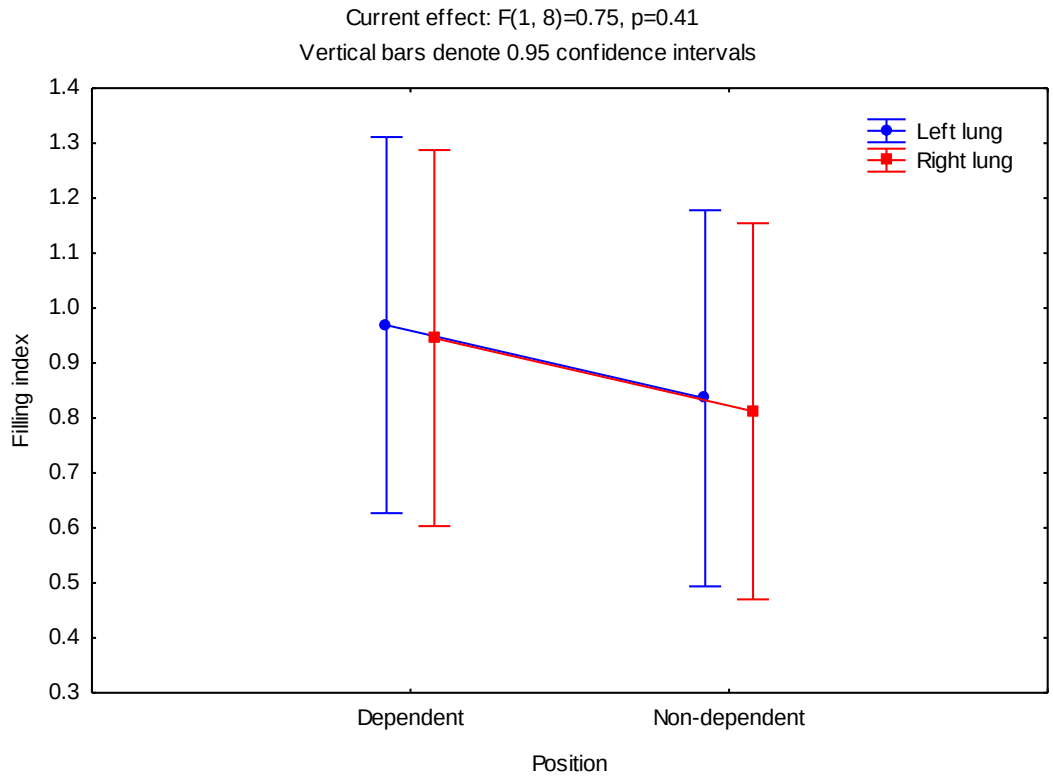


Figure 5.5.3 Filling indices in left and right lung regions when in either the dependent or non-dependent position.

5.5.5.3.1.5 Respiratory muscle activity

There were no significant differences in left and right hemi-diaphragm activity in the left (p=1.00) and right (p=1.00) side lying positions (Table 5.5.3). No difference was found within the left-hemi-diaphragm, right hemi-diaphragm and intercostal activity between positions. No interaction between the effects of respiratory muscle activity and position on the pattern of activity was found (Figure 5.5.4).

Table 5.5.3 Mean muscle activity (μV) in side lying positions presented as medians and IQR

	Left side lying	**Right side lying**	**p-value [a]**
Left hemi-diaphragm	7.19 (5.48 – 8.13)	4.91 (3.63 – 4.98)	0.40
Right hemi-diaphragm	6.43 (3.78 – 7.21)	3.67 (2.96 – 5.44)	0.30
Intercostals	2.10 (2.01 – 5.94)	2.23 (1.28 – 2.43)	0.68

[a] between left and right side lying positions.

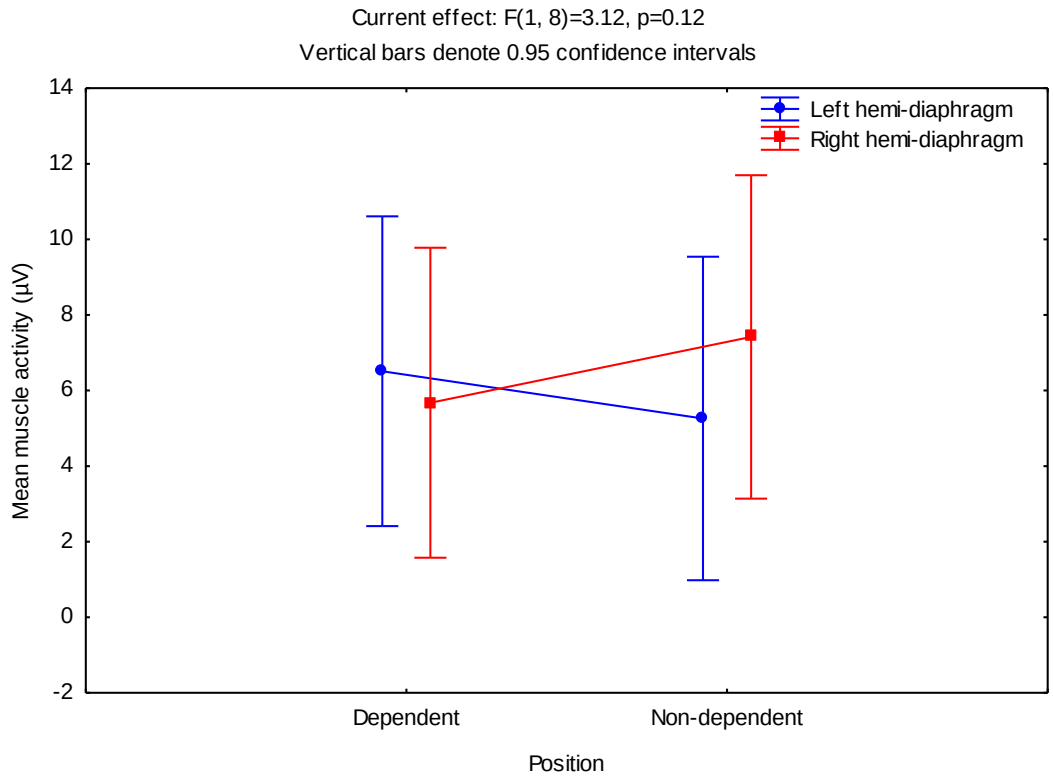


Figure 5.5.4 Mean activity of the left and right hemi-diaphragm when in the dependent or non-dependent in the side lying positions.

5.5.5.3.1.6 Interaction between respiratory muscle activity and regional ventilation

Respiratory muscle activity was not associated with the proportion of ventilation in either the left lung region (Table 5.5.4) or the right lung region (Table 5.5.5) in side lying positions.

Table 5.5.4 Interaction between intercostal and left hemi-diaphragm activity and the proportion of ventilation in the left lung region in side lying positions

	Coefficient	**95% Confidence interval**		**p-value**
	Estimate	Lower	Upper	
Intercept	77.13	44.51	109.75	0.00
Intercostals	1.15	-0.68	2.97	0.19
Left Hemi-diaphragm	-5.77	-12.30	0.75	0.08

Table 5.5.5 Interaction between intercostal and right hemi-diaphragm activity and the proportion of ventilation in the right lung region in side lying positions

	Coefficient	95% Confidence interval		p-value
	Estimate	Lower	Upper	
Intercept	45.59	19.49	71.68	0.00
Intercostals	-0.62	-4.55	3.32	0.73
Right Hemi-diaphragm	1.21	-5.59	8.00	0.70

5.5.5.3.2 Supine and prone positions

5.5.5.3.2.1 Pattern followed

Of the four children in whom measurements were obtained in both positions, half of the children (2, 50%) showed greater ventilation of the dorsal lung region, while the remaining two each showed consistently greater ventilation of either the dependent or non-dependent lung region (Figure 5.5.5).

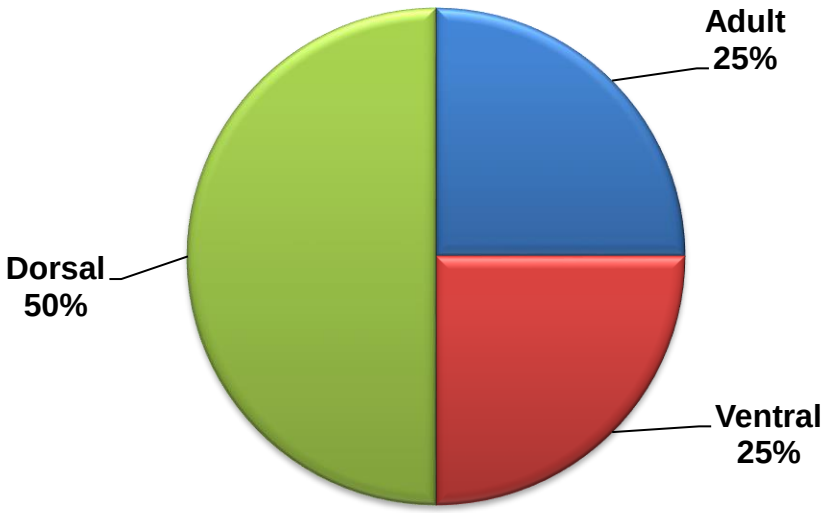


Figure 5.5.5 Proportion of infants and children demonstrating consistently greater ventilation in the dependent lung ("adult pattern"), ventral lung region, and dorsal lung region in the supine and prone positions.

5.5.5.3.2.2 Mean relative impedance change

Global ventilation was unaffected by position (p=0.67) (Table 5.5.6). There was no significant difference in ventilation within the ventral (p=0.89) and dorsal (p=0.67) lung regions, respectively. Ventilation between the ventral and dorsal lung regions was similar in

the supine (p=0.67) and prone (p=0.89) positions respectively. GI was not significantly different between supine and prone positions (p=0.86).

There was no significant interaction between the effects of lung region and position on the distribution of ventilation in the supine and prone positions (Figure 5.5.6). Ventilation was no different between ventral and dorsal lung regions when each lung was in the dependent (p=0.67) and non-dependent (p=0.67) positions.

Table 5.5.6 Mean relative impedance change, filling indices and global inhomogeneity indices in supine and prone positions presented as medians and IQR

	Supine position	**Prone position**
Ventral lung region		
ΔZ	14.43 (10.80 – 14.78)	20.20 (12.28 – 36.61)
Filling index	0.74* (0.68 – 0.77)	0.91 (0.77 – 1.05)
Dorsal lung region		
ΔZ	20.90 (17.63 – 22.57)	22.66 (14.13 – 29.32)
Filling index	1.04 (1.01 – 1.10)	0.87 (0.73 – 1.01)
Global ΔZ	35.67 (28.43 – 41.48)	44.27 (26.41 – 65.93)
GI	0.91 (0.87 – 0.93)	0.90 (0.86 – 0.93)

* p=0.02 between ventral and dorsal lung regions

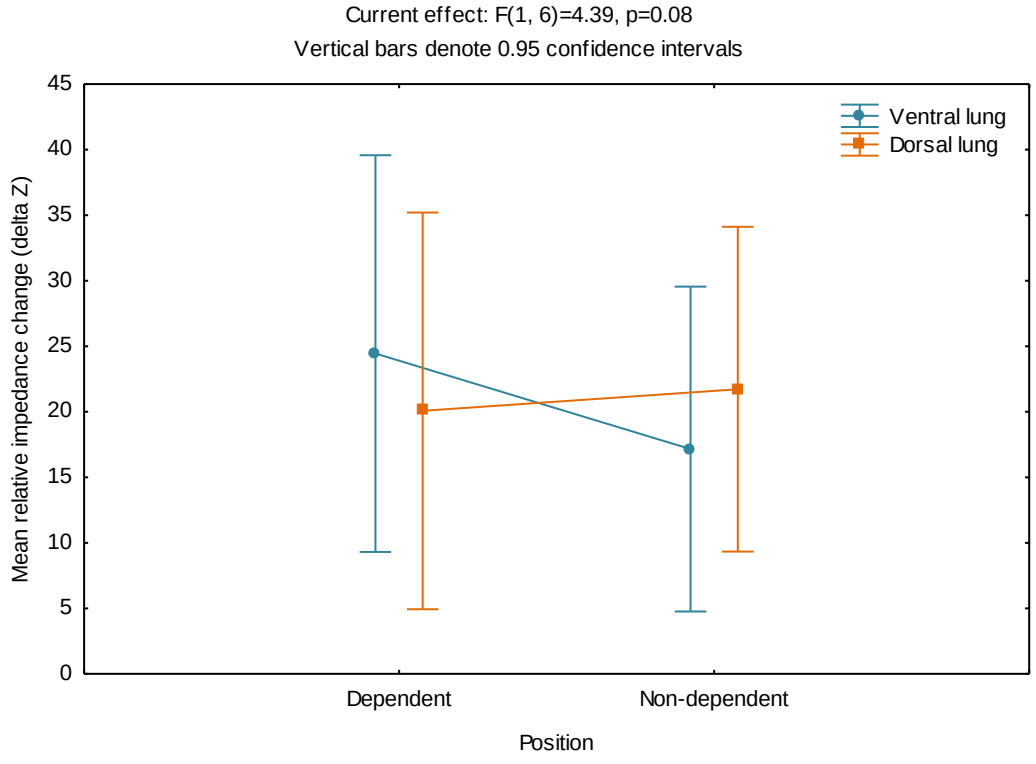


Figure 5.5.6 Ventilation (mean relative impedance change) in the ventral and dorsal lung regions when the dependent and non-dependent positions.

5.5.5.3.2.3 Regional filling

The dorsal lung region had a significantly higher filling index in the supine position compared to the ventral lung (p=0.02) (Table 5.5.6). No difference between the lung regions was found in the prone position (p=0.67). Regional filling within the ventral (p=0.18) and dorsal (p=0.18) lung regions was similar between supine and prone positions. No difference in regional filling was observed between ventral and dorsal lung regions when each lung was in the dependent (p=0.27) or non-dependent (p=0.27) position (Figure 5.5.7).

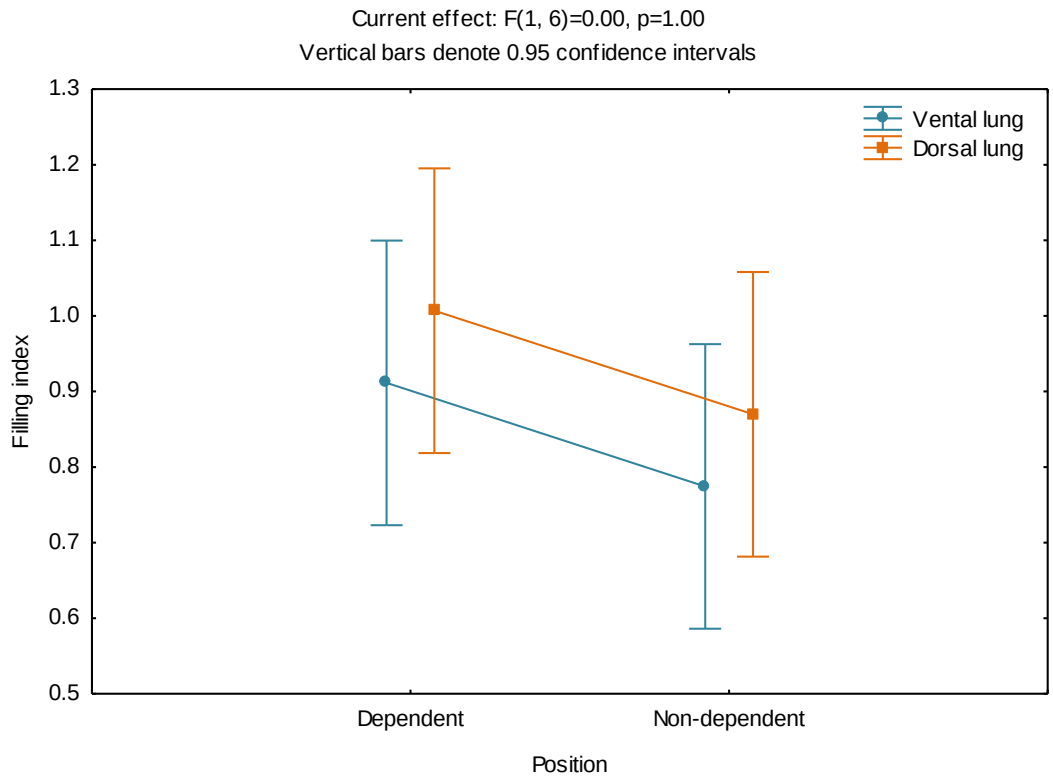


Figure 5.5.7 Filling indices in the ventral and dorsal lung regions in the dependent or non-dependent positions.

5.5.5.3.2.4 Global inhomogeneity index

The GI was similar in supine and prone positions (p=1.00) (Table 5.5.6).

5.5.5.3.2.5 Respiratory muscle activity

The ventral hemi-diaphragm showed significantly greater activity in the supine position compared to the dorsal diaphragm (p=0.04, Table 5.5.7). There was no significant difference in ventral and dorsal hemi-diaphragm activity in the prone position (p=0.47, Table 5.5.7). No difference was found within the ventral hemi-diaphragm, dorsal hemi-diaphragm and intercostal activity between positions. The interaction of the effects of respiratory muscle and position on muscle activity was not significant (p=0.11, Figure 5.5.8).

Table 5.5.7 Mean muscle activity (μV) in the supine and prone positions presented as medians and IQR

	Supine position	Prone position	p-value [a]
Ventral hemi-diaphragm	4.64 (4.01 – 4.89) *	4.44 (3.27 – 6.28)	0.90
Dorsal hemi-diaphragm	2.89 (2.84 – 3.02)	3.35 (2.67 – 5.35)	0.54
Intercostals	4.31 (4.28 – 4.65)	6.07 (3.56 – 9.66)	1.00

[a] between supine and prone positions * p=0.04 between ventral and dorsal hemi-diaphragm

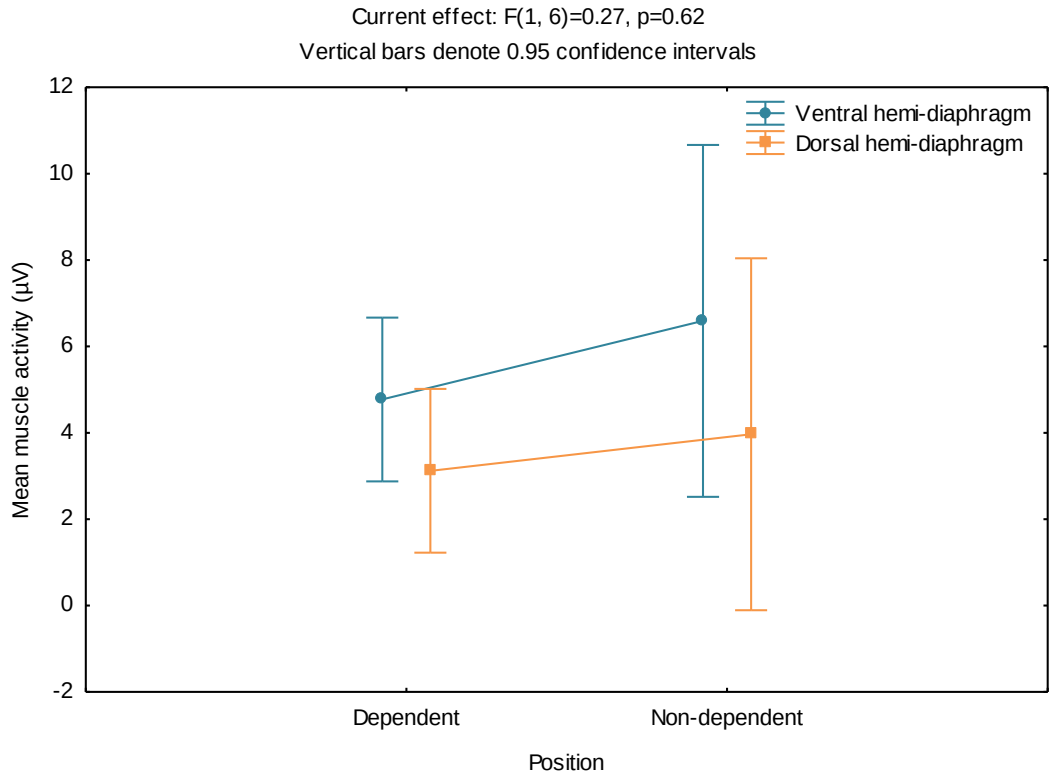


Figure 5.5.8 Mean muscle activity of ventral and dorsal hemi-diaphragms when in the dependent and non-dependent position

5.5.5.3.2.6 Interaction between respiratory muscle activity and regional ventilation

The proportion of ventilation in the ventral and dorsal lung regions was significantly affected by intercostal activity. Intercostal muscle activity was associated with an increase in the proportion of ventilation in the ventral lung region (p=0.01), whilst it was associated with a reduction of ventilation in the dorsal lung region (p=0.009). Activity of the ventral and dorsal hemi-diaphragms was not associated with the proportion of ventilation in the ventral (Table 5.5.8) and dorsal (Table 5.5.9) lung regions, respectively.

Table 5.5.8 Interaction between intercostal and ventral hemi-diaphragm activity and the proportion of ventilation in the ventral lung region in the supine and prone positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	31.00	22.81	39.17	0<01
Intercostals	1.95	0.58	3.32	0.01
Ventral Hemi-diaphragm	0.72	-0.90	2.33	0.34

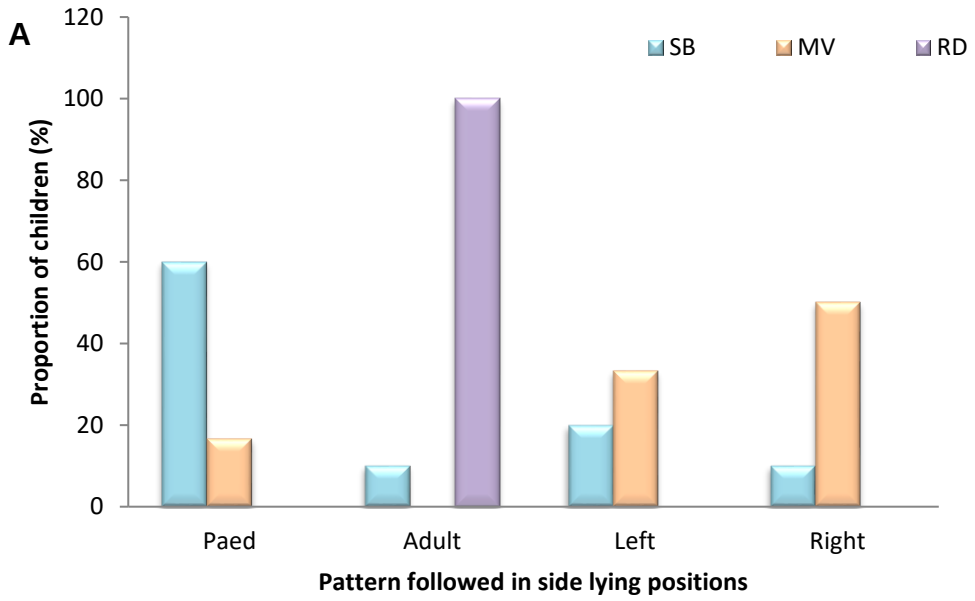
Table 5.5.9 Interaction between intercostal and dorsal hemi-diaphragm activity and the proportion of ventilation in the dorsal lung region in the supine and prone positions

	Coefficient Estimate	95% Confidence interval		p-value
		Lower	Upper	
Intercept	66.17	56.39	75.96	0<01
Intercostals	-2.62	-4.39	-0.85	0.01
Dorsal Hemi-diaphragm	0.87	-3.26	4.99	0.65

5.5.5.4 Differences in regional ventilation compared to Study one, Study two and Study three

5.5.5.4.1 Side lying positions

The pattern of ventilation followed was similar in children with respiratory disease and healthy children (Figure 5.5.9). There was only one infant with respiratory disease, who followed the adult pattern in side lying positions, therefore statistical analysis was not performed.



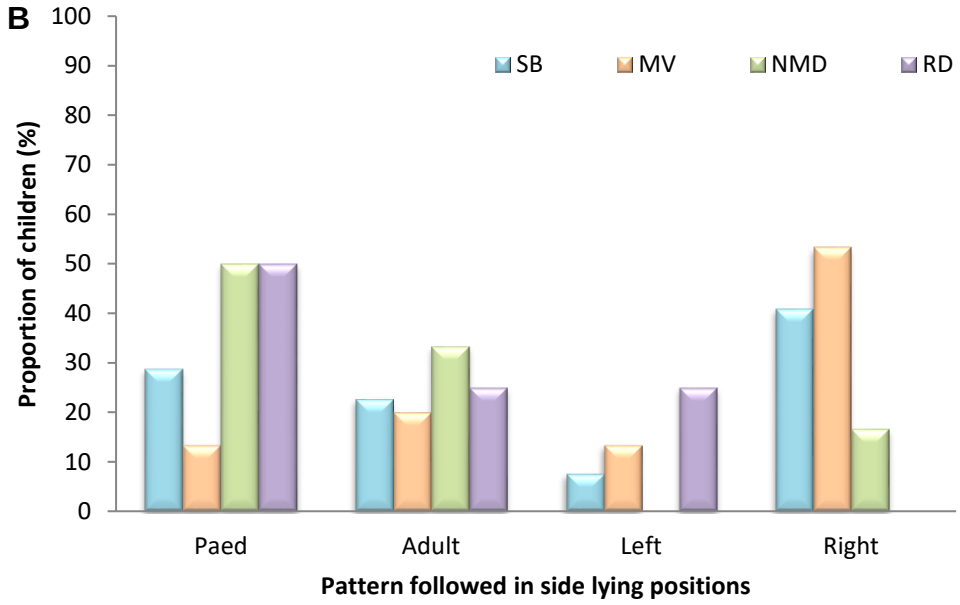


Figure 5.5.9 Pattern of ventilation consistently followed by healthy, spontaneously breathing (SB), mechanically ventilated (MV), children with neuromuscular disease (NMD) and children with respiratory disease (RD) in infants (A) and children (B).

5.5.5.4.2 Supine and prone positions

The patterns of ventilation followed in children with respiratory disease were not significantly different to those followed by healthy children, mechanically ventilated children and those with NMD (Figure 5.5.10).

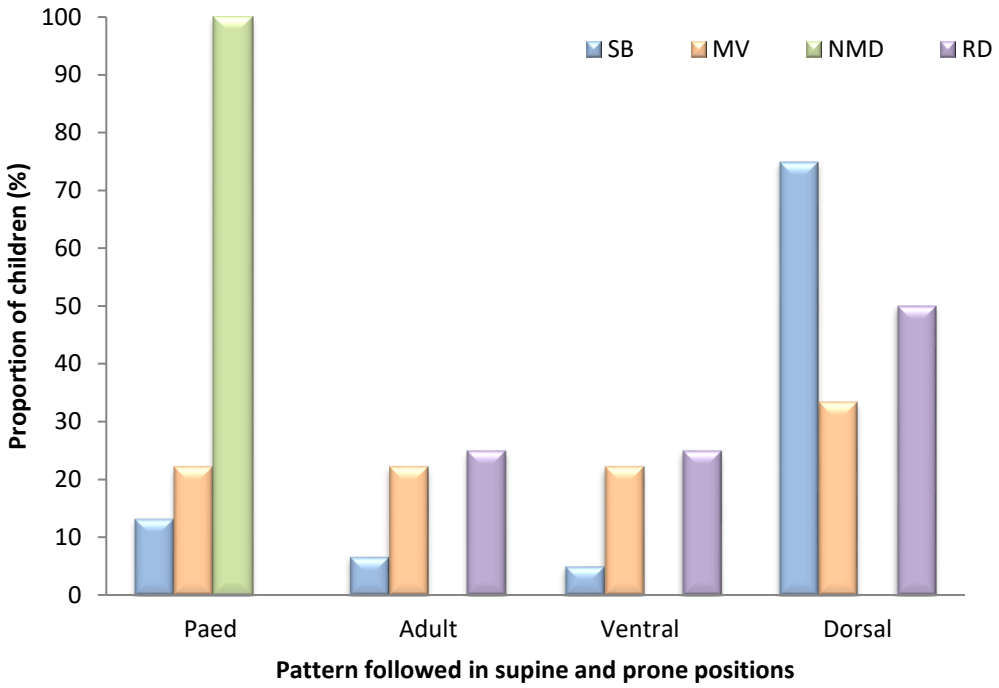


Figure 5.5.10 Pattern of ventilation consistently followed by healthy, spontaneously breathing (SB), mechanically ventilated (MV), children with neuromuscular disease (NMD) and children with respiratory disease (RD).

5.5.6 Discussion

Since the 1980's, this is the first study to examine the effect of body position on regional ventilation in older infants and children with respiratory disease. Although the results cannot be applied to all children with respiratory disease, due to the small sample size, these results suggest the distribution of ventilation in children with respiratory disease is not as uniform as previously thought.

5.5.6.1 Regional ventilation distribution

The pattern of ventilation consistently followed by infants and children with respiratory disease in different body positions is variable. This is contrary to the teaching based on the studies of Heaf et al. (1983) and Davies et al. (1985), but is in keeping with the other studies presented in this thesis. Although no significant differences were detected, owing to the small sample size, mean relative impedance change was higher in the dependent lung regions in the side lying positions. In the supine and prone positions, although not significant, the ventral lung showed greater ventilation when dependent, whereas the dorsal lung showed slightly better ventilation non-dependent. These findings need to be confirmed in a larger sample. Although none of the children with respiratory disease showed consistently greater ventilation of the left lung region, ventilation distribution was similar to that observed in healthy children in side lying and in the supine and prone positions in this cohort of children.

5.5.6.2 Regional filling characteristics

In keeping with the observations of mean relative impedance change, filling indices in the dependent lung regions were slightly higher, which may explain the greater ventilation in these regions. However, these were not significant and therefore this requires confirmation. The dorsal lung region had a significantly higher filling index in the supine position when compared to the ventral lung region. This is in keeping the notion that the dependent lung regions are placed lower on the pressure-volume curve, and therefore experience slower initial filling which increases as the volume delivered increases (Milic-Emili et al., 1966).

5.5.6.3 Respiratory muscle activity

Respiratory muscle activity was unaffected by side lying positions. Significantly greater activity was seen in the ventral hemi-diaphragm in the supine position. This finding is in keeping with the studies in healthy children and those receiving mechanical ventilation. Greater activity may be related to the more compliant anterior chest wall, particularly in children where work of breathing may be increased. While diaphragm activity was not associated with the distribution of ventilation, intercostal muscle activity was associated with the distribution of ventilation in the ventral and dorsal lung regions. In the ventral lung region, intercostal muscle activity was associated with an increase in the proportion of ventilation. This may be attributed to the stabilising effect the intercostal muscles have on the rib cage and therefore may facilitate the greater ventilation in the ventral lung region. The opposite was observed in the dorsal lung region, where intercostal activity was associated with a reduction in ventilation. Given the small sample size we can only speculate reasons for the effect of intercostal activity on ventilation distribution, and this finding would need to be confirmed in a larger sample.

5.5.6.4 Limitations

The sample size is a major limitation, and the results of this pilot study need to be confirmed in a larger cohort, before reasonable conclusions can be drawn and applied. Nevertheless, these results provide new insights, and provide baseline data to guide further studies. Methodological and instrument related limitations are similar to those previously discussed (Chapter 5.2.7).

5.5.7 Clinical implications and future research

Based on the small sample size, limited recommendations for clinical practice can be made. These results, in keeping with the rest of the studies in this thesis, suggest that the distribution of ventilation is variable in children, and therefore the choice of position in clinical practice should be based on the individual's response.

5.5.8 Conclusion

Whilst only a pilot study, these results are contrary to what has formed the basis of the choice of positioning in the management of infants and children with respiratory disease. These results are in keeping with the results of the other studies in this thesis, with infants and children demonstrating variable patterns of ventilation distribution.

Chapter 6 Study Five - The distribution of ventilation during prone positioning in infants and children with ARDS

6.1 Introduction

The improvement in oxygenation associated with prone turning in ARDS is said to occur as a result of recruitment of the previously collapsed dorsal lung regions, resulting in a more homogenous distribution of ventilation and thereby improved ventilation/perfusion matching (Matthews & Noviski, 2001; Pelosi, Brazzi & Gattinoni, 2002). In ARDS there is increased lung mass, as a result of oedema, and consequently increased superimposed pressure on the dependent lung regions. This increased pressure results in compression atelectasis of the dependent lung regions (Pelosi, Brazzi & Gattinoni, 2002; Gattinoni et al., 2006). Since there is a greater amount of lung tissue in the dorsal regions, atelectasis in these regions can have a significant impact on ventilation/perfusion matching and oxygenation. Adult studies have shown that when a patient is turned into the prone position, there is a more uniform distribution of the lung tissue from dorsal to ventral (Pelosi, Brazzi & Gattinoni, 2002) aiding in improved ventilation/perfusion matching. In addition to the changes to the lung tissue; there is decreased compression on the left lower lobe by the heart; decreased chest wall compliance and reduced effects of abdominal pressure on the thorax in the prone position (Matthews & Noviski, 2001; Gattinoni et al., 2013), all of which promote a more homogenous distribution of ventilation by minimising collapse of the dependent lung regions. Most of the studies have used computed tomography to measure differences in the lung inflation and ventilation. Although useful, this technique requires repeated radiation exposure and transport of the patients out of the critical care unit, making it unsuitable for use in infants and children. To date, there have been no studies examining the effects of prone positioning in infants and children with ARDS on the distribution of ventilation.

The beneficial short term effects, such as improved oxygenation and a reduction of dead space, of proning patients with ARDS have been established (refer to Section 2.5), it has also been noted that these benefits are not consistently seen in all patients. Until recently, a beneficial effect of prone positioning on important clinical outcomes, such as mortality, ventilator free days and length of ICU and hospital stay, particularly in the paediatric population, had not been confirmed (Gattinoni et al., 2001; Curley et al., 2005; Guérin et al., 2013). Improved survival is likely to occur as a result of improved ventilation homogeneity and a reduction in regional stress and strain in the lung (Albert et al., 2014). Based on the potential of prone positioning to reduce ventilator induced lung injury (VILI) and improve survival, Albert et al. (2014) suggested that prone positioning should be used routinely in early severe ARDS, and these benefits may extend to less severe cases as well. In the paediatric population, however, based on the lack of long term clinical improvement from

prone positioning, it has been recommended that it should not be used routinely in clinical practice (Curley et al. 2005). However, intermittent prone positioning appears to have some benefit to hypoxic patients with ARDS (Fineman et al., 2006).

The effect of prone positioning on ventilation distribution in paediatric ARDS (PARDS) has not been studied. This lack of knowledge is largely due to challenges and ethical implications of obtaining this data in the paediatric population. EIT provides the opportunity to gain insight and understanding into the effects of prone position on ventilation distribution in this population.

6.2 Aim

To determine the effect of turning from supine to prone positions on the regional distribution of ventilation in hypoxic children with ARDS.

6.3 Objectives

1. To measure the changes in regional ventilation distribution in response to turning into the prone position in hypoxic children with ARDS.
2. To correlate the changes in regional ventilation distribution to changes in haemodynamics, oxygen saturation, PaO_2, and ventilation parameters.
3. To examine possible factors which may identify infants and children more likely to respond to prone positioning.

6.4 Methods

6.4.1 Study design

This was a prospective cross-sectional observational study.

6.4.2 Sample

Infants and children in the paediatric intensive care unit at RCWMCH between March 2012 and November 2015 were screened and included in the study if they met the criteria listed below and written informed consent was obtained from their parent/legal guardian.

6.4.2.1 Inclusion criteria

- Mechanically ventilated infants and children with an arterial line in-situ
- Mild to severe ARDS, as determined by a $PaO_2/F_iO_2 \leq 300$ (the PARDS definition was not yet published at study conception and the start of data collection therefore this definition was used).

6.4.2.2 Exclusion criteria

- Haemodynamic instability (changes in mean arterial blood pressure, oxygen saturation and heart rate >20% over the previous 12 hours)
- Pulmonary oedema/haemorrhage

- Cardio-thoracic surgery during current admission or within the previous three months
- Raised intracranial pressure (>15mmHg or evident by a raised fontanel)
- Recent intracranial surgery (during current admission)
- Dressings, wounds or drains (including intercostal drains) in the thoracic region which would impede correct placement of EIT electrodes.

6.4.2.3 Sample size

At the commencement of the study no data was available to perform a sample size calculation; therefore, a *post-hoc* power analysis was conducted after seven participants had been enrolled. Based on the data obtained from the first seven participants it was calculated, using G*Power (v3.1.9.2, Germany), that a sample of 10 participants was needed to determine an effect size of 1.08 in a repeated measures within factor analysis (α=0.05, power=0.95) to determine a difference in dorsal relative impedance change from baseline to 60 minutes in the prone position between responders and non-responders. In order to increase rigor, it was decided to collect data from an additional seven participants making the total sample size 14.

6.4.3 Outcome measures

The primary outcome measure was regional ventilation distribution as determined by EIT, which has been described in Chapter 3.

Oxygenation index (OI) was used to determine the response to prone position as this takes into account changes in PaO_2, FiO_2 and airway pressures. Furthermore, it has been shown to better predict mortality than PF ratio in the paediatric population (Khemani et al., 2015). The morning PaO_2 values from arterial blood gas (ABG) analysis (ABL800 Basic, Radiometer, Denmark), which are taken daily as part of standard practice in the PICU, were used for the pre-intervention measurement and an additional ABG was done at one-hour post-intervention. A change in OI from baseline of more than 10% was considered to be clinically meaningful, in keeping with previous studies (Curley, Thompson & Arnold, 2000; Curley et al., 2005). Therefore, children who had a reduction of 10% or more from their baseline OI were classified as “responders”. Children who showed an increase of 10% or more from their baseline OI were classified as “non-responders”. Infants and children who displayed a change of less than 10% were classified as “no change”.

Physiological parameters, including heart rate, respiratory rate, blood pressure and oxygen saturation, which are continuously monitored in the PICU, were also recorded pre- and post-intervention (Appendix 4.2).

6.4.4 Study procedure

Potential participants were identified by the investigators or doctors overseeing their care. Parents or legal guardians of infants and children who met the inclusion criteria were approached. The study was explained to them and written informed consent was obtained (Appendix 3.5).

EIT measures (as described Chapter 4.5.1) were taken in the supine position as the baseline measurement. The infant/child was then turned into the prone position by a team of staff, ensuring that all lines and invasive devices remained secure throughout the manoeuvre. The infant/child was placed in the prone position with their head rotated to either the left or right, according to convenience. A small roll was placed under the upper third of their thorax to maintain a neutral neck position and the abdomen was not free. Measurements were then repeated at 5 minutes, 20 minutes and 60 minutes after being turned into the prone position. Each EIT measurement was taken for approximately one minute or until a series of at least five reproducible breaths was obtained. The morning ABG (or the most recent if available) was used as a baseline measure of pH, PaO_2 and $PaCO_2$. Another ABG was taken 60 minutes after being turned into the prone position and change in pH, PaO_2 and $PaCO_2$ was documented to determine the response to being turned into the prone position. Additional data that was collected and monitored throughout the process included haemodynamics and ventilatory settings (Appendix 4.2).

6.4.5 Ethical considerations

Ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town (Appendix 2.2). Approval was obtained from the medical superintendent of RCWMCH and the director of the PICU. Information regarding the study was provided in the preferred language of the parent or legal guardian and written informed consent was obtained. This study was in keeping with the principles laid out in the Declaration of Helsinki (2013).

Interventions carried out in this study form part of the standard care in the PICU at RCWMCH and therefore added no additional risk to participants. There are no known harmful effects associated with the use of EIT (Pillow, Frerichs & Stocks, 2006).

6.4.6 Data and statistical analysis

6.4.6.1 Mean relative impedance change

The mean relative impedance change for the ventral and dorsal lung regions was calculated for each measurement, comprising of five consecutive breaths of similar amplitude (Heinrich et al., 2006), from the fEIT images. The proportion of ventilation, relative to global ventilation, was then calculated for each infant/child to take into account age-related

differences in lung volume and allow for comparison between participants, this value was used in the analysis (Equation 6.4.1).

$$Proportion\ of\ ventilation\ (\%) = \frac{Mean\ regional\ relative\ impedance\ change}{Mean\ global\ relative\ impedance\ change} * 100$$

Equation 6.4.1 Calculation of the proportion of ventilation.

6.4.6.2 Global inhomogeneity index (GI)

The GI was calculated from the fEIT data, as previously described in Chapter 4.5.1, for the entire (global) lung region. This has recently been shown to reliably determine ventilation inhomogeneity and recruitable lung in adult patients with ARDS (Zhao et al., 2014).

The co-efficient of variation (CV) was calculated for the GI among the responders, non-responders and those that showed no change, respectively (Equation 6.4.2).

$$Co - efficient\ of\ variation = \frac{Standard\ deviation}{Mean}$$

Equation 6.4.2 Calculation of the co-efficient of variation.

6.4.6.3 Regional filling characteristics

To determine regional filling characteristics of the ventral and dorsal lung regions relative to global filling, plots of regional relative impedance change versus global relative impedance change during inspiration were plotted (Frerichs et al., 2001; Hinz et al., 2007). The raw relative impedance change values were taken from five consecutive breaths, to which a filter was applied to remove any biological noise such as the heartbeat. Regional (ventral and dorsal lung regions) and global relative impedance change were normalised to a fraction of 1.0 to allow for inter-individual comparison (Hinz et al., 2007). These plots were then fitted to a polynomial function to the second degree ($y = ax^2+bx+c$). The polynomial co-efficient of the second degree (*'a'*) is representative of the curvature of the tracing. A positive polynomial coefficient indicates initially slow filling, relative to global, and may indicate possible recruitable lung. A negative polynomial co-efficient indicates rapid filling of the region relative to global filling and may indicated possible hyperinflated lung. A polynomial co-efficient of almost zero indicates homogenous filling and is indicative of optimal, protective ventilation (Figure 6.4.1) (Hinz et al., 2007).

Regional filling characteristics (relative to global) for the ventral and dorsal lung regions were calculated for each measurement period. The correlation co-efficient (R^2) was also calculated for each plot.

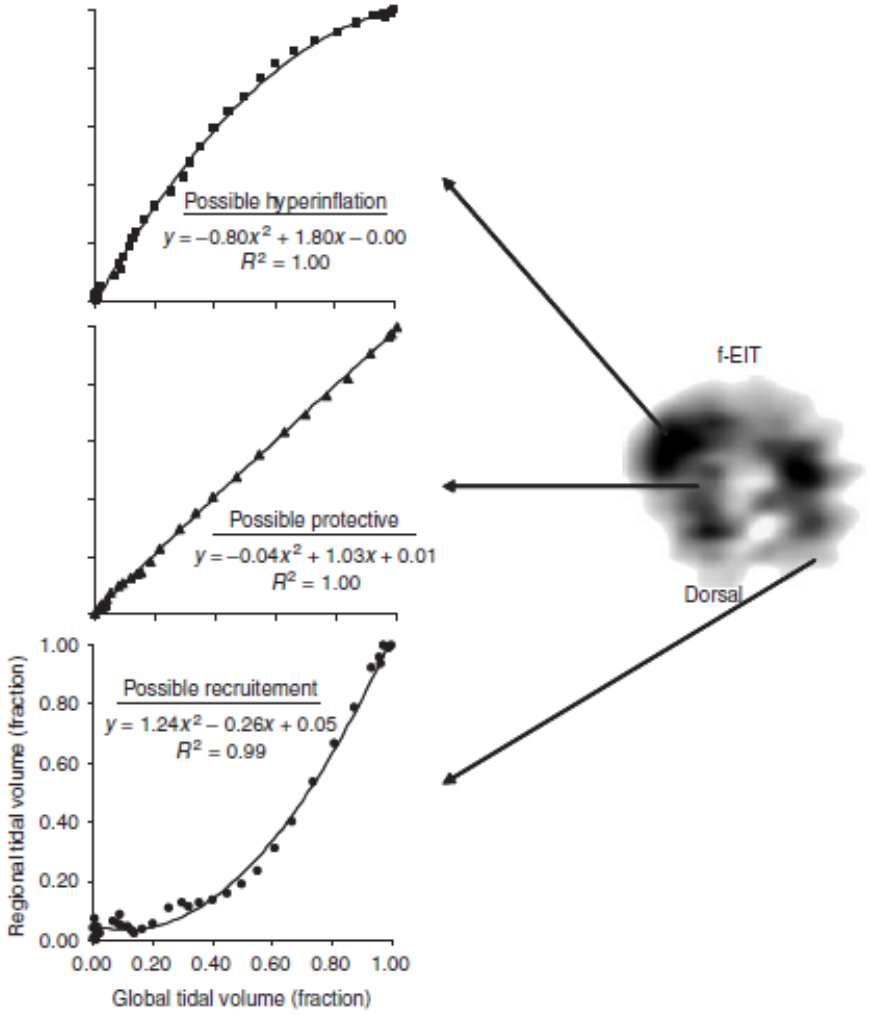


Figure 6.4.1 An example of the polynomial function derived from the plots of regional vs global tidal volume from an EIT image. Used with permission from Hinz et al. (2007).

6.4.6.4 Statistical analysis

Data were tested for normality using the Shapiro-Wilks W test. Differences in total ventilation induced impedance change globally and per region (ΔZ) at the four measurements were determined using two-way (within- and between groups) ANOVA for repeated measures. To account for possible age-related differences, the proportion of ventilation (Equation 6.4.1) was used to allow for inter-individual comparison. Post hoc t-tests or Mann-Whitney U tests were used to determine where significant differences occurred (Stastica12, Statsoft, Tulsa, USA). To determine the differences in the co-efficient of variation for the GI, between the two groups, a two-sided z-test was performed. A Bonferroni correction was applied for multiple comparisons where appropriate.

6.5 Results

6.5.1 Plain language summary of results

Twelve children were studied. Varied responses to prone positioning were found. Four children demonstrated a reduction in OI (responders), three showed an increased in OI (non-responders) and five showed no change. Ventilation increased in the dorsal lung regions and decreased in the ventral lung regions in all response groups in the prone position. Ventilation distribution tended to be more heterogeneous at baseline in those that responded to prone positioning. Regional filling appeared to be more homogenous at baseline in non-responders and those that showed no change at baseline compared to responders. With time in the prone position, regional filling became more homogenous in the responders. No significant differences were found in any measures of ventilation distribution between the response groups.

6.5.2 Demographics

Data were tested for normality and were normally distributed; therefore, data are presented as means and standard deviations (SD).

Twelve infants/children (9 male, 75%) were studied (Figure 6.5.1). The mean age was 39 ± 41 months. Varying degrees of severity of ARDS were observed, with the majority of children falling into the mild category (Table 6.5.1). Infants and children included in this study required mechanical ventilation for respiratory failure, with the most common primary admission diagnosis of pneumonia (6, 50%) (Table 6.5.2).

Four infants/children (2 male) with a mean age of 63 ± 56 months were “responders”, demonstrating a decrease of 39 ± 21% in OI after 60 minutes in the prone position. Three infants/children (3 male) with a mean age of 22 ± 16 months were “non-responders” demonstrating an increase of 61± 57% in OI after 60 minutes. Five infants/children (4 male) with a mean age of 37 ± 29 months showed “no change”. Characteristics of the different responses are shown in Table 6.5.3. After applying a Bonferroni correction ($p<0.003$ considered significant), all types of responders displayed similar characteristics with regards to ventilation settings, ABG’s and measures of oxygenation, with no significant differences between groups at baseline or at 60 minutes (Appendix 6.1). Although responders showed improved PF ratio, SF ratio and OI, whilst non-responders showed deterioration in their PF ratio, SF ratio and OI, these differences were not significant. No adverse events occurred during the study.

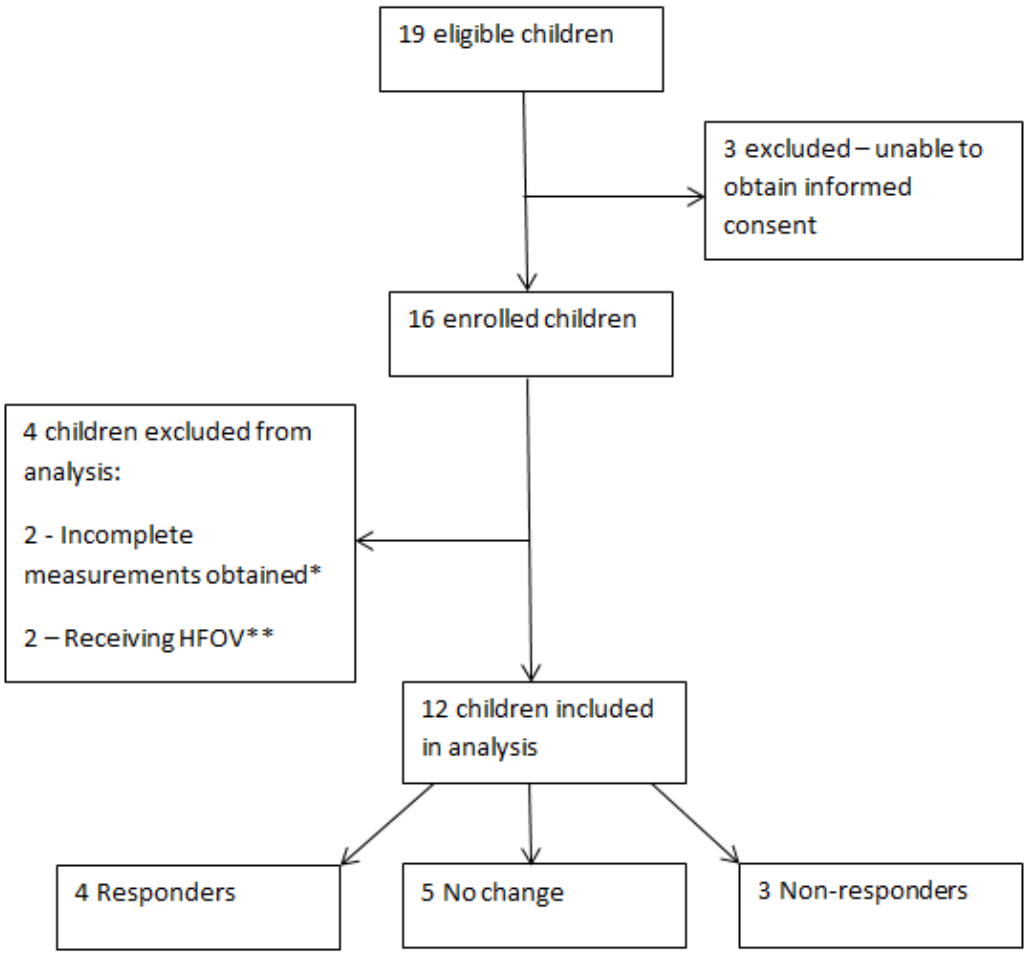


Figure 6.5.1 Flow of children through the study. *1 – doctors need to perform a procedure during study; 1 – unable to obtain final blood gas due to machine undergoing maintenance. ** These were excluded to improved data homogeneity, since five tidal breaths could not be selected.

Table 6.5.1 Classification of ARDS based on OI index (Khemani et al., 2015)

ARDS severity	Responders	Non - Responders	No change	Total
Mild (4 ≤ OI ≥ 8)	2	1	5	8
Moderate (8 ≤ OI ≥ 16)	1	1	0	2
Severe (OI ≥ 16)	1	1	0	2

Table 6.5.2 Primary diagnosis of infants/children enrolled into the study

Primary diagnosis	Number of infants/children
Pneumonia	6
Bronchopneumonia	2
Bronchiolitis	1
Sepsis	1
Interstitial lung disease	1
Acute flaccid paralysis	1

Table 6.5.3 Characteristics of different response groups at baseline and 60 minutes after being turned into the prone position (mean ± SD).

	Responders			Non-responders			No change		
	Baseline	60 Minutes	p-value*	Baseline	60 Minutes	p-value*	Baseline	60 Minutes	p-value*
Age (months)	63 ± 56	-	-	22 ± 16	-	-	37 ± 49	-	-
Vitals									
HR (beats/min)	117 ± 39	107 ± 19	0.66	119 ± 31	120 ± 33	0.98	125 ± 13	131 ± 10	0.55
MABP (mmHg)	84 ± 9	74 ± 14	0.26	65 ± 4	61 ± 8	0.35	60 ± 14	59 ± 9	0.95
SpO2 (%)	98 ± 3	98 ± 2	0.81	89 ± 6	94 ± 5	0.22	88 ± 6	89 ± 3	0.67
Ventilator settings									
PIP (cmH_2O)	23 ± 6	21 ±5	0.66	18 ± 2	18 ± 2	0.90	29 ± 4	32 ± 10	0.63
PEEP (cmH_2O)	7 ± 2	7 ±2	1.00	5 ± 1	5 ± 1	1.00	12 ± 5	13 ± 6	0.84
MAP (cmH_2O)	13 ± 4	12 ±4	0.72	10 ± 1	10 ± 1	0.31	17 ± 5	20 ± 8	0.69
FiO_2	0.55 ± 0.20	0.44 ± 0.13	0.38	0.53 ± 0.24	0.53 ± 0.14	1.00	0.41 ± 0.10	0.38 ± 0.08	0.61
Arterial blood gas									
pH	7 ±1	7 ± 0	0.77	7 ± 0	7 ± 0	0.54	7 ± 0	7 ± 0	0.98
PaO_2 (kPa)	11 ± 3	14 ± 3	0.17	9 ± 2	8 ± 0	0.99	11 ± 2	8 ± 0	0.10
$PaCO_2$ (kPa)	7 ± 2	7 ± 1	0.67	6 ± 1	7 ± 1	0.29	7 ± 1	7 ± 1	0.95
OI	10 ± 8	5 ± 2	0.23	6 ± 1	6 ± 1	0.99	14 ± 11	20 ± 14	0.60
% change in OI	-	-39 ± 21	-	-	61 ± 57	-	-	0 ± 5	-
PF ratio	170 ± 92	247 ± 80	0.26	173 ± 37	182 ± 30	0.70	173 ± 98	114 ± 28	0.37
SF ratio	200 ± 80	240 ± 73	0.49	187 ± 82	176 ± 45	0.57	187 ± 82	176 ± 45	0.83

* p-value is between baseline and 60 minutes within each group. HR – heart rate; MABP – mean arterial blood pressure; SpO2 oxygen saturation; PIP – peak inspiratory pressure; PEEP – positive end expiratory pressure; MAP – mean airway pressure; FiO_2 – fraction of inspired oxygen; PaO_2 – partial pressure of oxygen; $PaCO_2$ – partial pressure of carbon dioxide; OI – oxygenation index; PF ratio – partial pressure of oxygen/fraction of inspired oxygen; SF ratio – oxygen saturation/fraction of inspired oxygen.

6.5.3 Mean relative impedance change in ventilation distribution

The interactions between the effects of time in the prone position and type of response on the proportion of ventilation in the ventral (Figure 6.5.2) and dorsal (Figure 6.5.3) lung regions were not significant. Within the ventral and dorsal lung regions, no significant differences were found between response groups at baseline, 5 minutes, 20 minutes and 60 minutes (Table 6.5.4). Irrespective of type of response to prone positioning, ventilation in the dorsal lung region tended to increase and ventilation in the ventral lung region decreased, resulting in a relatively equal proportion of ventilation occurring in each lung region with time in the prone position.

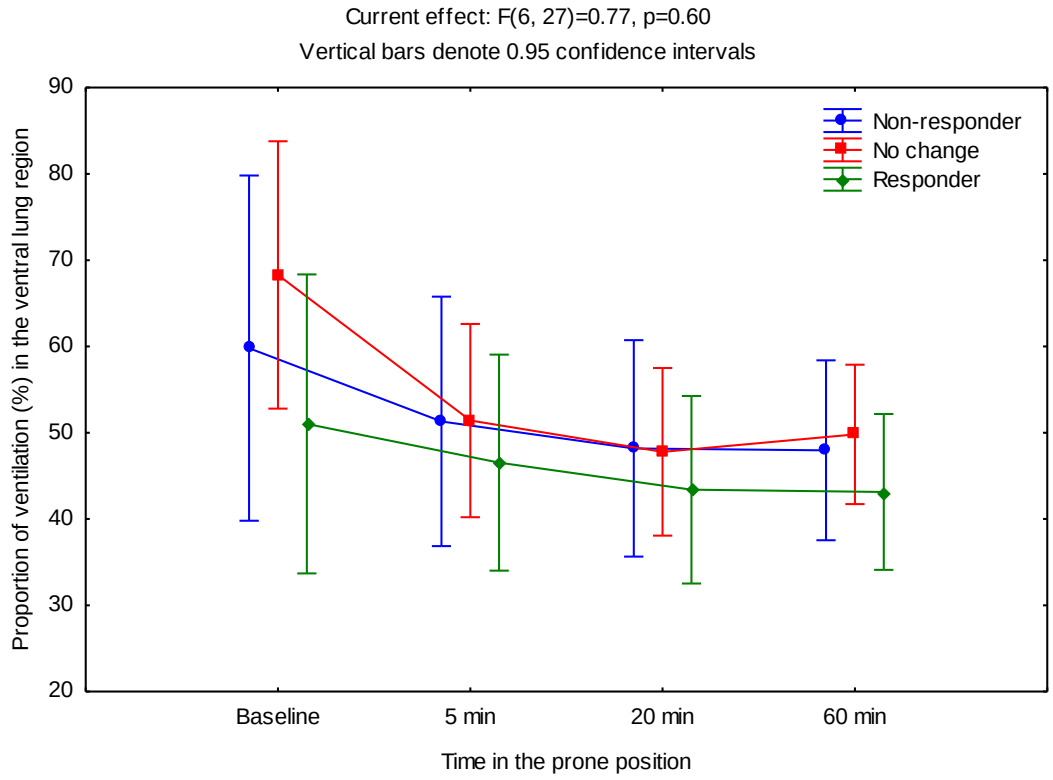


Figure 6.5.2 Proportion of ventilation occurring in the ventral lung region over time in the prone position between response groups

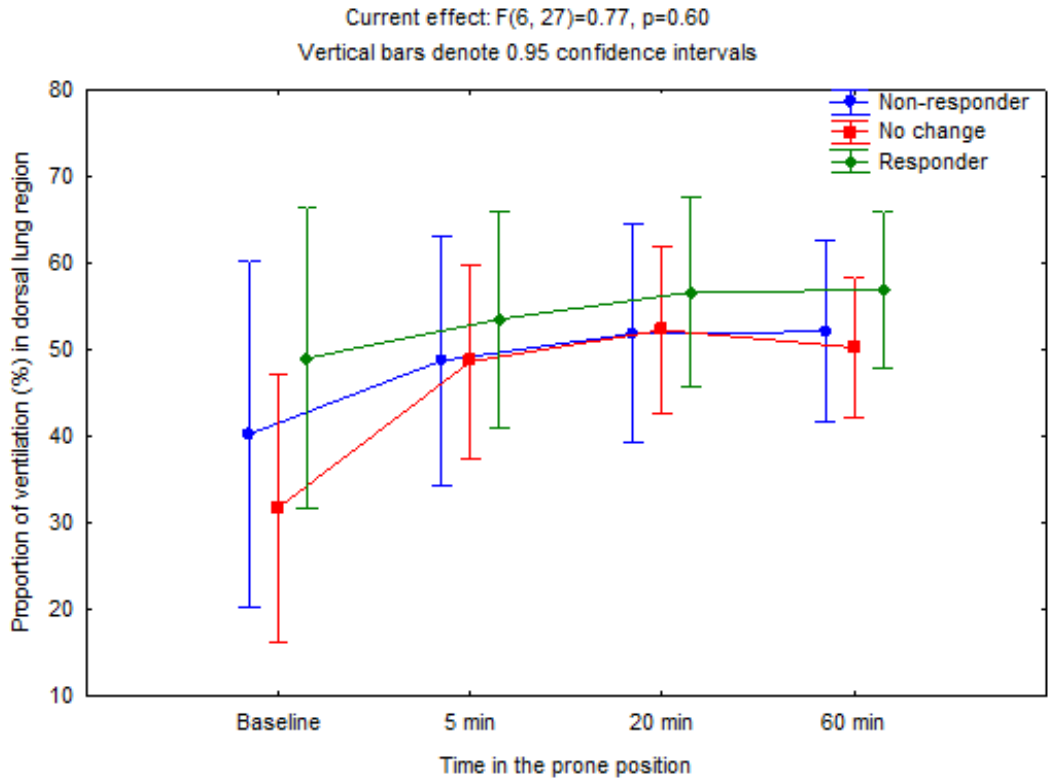


Figure 6.5.3 Proportion of ventilation occurring in the dorsal lung region with time in the prone position between response groups.

Table 6.5.4 Regional ventilation characteristics in all response groups

		Baseline	5 minutes	20 minutes	60 minutes
Responders (n=4)	GI index	1.06 ± 0.31	0.98 ± 0.18	1.08 ± 0.27	1.03 ± 0.22
	Ventral lung				
	Ventilation (%)	51.03 ± 21.93	46.53 ± 3.33	43.40 ± 3.66	43.14 ± 5.39
	Polynomial co-eff	0.20 ± 0.37	0.15 ± 0.13	0.14 ± 0.11	0.09 ± 0.14
	Correlation co-eff	0.86 ± 0.24	0.95 ±0.06	1.00 ± 0.00	0.98 ± 0.02
	Dorsal lung region				
	Ventilation (%)	48.97 ± 21.93	53.47 ± 3.33	56.60 ± 3.66	56.86 ± 5.39
	Polynomial co-eff	-0.06 ±0.17	-0.14 ± 0.12	-0.11 ± 0.07	-0.05 ± 0.09
	Correlation co-eff	0.91 ± 0.15	0.96 ± 0.05	1.00 ± 0.00	0.99 ± 0.01
Non-responders (n=3)	GI index	0.97 ± 0.17	0.95 ± 0.10	0.90 ± 0.09	0.89 ± 0.09
	Ventral lung				
	Ventilation (%)	59.80 ± 16.07	51.32 ± 16.08	48.18 ± 16.53	47.96 ± 12.95
	Polynomial co-eff	0.50 ± 0.86	0.12 ± 0.07	0.06 ± 0.04	0.05 ± 0.07
	Correlation co-eff	0.93 ± 0.12	0.99 ± 0.01	0.99 ± 0.00	1.00 ± 0.00
	Dorsal lung region				
	Ventilation (%)	40.20 ± 16.07	48.68 ± 16.08	51.82 ±16.53	52.04 ± 12.95
	Polynomial co-eff	0.06 ± 0.92	-0.15 ± 0.15	-0.07 ± 0.06	-0.07 ± 0.12
	Correlation co-eff	0.96 ± 0.04	0.99 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
No change (n=5)	GI index	0.91 ± 0.12	0.94 ± 0.09	0.98 ± 0.20	0.95 ± 0.11
	Ventral lung				
	Ventilation (%)	68.28 ± 6.17	51.41 ± 11.74	47.79 ± 7.81	49.81 ±6.15
	Polynomial co-eff	0.02 ± 0.14	0.21 ± 0.15	0.28 ± 0.27	0.34 ± 0.32
	Correlation co-eff	1.00 ± 0.00	0.99 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
	Dorsal lung region				
	Ventilation (%)	31.72 ± 6.17	48.59 ± 11.74	52.12 ± 7.81	50.19 ±6.15
	Polynomial co-eff	0.01 ± 0.38	-0.27 ± 0.26	-0.33 ± 0.38	-0.35 ± 0.35
	Correlation co-eff	1.00 ± 0.00	0.98 ± 0.01	1.00 ± 0.00	1.00 ± 0.00

GI - Global inhomogeneity

6.5.4 Global inhomogeneity index

GI index within the three different groups of responses remained similar at all measurement points, with no significant differences found, within and between groups (Table 6.5.4). Although the GI in the responders was not significantly different to the non-responders or those that showed no change at all measurement points, there is a larger data range in the responders compared to the other groups (Table 6.5.4 and Figure 6.5.4).

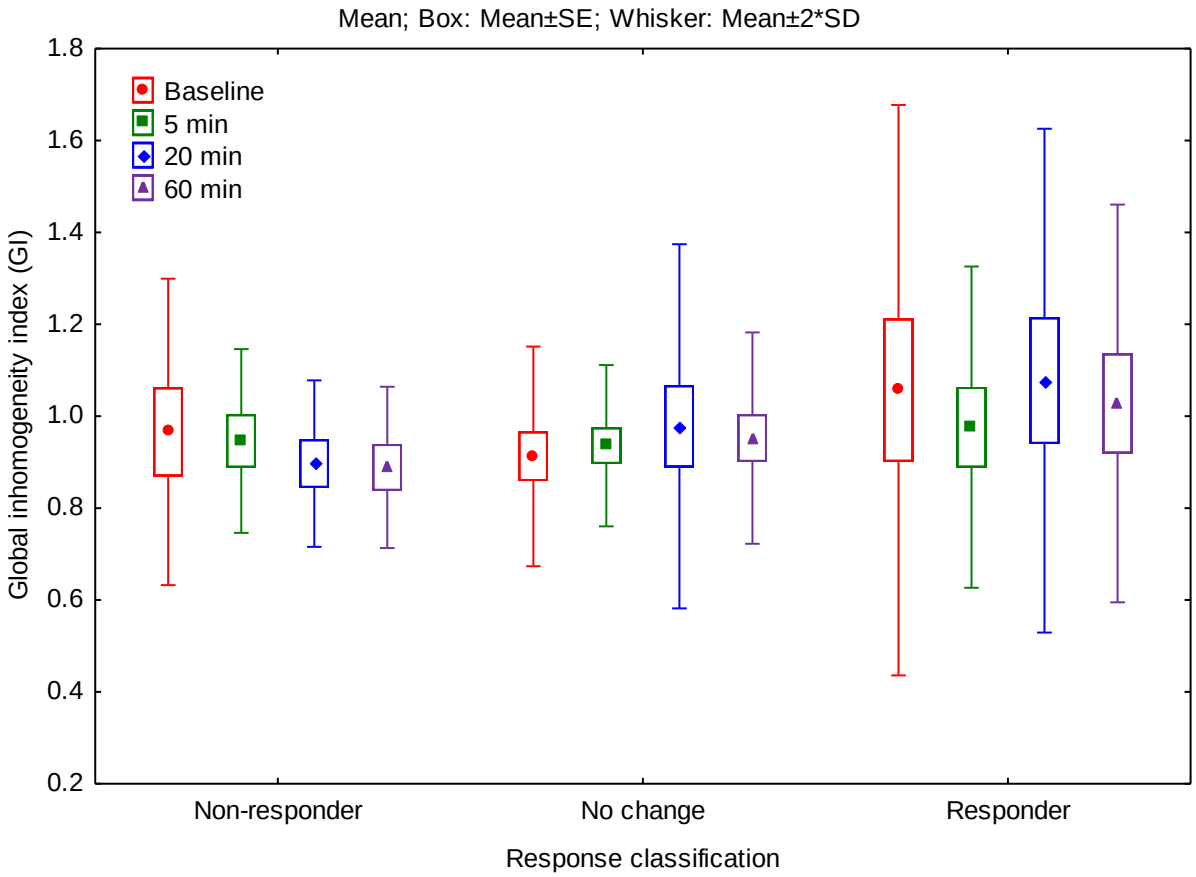


Figure 6.5.4 Global inhomogeneity index between different response groups at different time points in the prone position.

Responders showed a greater degree of variation in ventilation homogeneity as indicated by the co-efficient of variation of the GI index at baseline compared to non-responders or those that showed no change, however this was not significant (Table 6.5.5). Although not significant, the variation decreased with time in the prone position in both the responders and non-responders, whilst it remained unchanged in those that showed no change.

Table 6.5.5 Co-efficient of variation (CV) for GI index for the different response groups at the different measurement points

	Baseline	5 Minutes	20 Minutes	60 Minutes
Responder	0.35	0.22	0.24	0.24
No change	0.11	0.16	0.16	0.11
Non-responder	0.17	0.11	0.10	0.10

6.5.5 Regional filling characteristics

The mean polynomial and correlation co-efficients were similar between all three response groups. Most of the polynomial co-efficients fall within the “negligible range” of -0.20 to 0.20 (Hinz et al., 2007) indicating relatively equal rates of filling between the respective lung region and that of global filling. An example of the difference between the regional filling characteristics of a responder and non-responder between baseline and 60 minutes in the prone position are shown in the plots of regional inflation during five breaths (Figure 6.5.5). Of note in the plots is the difference in breath by breath variability between responders and non-responders and the improvement in this variability in the responders with time in the prone position.

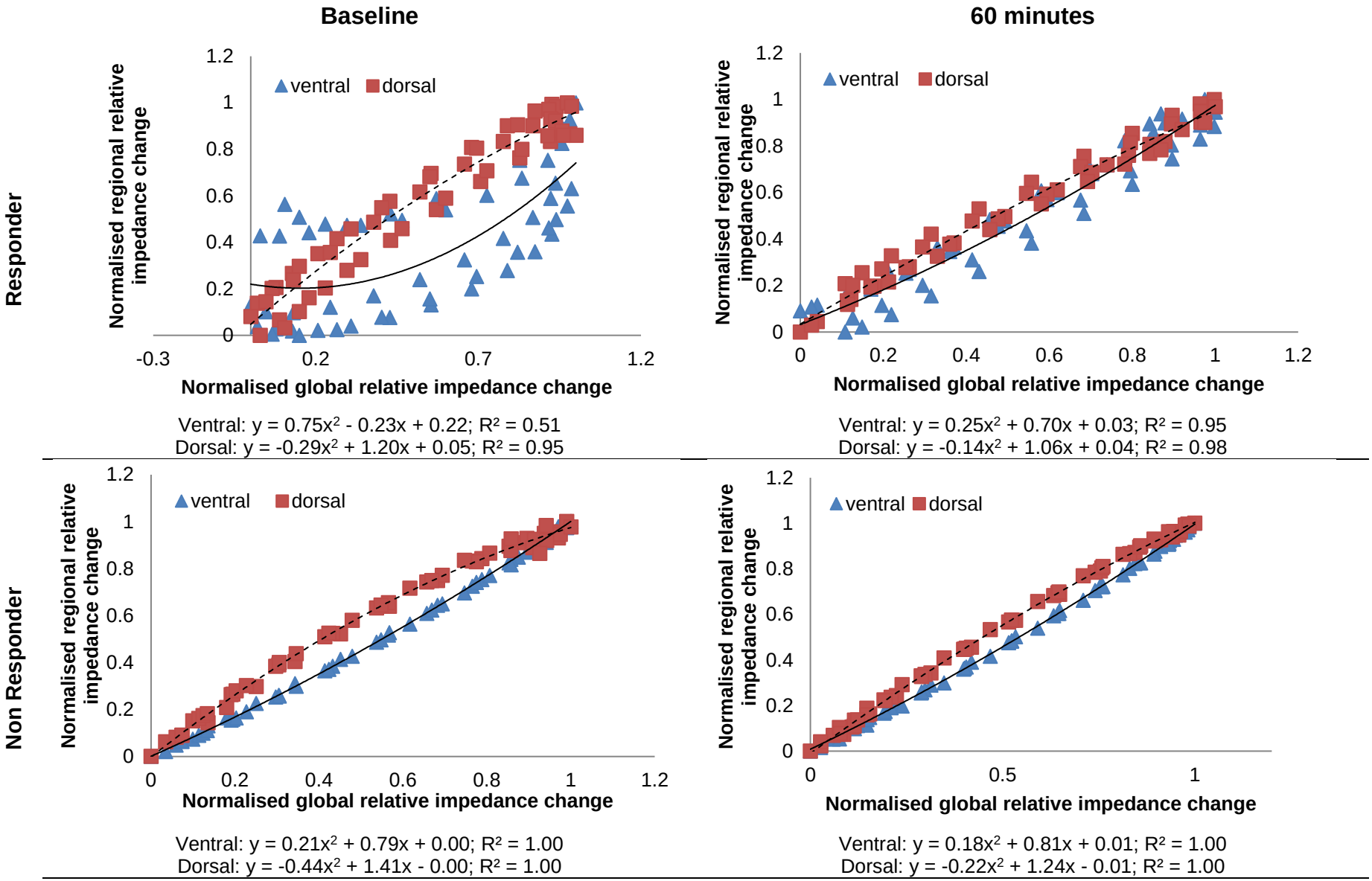


Figure 6.5.5 Examples of regional filling plots for five breaths in a responder and non-responder at baseline and after 60 minutes in the prone position. Included are the polynomial functions to the second degree for the ventral and dorsal lung regions as well as the corresponding correlation co-efficient

6.6 Discussion

This is the first study to report the effects of prone positioning on regional and global ventilation distribution in infants and children with ARDS. Although limited by a small heterogeneous sample, the results provide new insight into the effects of prone positioning on ventilation distribution in children with ARDS. Findings suggest that positive response to prone turning may not necessarily only be related to improved ventilation in the dorsal lung regions, but also improved homogeneity of ventilation throughout the lung. Results from this study are not powered sufficiently to adequately inform clinical practice, however they do provide new information which can assist in the development of future, well-designed studies on this important topic.

The observed improvement in ventilation homogeneity, as suggested by the change in the proportion of ventilation and GI index in the prone position, are in keeping with adult studies which have reported improved inflation throughout the lung in the prone position (Gattinoni et al., 1991; Pelosi et al., 1994). Uniformity of transpulmonary pressure gradients and reduced hydrostatic pressures in the dependent lung regions are thought to account for the improved inflation (Mutoh et al., 1992; Pelosi, Brazzi & Gattinoni, 2002). Since we did not take direct measures of these factors, we can only speculate that these may have contributed to the findings of improved ventilation homogeneity. In infants and children who have an inherently more compliant chest wall, prone positioning may aid in limiting movement of the anterior portion of the chest wall, resulting in a more homogenous distribution of ventilation, as was seen by the reduction of ventilation occurring in the ventral lung region. Furthermore, limiting the movement of the anterior chest wall may also result in more effective respiratory muscle activity.

An interesting and notable observation was that responders tended to have greater ventilation inhomogeneity in the supine position (baseline) compared to the non-responders as seen in the larger standard deviations in both R^2 and GI values. This inhomogeneity improved with time spent in the prone position and was similar to that of the non-responders after 60 minutes. This observation supports the notion that improved ventilation homogeneity in the prone position may account for the improved oxygenation seen. Furthermore, measures of baseline inhomogeneity may guide practitioners in identifying which children may be more likely to respond positively to being turned prone. Given the increase in OI observed in the non-responders, being able to identify children who are more likely to respond may prevent potentially detrimental manoeuvres. These observations require confirmation from further studies with larger samples. Kavanagh (2005) proposed that factors other than oxygenation should be considered when trying to determine the effect

of prone positioning on clinical outcomes, these results suggest that perhaps ventilation homogeneity should be considered as an outcome measure.

Several factors may explain the minimal change in OI in the “no change” group. Firstly, all these children had mild ARDS, therefore may not have had the same degree of ventilation inhomogeneity as those in the other two groups. Secondly, this group had relatively high PEEP settings compared to responders and non-responders (12cmH_2O vs 7 cmH_2O and 5cmH_2O). The application of PEEP helps ameliorate collapse of dependent lung regions and improve EELV, which may help improve overall ventilation homogeneity (Gattinoni et al., 1993; Hinz et al., 2005; Frerichs et al., 2007).

It has been postulated that prone positioning may be effective in improving oxygenation by recruiting previously collapsed dorsal lung regions (Pelosi et al., 2001). This is not supported by our results. Although ventilation in the dorsal lung regions increased with time in the prone position, the change was no different between responders, non-responders and those that showed no change. At 60 minutes both lung regions were contributing relatively equally to overall ventilation in all positive responders, which suggests that ventilation becomes more homogenous in the prone position.

The degree of collapse or potentially recruitable lung is related to the severity of ARDS or degree of impaired oxygenation as indicated by the PF ratio and is variable between patients (Gattinoni et al., 2006). The regional filling data suggests that there was relatively equal filling between ventral and dorsal lung regions, with no hyperinflated or recruitable areas, based on the range of -0.2 to 0.2 as suggested by Hinz et al. (2007). Since we included children at various stages of ARDS and with varying degrees of severity, with the majority being classified as moderate to mild, it is likely that they would have had less collapse and therefore less “recruitable” lung. Our findings suggest that ventilation redistribution rather than regional recruitment occurs, where a balance is reached between poorly aerated, but open, lung regions and over-aerated lung regions (Santini et al., 2015).

6.6.1 Limitations

There are several limitations to this study. Despite calculating that a sample of 14 children would provide adequate power to determine a difference between the change in dorsal and ventral ventilation, this study was of a small sample in a single institution. Although a positive response to being in the prone position has been reported after only half an hour, other studies suggests that longer periods in the early stages are more beneficial (Guerin, 2014; Lee et al., 2014). Previous paediatric studies report varying response times, with the majority of children (56%) showing a progressive response over 19 hours in the study by Curley, Thompson & Arnold (2000) and a third of responders (n=18) only showing an

improvement in OI after successive periods in the prone position (Casado-Flores et al., 2002). Children in this study were only assessed for a period of 60 minutes in the prone position; therefore, slower responders may have been misclassified as having "no change" in response to prone tuning.

There was a delay of approximately 3 hours between the morning blood gas and turning the patient prone. While ventilation settings remained the same during this time, it is possible that the PaO_2 may have changed. An alternative to using PaO_2 is to use measures such as the SF ratio or oxygen saturation index (OSI), which are non-invasive. Although saturation data was collected during the study; FiO_2 was not titrated to maintain a saturation of ≤97% as recommended (Khemani et al., 2015), and this outcome measure were therefore not considered appropriate to use *post hoc*. The use of such measures may, however, improve sample size in future studies, as a number of children (~5) had to be excluded owing to the absence of indwelling arterial lines. The change in dead space, measured via volumetric capnography, may also be useful as a surrogate measure for response in future studies, especially given the greater inhomogeneity noted in responders. Furthermore, in adults a reduction in dead space has been shown to be associated with improved mortality (Gattinoni et al., 2003). We calculated the corrected minute ventilation (Appendix 6.2); however volumetric capnography may have provided more accurate measurements.

Adult studies suggest that prone positioning may be more advantageous in those with "severe ARDS" (Guerin, 2014). Since we included children of varying degrees of ARDS severity (majority of which were mild to moderate), it is unclear whether similar or more notable results would be observed in those with "severe ARDS" and the small sample size did not allow for meaningful sub-analysis based on ARDS severity. These results, therefore, need to be substantiated in larger sample size studies with moderate to severe ARDS.

6.7 Future research

This study highlights some important areas for future research. Firstly, the results of this study should be confirmed in a larger sample with varying degrees of severity of ARDS and powered to detect changes in markers of ventilation homogeneity, such as GI. Future studies should include measures of chest wall mechanics (motion and compliance) together with changes in regional ventilation to clarify the contribution of chest wall mechanics to the observed response to prone turning. Alternative measures of determining the response to being turned into the prone position, such as the SF ratio, OSI and dead space, should also be examined. This study also highlights the potential for EIT guided titration of ventilation settings, such as PEEP, to achieve ventilation homogeneity, thereby reducing lung stress and strain, and to determine whether this has the same effect on oxygenation as prone

positioning. As has been highlighted in other studies, future studies should examine the effects of a positive response to prone positioning on clinically meaningful outcomes such as the incidence of ventilator induced lung injury, the duration of ventilation or number of ventilator free days and hospital stay, and survival.

6.8 Conclusion

This study provides novel insights into the distribution of ventilation in children with ARDS in response to being turned into the prone position. To the best of my knowledge it is the first to report the effects of prone positioning in ARDS on regional ventilation distribution in infants and children. These results confirm that not all infants and children respond positively to being turned into the prone position and that the degree of response is variable. Results do not support the notion that the dorsal lung regions are “recruited” during a prone manoeuvre in those that do respond positively. Rather, the results suggest that improvement in oxygenation may occur as a result of ventilation redistribution, which becomes more homogenous in the prone position. The results of this study should be confirmed in a larger cohort which also examines the possible mechanisms which may determine the effects of and response to prone positioning. In addition, alternative methods, which may achieve the same effect of prone positioning, should be investigated.

Chapter 7 Conclusion

7.1 Clinical implications

While these studies provide new knowledge on the distribution of ventilation in infants and children beyond neonatal age, they also raise a number of questions regarding factors influencing ventilation distribution. These results highlight that ventilation distribution is not merely determined by gravity and the body's orientation to gravity. Rather, they support the notion that ventilation distribution may be the result of a complex interplay of chest wall and lung mechanics, which vary between individuals, particularly in children where variations in respiratory rate and pattern are common.

7.1.1 Positioning

These studies refute the previous school of thought and clinical practice which has existed in the paediatric population for the last 30 years. These studies do not support the principle that *all* children, regardless of disease state, preferentially ventilate the non-dependent lung region in all body positions (Heaf et al., 1983; Davies et al., 1985). While there was no effect of age beyond 12 months on ventilation distribution; results of the present studies in healthy infants and children suggest that infants may be more likely to follow the previously described paediatric pattern, particularly in side lying positions. It must be noted that although on average infants showed a paediatric pattern, there is still individual variation within the group. In spontaneously breathing, healthy infants and children, there tends to be greater ventilation in the right lung region, particularly in left side lying position. Ventilation distribution in response to positioning is variable in infants and children with no clear, consistent pattern observed.

No statistically significant effect of head position on the distribution of ventilation between left and right lung regions in the supine and prone positions was found in healthy or mechanically ventilated infants and children, and therefore, head position may be chosen based on patient preference. Results in healthy, spontaneously breathing infants and children, suggest that turning the head to the left in the supine position may result in a reduction in ventilation to the left lung region, however this requires confirmation in a large, adequately powered sample.

Respiratory muscle activity is variably affected by body position with significant differences in activity found in the supine and/or prone positions, while no significant differences were found in the side lying positions in both spontaneously breathing, mechanically ventilated

children and children with NMD. The interaction between respiratory muscle activity and ventilation was variable and requires further investigation.

In the critical care setting, where infants and children may be receiving mechanical ventilation, the degree of spontaneous breathing effort from the patient needs to be considered when choosing a suitable therapeutic position. Infants and children who make spontaneous breathing efforts also show a variable pattern of ventilation as shown in Study Two, whereas those who make no spontaneous effort or are paralysed may be more likely to preferentially ventilate the non-dependent lung (Humphreys et al., 2011). The latter observation requires confirmation in different body positions.

Given the observed variability in ventilation distribution, the response to positioning could be determined clinically by monitoring of vital signs; gaseous exchange; observation of breathing pattern and work of breathing; auscultation; lung compliance, peak airway pressures and tidal volumes; and the child's level of comfort. Since the association between the above-mentioned factors and improved ventilation distribution is not yet known, EIT has considerable potential for use in the clinical setting.

7.1.2 Prone positioning in ARDS

Results from the study examining prone positioning in children with ARDS support the notion that prone positioning has beneficial short term effect on oxygenation by improving the homogeneity of ventilation throughout the lung in some infants/children. This is contrary to the idea that improved oxygenation in the prone position is caused by improved ventilation (recruitment) in the dorsal lung regions. It is suggested that infants and children who are more likely to respond positively to prone turning are those with greater ventilation inhomogeneity at baseline in the supine position. To date, adult studies showing improved inflation in the prone position in ARDS have used static imaging, such as CT scanning (Pelosi, Brazzi & Gattinoni, 2002). Not only is this the first study to examine ventilation distribution during prone positioning in infants/children with ARDS, but it is also the first to show improved ventilation homogeneity using functional imaging. EIT could be a useful tool in the clinical setting to determine baseline ventilation distribution, and potentially determine the likelihood of responding to prone positioning and guide further management. This requires further investigation. However, in the absence of EIT, other methods of determining the degree of ventilation inhomogeneity need to be determined. These results suggest that PEEP settings may be able to achieve the same/similar degree of homogeneity as prone positioning, and this requires further study. Since we did not examine clinical outcomes in this study, no clear clinical recommendations can be made.

7.2 Limitations

While these studies provide novel insight into the distribution of ventilation in infants and children under different conditions, there are a number of limitations that need to be considered.

Despite the sample size being similar to studies in the neonatal populations (Frerichs et al., 2003; Pham et al., 2011; Hough et al., 2012; Hough et al., 2013), the studies in this thesis were underpowered, mostly likely as a result of the age range in the present studies. The lack of data in older infants and children made it difficult to make accurate sample size calculations *a priori*. Nevertheless, these results provide novel insights into ventilation distribution in older infants and children, and more importantly provide some baseline data that can be used to calculate appropriate sample sizes for future studies.

Body positioning was not absolutely standardised between participants, and given that these were awake children, restraining them in a position would have been difficult to justify. Positioning was reproducible between participants and co-operation was easily obtained when children were distracted with media. This type of positioning may reflect clinical practice more accurately. Individual variations in EELV, tidal volumes and flow rates may account for some of the variability found and measurements of these factors may have helped explain the variability found in all groups of infants and children. Alternatively, EIT measurement could be taken during NREM sleep when breathing is more regular. The placement of EIT electrodes may also have affected the measurements, however in all children electrodes were placed at the nipple line; therefore, electrode placement was consistent in these studies. Small differences in electrode placement do not significantly affect the results of the measurements obtained (Reifferscheid et al., 2011). Although good correlation has been found between EIT and other imaging tools, the images and data obtained only represent a cross sectional slice of the thorax. Therefore, EIT using one electrode plane may not be suitable for guiding positioning to specific lung regions (e.g. upper lobe).

The effect of time in a position was not examined and may influence the distribution of ventilation. Recently it has been reported that ventilation takes approximately 15 minutes to settle and after three hours a significant difference was no longer found (Caruana et al., 2015; van der Burg et al., 2016). Although no differences were found between two EIT measurements, taken approximately five minutes apart, whether more time was necessary for ventilation to settle is unclear. This too may explain some of the variability found.

Given the number of positions examined, it was not possible to examine the effect of the order of positioning on ventilation distribution. Position order may have had a significant effect on ventilation distribution. This should be investigated further in either larger samples, or examining fewer positions at a time.

The placement of electrodes, particularly for the intercostals, for the sEMG measurements, although consistent, may have resulted in contamination from other muscles, especially with small movements. Although studies have shown that the placement used in this study accurately reflects intercostal and diaphragm activity, the influence of crosstalk requires investigation in more rigorous studies. As mentioned in the individual studies, since children have higher heart rates, which may be exacerbated in illness or anxiety, portions of the sEMG signal may be lost during the removal of the QRS complex during gating (Sprikkelman et al., 1998; Maarsingh et al., 2000). Unfortunately, there is no immediate solution to this and this problem is common to all methods of respiratory muscle monitoring using EMG. Although response of muscle activity to different body positions and the subsequent effect on ventilation distribution provides new information, other or concurrent measures of muscle function (such as ultrasonography and maximal inspiratory pressures) may provide more clinical meaningful information upon which therapeutic interventions can be implemented. Moreover, these additional measures would be able to be performed simultaneously with EIT measurements, allowing for more accurate conclusions regarding the impact of muscle activity/function on ventilation distribution. In retrospect, analysis of the sequence of respiratory muscle activity rather than just the amplitude may have provided a more accurate assessment of their contribution to ventilation distribution.

7.3 Future directions

While these studies have provided new insights into the ventilation distribution in infants and children, they have also highlighted important areas that require further investigation.

7.3.1 Positioning

Despite providing new knowledge on the distribution of ventilation in infants and children in different body positions and in different disease states, these studies also raise a number of questions regarding the possible mechanisms that may determine ventilation distribution. Some of these questions include: does time in a position impact on ventilation distribution and is there an optimal time limit? Is ventilation distribution different with different modes of ventilation? Is ventilation distribution different in different stages of NMD? Is ventilation distribution different in the presence of different respiratory conditions (e.g. atelectasis, pneumonia, bronchiolitis, and chronic lung disease)? All of these require further investigation. Furthermore, direct measures of factors such as lung volumes, lung

compliance, airway resistance, secretion characteristics and fluid balance and the consequent effect on ventilation distribution in response to position change should be examined.

Given the variable effect of position changes on ventilation distribution in infants and children objectives measures to determine the response to position change require further investigation. These measures may include changes in vital signs, auscultation and ventilatory parameters with improved ventilation distribution. This may help better guide clinical practice where EIT is not available. Furthermore, the effects of positioning on clinical outcomes should also be investigated, since it is a widely-used modality with little evidence supporting its efficacy.

Further investigation is required in the use of prone positioning in ARDS in infants and children. Methods of identifying potential responders, determining the optimal time in the prone position and the effects of prone positioning on clinically meaningful outcomes such as duration of ventilation, length of PICU and hospital stay and mortality require further study. The use of EIT guided titration of ventilatory settings in ARDS with or without prone positioning, and the subsequent effects on clinical outcomes, requires investigation.

7.3.2 Instruments

These studies repeatedly highlight the potential clinical utility of EIT in guiding and optimising interventions such as positioning, response to therapeutic interventions and mechanical ventilation.

To substantially grow the evidence for EIT in clinical practice, it may be worthwhile obtaining consensus amongst EIT research groups on standardised analysis and presentation of EIT data with regards to ventilation distribution. Guidelines regarding the clinical use and measurement procedures for EIT have recently been published (Frerichs et al., 2017). However, several methods of analysis and data presentation exist in the literature, making comparison between studies difficult.

Although not a primary outcome measure, sEMG was found to be feasible, in terms of ease of set-up and patient tolerance, for use in older infants and children. However, the current methods of data analysis are complex and not suited for bedside monitoring at the present. Further validation of sEMG in this population and in the critical care setting is required.

7.4 Conclusion

In order to correctly and effectively apply therapeutic interventions, an understanding of the underlying physiology and mechanisms by which the intervention may work is required.

Positioning is a frequently used component of the management of infants and children with respiratory disease and critical illness, to improve ventilation, improve VQ matching and improve oxygenation. Until recently, our understanding of ventilation distribution in the older paediatric population has been limited and based on several studies approximately 30 years old. To correctly position infants and children to achieve the aforementioned aims, an understanding of the distribution of ventilation is paramount. Therefore, this thesis aimed to investigate the distribution of ventilation in infants and children in different positions in different disease states.

Two observational studies and two pilot studies revealed that the distribution of ventilation in healthy infants and children, those who were mechanically ventilated and those with respiratory or neuromuscular disease is not as straightforward as previously thought. Results indicate that the pattern of ventilation distribution is variable amongst infants and children. Head position had no significant effect on the distribution of ventilation in older infants and children. Age had a variable, although not significant, effect on ventilation distribution, with healthy infants tending to show preferential ventilation of the non-dependent lung region, although this was not a uniform finding amongst all participants. Mechanical ventilation, respiratory disease and neuromuscular disease did not alter ventilation distribution significantly when compared to healthy infants and children.

An observational study investigating the effect of prone positioning on ventilation distribution in mechanically ventilated infants and children with ARDS, demonstrated that prone positioning did not clearly result in recruitment of the dorsal lung regions, rather it resulted in a more homogeneous distribution of ventilation throughout the lungs. Results suggest that a positive response to prone positioning is related to the baseline degree of ventilation inhomogeneity.

The results of this thesis have contributed new knowledge regarding ventilation distribution in infants and children. This knowledge may help guide clinical practice and improve the management of infants and children with respiratory disease, critical illness and ARDS. These studies also highlight the suitability of EIT for paediatric research and its potential for clinical use in the future. Lastly, these studies provide baseline data and highlight important areas for future research to further enhance the efficacy of our management of infants and children.

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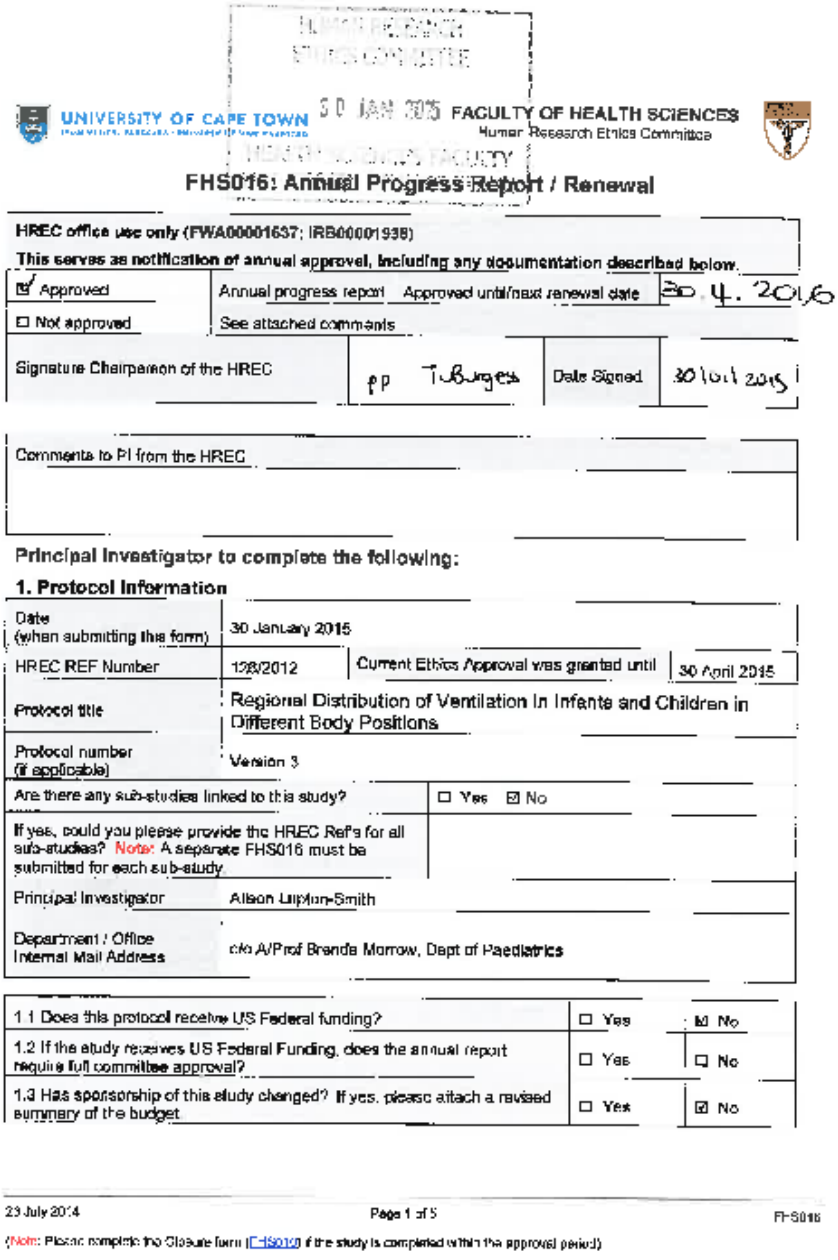
APPENDICES

Appendix 1. Ethical Approval

1.1. Studies One - Four



UNIVERSITY OF CAPE TOWN

30 JAN 2015

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)

This serves as notification of annual approval, including any documentation described below.

☑ Approved	Annual progress report Approved until/next renewal date	30 4. 2016	
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	pp T Burgess	Date Signed	30 Oct 2015

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	30 January 2015		
HREC REF Number	128/2012	Current Ethics Approval was granted until	30 April 2015
Protocol title	Regional Distribution of Ventilation in Infants and Children in Different Body Positions		
Protocol number (if applicable)	Version 3		
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study			
Principal Investigator	Alison Lupton-Smith		
Department / Office Internal Mail Address	c/o A/Prof Brenda Morrow, Dept of Paediatrics		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget	☐ Yes	☑ No

23 July 2014 Page 1 of 5 FHS016

(Note: Please complete the Closure form (FHS019) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

30 JAN 2015

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)

This serves as notification of annual approval, including any documentation described below.

☑ Approved	Annual progress report	Approved until/next renewal date	28.2.2016
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	pp T Burgess	Date Signed	30/01/2015

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	30 January 2015		
HREC REF Number	094/2013	Current Ethics Approval was granted until	14 March 2015
Protocol title	Respiratory muscle activity and the distribution of ventilation in infants and children with neuromuscular disease in different body positions.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS01B must be submitted for each sub-study			
Principal Investigator	Alison Lupton-Smith		
Department / Office Internal Mail Address	c/o A/Prof Brenda Morrow, Dept of Paediatrics		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☐ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☑ No

(Note: Please complete the Closure form (FHS01C) if the study is completed within the approval period)

1.2. Study Five

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

Form FHS007: Amendment – study staff

HREC office use only (FWA00001637; IRB00001938)			
☐ Approved			
This serves as notification that all changes to the study staff and documentation described below are approved.			
Chairperson of the HREC signature		Date	2/12/2015

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	
HREC REF Number	269/2008
Protocol title	An investigation into the effects of chest physiotherapy modalities on regional distribution of ventilation in infants and children with pulmonary disease.
Protocol number (if applicable)	
Principal Investigator	Alison Lupton-Smith
Department / Office Internal Mail Address	c/o Brenda Morrow, School of Child and Adolescent Health

1.1 Does this protocol receive US Federal funding?	☐ Yes	✓ No

2.1 Staff changes (tick ✓)

Are new personnel being added to this research?	☐ Yes	✓ No
Are current personnel being removed from this research?	☐ Yes	✓ No
Is the principal investigator for this research being changed? If yes, please attach revised conflict of interest and PI declaration statements. (Refer: sections 7 and 8.4 in the New Protocol Application Form)	✓ Yes	☐ No
Do the consent and assent forms need modification to reflect these staff changes? If yes, please attach copies of the revised forms, with all changes highlighted or tracked and listed in the documents for approval.	☐ Yes	✓ No

Appendix 2. Institutional approval

Dr TA Blake
Manager: Medical Services
Email: Thomas.Blake@pgwc.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166

Ms A LUPTON-SMITH

RESEARCH PROPOSAL

To whom it may concern,
This letter serves to confirm that the bearer (Ms A Lupton-Smith) has approval to conduct research at the Red Cross War Memorial Children's Hospital.

The tests are to monitor, non-invasively, the respiration of children using externally placed electrical probes.

Yours faithfully

Dr Thomas Blake
Manager: Medical Services

18 July 2012
Date

Appendix 3. Information sheet, consent form and assent forms

3.1. Study One

University of Cape Town

Division of Paediatrics and Child Health

Regional ventilation and respiratory muscle activity in children in different body positions

Informed consent – spontaneously breathing children

The University of Cape Town will be conducting a study at Red Cross Children's Hospital. This study is for a PhD degree.

We would like to find out where the air moves in the lungs in children and which muscles are working when they lie in different positions or sit. The different positions are when the child lies on their back, stomach, sides and when they are sitting.

How will we do this?

To do this, we will place 23 small stickers (electrodes) on your child's skin around their chest in line with their nipples. We will need to take off your child's clothes so we can see their chest. A very small electrical current is sent through the stickers by the machine. Your child will not feel anything when this happens and it is not sore. This shows where the air is moving in and out of the lungs and which muscles are working on a computer. We will keep this information on the computer. We will see where the air is moving by using Electrical Impedance Tomography (EIT) and will use Electromyography (sEMG) to see which muscles are working. This will be done while your child is lying on their stomach, back and sides.

This should take about 40 minutes. If your child lies still it may take less time and if they wriggle around it may take longer. If your child becomes upset during the measurements we will stop.

We will also ask you a few questions about your baby/child's birth and medical history or we will get this information from their hospital folder, with your permission. We will ask a few questions about what their home is like.

If we find anything wrong in your child's lungs while the measurements are being taken, we will send your child to their doctor so that they get the right medicine or care.

Who will take part in the study?

We are hoping to look at 22 different babies and children. We will be looking at babies and children between the ages of six (6) months and nine (9) years old who do not have anything wrong with their chest.

What are the risks? (Can anything go wrong?)

There is nothing that we know of that can go wrong with EIT or sEMG. Your child will not feel uncomfortable or any pain while the measurements are taken. No radiation is involved (it is not like an X-Ray).

What good things can we learn from this?

This study will help us better understand where the air moves in and out of the lungs and which muscles are working in babies and children who do not have anything wrong with their chest when they lie or sit. This will also help us know what to look for when studies are done on children who are ill with chest infections. It may also help us look after children who are sick with chest infections better than we can now.

Is what we find kept private?

No one will know that the information comes from your child (it is confidential). None of the children's names will be in the article if it is written.

Contact Information of Researchers

If you have any problems or questions, you may contact the investigators (Ass Prof B Morrow or Alison Lupton-Smith) at the following number 021 658 5074 or Prof Marc Blockman (Chairperson, FSH Research Ethics Committee) at 021 406 6626

You may choose not to allow your child to take part in this study; this decision will not affect the care of your child in any way. You may also stop child from taking part in this study at any time, without giving reasons.

There is no payment for taking part in this study.

Division of Paediatrics and Child Health

Regional ventilation and respiratory muscle activity in children in different body positions

Informed consent – spontaneously breathing children

Consent/ Agreement to take part in the study

I agree that the exact processes/procedures, benefits and possible risks of this study have been fully explained to me.

I understand that I/my child are free to ask any questions I/my child at any time during the study.

I understand that at any time I may take my child out of the study, should I wish to.

I understand that no one will know that the information comes from my child and that my child's name will not be in the article when it is written.

I have carefully read this form/ had it read to me. I understand what the study is about. I agree to my child taking part in this study of the UCT Division of Child Health.

Name (in full) of Parent/Legal Guardian: _____

Signature of Parent/Legal Guardian: _____

Relationship to Infant/Child: _____

Name (in full) of witness: _____

Signature of witness: _____

Date: _____

University of Cape Town

Division of Paediatrics and Child Health

Regional ventilation and muscle activity in children in different body positions

Assent form

My name is Alison and I am studying at the University of Cape Town. For my studies I want to see where the air moves in and out of your chest when you breathe in and out. I also would like to see which muscles are working when you breathe. I will see this when you lie on your back, tummy, sides and when you sit.

To do this, I will put white/blue stickers around your chest and a computer will show us with pictures where the air is going and which muscles are working. It is not sore. It will take about 40 minutes. .

It is ok if you do not want me to do this. If you start and want to stop later that is also ok.

You may have some questions; you can ask these at any time.

If you are helping with the study, I will not tell anyone your name and that the pictures belong to you.

Signing this form means that you are happy for me to see where the air is coming in and out of your chest and which muscles are working while you lie on your back, tummy and sides and also while you sit.

Name of Participant: _____

Signature of Participant: _____

Date: _____

Name of Investigator: _____

Signature of Investigator: _____

Date: _____

3.2. Study Two

University of Cape Town

Division of Paediatrics and Child Health

Regional Ventilation and respiratory muscle activity in children in different body positions

Informed consent – mechanically ventilated children

Your child is currently being mechanically ventilated by a machine to help his/ her breathing. The University of Cape Town will be conducting a study at Red Cross Children's Hospital. This study is for a PhD degree.

We would like to find out where the air moves in the lungs in the different positions and which muscles are working. The different positions are when your child lies on their back, sides and stomach, if possible. We would also like to see if turning their head to the left or right (when they are lying on their stomach or back) changes the where the air moves in the lungs.

How will we do this?

To do this, we will place 23 small stickers (electrodes) on your child's skin around their chest in line with their nipples. We will need to take off your child's clothes so we can see their chest. A very small electrical current is sent through the stickers by the machine. Your child will not feel anything when this happens and it is not sore. This shows where the air is moving in and out of the lungs on a computer. We will keep this information on the computer. This is called Electrical Impedance Tomography. This will be done while your child is lying on their stomach (if possible), back and sides.

This should take about 40 minutes. If your child lies still it may take less time and if they wriggle around it may take longer. If your child becomes upset during the measurements we will stop.

We will also ask you a few questions about your baby/child's birth and medical history or we will get this information from their hospital folder, with your permission. We will ask a few questions about what their home is like.

If we find anything wrong in your child's lungs while the measurements are being taken, we will send your child to their doctor so that they get the right medicine or care.

Who will take part in the study?

We are hoping to look at 22 different babies and children. We will be looking at babies and children between the ages of three (3) months and nine (9) years old who do not have anything wrong with their chest.

What are the risks? (Can anything go wrong?)

There is nothing that we know of that can go wrong with EIT. Your child will not feel uncomfortable or any pain while the measurements are taken. No radiation is involved (it is not like an X-Ray).

What good things can we learn from this?

This study will help us better understand where the air moves in and out of the lungs in babies and children who are being helped to breathe by a machine (ventilator). This will also help us know what to look for when studies are done on children who are ill with chest infections and also need help breathing. It may also help us look after children who are sick with chest infections better than we can now.

Is what we find kept private?

No one will know that the information comes from your child (it is confidential). None of the children's names will be in the article if it is written.

Contact Information of Researchers

If you have any problems or questions, you may contact the investigators (Ass Prof B Morrow or Alison Lupton-Smith) at the following number 021 658 5074 or Prof Marc Blockman (Chairperson, FSH Research Ethics Committee) at 021 406 6626

You may choose not to allow your child to take part in this study; this decision will not affect the care of your child in any way. You may also stop child from taking part in this study at any time, without giving reasons.

There is no payment for taking part in this study.

University of Cape Town

Division of Paediatrics and Child Health

Regional ventilation and respiratory muscle activity in children in different body positions

Informed consent – mechanically ventilated children

Consent/ Agreement to take part in the study

I agree that the exact processes/procedures, benefits and possible risks of this study have been fully explained to me.

I understand that I/my child are free to ask any questions I/my child at any time during the study.

I understand that at any time I may take my child out of the study, if I would like to.

I understand that no one will know that the information comes from my child and that my child's name will not be in the article when it is written.

I have carefully read this form/ had it read to me. I understand what the study is about. I agree to my child taking part in this study of the UCT Division of Child Health.

Name (in full) of Parent/Legal Guardian: _____

Signature of Parent/Legal Guardian: _____

Relationship to Infant/Child: _____

Name (in full) of witness: _____

Signature of witness: _____

Date: _____

3.3. Study Three

University of Cape Town

Division of Paediatrics and Child Health

Regional Ventilation and respiratory muscle activity in children with neuromuscular disease in different body positions

Informed consent – Neuro-muscular Disease

The University of Cape Town will be conducting a study at Red Cross Children's Hospital. This study is for a PhD degree.

We would like to find out where the air moves in the lungs in children, who may have some muscle weakness and which muscles are working when they lie in different positions or sit. The different positions are when the child lies on their back, stomach, sides and when they are sitting.

How will we do this?

To do this, we will place 23 small stickers (electrodes) on your child's skin around their chest in line with their nipples. We will need to take off your child's clothes so we can see their chest. A very small electrical current is sent through the stickers by the machine. Your child will not feel anything when this happens and it is not sore. This shows where the air is moving in and out of the lungs and which muscles are working on a computer. We will keep this information on the computer. We will see where the air is moving by using Electrical Impedance Tomography (EIT) and will use Electromyography (EMG) to see which muscles are working. This will be done while your child is lying on their stomach, back and sides.

This should take about 40 minutes. If your child lies still it may take less time and if they wriggle around it may take longer. If your child becomes upset during the measurements we will stop.

We will also ask you a few questions about your baby/child's birth and medical history or we will get this information from their hospital folder, with your permission. We will ask a few questions about what their home is like.

If we find anything wrong in your child's lungs while the measurements are being taken, we will send your child to their doctor so that they get the right medicine or care.

Who will take part in the study?

We are hoping to look at 22 different babies and children. We will be looking at babies and children between the ages of six (6) months and nine (9) years old who do not have anything wrong with their chest.

What are the risks? (Can anything go wrong?)

There is nothing that we know of that can go wrong with EIT or EMG. Your child will not feel uncomfortable or any pain while the measurements are taken. No radiation is involved (it is not like an X-Ray).

What good things can we learn from this?

This study will help us better understand where the air moves in and out of the lungs and which muscles are working in babies and children who may have some muscle weakness when they lie or sit. It may also help us look after children, who may have muscle weakness and are sick with chest infections better than we can now.

Is what we find kept private?

No one will know that the information comes from your child (it is confidential). None of the children's names will be in the article if it is written.

Contact Information of Researchers

If you have any problems or questions, you may contact the investigators (Ass Prof B Morrow or Alison Lupton-Smith) at the following number 021 658 5074 or Prof Marc Blockman (Chairperson, FSH Research Ethics Committee) at 021 406 6626

You may choose not to allow your child to take part in this study; this decision will not affect the care of your child in any way. You may also stop child from taking part in this study at any time, without giving reasons.

There is no payment for taking part in this study.

University of Cape Town

Division of Paediatrics and Child Health

Regional ventilation and respiratory muscle activity in children in different body positions

Informed consent – Neuro-muscular Disease

Consent/ Agreement to take part in the study

I agree that the exact processes/procedures, benefits and possible risks of this study have been fully explained to me.

I understand that I/my child are free to ask any questions I/my child at any time during the study.

I understand that at any time I may take my child out of the study, should I wish to.

I understand that no one will know that the information comes from my child and that my child's name will not be in the article when it is written.

I have carefully read this form/ had it read to me. I understand what the study is about. I agree to my child taking part in this study of the UCT Division of Child Health.

Name (in full) of Parent/Legal Guardian: _____

Signature of Parent/Legal Guardian: _____

Relationship to Infant/Child: _____

Name (in full) of witness: _____

Signature of witness: _____

Date: _____

University of Cape Town

Division of Paediatrics and Child Health

Regional ventilation and muscle activity in children in different body positions

Assent form

My name is Alison and I am studying at the University of Cape Town. For my studies I want to see where the air moves in and out of your chest when you breathe in and out. I also would like to see which muscles are working when you breathe. I will see this when you lie on your back, tummy and sides.

To do this, I will put white/blue stickers around your chest and a computer will show us with pictures where the air is going and which muscles are working. It is not sore. It will take about 40 minutes.

It is ok if you do not want me to do this. If you start and want to stop later that is also ok.

You may have some questions; you can ask these at any time.

If you are helping with the study, I will not tell anyone your name and that the pictures belong to you.

Signing this form means that you are happy for me to see where the air is coming in and out of your chest and which muscles are working while you lie on your back, tummy and sides and also while you sit.

Name of Participant: _____

Signature of Participant: _____

Date: _____

Name of Investigator: _____

Signature of Investigator: _____

Date: _____

3.4. Study Four

University of Cape Town

Division of Paediatrics and Child Health

Regional Ventilation and respiratory muscle activity in children with respiratory disease in different body positions

Informed consent

The University of Cape Town will be conducting a study at Red Cross Children's Hospital. This study is for a PhD degree.

We would like to find out where the air moves in the lungs in children and which muscles are working when they lie in different positions or sit. The different positions are when the child lies on their back, stomach, sides and when they are sitting.

How will we do this?

To do this, we will place 23 small stickers (electrodes) on your child's skin around their chest in line with their nipples. We will need to take off your child's clothes so we can see their chest. A very small electrical current is sent through the stickers by the machine. Your child will not feel anything when this happens and it is not sore. This shows where the air is moving in and out of the lungs and which muscles are working on a computer. We will keep this information on the computer. We will see where the air is moving by using Electrical Impedance Tomography (EIT) and will use Electromyography (sEMG) to see which muscles are working. This will be done while your child is lying on their stomach, back and sides.

This should take about 40 minutes. If your child lies still it may take less time and if they wriggle around it may take longer. If your child becomes upset during the measurements we will stop.

We will also ask you a few questions about your baby/child's birth and medical history or we will get this information from their hospital folder, with your permission. We will ask a few questions about what their home is like.

If we find anything wrong in your child's lungs while the measurements are being taken, we will send your child to their doctor so that they get the right medicine or care.

Who will take part in the study?

We are hoping to look at 22 different babies and children. We will be looking at babies and children between the ages of six (6) months and nine (9) years old who do not have anything wrong with their chest.

What are the risks? (Can anything go wrong?)

There is nothing that we know of that can go wrong with EIT or sEMG. Your child will not feel uncomfortable or any pain while the measurements are taken. No radiation is involved (it is not like an X-Ray).

What good things can we learn from this?

This study will help us better understand where the air moves in and out of the lungs and which muscles are working in babies and children who have chest infections when they lie or sit. It may also help us look after children who are sick with chest infections better than we can now.

Is what we find kept private?

No one will know that the information comes from your child (it is confidential). None of the children's names will be in the article if it is written.

Contact Information of Researchers

If you have any problems or questions, you may contact the investigators (Ass Prof B Morrow or Alison Lupton-Smith) at the following number 021 658 5074 or Prof Marc Blockman (Chairperson, FSH Research Ethics Committee) at 021 406 6626

You may choose not to allow your child to take part in this study; this decision will not affect the care of your child in any way. You may also stop child from taking part in this study at any time, without giving reasons.

There is no payment for taking part in this study.

University of Cape Town

Division of Paediatrics and Child Health

Regional Ventilation and respiratory muscle activity in children with respiratory disease in different body positions

Informed Consent – Respiratory Disease

Consent/ Agreement to take part in the study

I agree that the exact processes/procedures, benefits and possible risks of this study have been fully explained to me.

I understand that I/my child are free to ask any questions I/my child at any time during the study.

I understand that at any time I may take my child out of the study, should I wish to.

I understand that no one will know that the information comes from my child and that my child's name will not be in the article when it is written.

I have carefully read this form/ had it read to me. I understand what the study is about. I agree to my child taking part in this study of the UCT Division of Child Health.

Name (in full) of Parent/Legal Guardian: _____

Signature of Parent/Legal Guardian: _____

Relationship to Infant/Child: _____

Name (in full) of witness: _____

Signature of witness: _____

Date: _____

University of Cape Town

Division of Paediatrics and Child Health

Regional ventilation and muscle activity in children in different body positions

Assent form

My name is Alison and I am studying at the University of Cape Town. For my studies I want to see where the air moves in and out of your chest when you breathe in and out. I also would like to see which muscles are working when you breathe. I will see this when you lie on your back, tummy and sides.

To do this, I will put white/blue stickers around your chest and a computer will show us with pictures where the air is going and which muscles are working. It is not sore. It will take about 40 minutes.

It is ok if you do not want me to do this. If you start and want to stop later that is also ok.

You may have some questions; you can ask these at any time.

If you are helping with the study, I will not tell anyone your name and that the pictures belong to you.

Signing this form means that you are happy for me to see where the air is coming in and out of your chest and which muscles are working while you lie on your back, tummy and sides and also while you sit.

Name of Participant: _____

Signature of Participant: _____

Date: _____

Name of Investigator: _____

Signature of Investigator: _____

Date: _____

3.5. Study Five

University of Cape Town

Division of Paediatrics and Child Health

An investigation into the effects of chest physiotherapy modalities on regional distribution of ventilation in infants and children with pulmonary disease

Patient information and consent form

You and your child are requested to participate in a medical research study that is being done at Red Cross Children's hospital. This study is being done by researchers in the School of Child and Adolescent Health of the University of Cape Town. The following information will describe the study and your child's role as a participant. Please read this carefully and feel free to ask any questions. The study will be conducted according to the Declaration of Helsinki.

What is the reason for the study and how will it be done?

Infants and children with severe chest infections are sometimes turned onto their stomachs to try and improve their breathing. The aim of this study is to measure changes in how children breathe, where the air goes in the lungs and oxygenation that occur during and after chest physiotherapy, which includes turning your child on their tummy.

For this study we will use Electrical Impedance Tomography, a new technology which safely scans the body without any radiation. At the same time a monitor will be attached to the tube connecting your child to the ventilator, in order to look at the way the lungs are working. We will take measurements at the start and 60 minutes after the treatment.

Before and after turning your child, a small amount of blood will be taken from the drip line to check oxygen content, which helps show us how well the lungs are working.

What does the study mean for your child?

We will look at your child's hospital folder for her/his medical information. Your child will receive the usual investigations and treatment in hospital; in addition, the study interventions as described above will be done.

What are the possible benefits to your child?

Turning your child may be helpful in improving his/her breathing. Even if you refuse to participate in the study, your child may still be turned if deemed necessary by the doctor.

The study may also benefit other children with chest infections, as we hope it will help us to identify which patients would be most likely to benefit from the procedure.

What are the possible risks to your child?

This study poses very little risk to your child. Besides the usual blood tests, a small amount of additional blood (less than half a teaspoon) will be drawn from the arterial line to check the blood gases only. The blood will then be discarded. Neither of the monitors are painful or uncomfortable to apply, and do not add any risk to your child.

Confidentiality

Your child's study records will be kept confidential. Neither you nor your child's name will appear in any publication that may arise from this study.

Voluntary participation

You may choose for your child to be in this study. If you choose not to be in the study then your child will get regular treatment for his/ her chest infection. Being in the study will not affect any other treatment that your child will receive.

Contact Information of Researchers

If you have any problems or questions, you may contact the investigators (Ass Prof B Morrow or Alison Lupton-Smith) at the following number 021 658 5074 or Prof Marc Blockman (Chairperson, FSH Research Ethics Committee) at 021 406 6626

University of Cape Town

Division of Paediatrics and Child Health

An investigation into the effects of chest physiotherapy modalities on regional distribution of ventilation in infants and children with pulmonary disease

Consent/ Agreement to take part in the study

I have read and understood this form. My questions have been answered. I voluntary consent to have my child participate.

I, _____, the parent/ legal guardian of _____ agree to allow her/him to participate in this study.

Signed: _____ Witness: _____

Date: _____ Date: _____

Patient sticker:

Appendix 4. Data Collection Sheets

4.1. Studies One – Four

University of Cape Town

Department of Child and Adolescent Health

Regional Ventilation in children in different body positions

Data collection sheet

Patient identifier:

Date:

Date of Birth: Age:

Gender:

Weight (kg):

Height (cm):

Spontaneously breathing / mechanically ventilated (circle)

Birth History (NVD/ C/S; Gestational age at birth; any complications):

Medical History:

Neuromuscular disease (if known):

Current:

Past:

Surgical History:

Family History (asthma; allergies; chronic lung disease):

Social History:

- Type of dwelling (tick appropriate) : Brick house/flat _____ Wendy _____ Other _____
- Number of people staying in house: _____
- Electricity : (circle appropriate) Yes / No

- If no, what is used : _____

- Are there smokers at home? (circle appropriate) Yes / No

Current/Chronic Medication:

Development:

Functional ability:

Skeletal Deformities (e.g. scoliosis, kyphosis):

Muscle Strength (upper limbs, lower limbs, trunk and neck - any known weakness)

Mechanically ventilated children:

Mode:

RR: Pre-set on Ventilator: Recorded (spontaneously):

FiO2:

PIP:

PEEP:

MAP:

SpO2

HR:

MABP:

Any adverse events:

_____

4.2. Study Five

University of Cape Town

Department of Child and Adolescent Health

Prone study – Data sheet

Patient Sticker: Date:

Study number: Pr

Primary diagnosis: Comorbidity:

Weight:
ETT size (mmID): Catheter size (FG):
Ventilation parameters before: IPPV / HFOV
PIP: PEEP: MAP:
RR: FiO2: Hz:
Culture result: BAL / Blood date:

	Before Rx	After Rx 5 min	After Rx 20 min	After Rx 1 hour
HR				
SpO2				
MABP				

Adverse events:

_____
_____
_____
_____
_____
_____
_____

	Before	After (if applicable)

CXR		

Blood gas:

	Before	After
PaO2:		
PaCO2:		
pH:		

Ventilation parameters 1 hour after: IPPV/HFOV

PIP: PEEP: MAP:

RR: FiO2: Hz:

	Baseline	5min	20min	60min
VTi				
Vte				
MVe (l/min)				
Cdyn				
WOB				
ETCO2				

EIT time codes

Measurement	Time code
Baseline	
Prone – 5 min	
Prone – 20 min	
Prone – 60 min	

Appendix 5. Residuals for ANOVA's

5.1. Study One

Figure 5.2.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

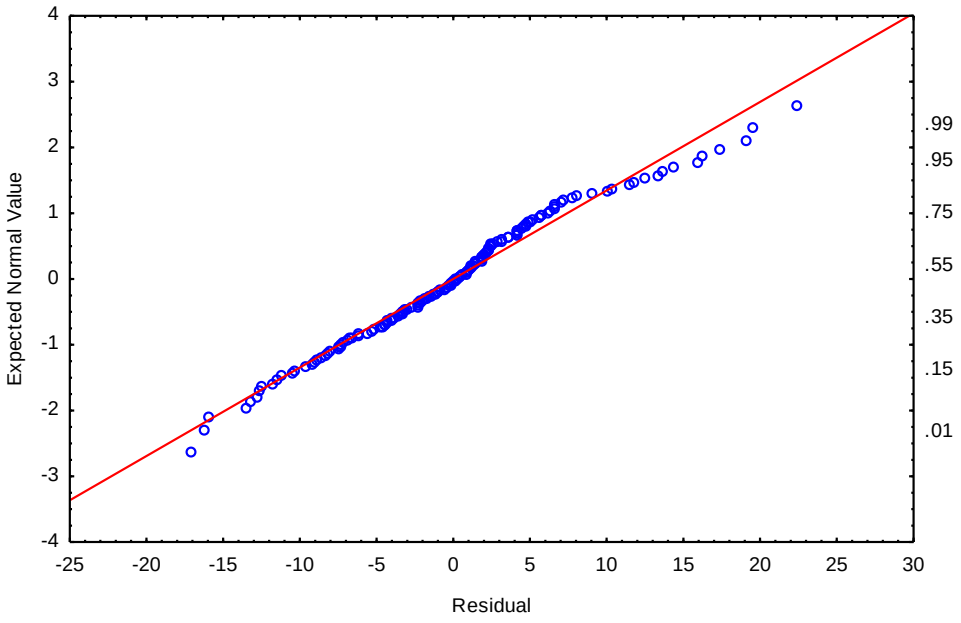


Figure 5.2.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine

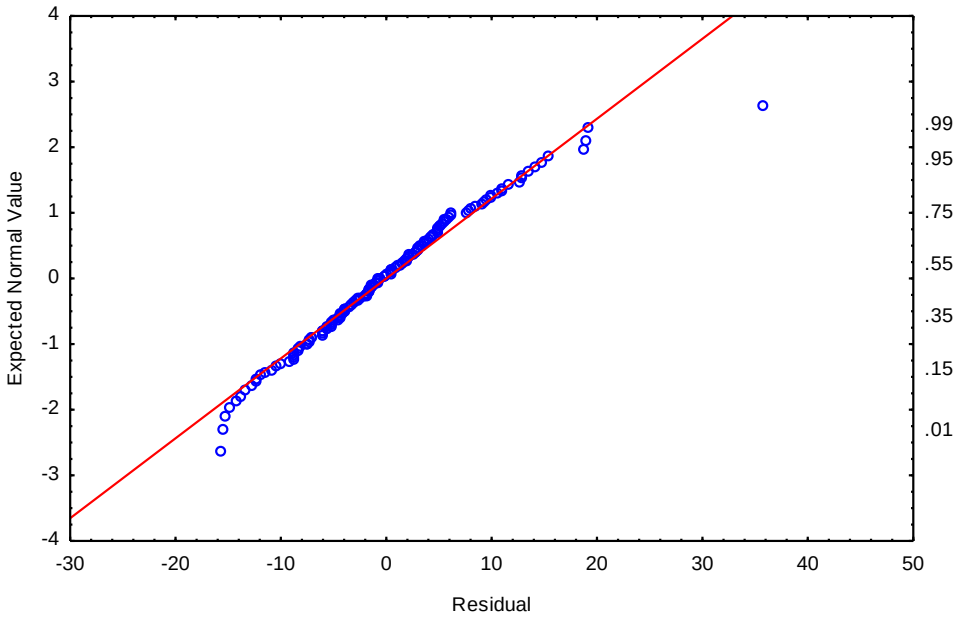


Figure 5.2.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

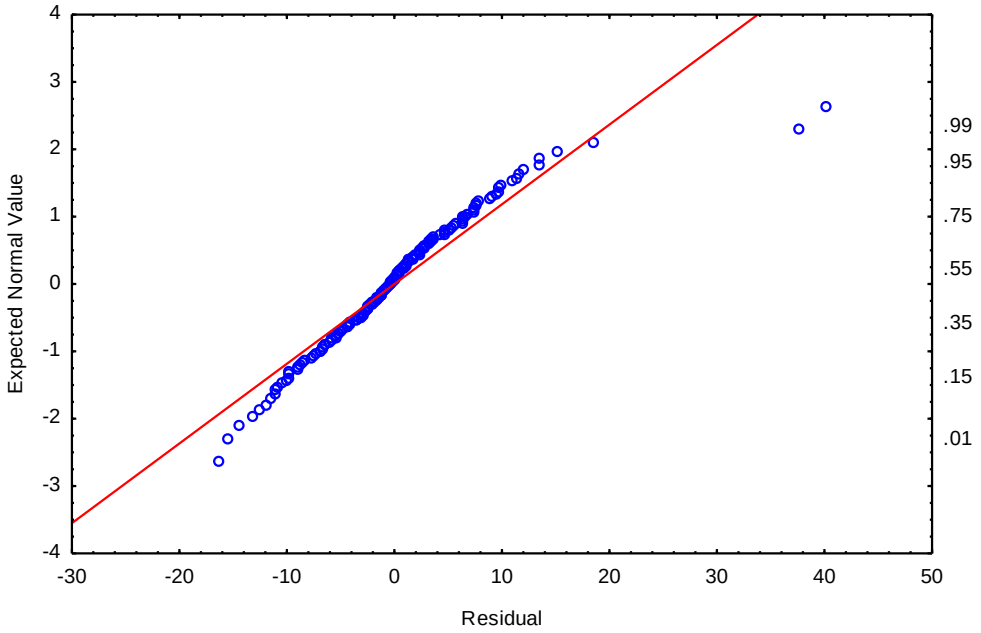


Figure 5.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

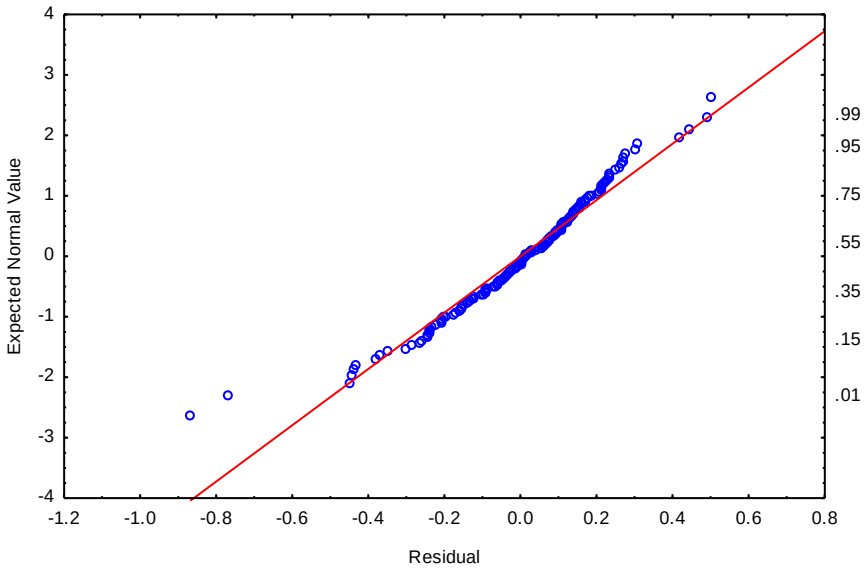


Figure 5.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Supine

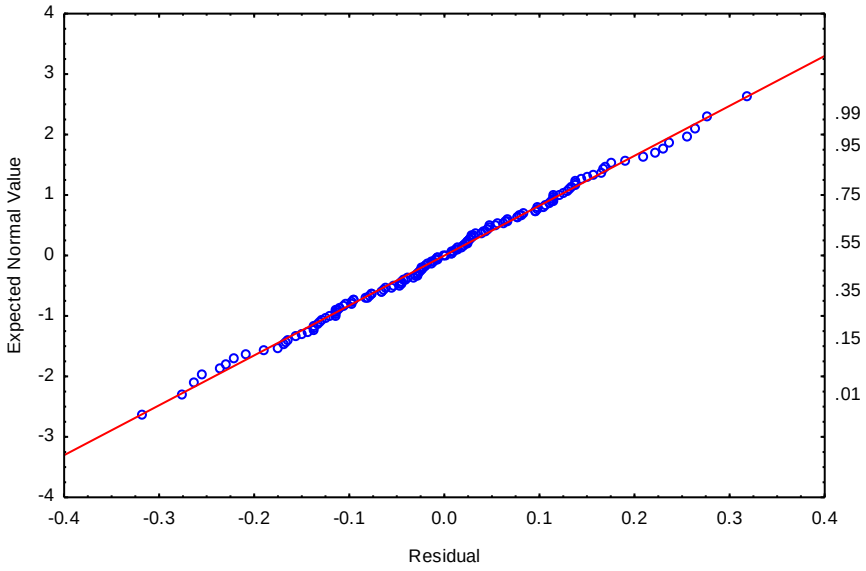


Figure 5.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

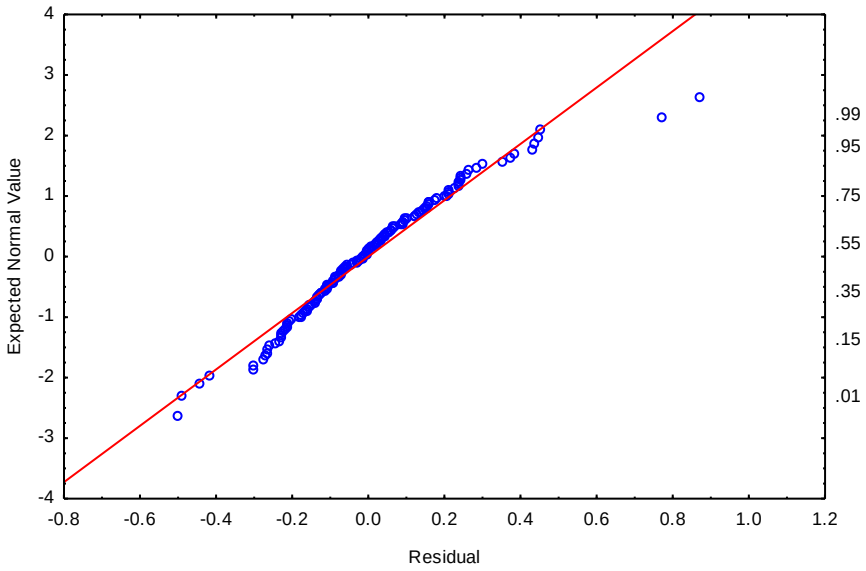


Figure 5.2.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

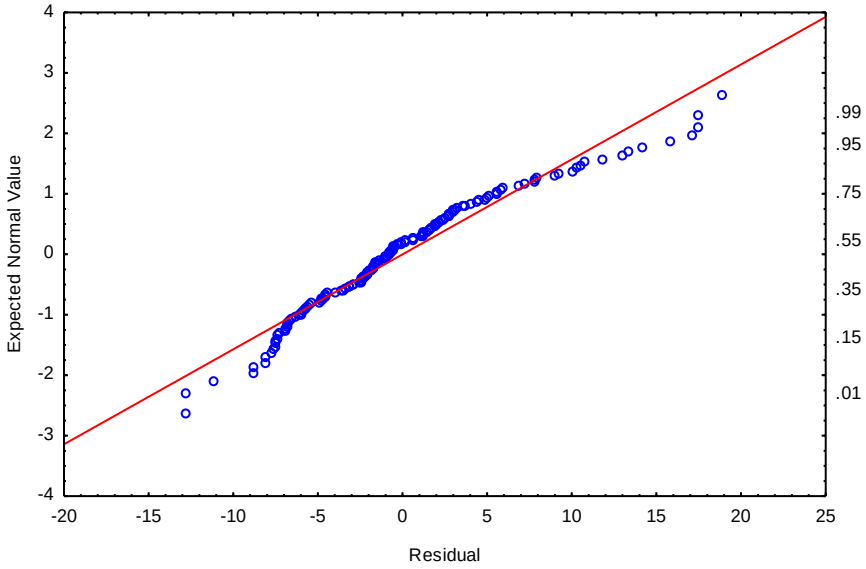


Figure 5.2.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine

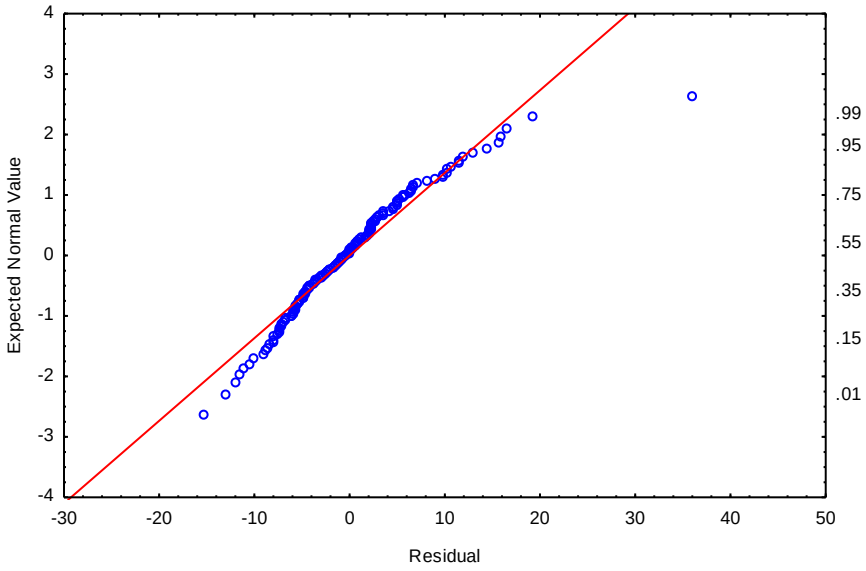


Figure 5.2.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

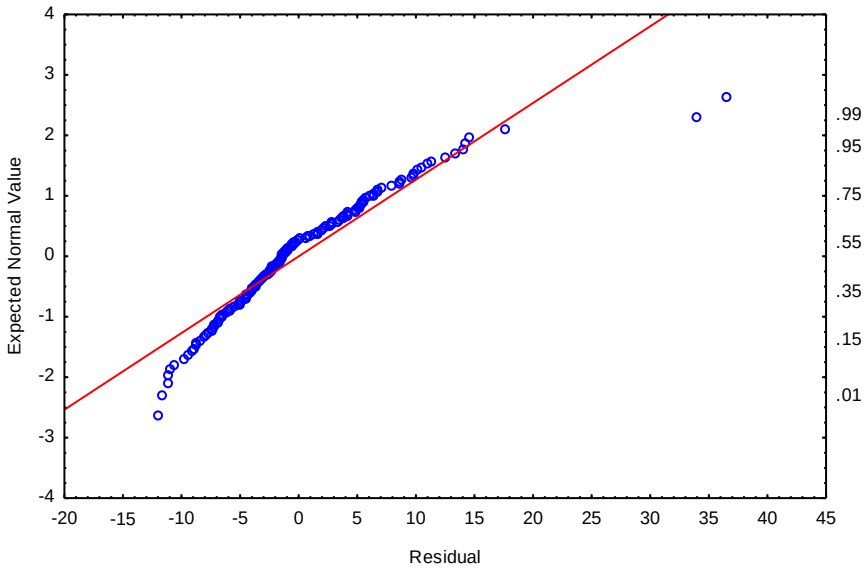


Figure 5.2.8
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

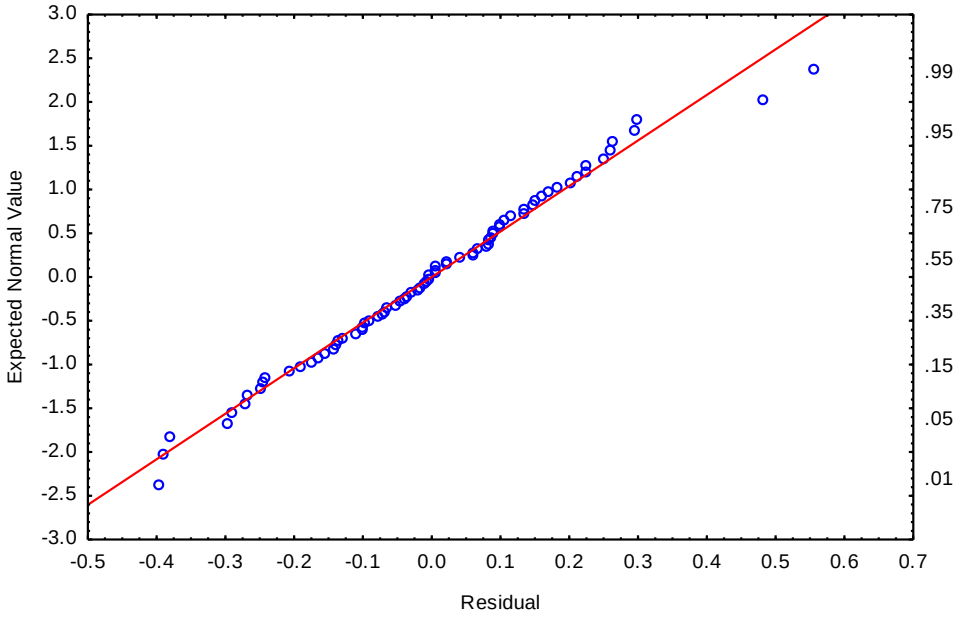


Figure 5.2.8
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine

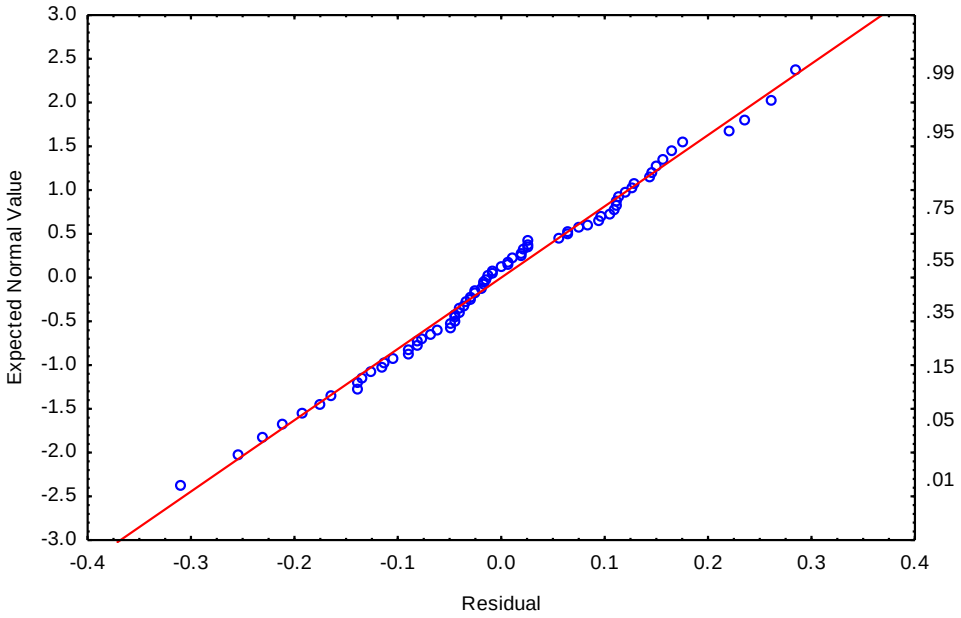


Figure 5.2.8
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

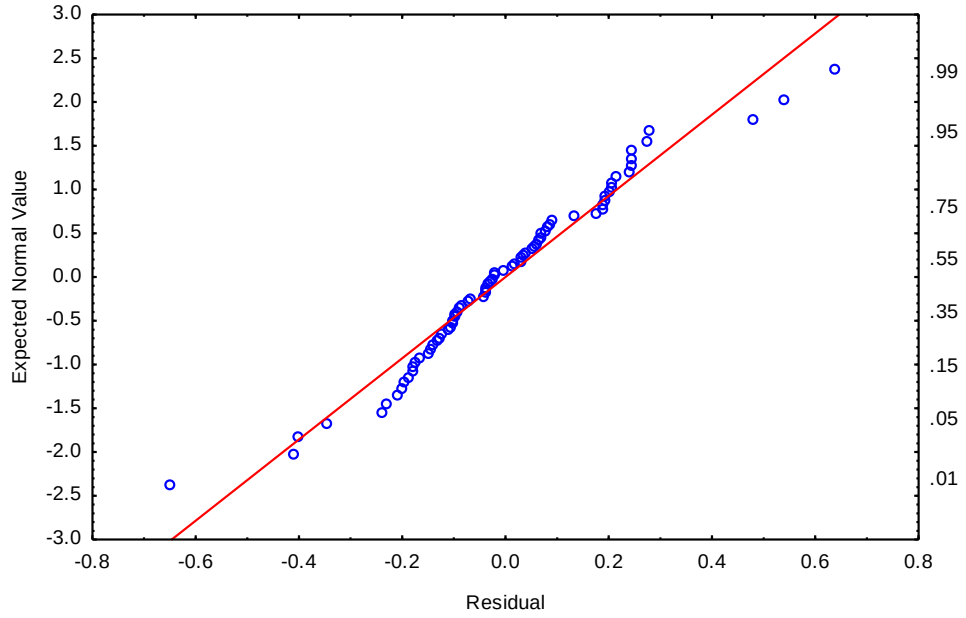


Figure 5.2.10
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Dependent

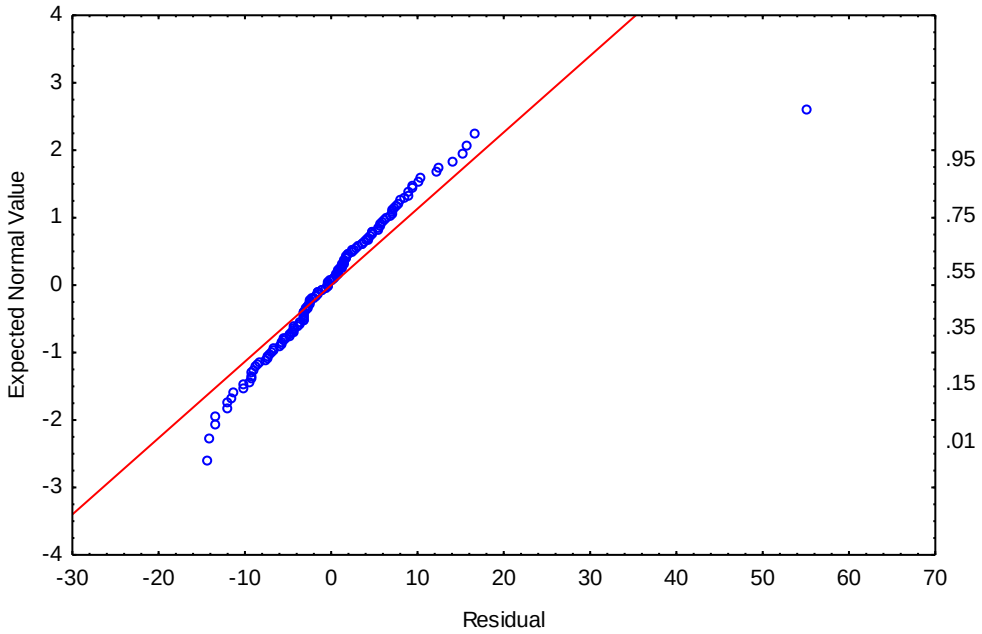


Figure 5.2.10
Normal Prob. Plot; Raw Residuals
Dependent variable: Supien/Prone - Non-dependent

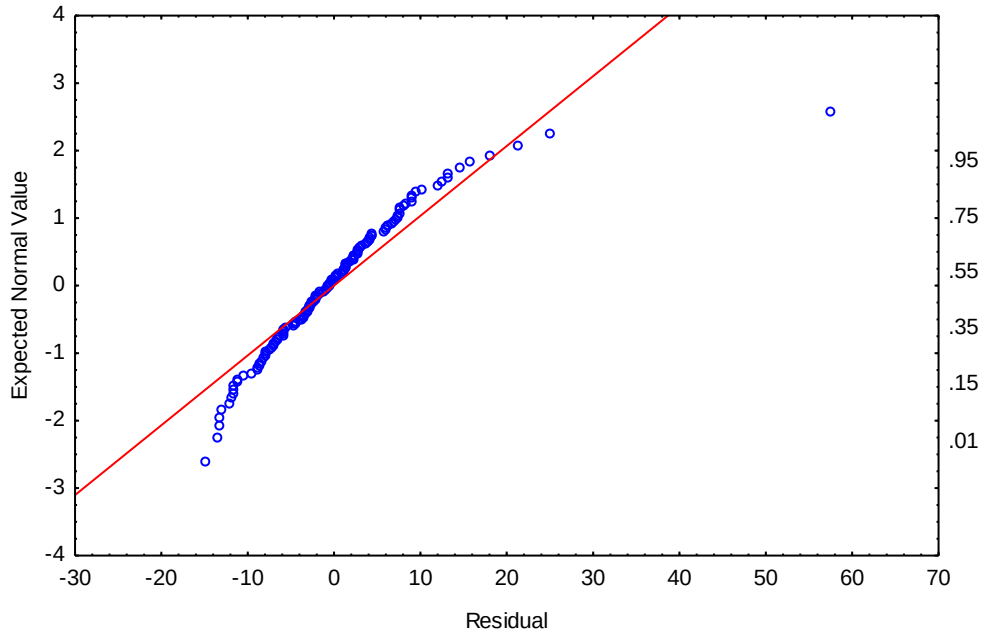


Figure 5.2.11
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

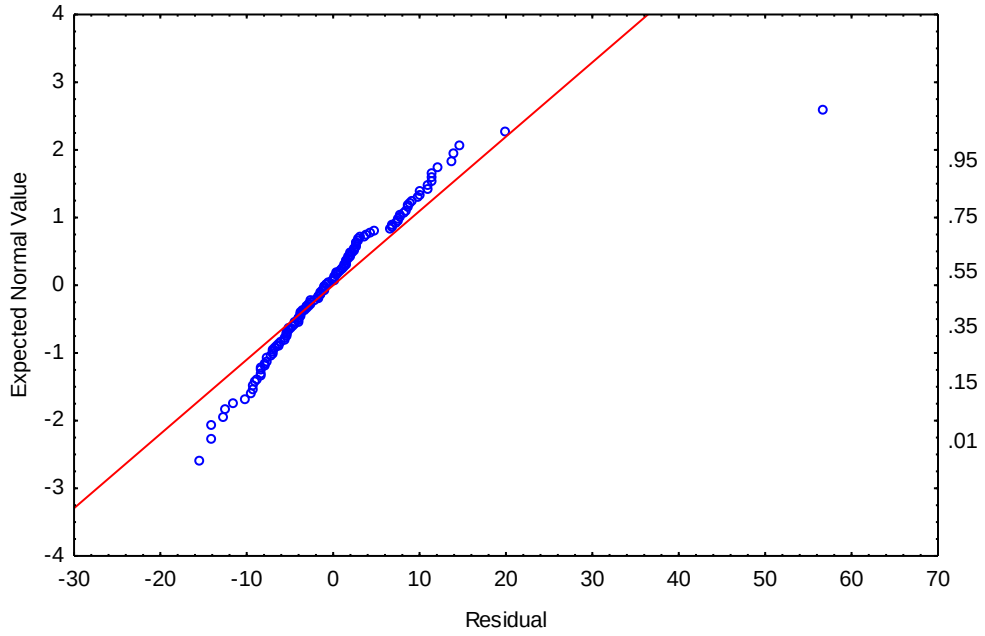


Figure 5.2.11
Normal Prob. Plot; Raw Residuals
Dependent variable: Side Lying - Non-dependent

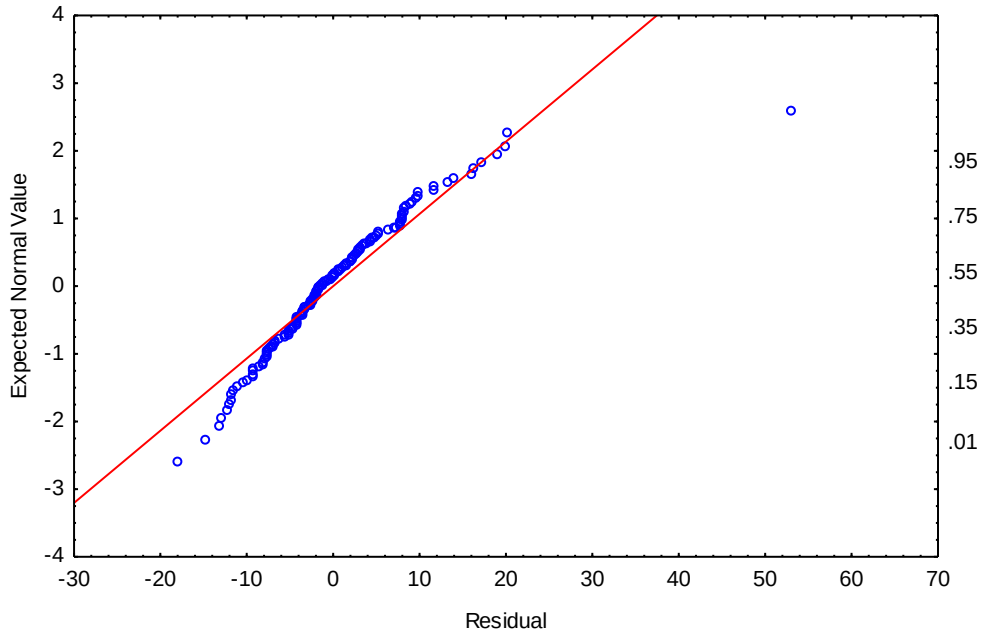


Figure 5.2.14
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Dependent

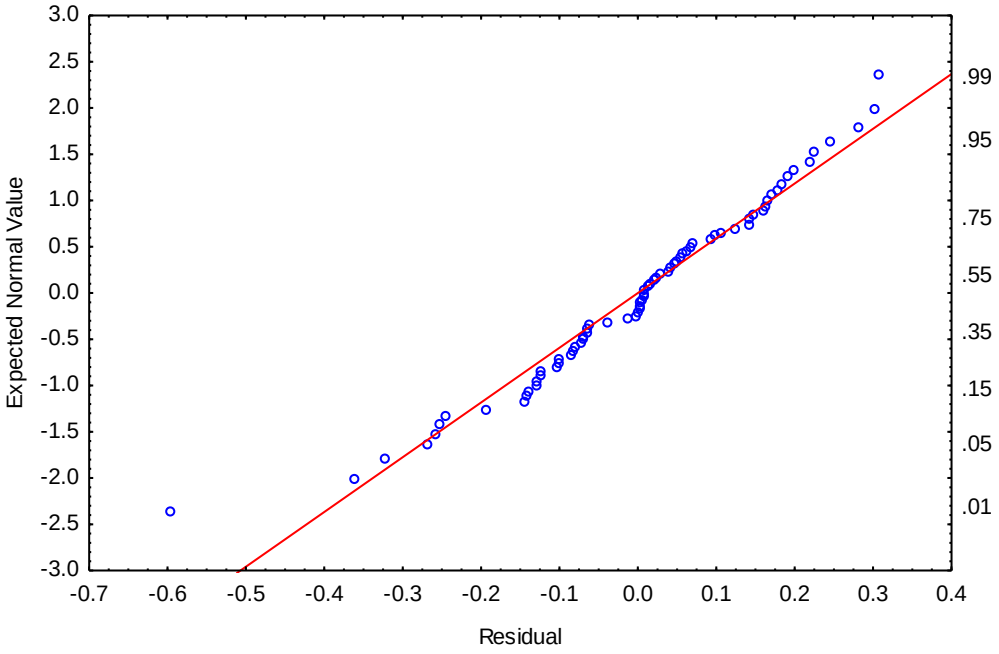


Figure 5.2.14
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Non-dependent

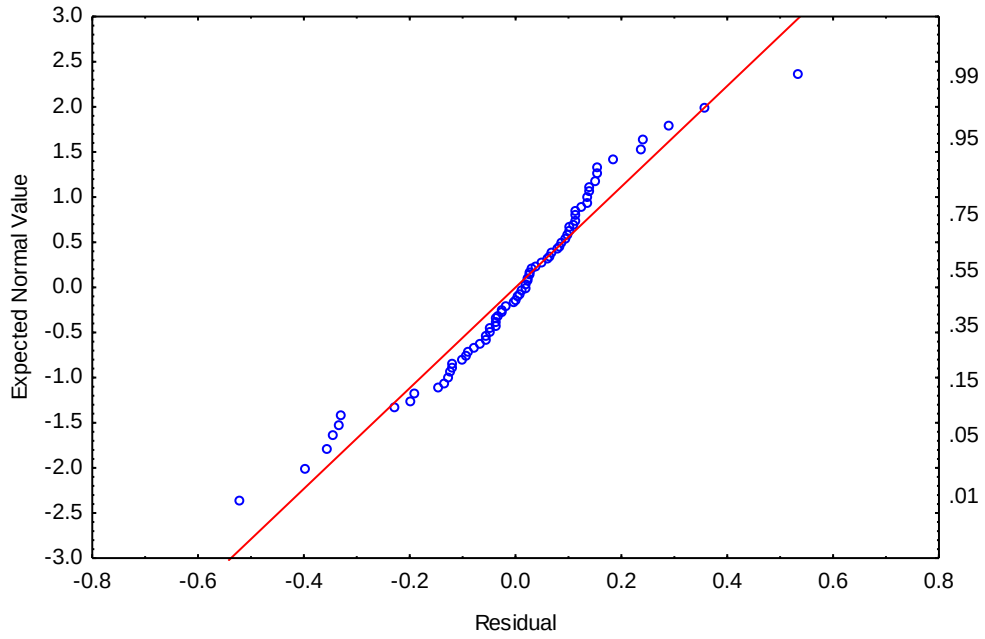


Figure 5.2.15
Normal Prob. Plot; Raw Residuals
Dependent variable: Left side lying - Left lung

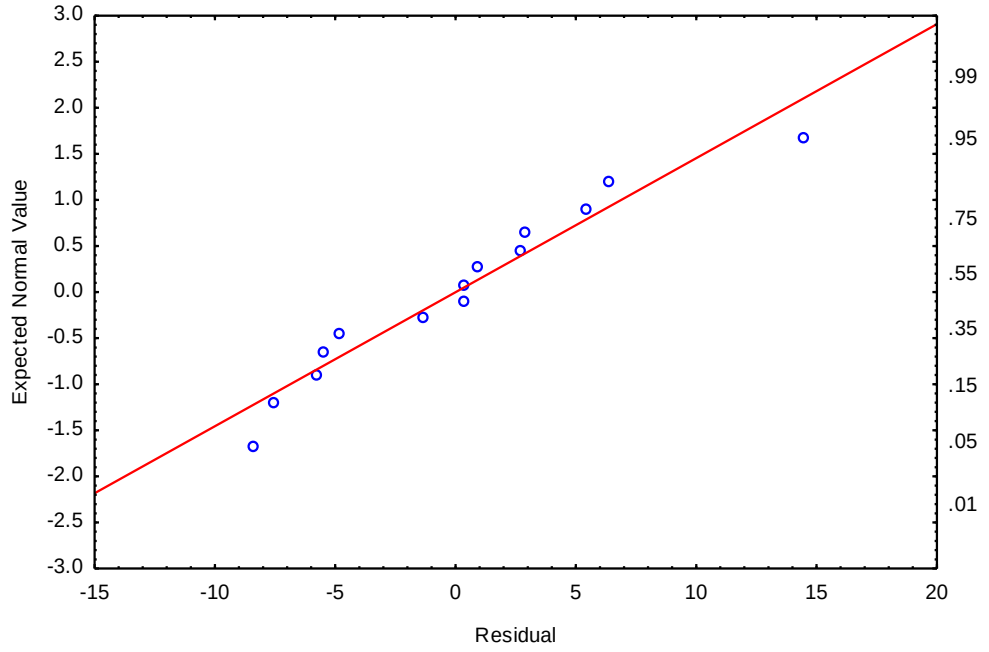


Figure 5.2.15
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine - Left lung

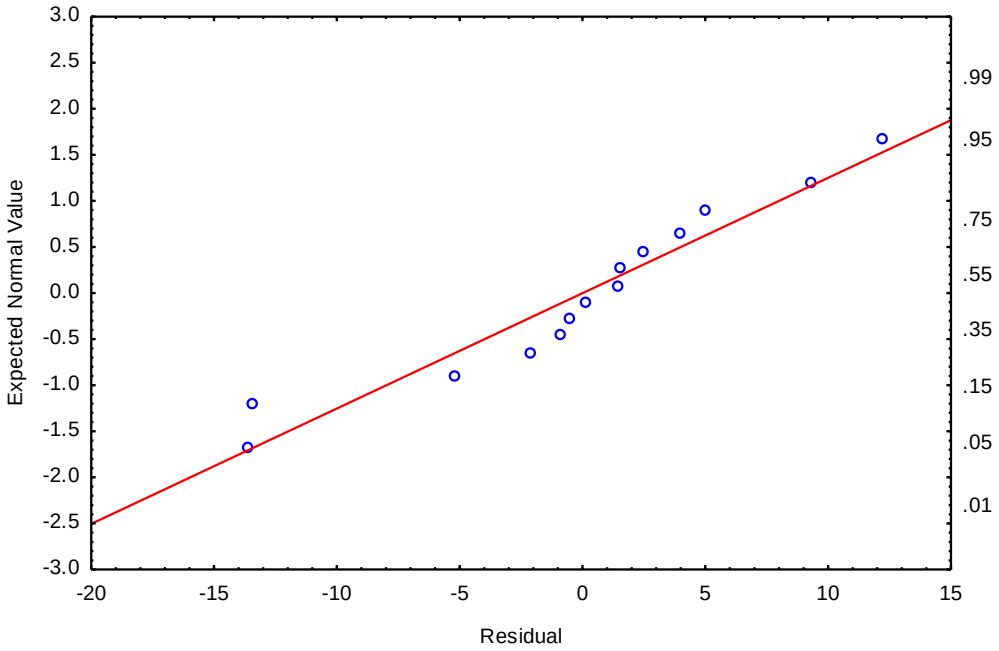


Figure 5.2.15
Normal Prob. Plot; Raw Residuals
Dependent variable: Right side lying - Left lung

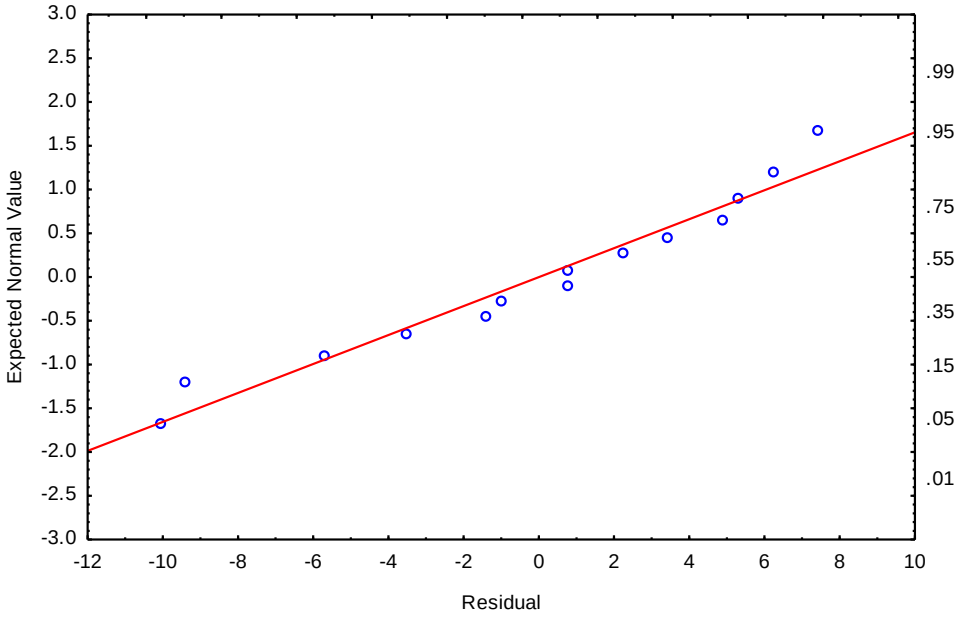


Figure 5.2.16
Normal Prob. Plot; Raw Residuals
Dependent variable: Left side lying - Right lung

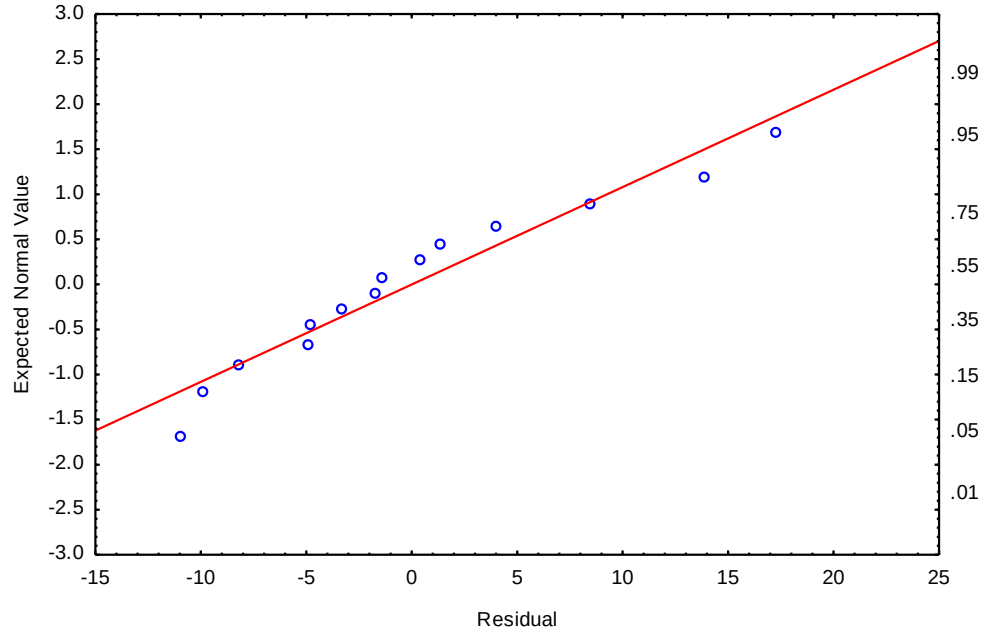


Figure 5.2.16
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine - Right lung

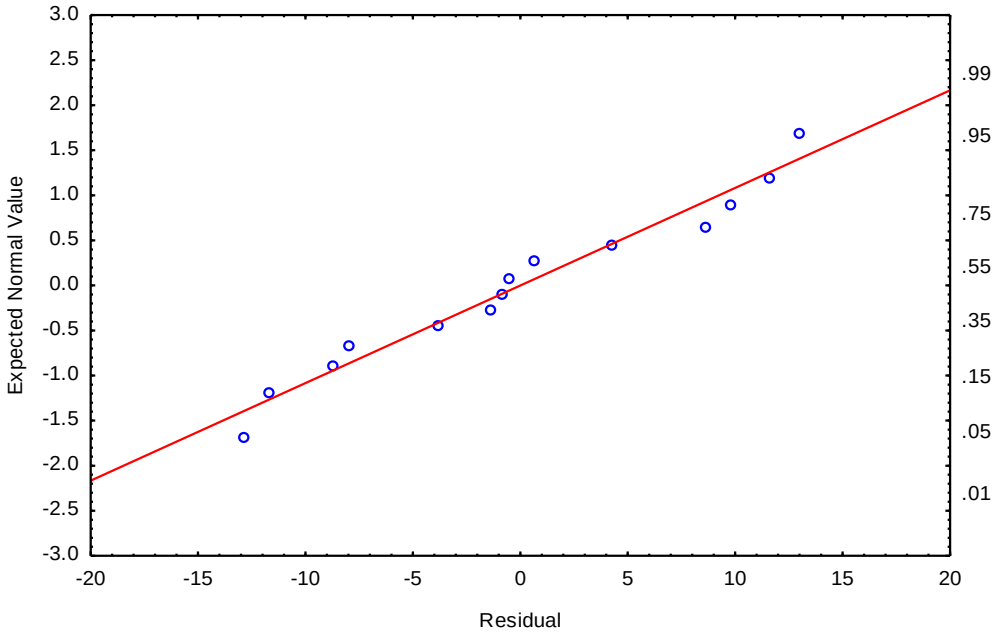


Figure 5.2.16
Normal Prob. Plot; Raw Residuals
Dependent variable: Right side lying - Right lung

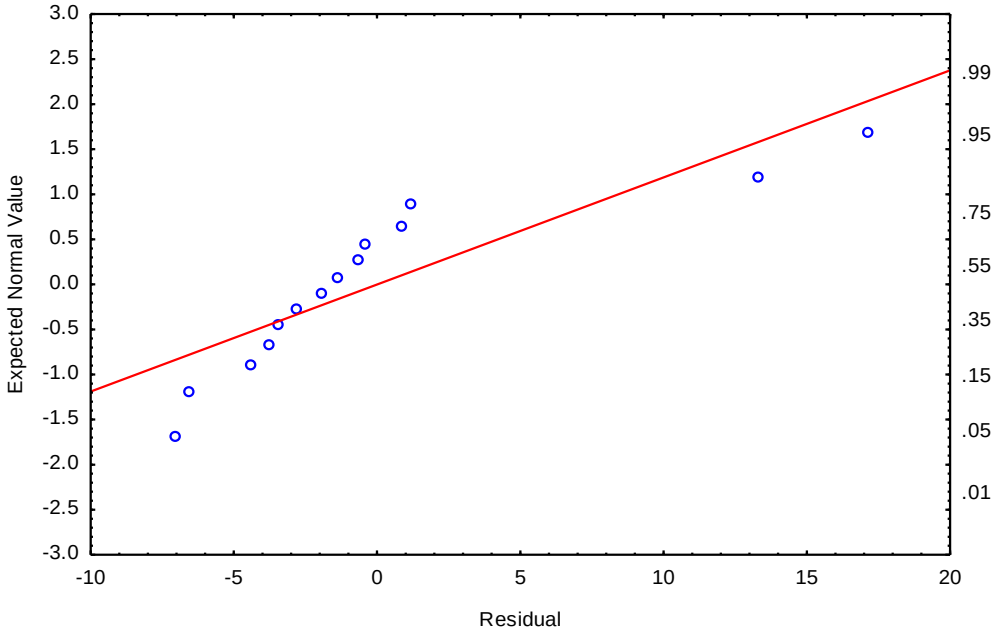


Figure 5.2.17
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

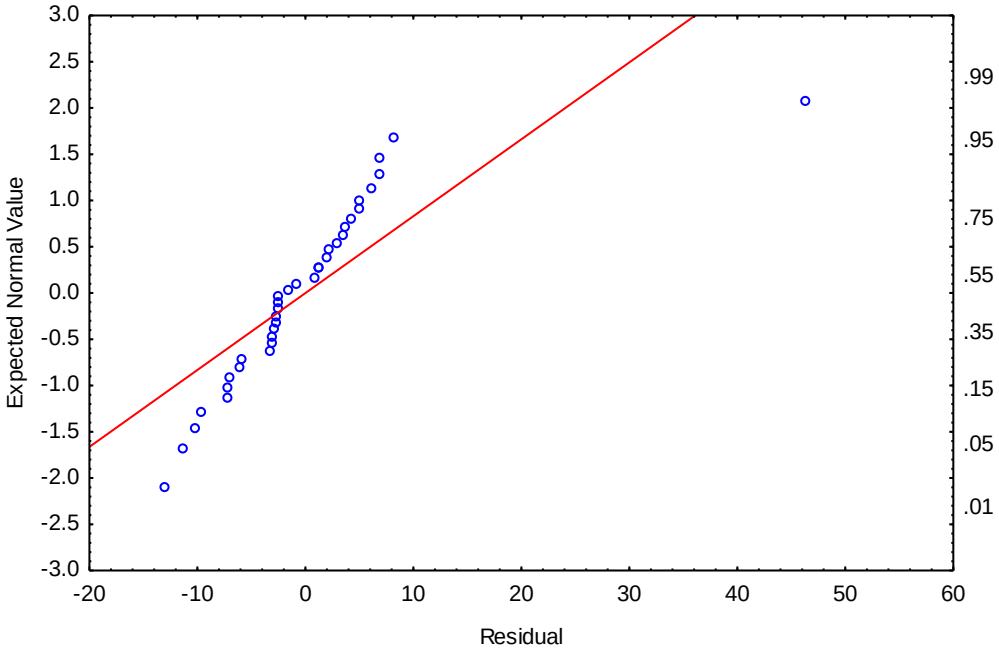


Figure 5.2.17
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

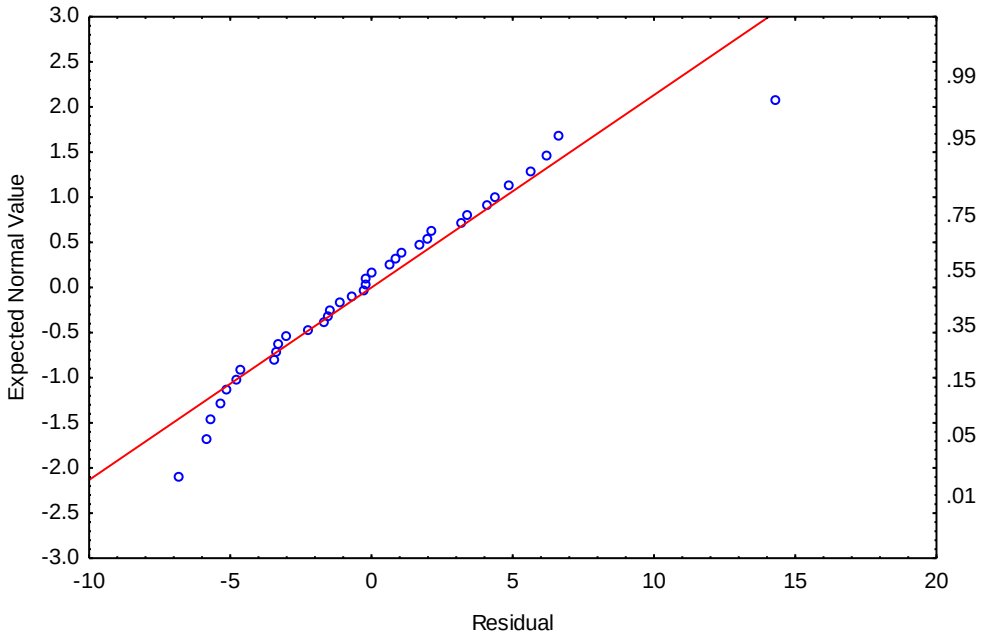


Figure 5.2.18
Normal Prob. Plot; Raw Residuals
Dependent variable: Left hemi-diaphragm - Left side lying

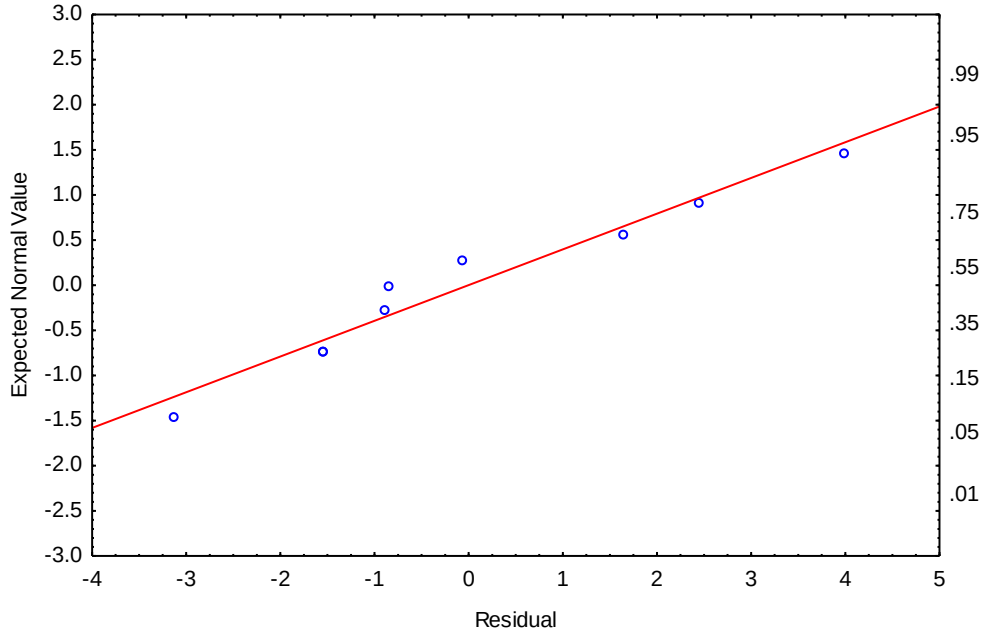


Figure 5.2.18
Normal Prob. Plot; Raw Residuals
Dependent variable: Left hemi-diaphragm - Right side lying

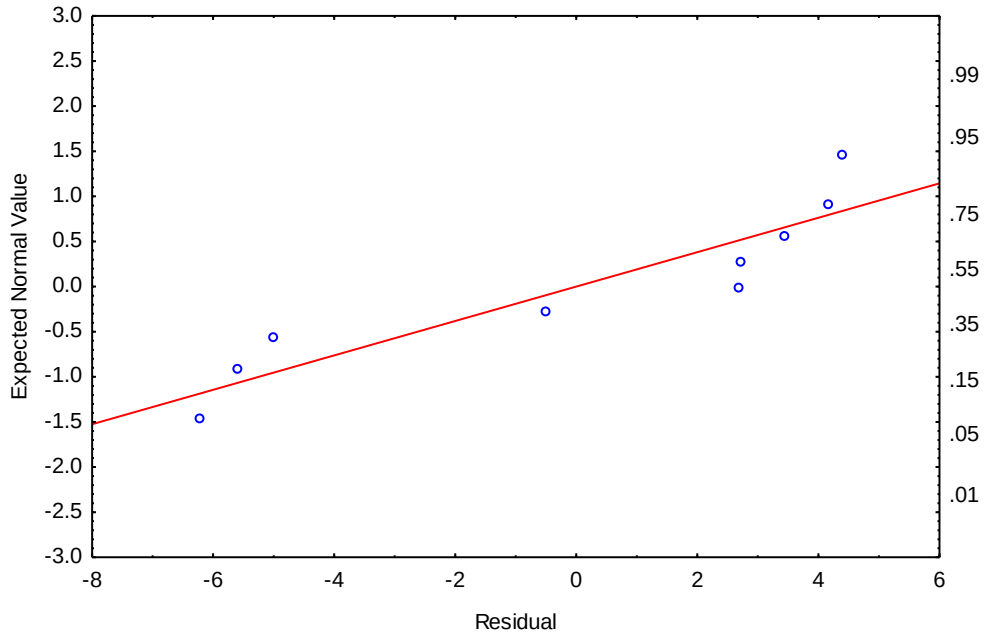


Figure 5.2.19
Normal Prob. Plot; Raw Residuals
Dependent variable: Right Hemi-diaphragm - Left side lying

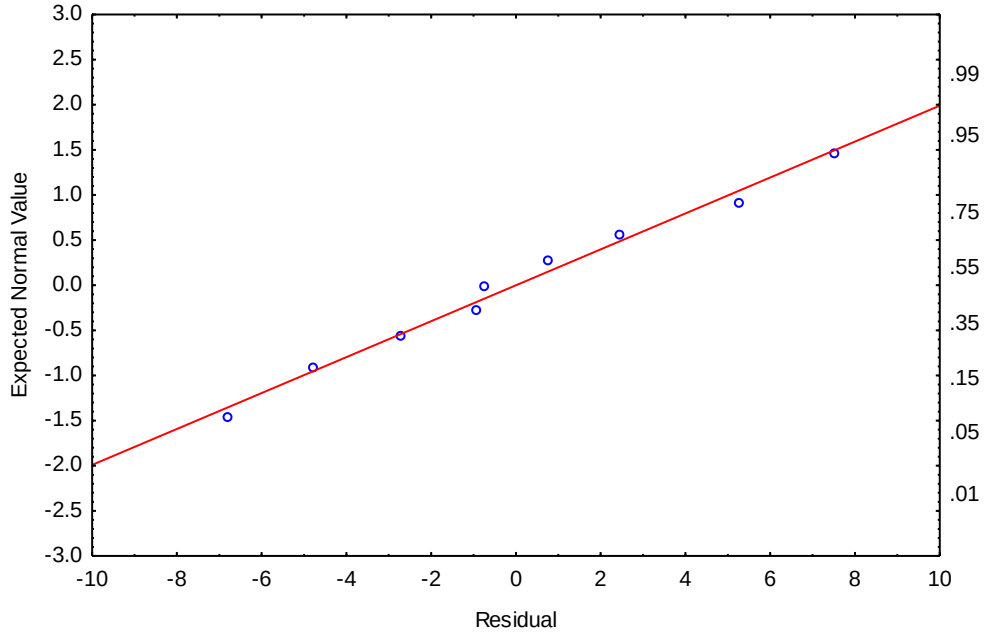


Figure 5.2.19
Normal Prob. Plot; Raw Residuals
Dependent variable: Right Hemi-diaphragm - Right side lying

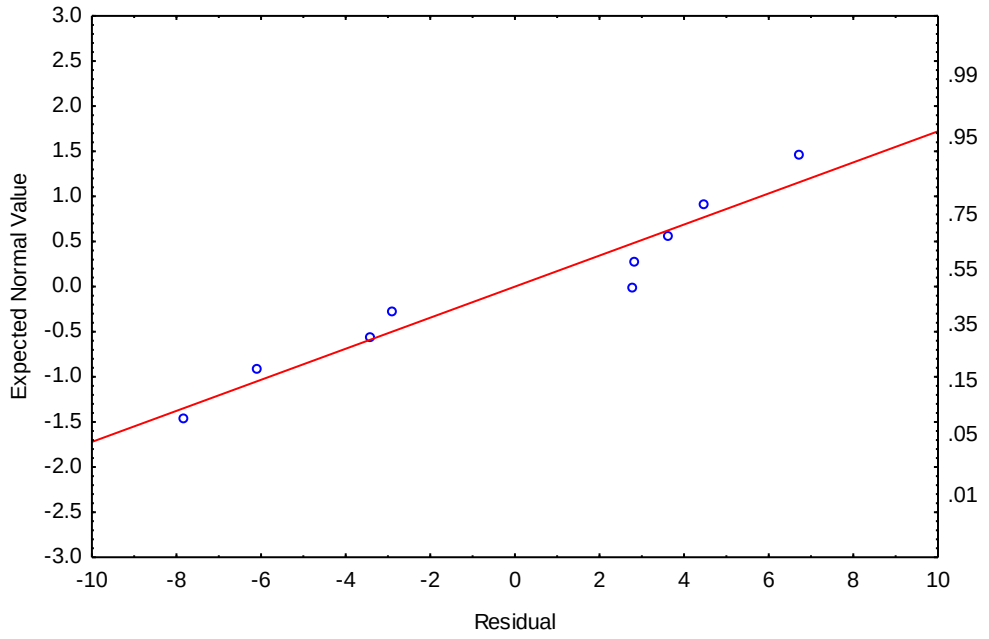


Figure 5.2.20
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine position - Ventral lung

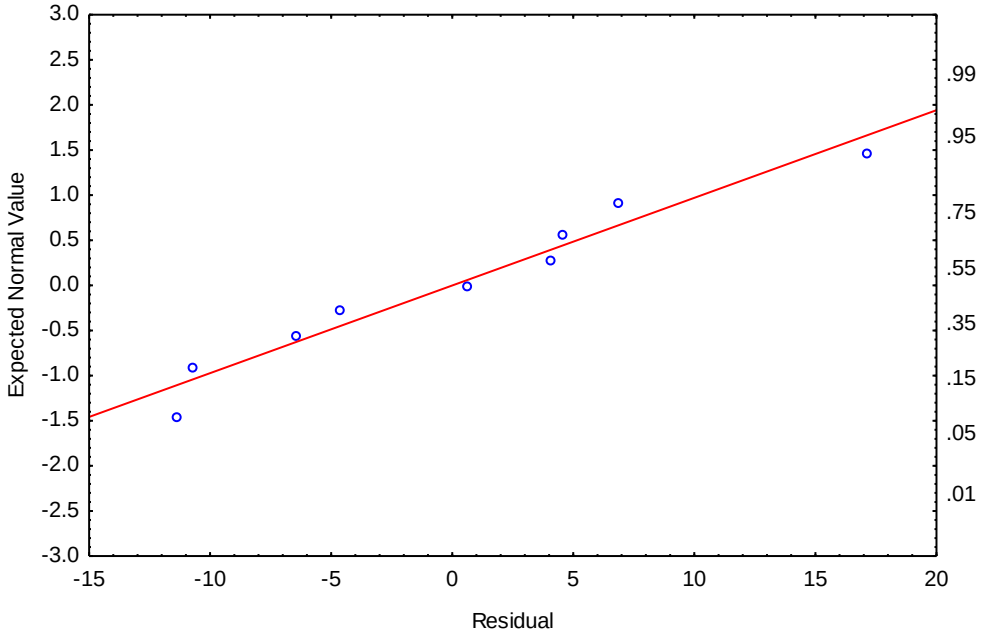


Figure 5.2.20
Normal Prob. Plot; Raw Residuals
Dependent variable: Prone position - Ventral lung

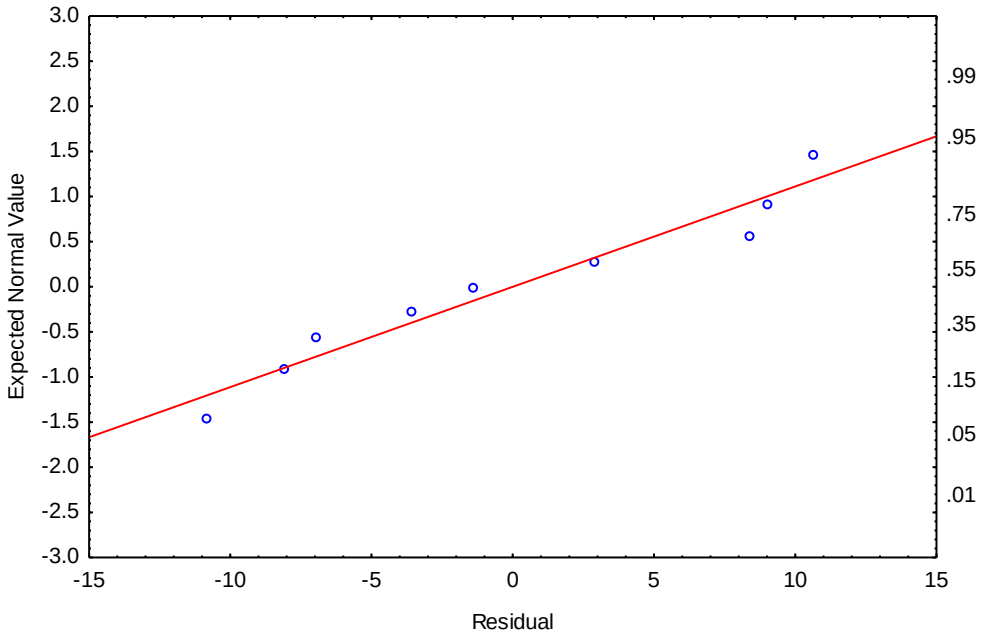


Figure 5.2.21
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine position - Dorsal lung

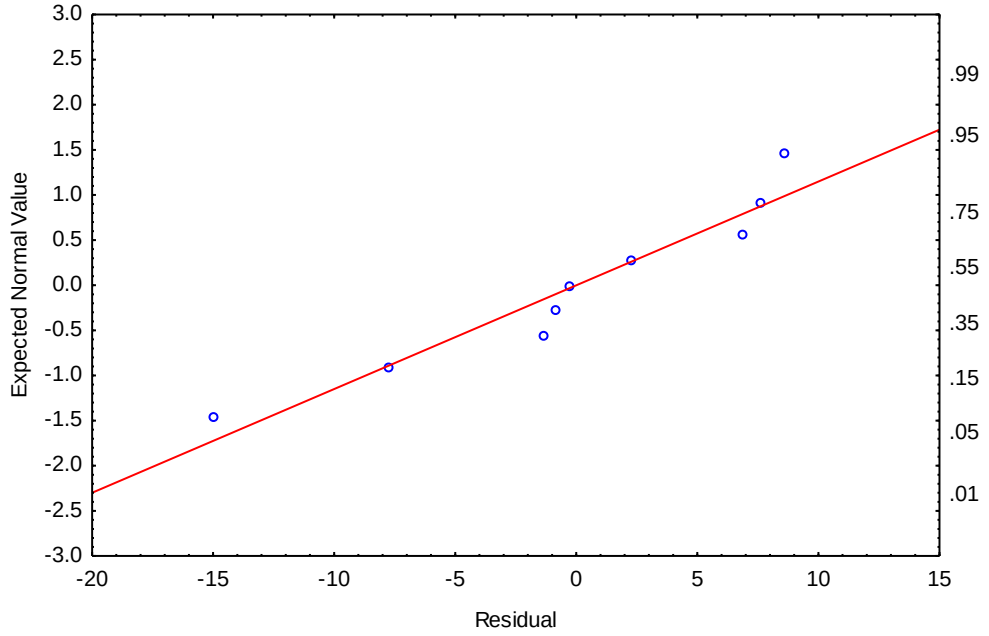


Figure 5.2.21
Normal Prob. Plot; Raw Residuals
Dependent variable: Prone position - Dorsal lung

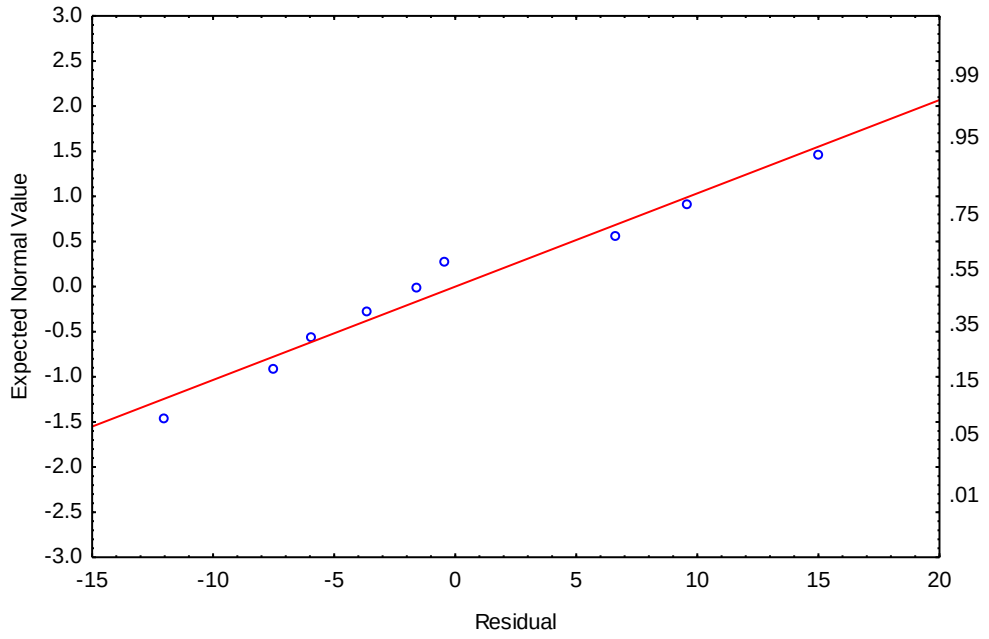


Figure 5.2.22
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Dependent

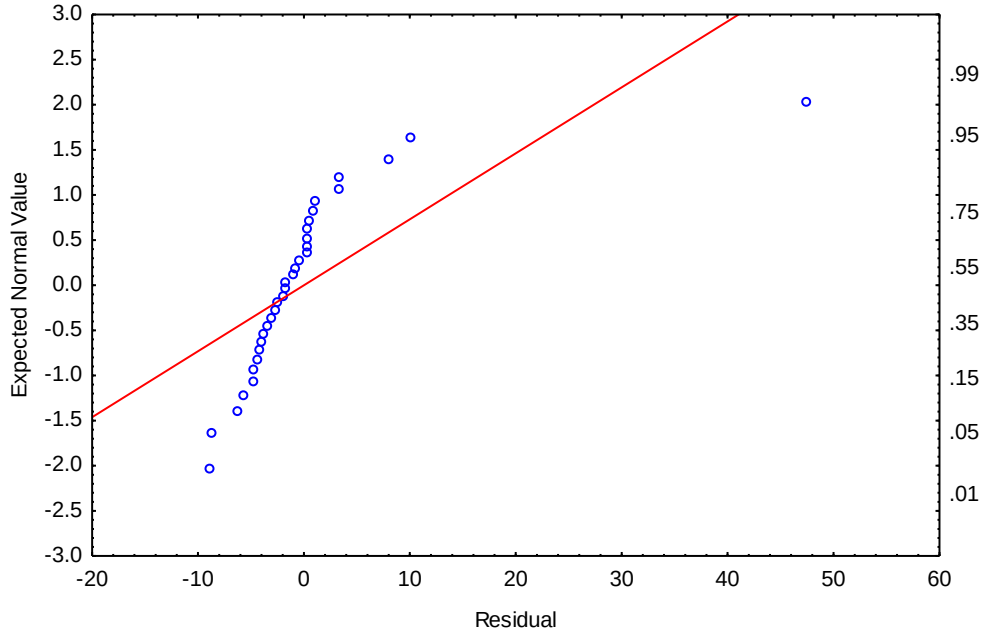
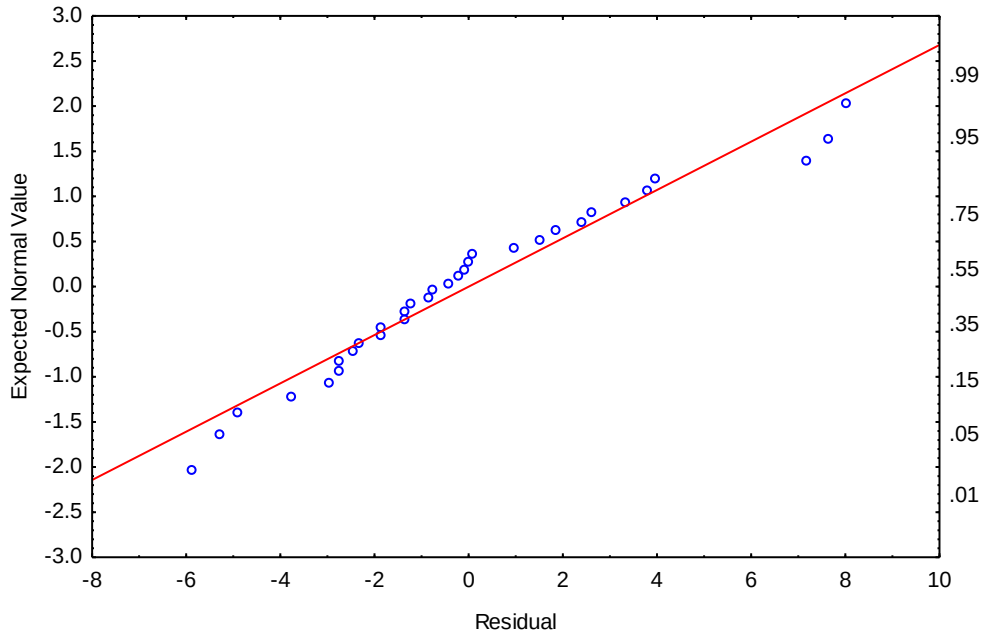
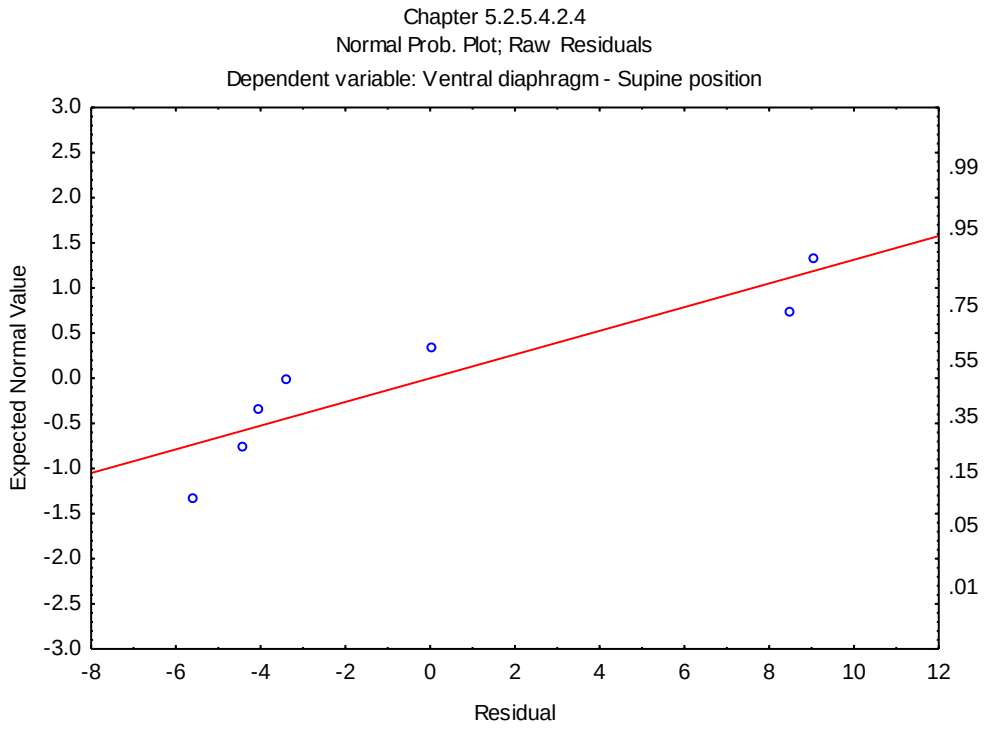


Figure 5.2.22
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Non-dependent




Chapter 5.2.5.4.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral diaphragm - Supine position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-8
-6
-4
-2
0
2
4
6
8
10
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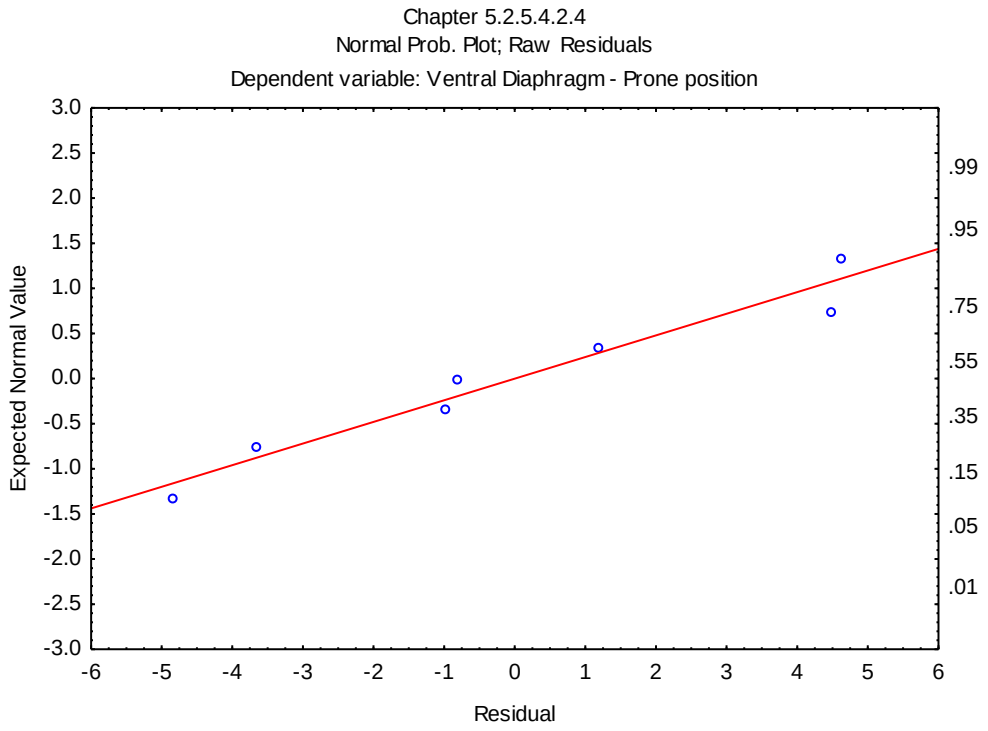
.75
.55
.35
.15
.05
.01


Chapter 5.2.5.4.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral Diaphragm - Prone position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-6
-5
-4
-3
-2
-1
0
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4
5
6
.99
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.75
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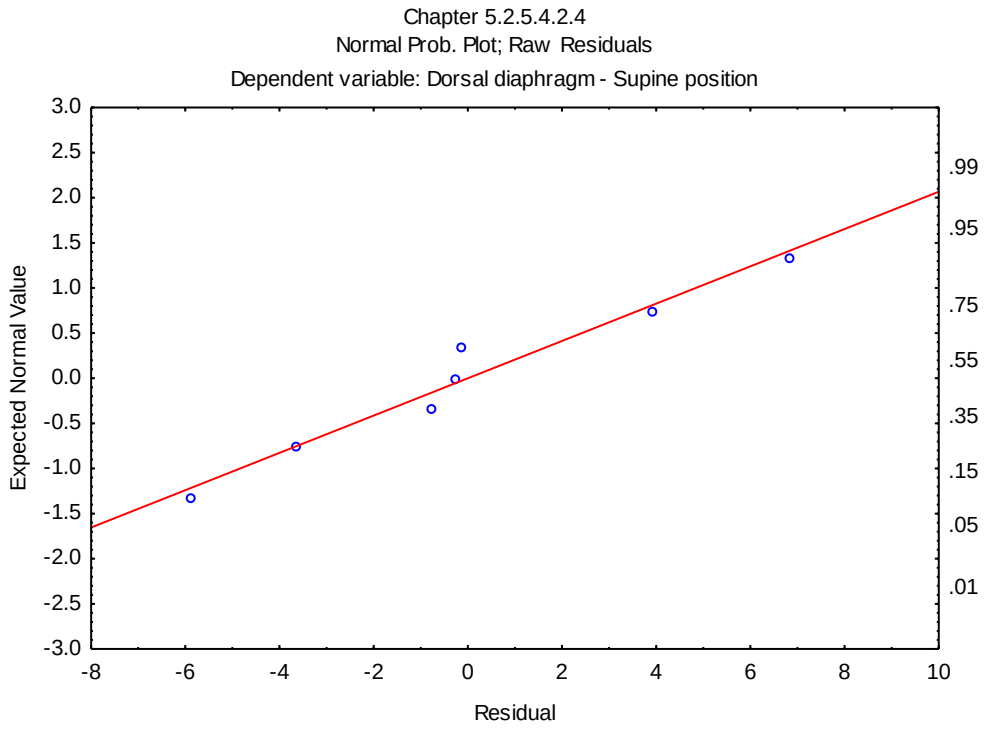
.05
.01


Chapter 5.2.5.4.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal diaphragm - Supine position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-8
-6
-4
-2
0
2
4
6
8
10
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.95
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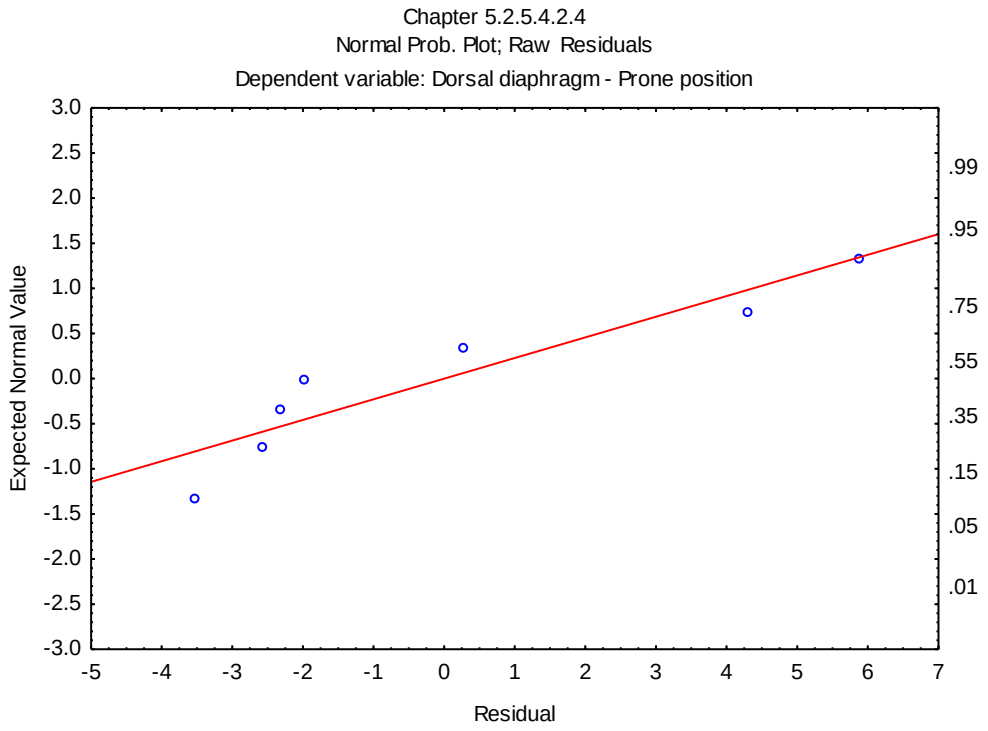
.55
.35
.15
.05
.01


Chapter 5.2.5.4.2.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal diaphragm - Prone position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
.99
.95
.75
.55
.35
.15
.05
.01

5.2. Study Two

Figure 5.3.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

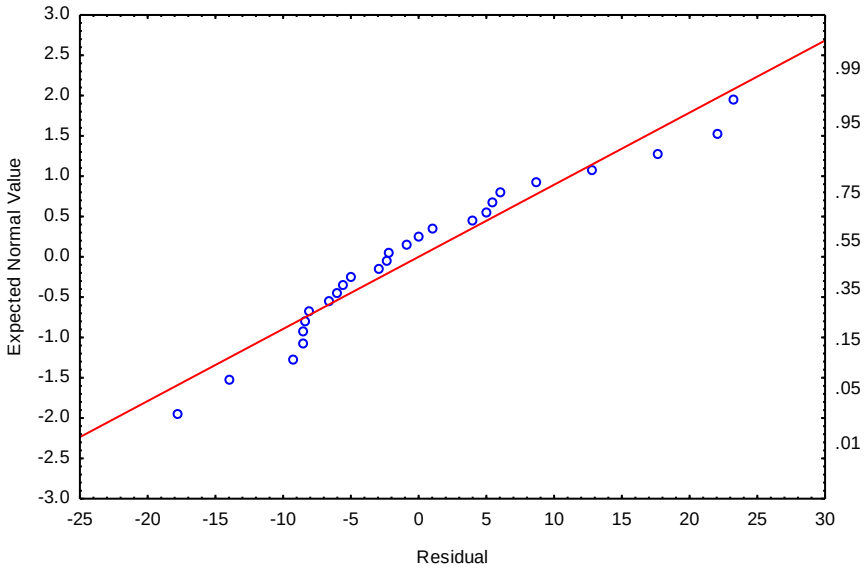


Figure 5.3.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine

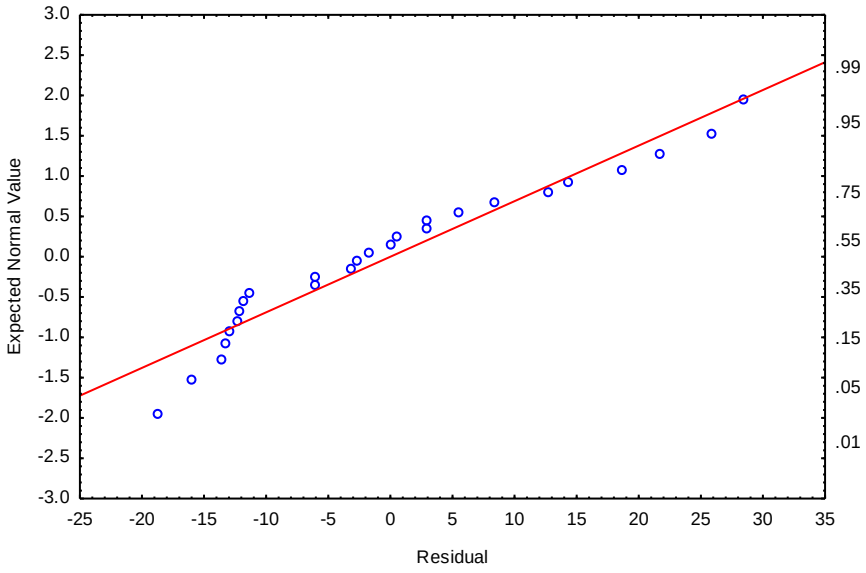
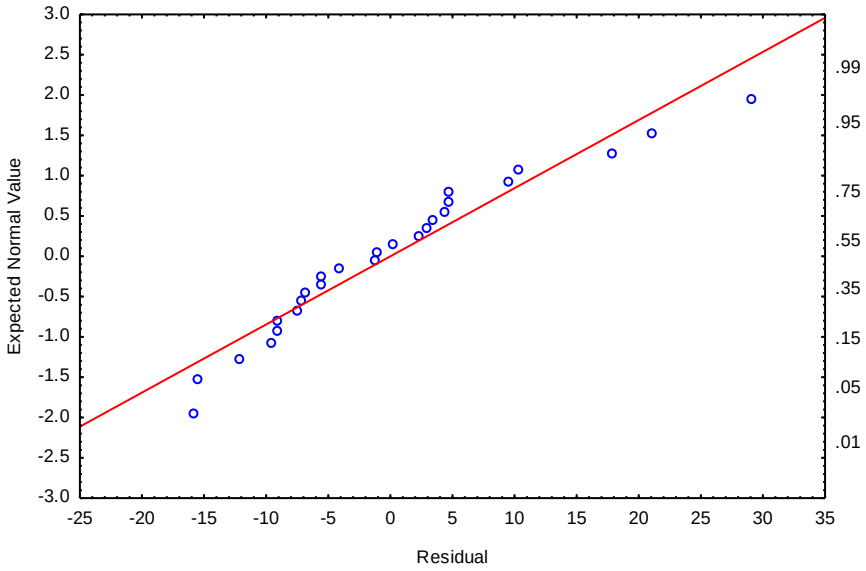
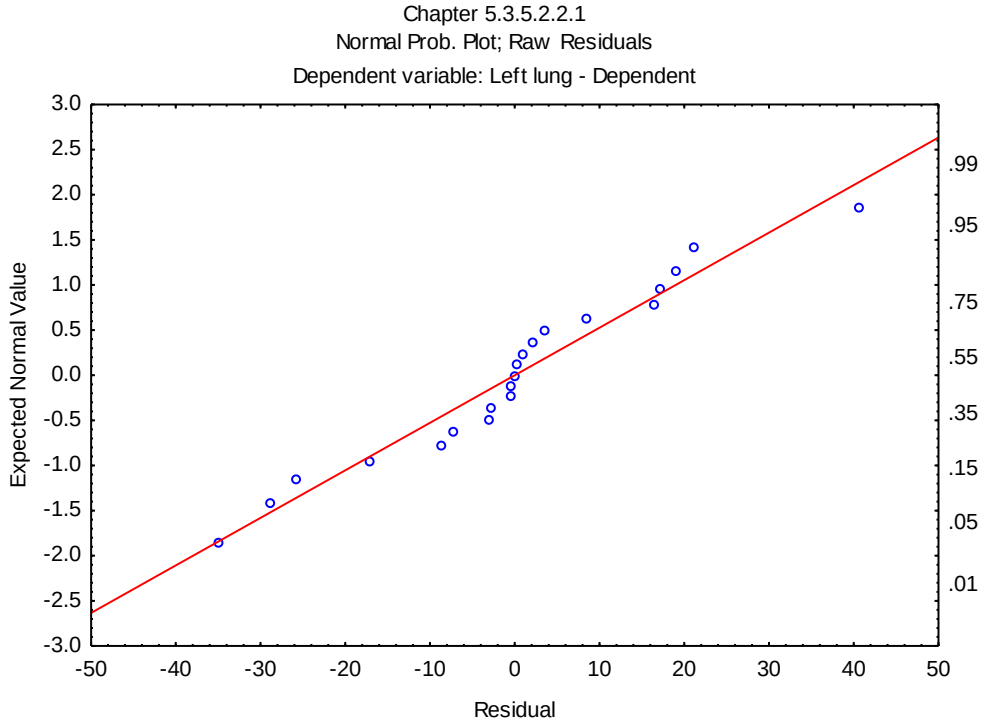


Figure 5.3.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent




Chapter 5.3.5.2.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Dependent
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-50
-40
-30
-20
-10
0
10
20
30
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.15
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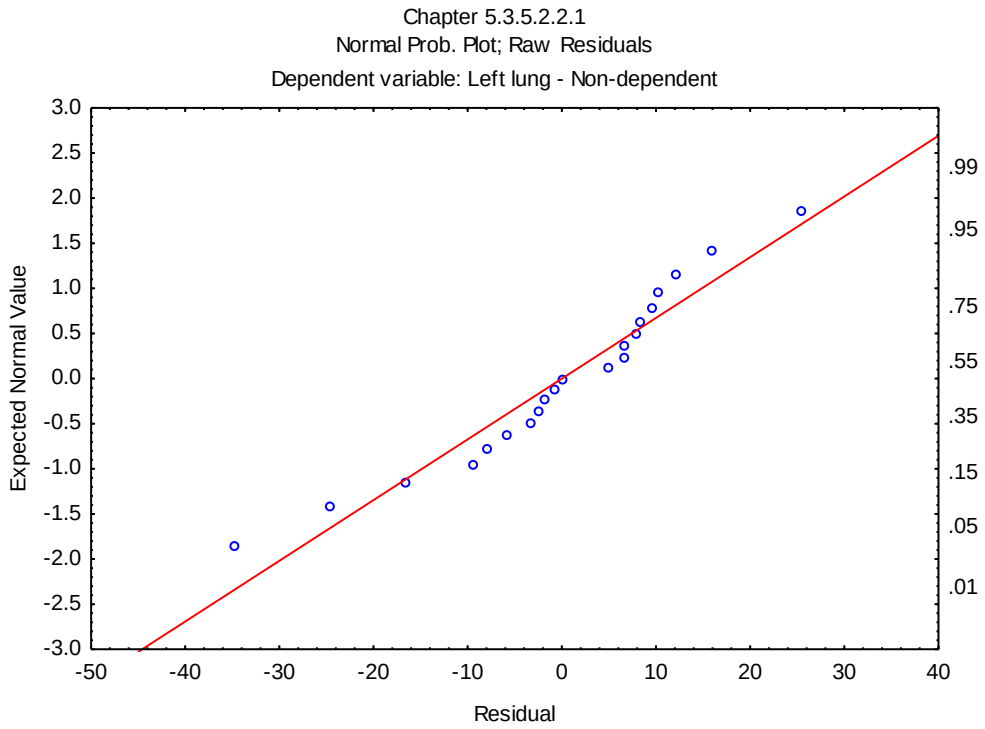
.01


Chapter 5.3.5.2.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Non-dependent
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-50
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0
10
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30
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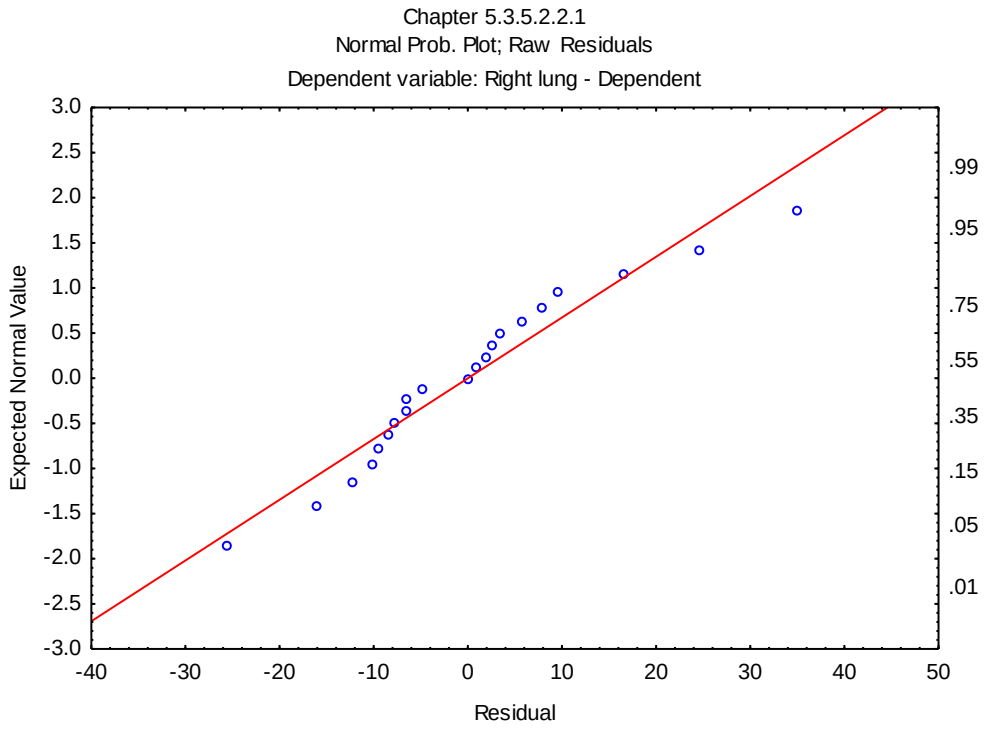
Chapter 5.3.5.2.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Dependent
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-40
-30
-20
-10
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10
20
30
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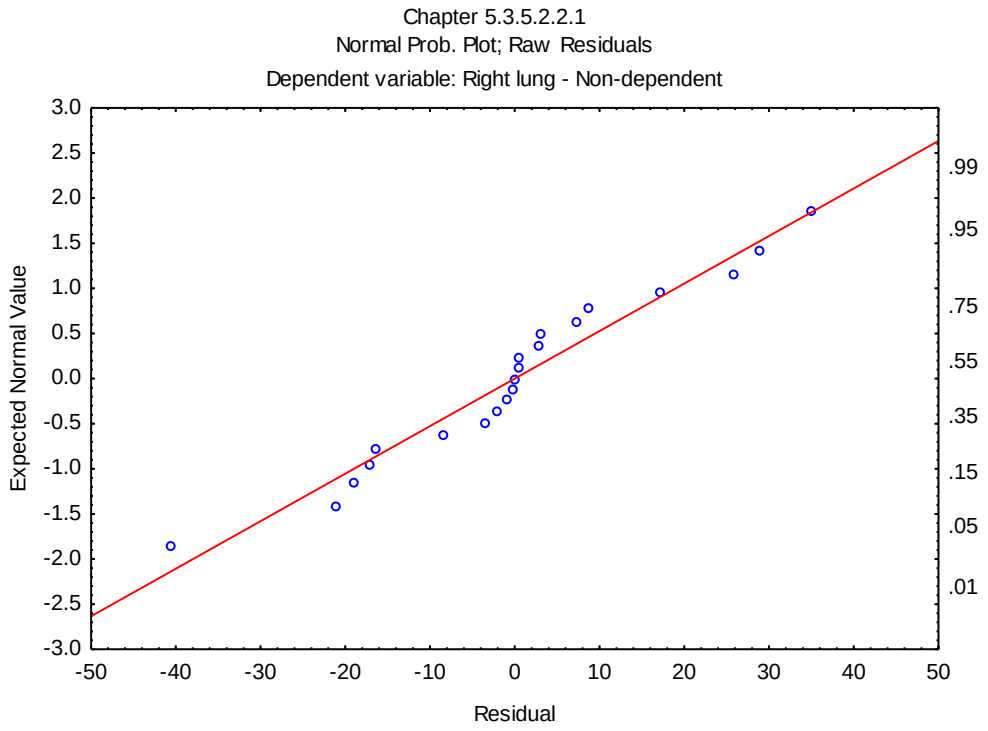
Chapter 5.3.5.2.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Non-dependent
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-50
-40
-30
-20
-10
0
10
20
30
40
50
.99
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.01

Figure 5.3.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Left side lying

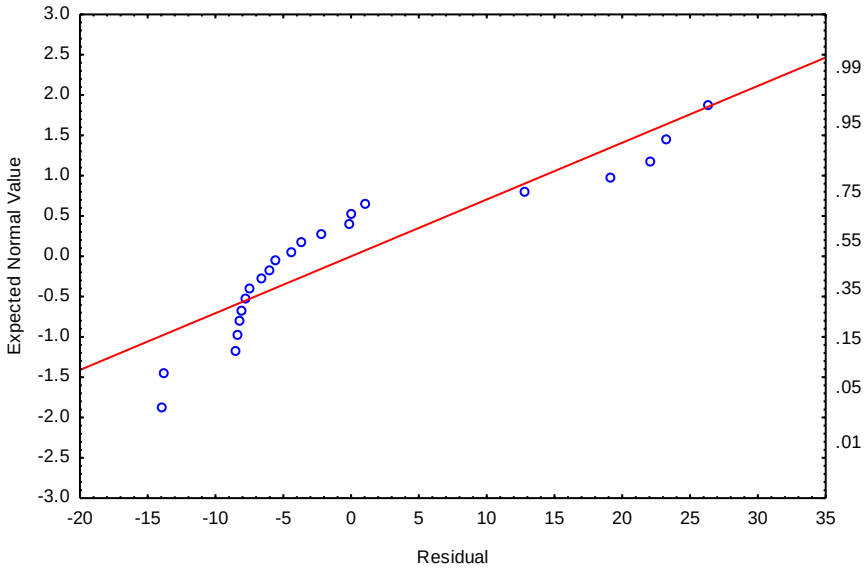


Figure 5.3.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Supine

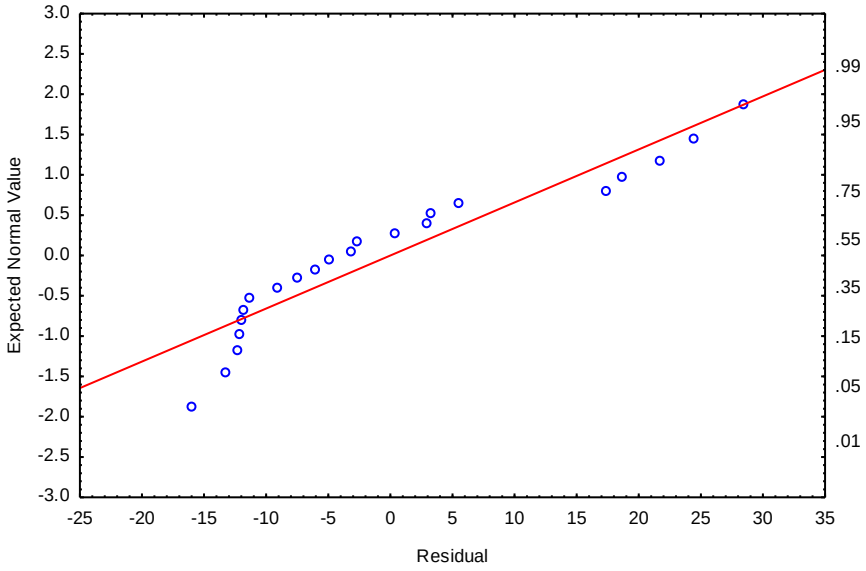


Figure 5.3.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Right side lying

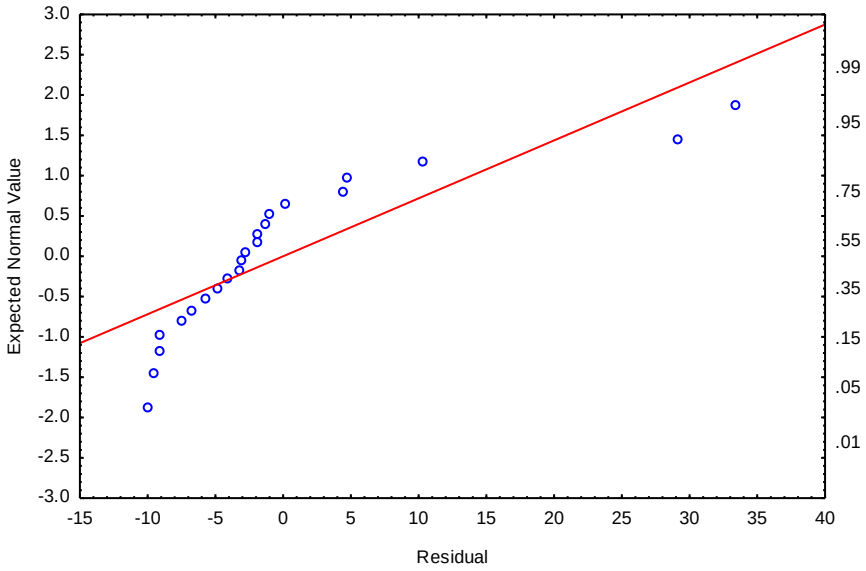


Figure 5.3.6
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Left side lying

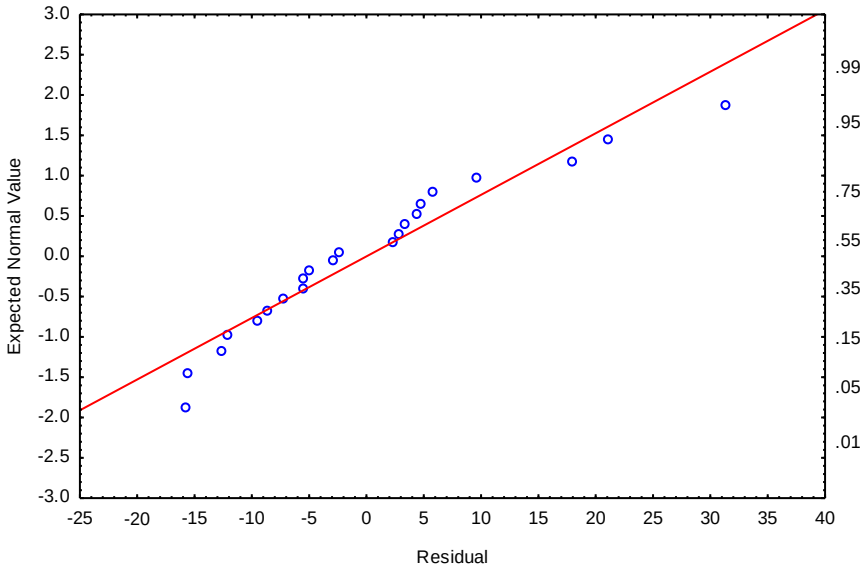


Figure 5.3.6
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Supine

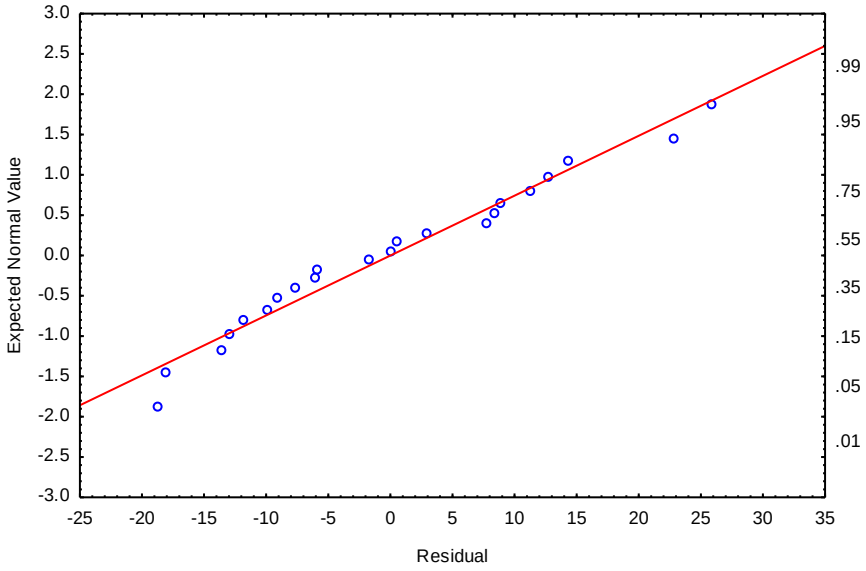


Figure 5.3.6
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Right side lying

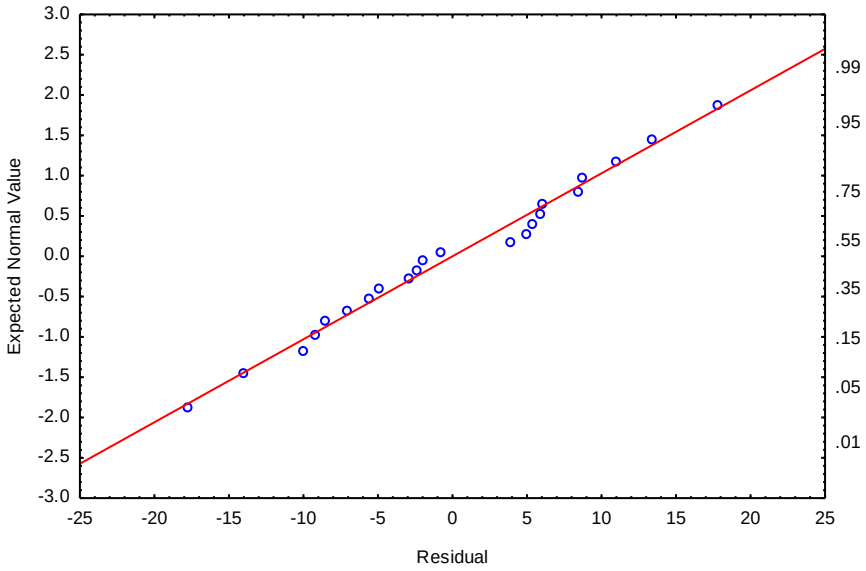


Figure 5.3.7
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

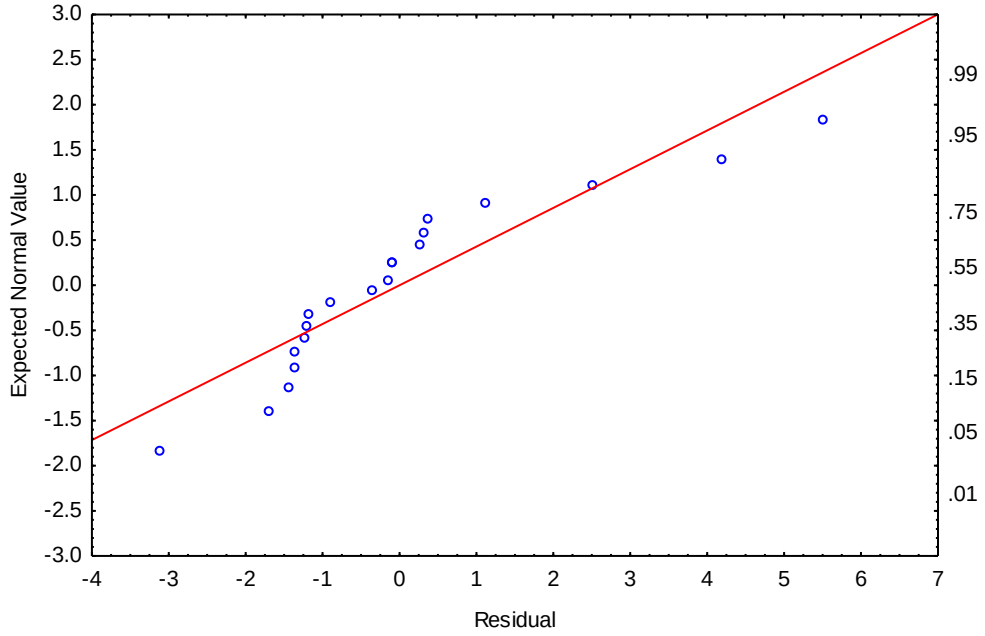
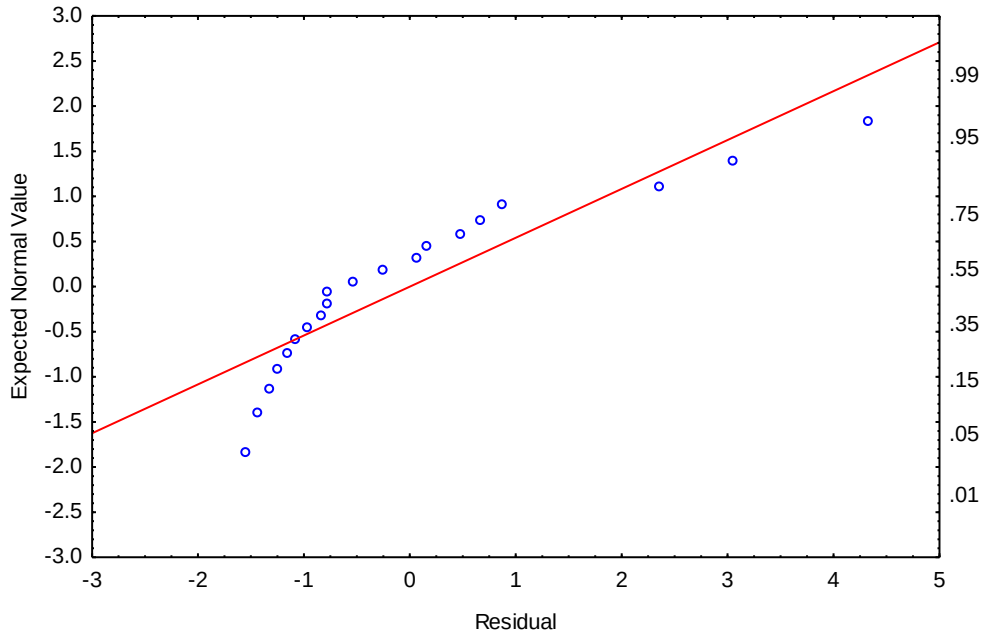
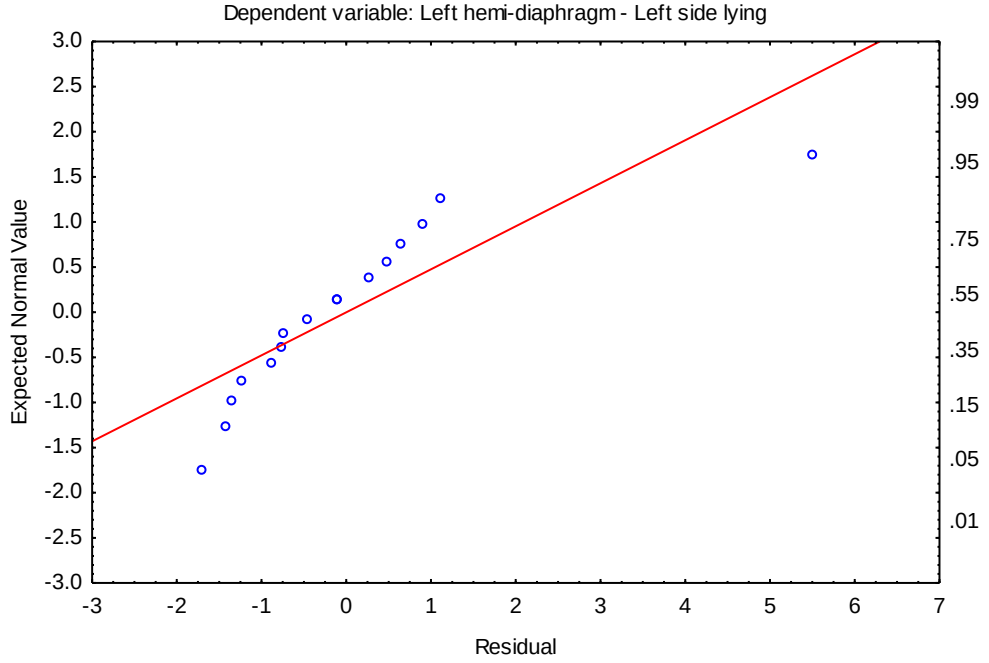


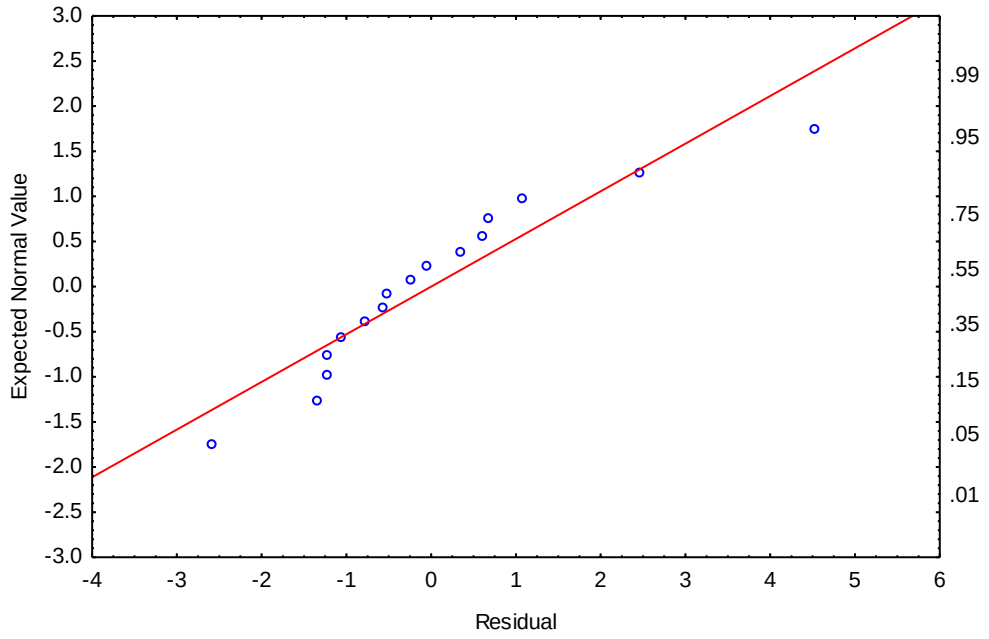
Figure 5.3.7
Normal Prob. Plot; Raw Residuals
Dependent variable: Non-dependent

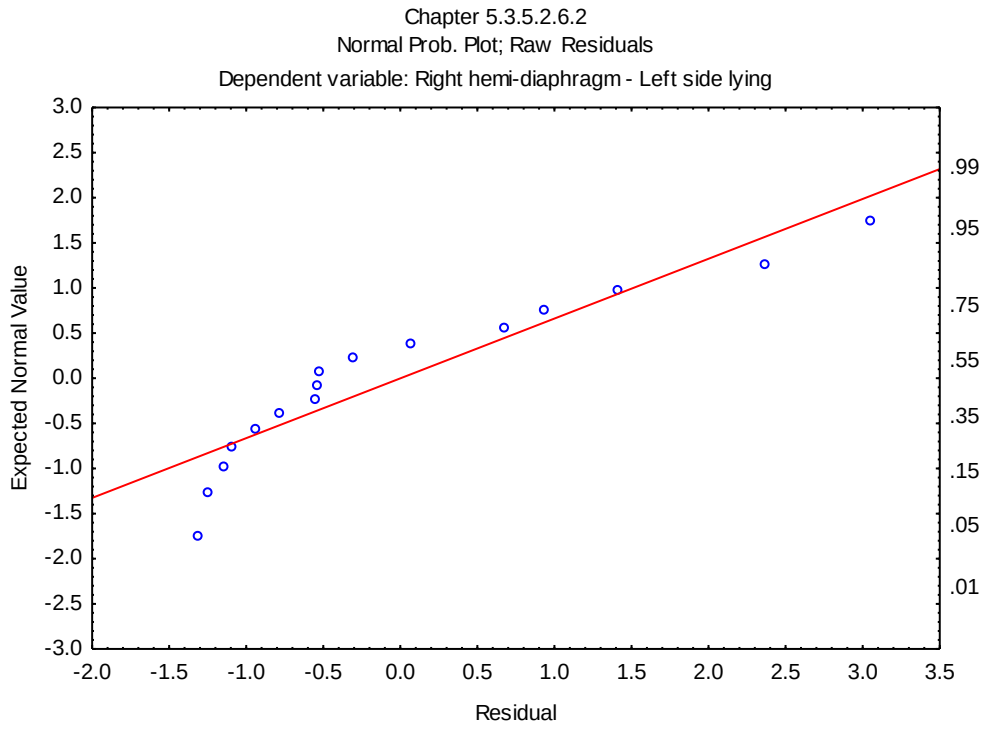


Chapter 5.3.5.2.6.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Left hemi-diaphragm - Left side lying



Chapter 5.3.5.2.6.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Left hemi-diaphragm - Right side lying




Chapter 5.3.5.2.6.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Right hemi-diaphragm - Left side lying
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-2.0
-1.5
-1.0
-0.5
0.0
0.5
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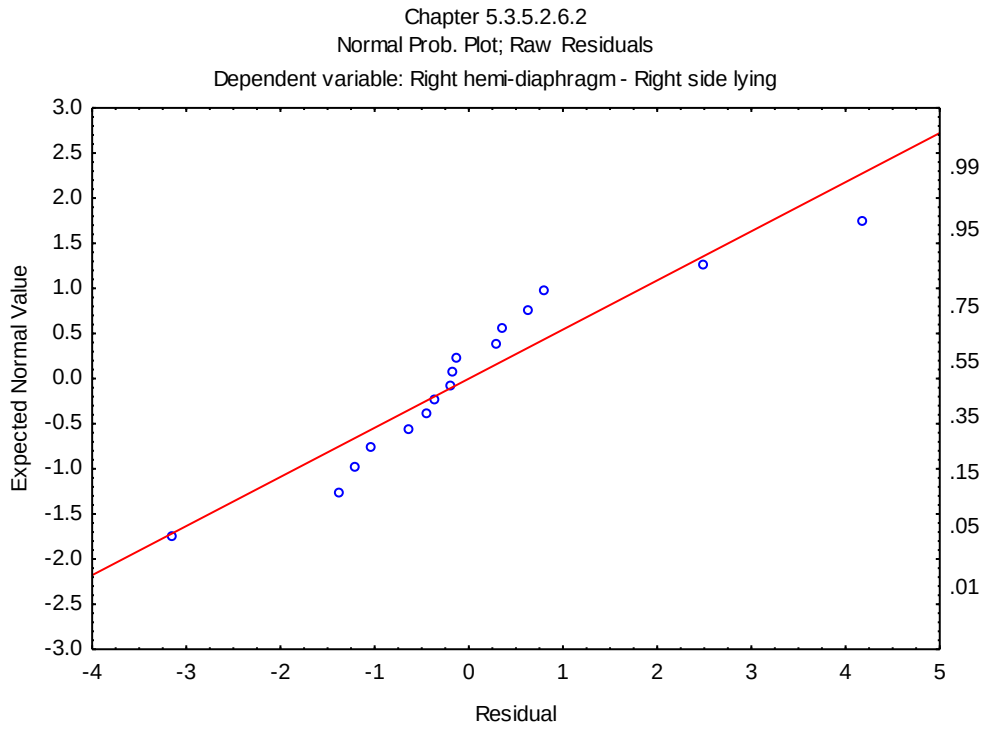
Chapter 5.3.5.2.6.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Right hemi-diaphragm - Right side lying
Expected Normal Value
Residual
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2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-4
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-2
-1
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1
2
3
4
5
.99
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.05
.01

Figure 5.3.9
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Dependent

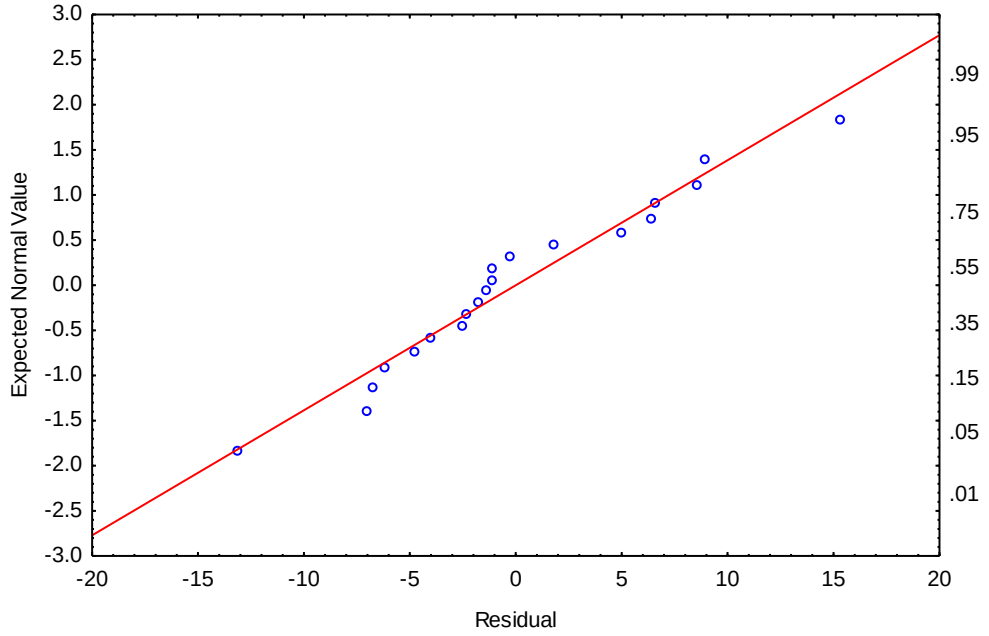
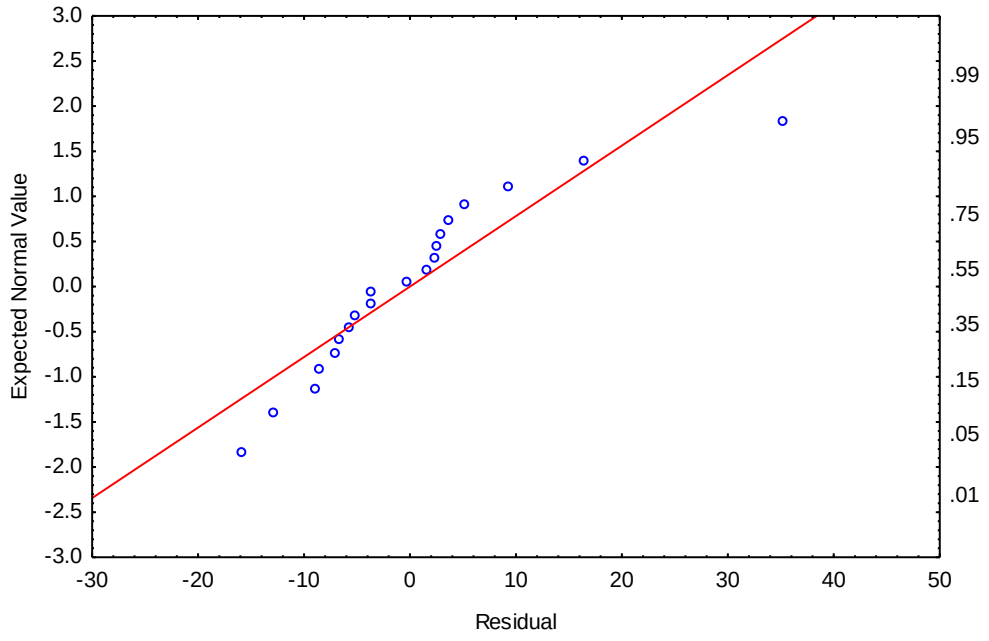
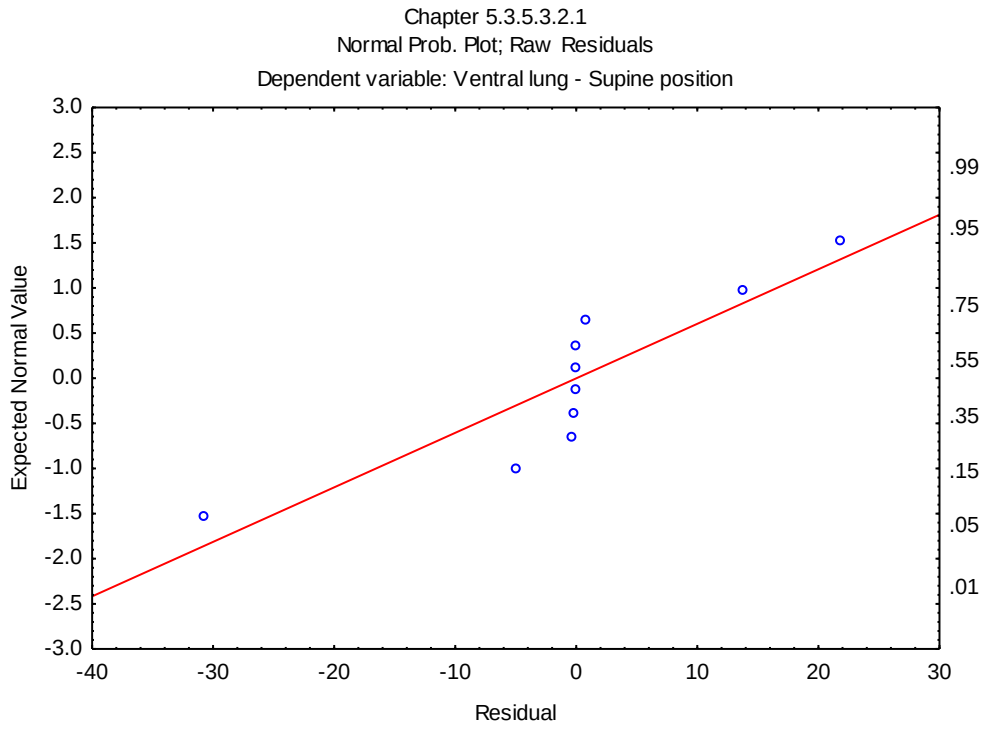


Figure 5.3.9
Normal Prob. Plot; Raw Residuals
Dependent variable: Nodependent




Chapter 5.3.5.3.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Supine position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-40
-30
-20
-10
0
10
20
30
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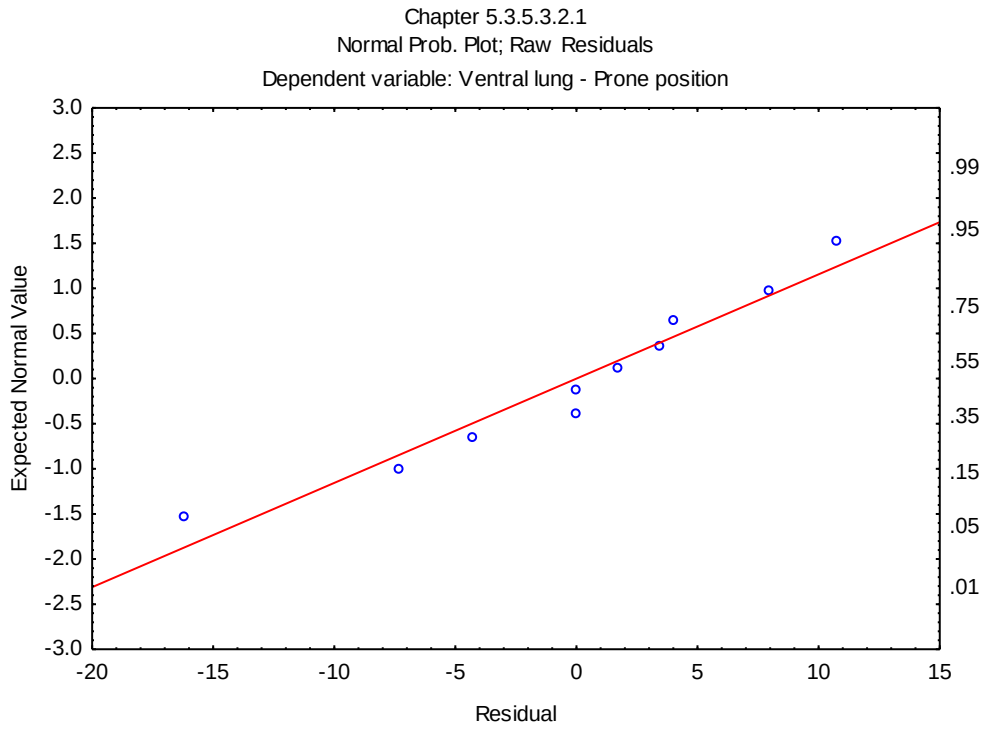
.01


Chapter 5.3.5.3.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Prone position
Expected Normal Value
Residual
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1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
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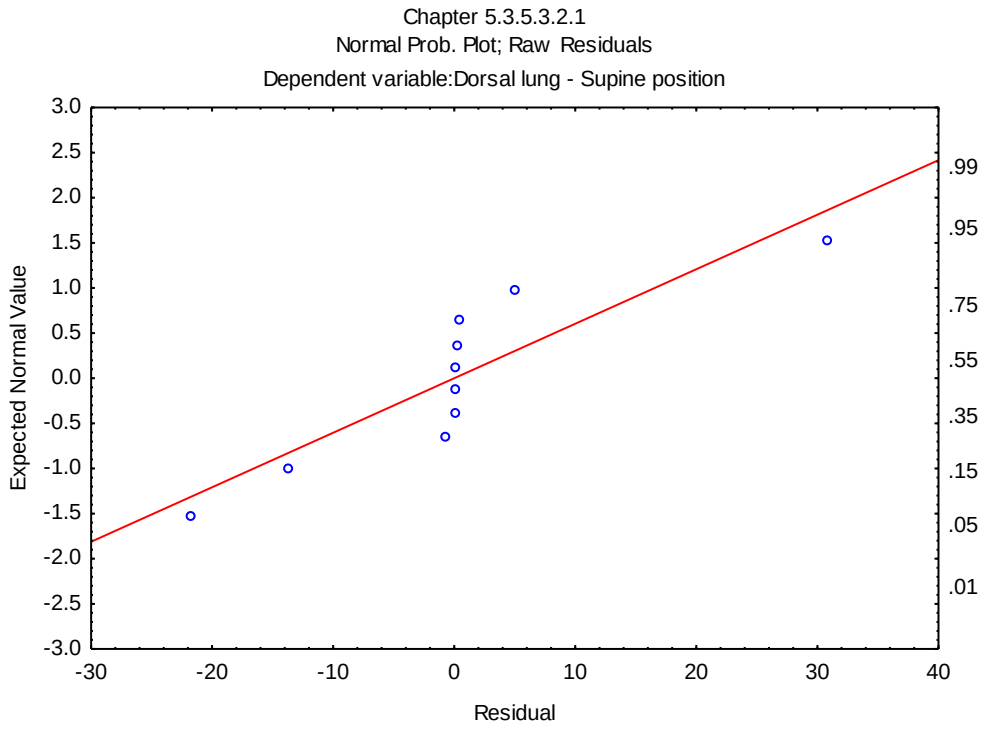
Chapter 5.3.5.3.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable:Dorsal lung - Supine position
Expected Normal Value
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1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
.99
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.05
.01
-30
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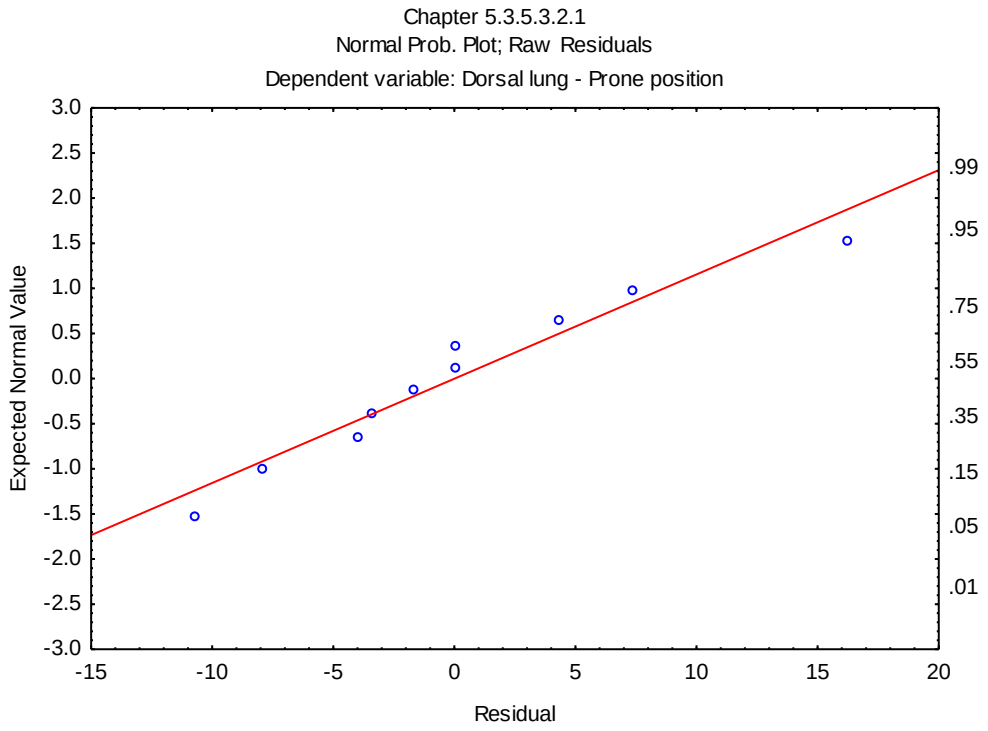
-10
0
10
20
30
40
Residual


Chapter 5.3.5.3.2.1
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Prone position
Expected Normal Value
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2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
.99
.95
.75
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.05
.01
-15
-10
-5
0
5
10
15
20
Residual

Figure 5.3.10
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Ventral lung

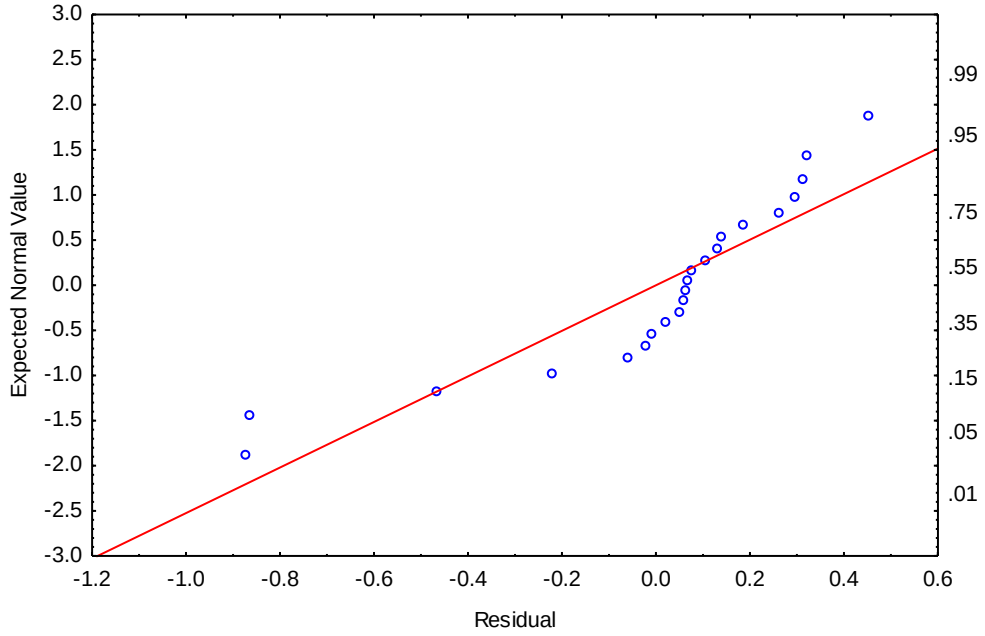


Figure 5.3.10
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Dorsal lung

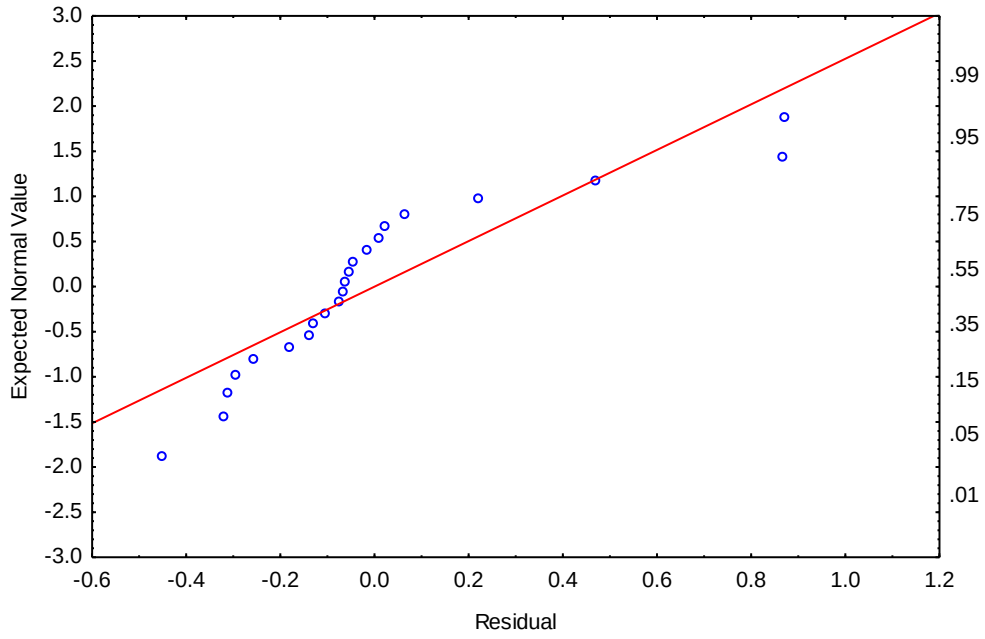


Figure 5.3.11
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Supine position

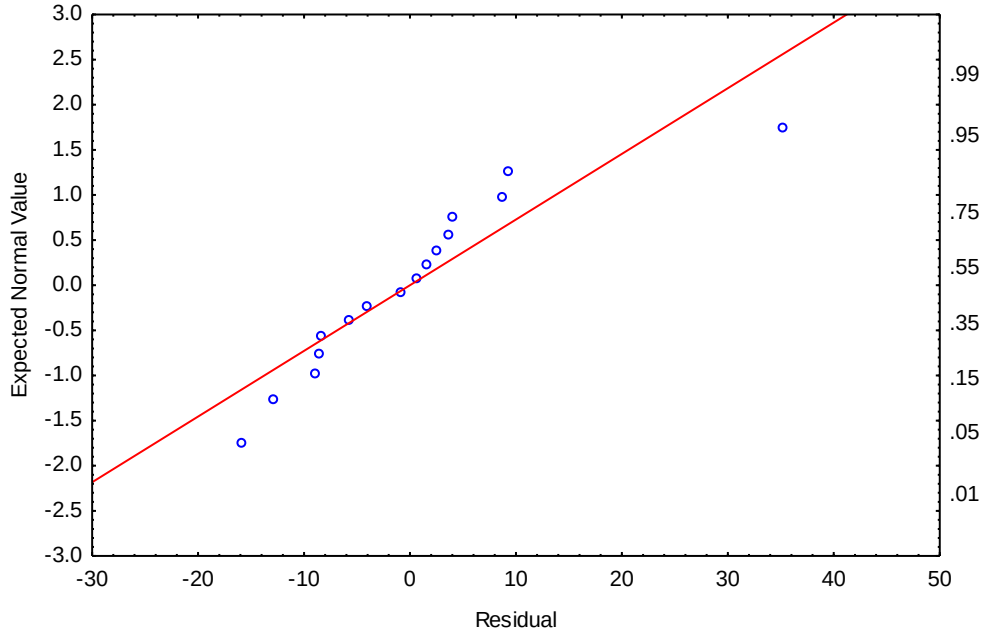


Figure 5.3.11
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Prone position

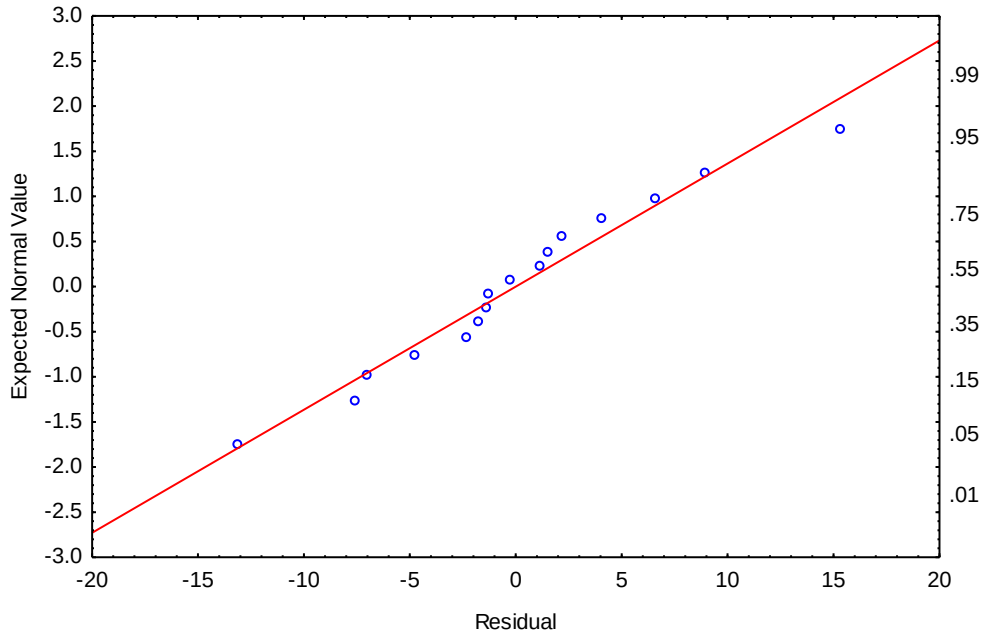


Figure 5.3.12
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Supine position

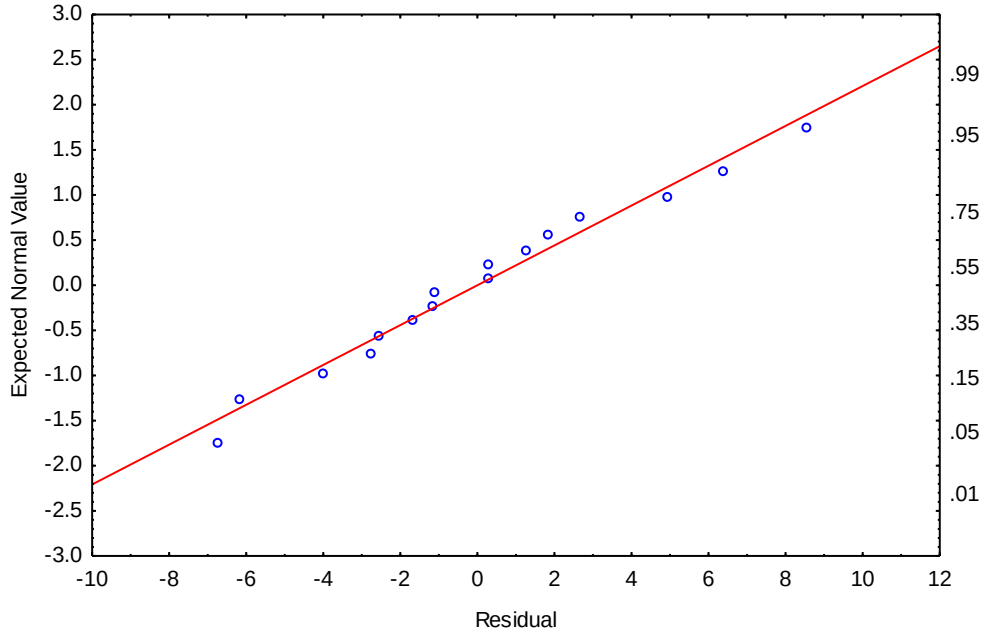


Figure 5.3.12
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Prone position

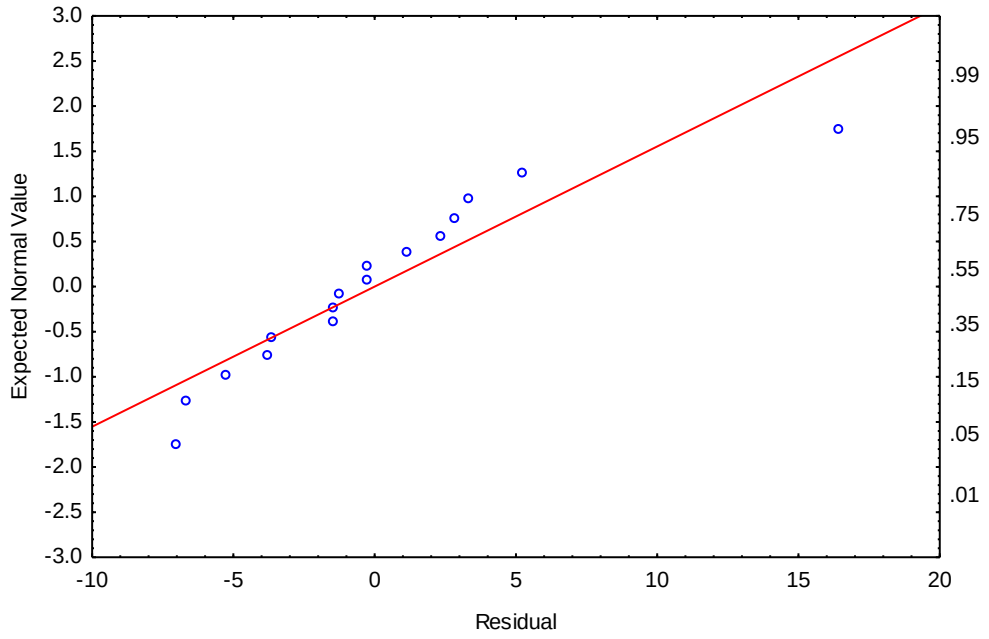


Figure 5.3.13
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Dependent

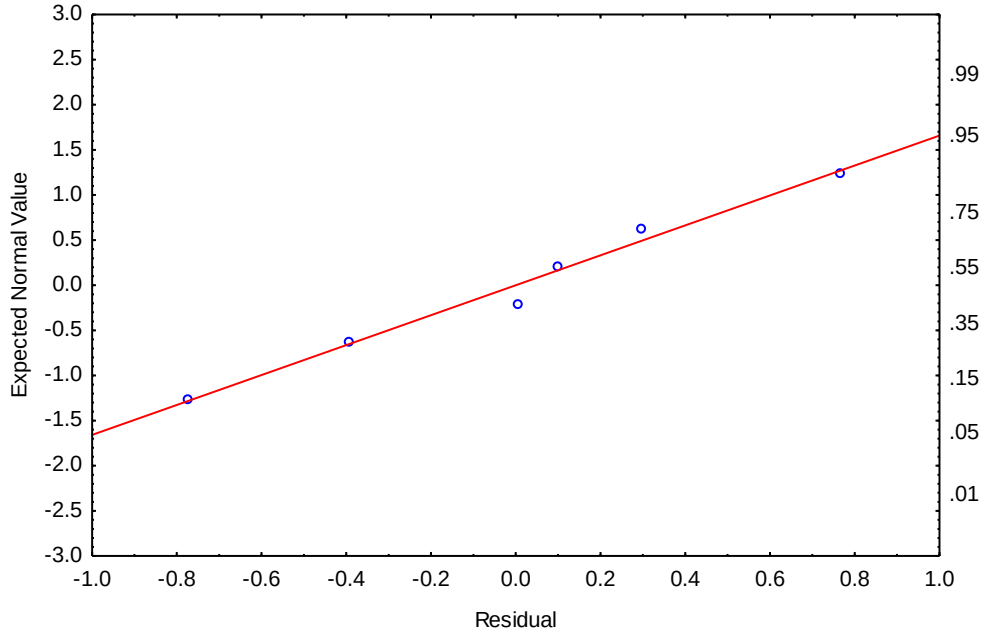
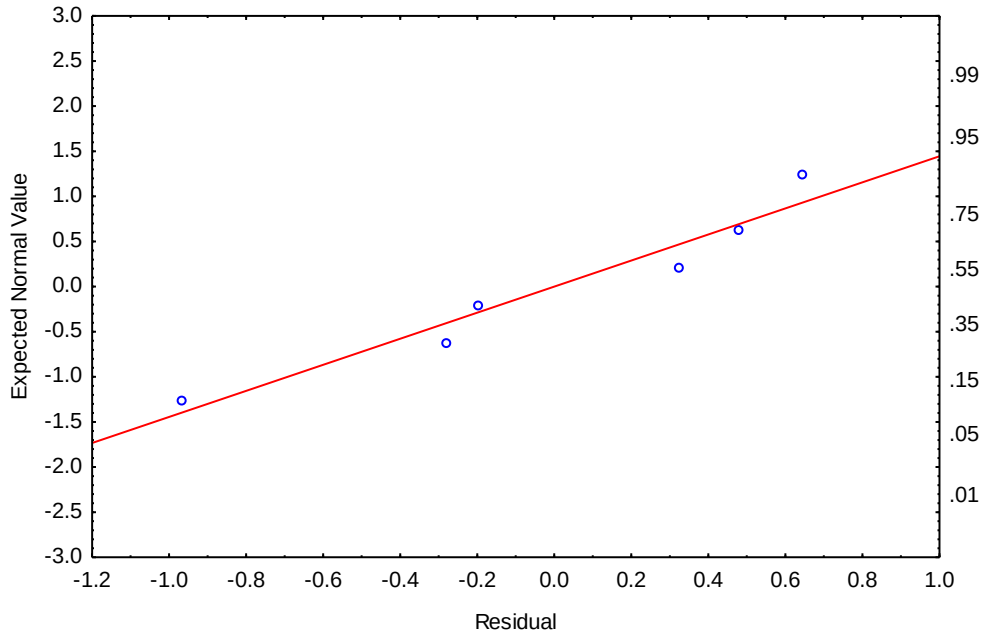
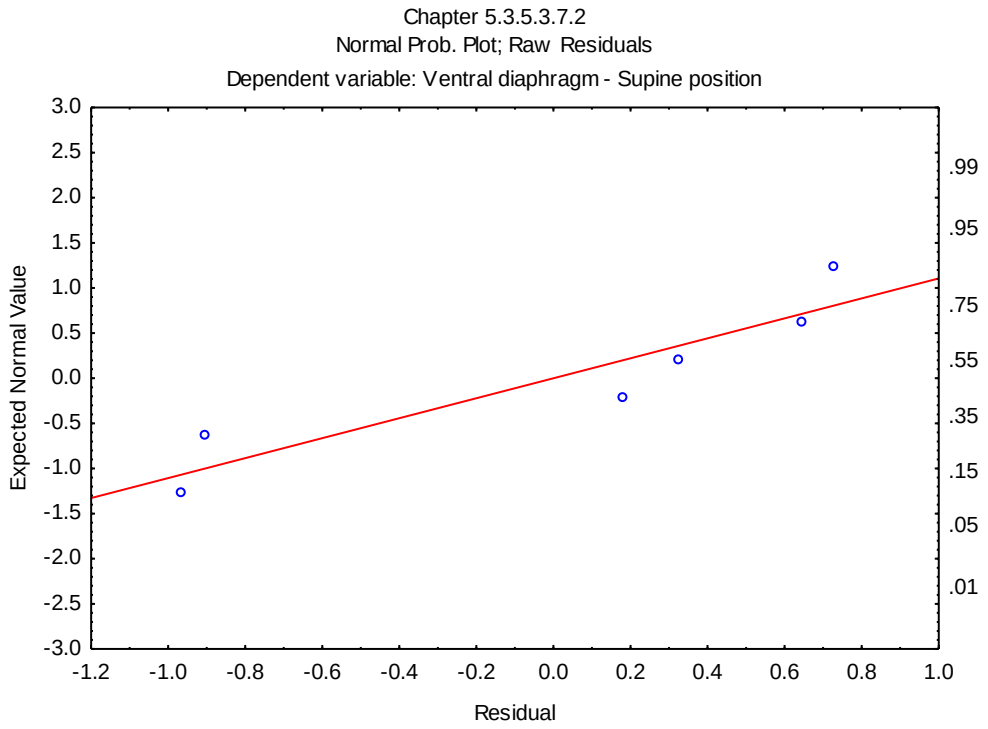
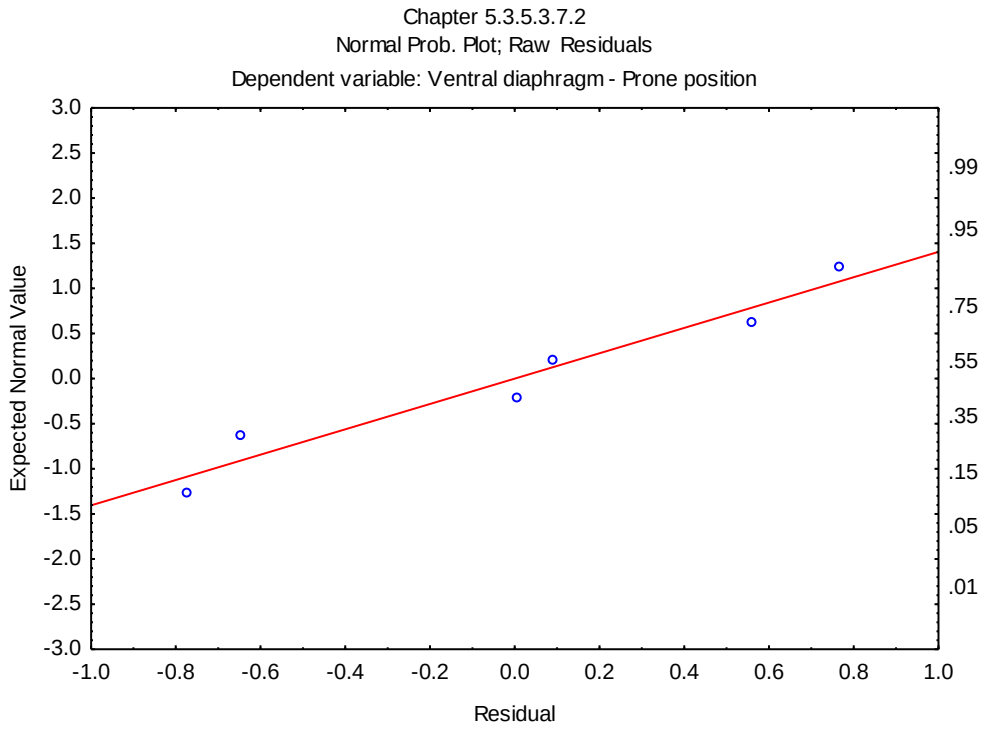
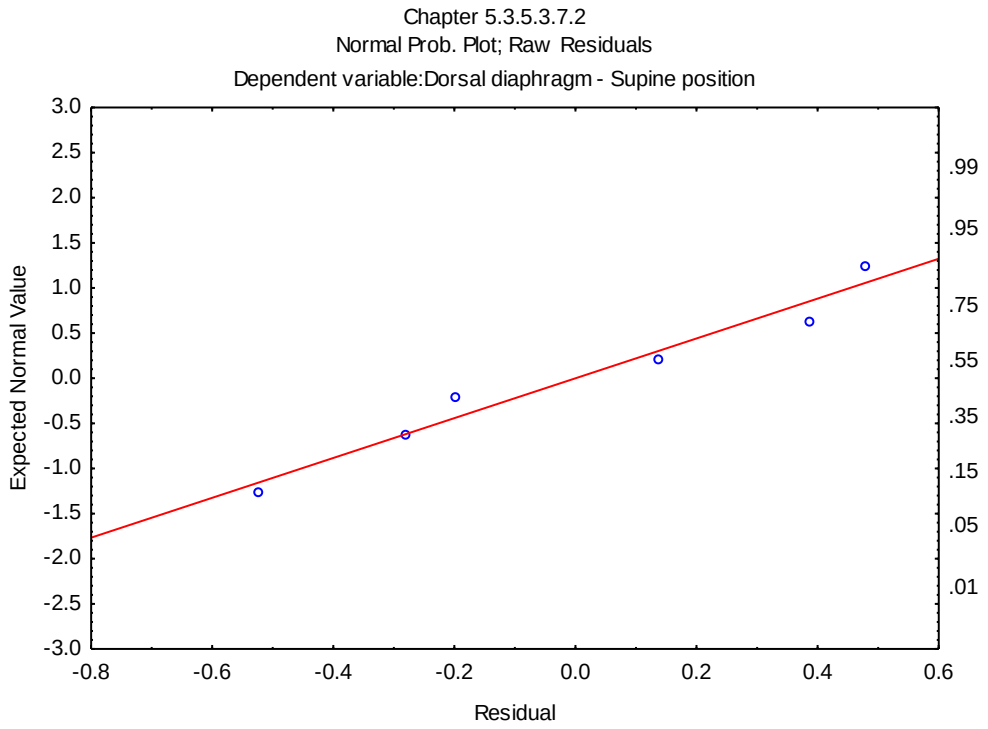


Figure 5.3.13
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine/Prone - Non-dependent




Chapter 5.3.5.3.7.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral diaphragm - Supine position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-1.2
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
.99
.95
.75
.55
.35
.15
.05
.01


Chapter 5.3.5.3.7.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral diaphragm - Prone position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-1.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
.99
.95
.75
.55
.35
.15
.05
.01


Chapter 5.3.5.3.7.2
Normal Prob. Plot; Raw Residuals
Dependent variable:Dorsal diaphragm - Supine position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
.99
.95
.75
.55
.35
.15
.05
.01

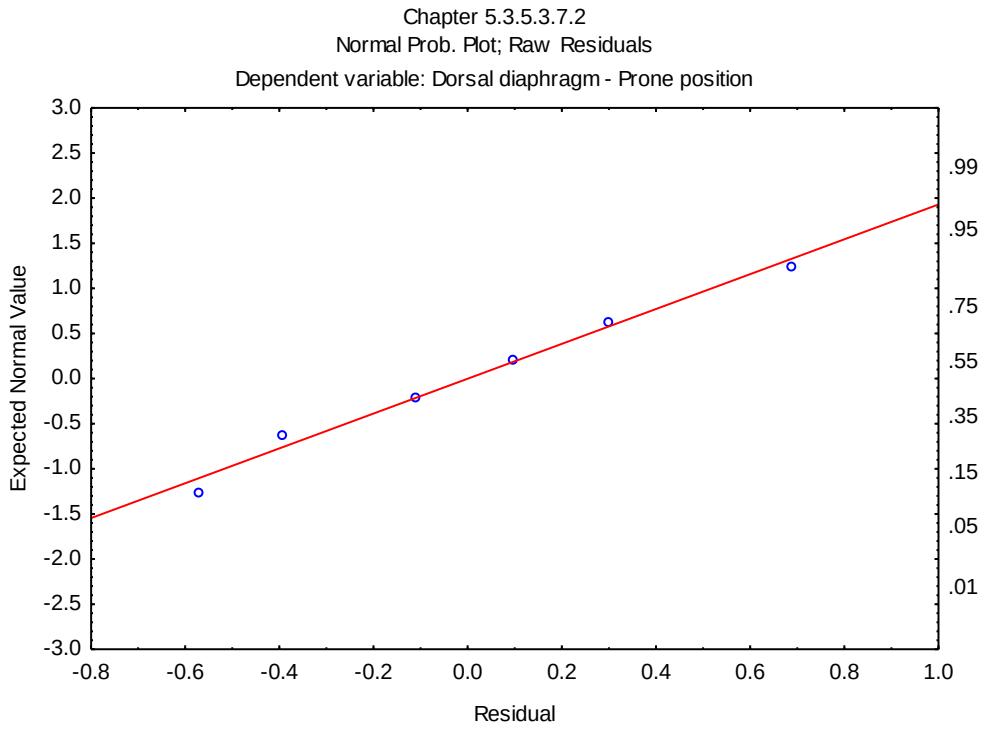

Chapter 5.3.5.3.7.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal diaphragm - Prone position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
.99
.95
.75
.55
.35
.15
.05
.01

Figure 5.3.15
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Left side lying

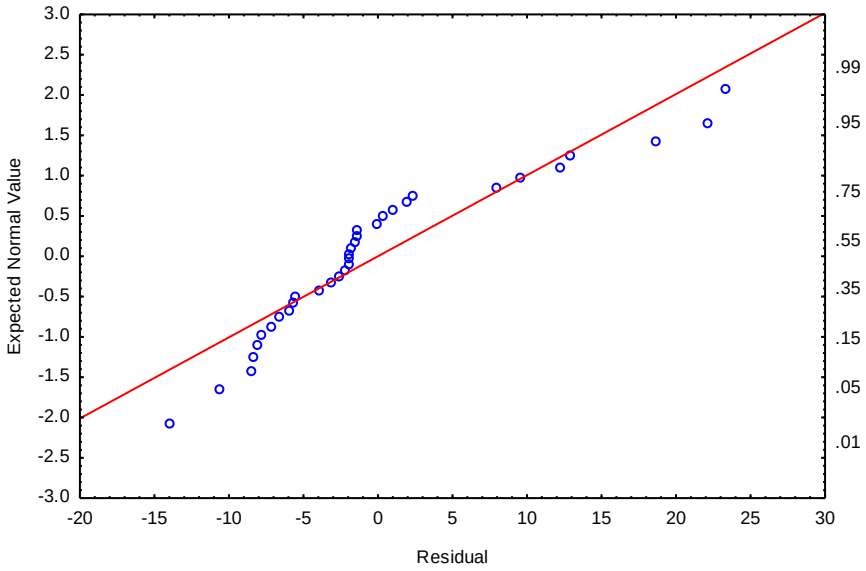


Figure 5.3.15
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Supine position

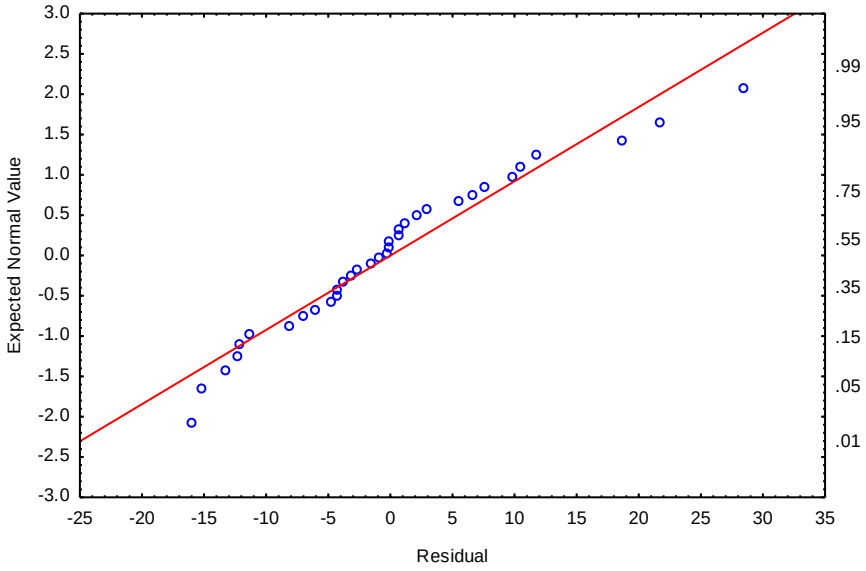


Figure 5.3.15
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Right side lying

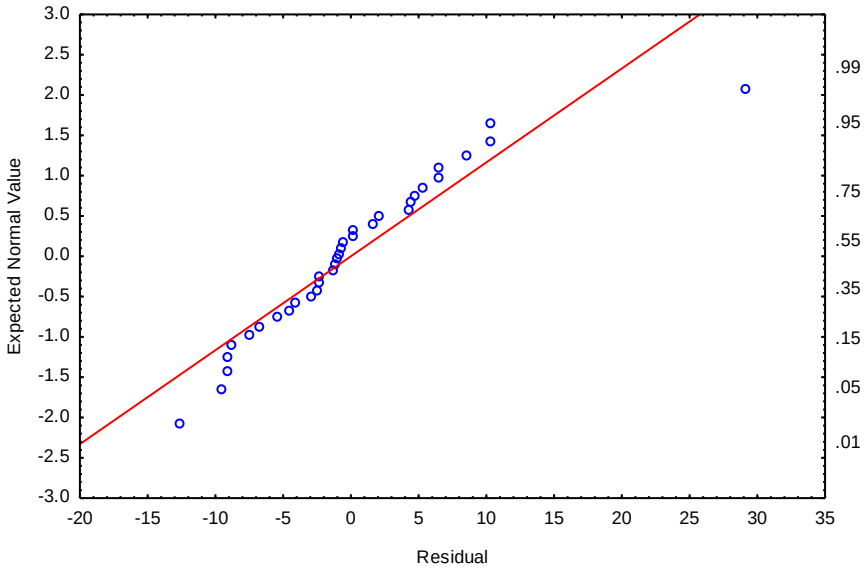


Figure 5.3.16
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Left side lying

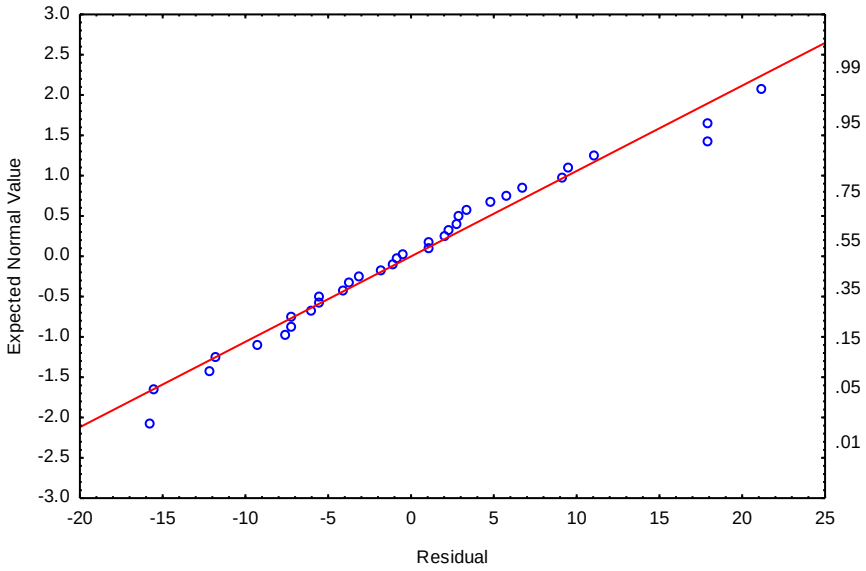


Figure 5.3.16
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Supine position

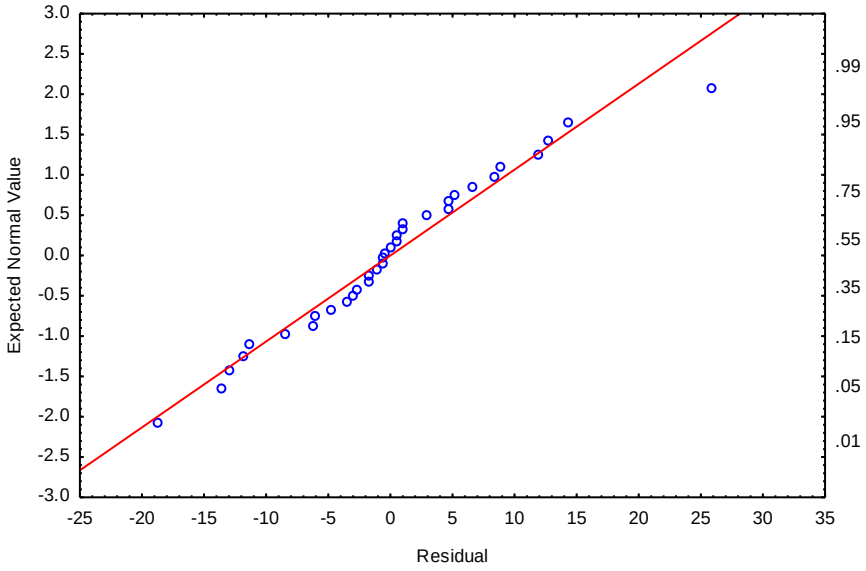


Figure 5.3.16
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Right side lying

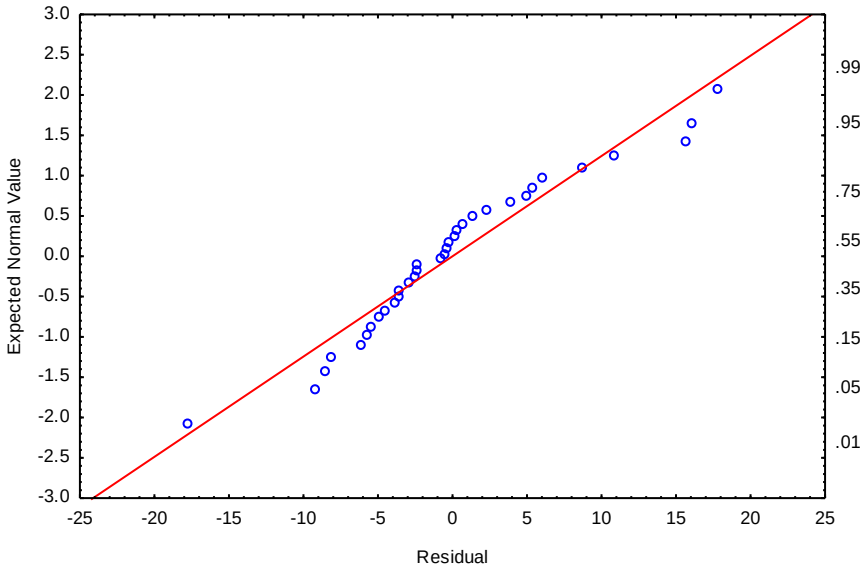


Figure 5.3.17
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Left side lying

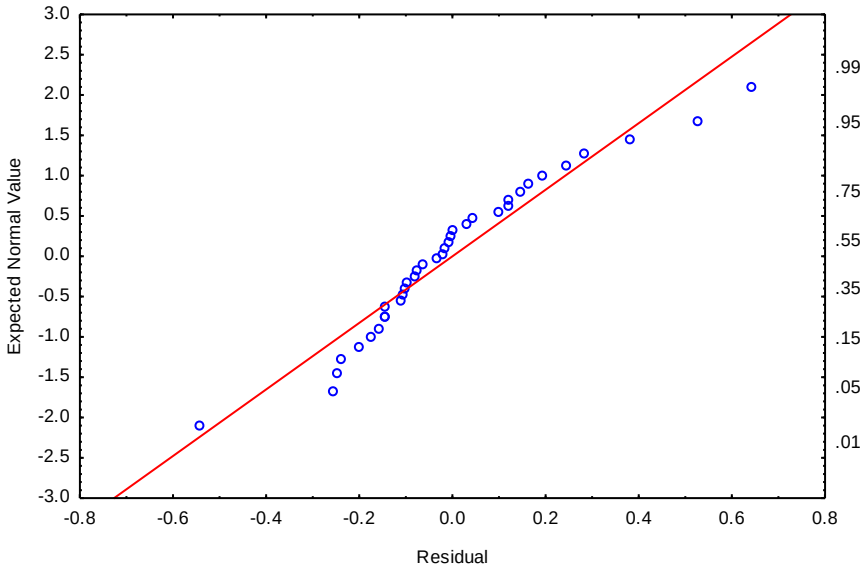


Figure 5.3.17
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Supine position

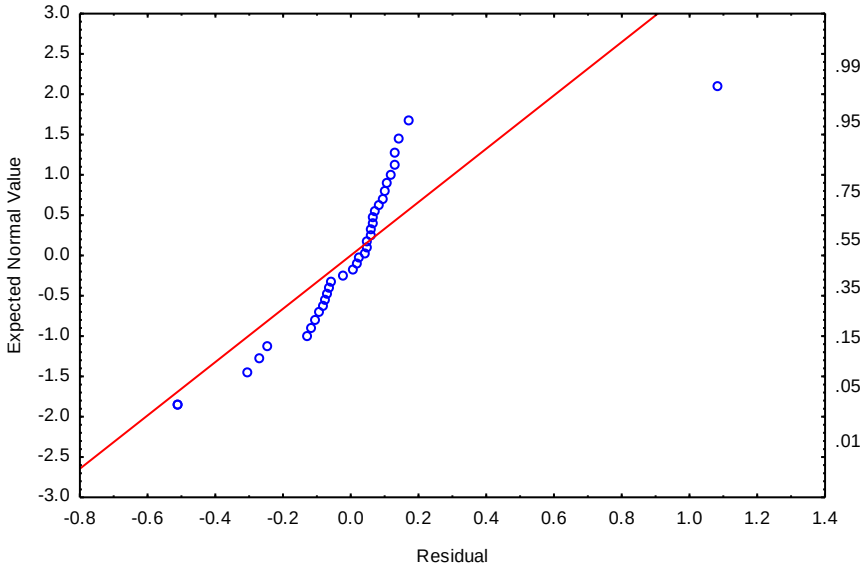


Figure 5.3.17
Normal Prob. Plot; Raw Residuals
Dependent variable: Left lung - Right side lying

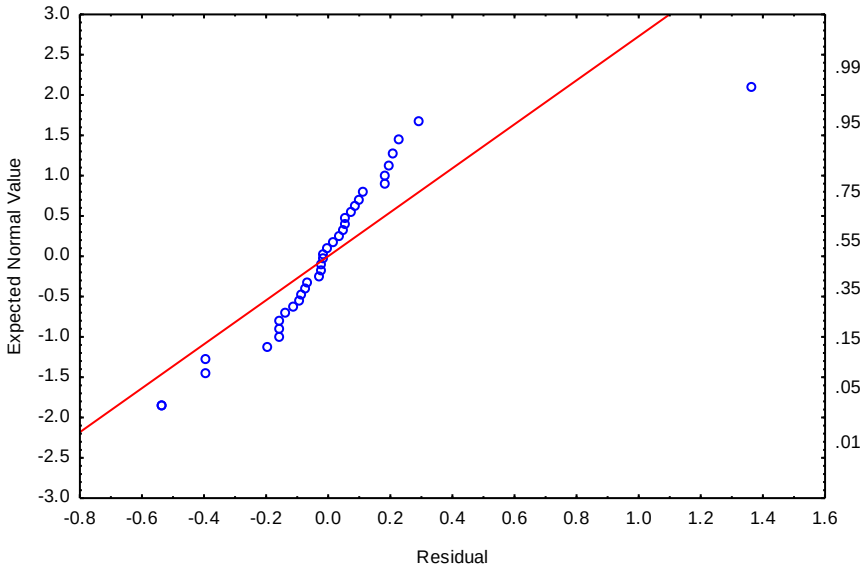


Figure 5.3.18
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Left side lying

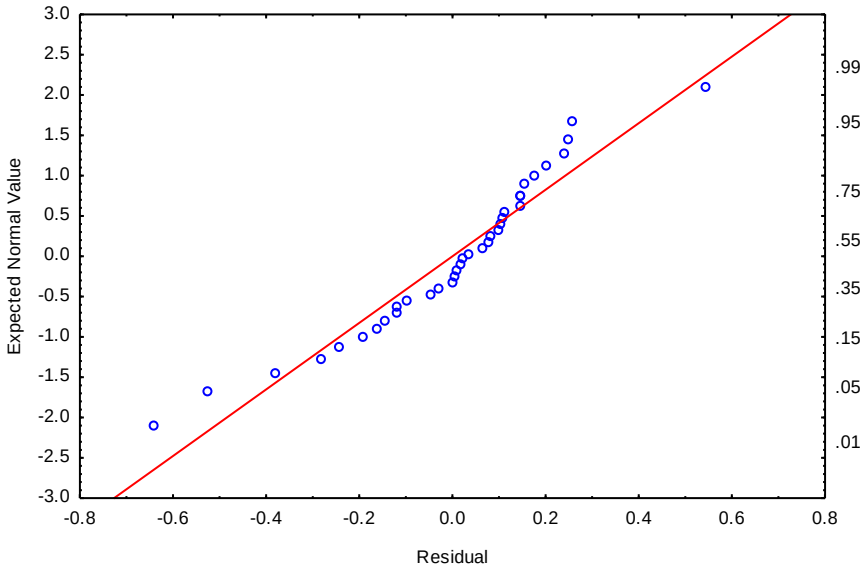


Figure 5.3.18
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Supine position

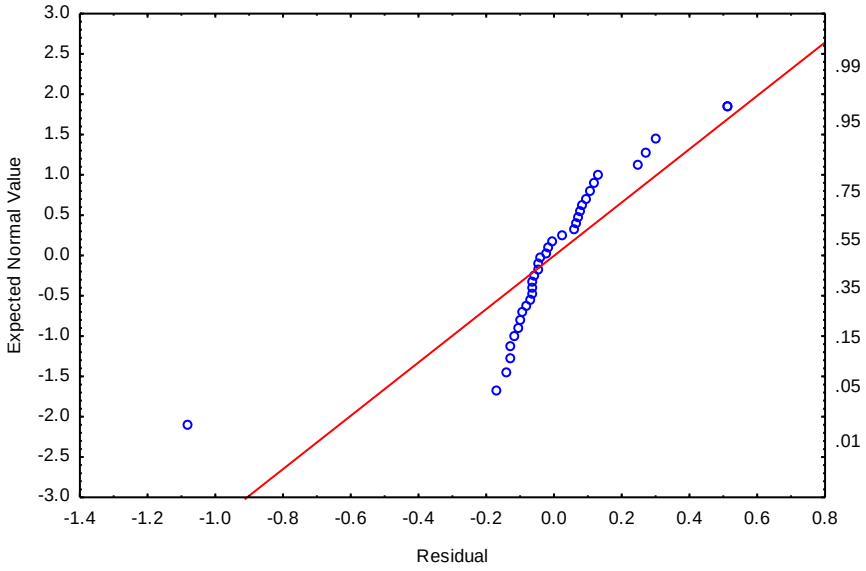


Figure 5.3.18
Normal Prob. Plot; Raw Residuals
Dependent variable: Right lung - Right side lying

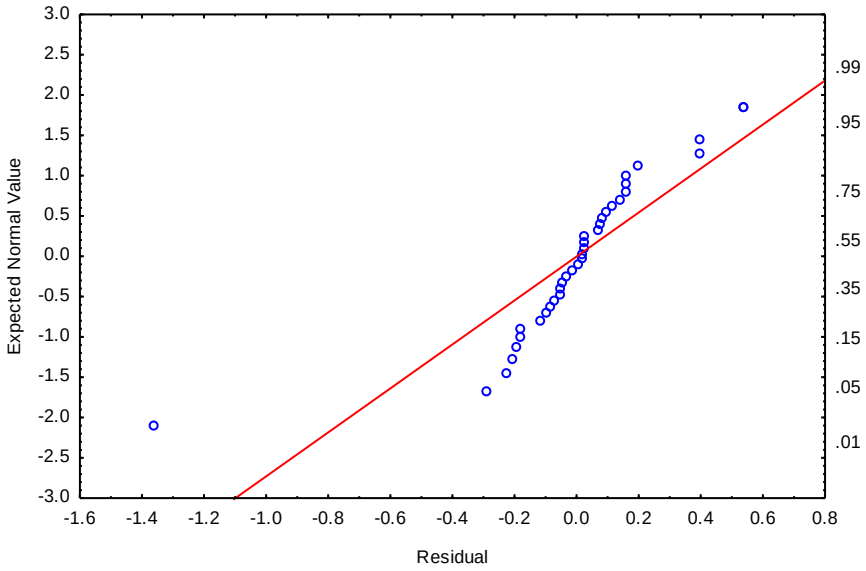


Figure 5.3.20
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Supine position

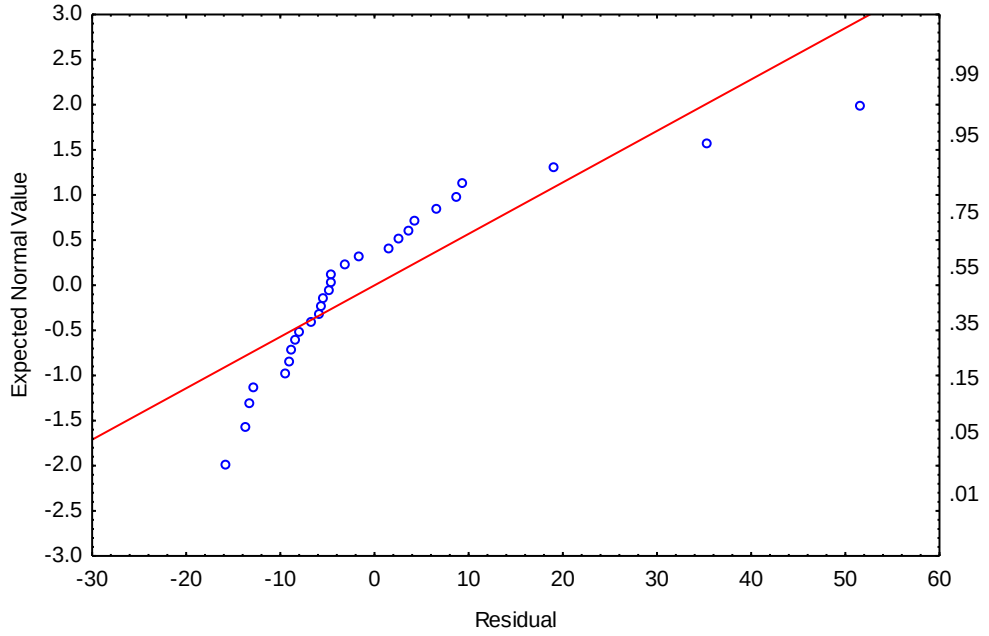


Figure 5.3.20
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Prone position

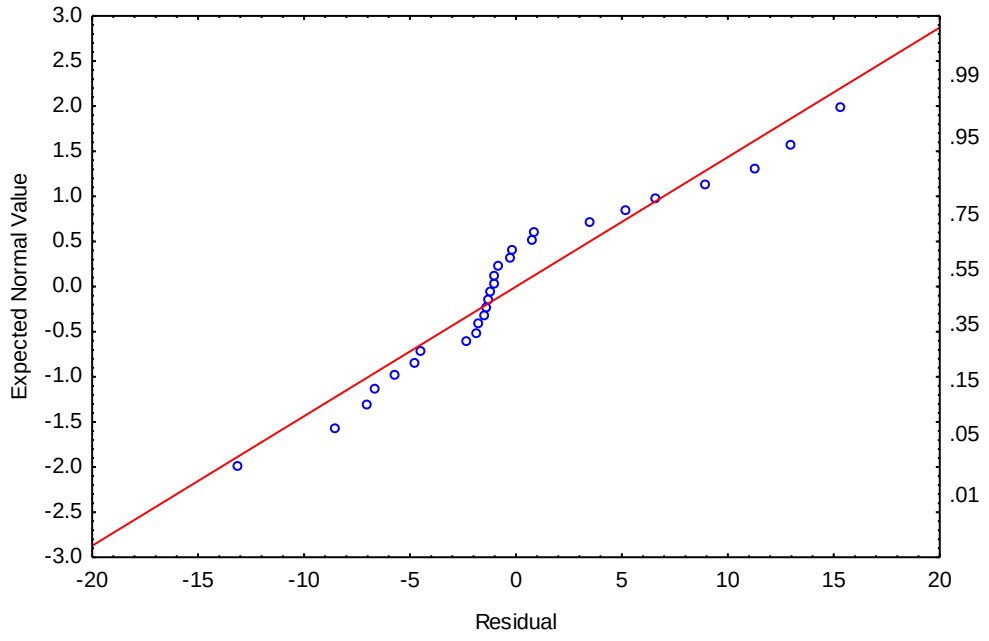


Figure 5.3.21
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Supine position

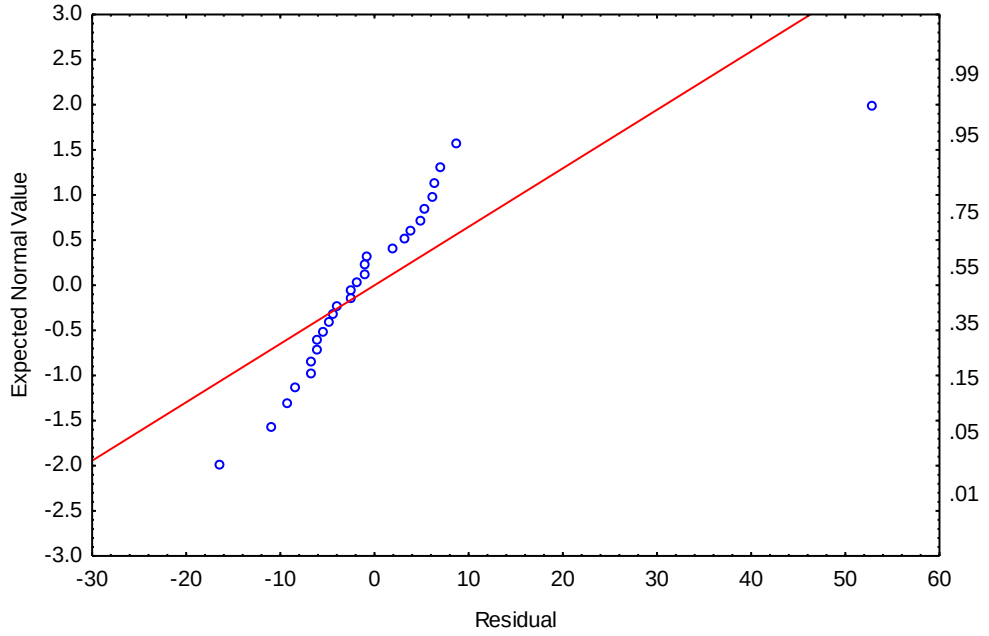


Figure 5.3.21
Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Prone position

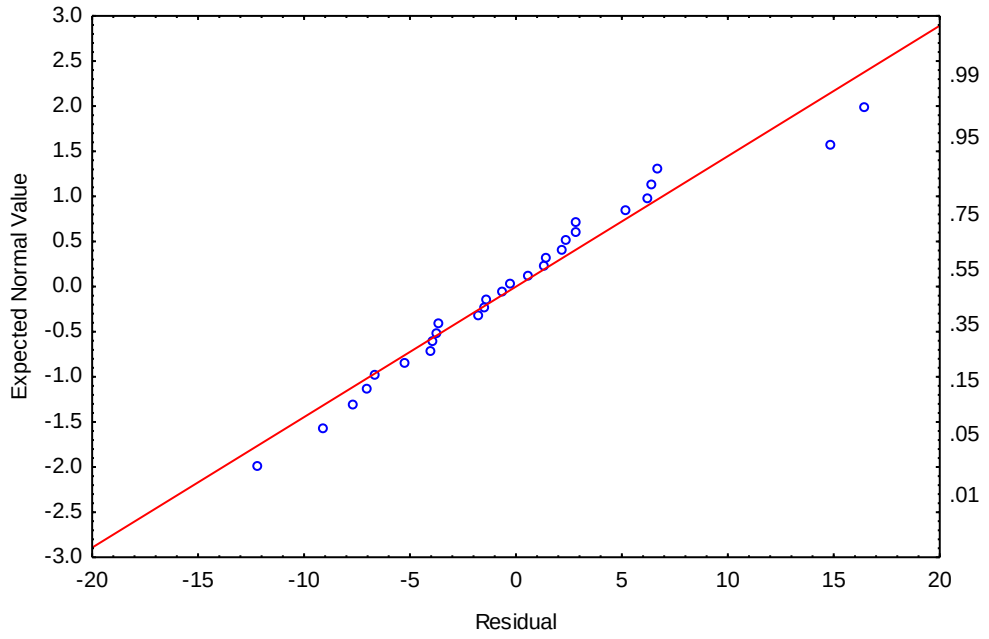


Figure 5.3.22
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Supine position

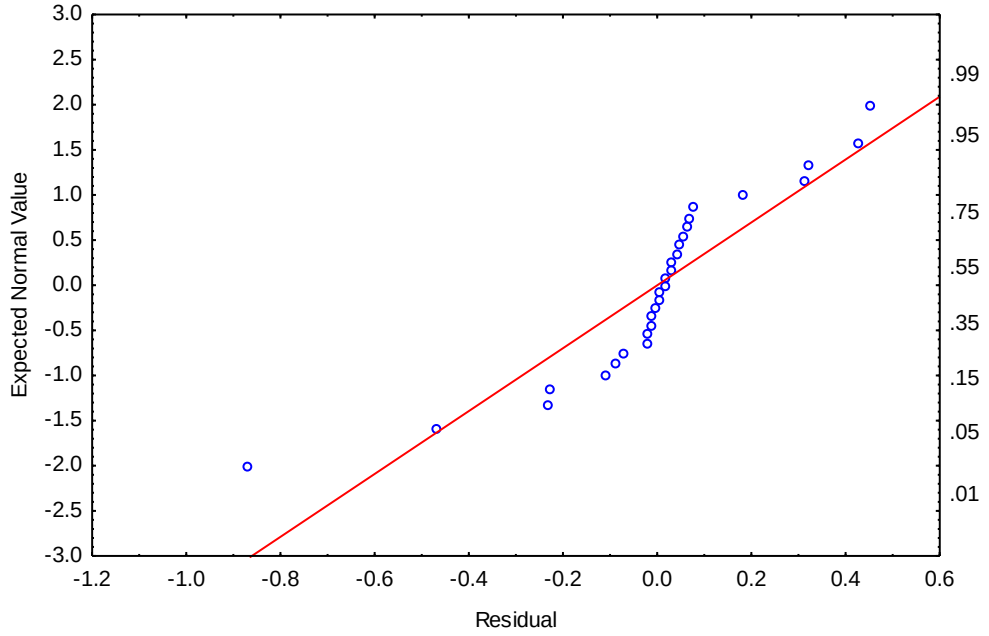
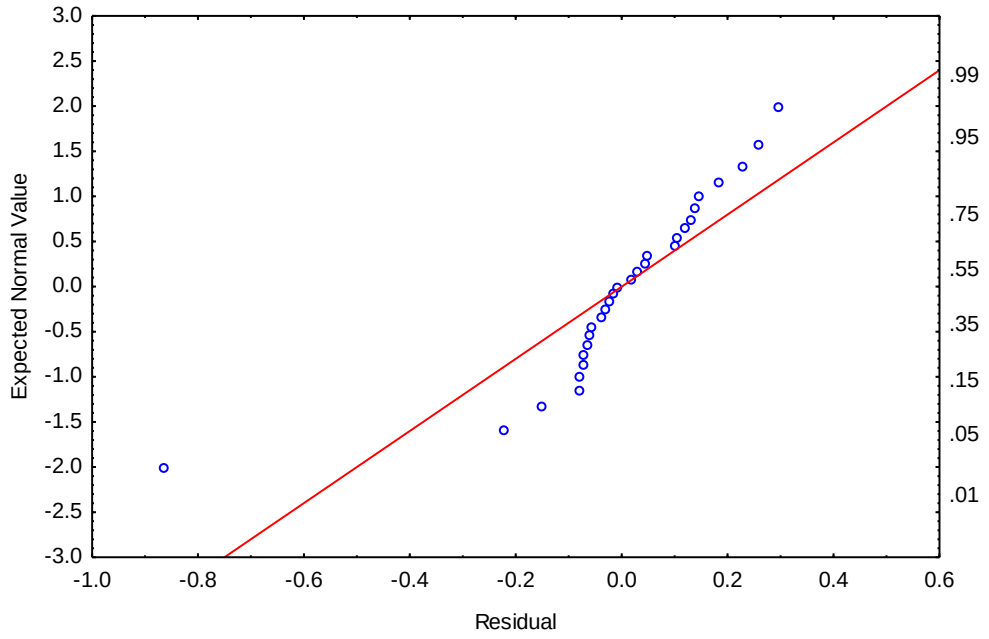


Figure 5.3.22
Normal Prob. Plot; Raw Residuals
Dependent variable: Ventral lung - Prone position



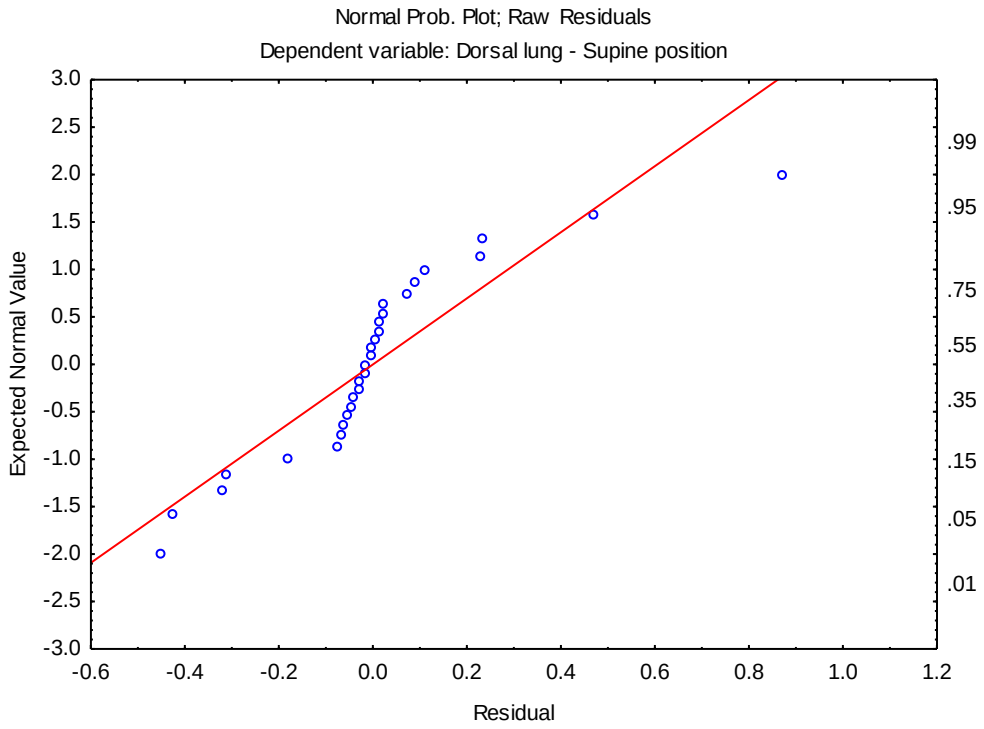
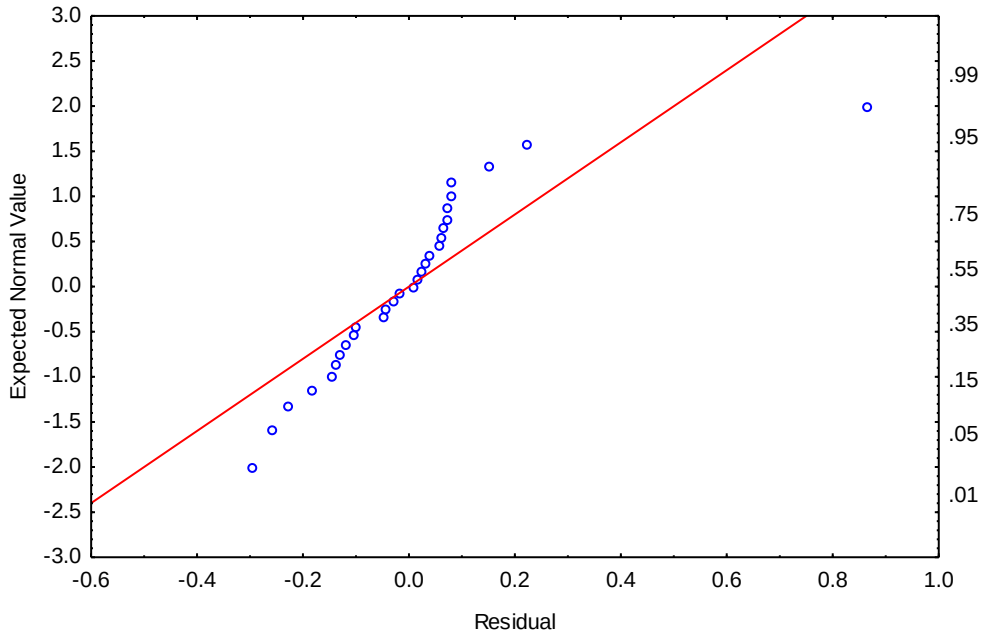

Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Supine position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
1.2
.99
.95
.75
.55
.35
.15
.05
.01

Figure 5.3.23


Normal Prob. Plot; Raw Residuals
Dependent variable: Dorsal lung - Prone position
Expected Normal Value
Residual
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
.99
.95
.75
.55
.35
.15
.05
.01

5.3. Study Three

Figure 5.4.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine

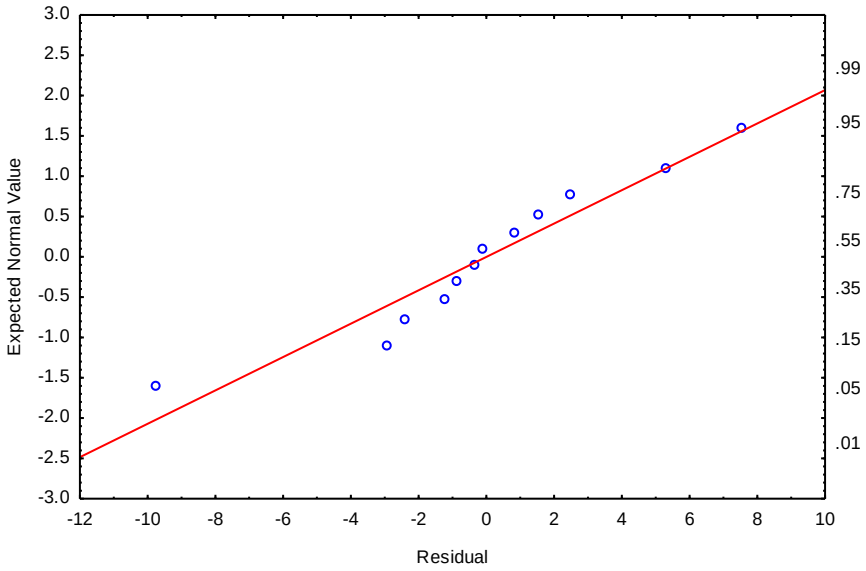


Figure 5.4.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

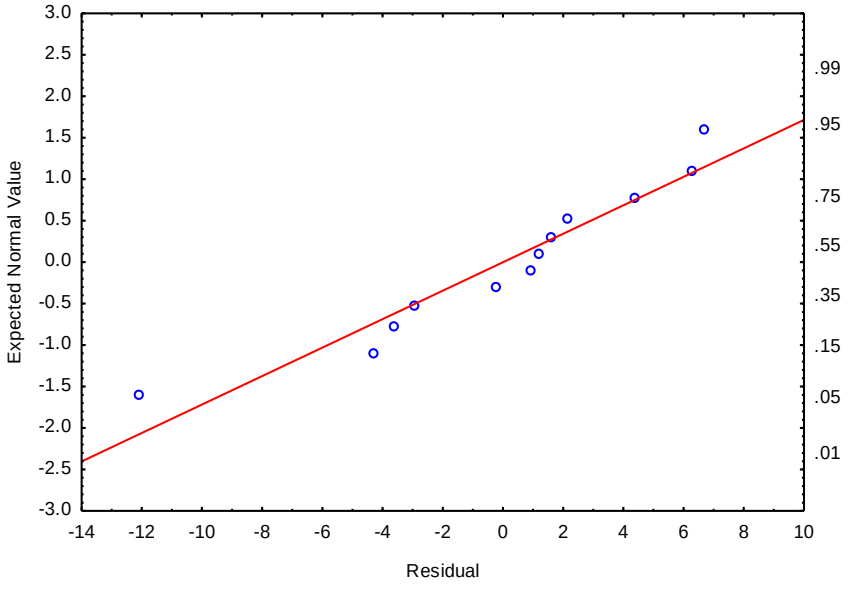


Figure 5.4.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

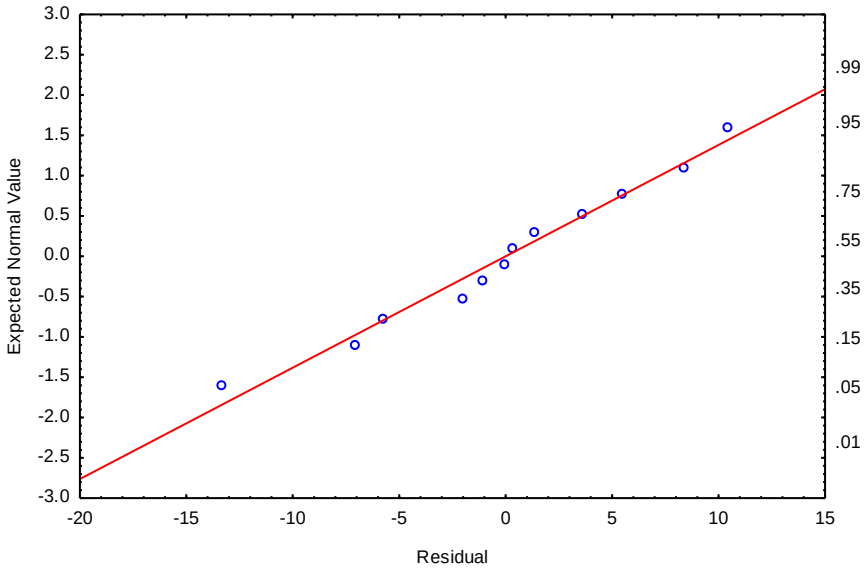


Figure 5.4.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

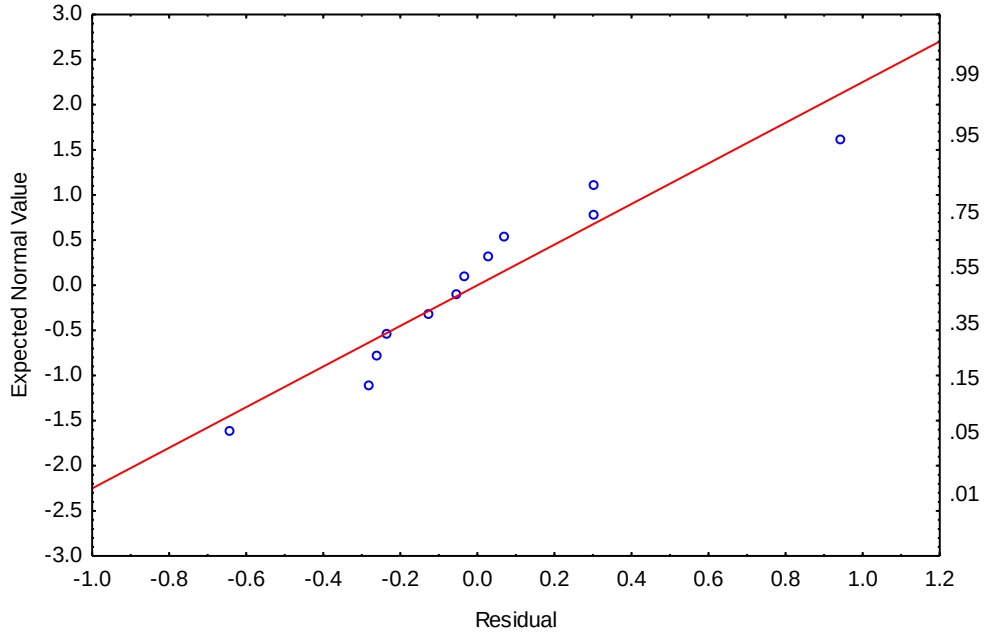


Figure 5.4.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

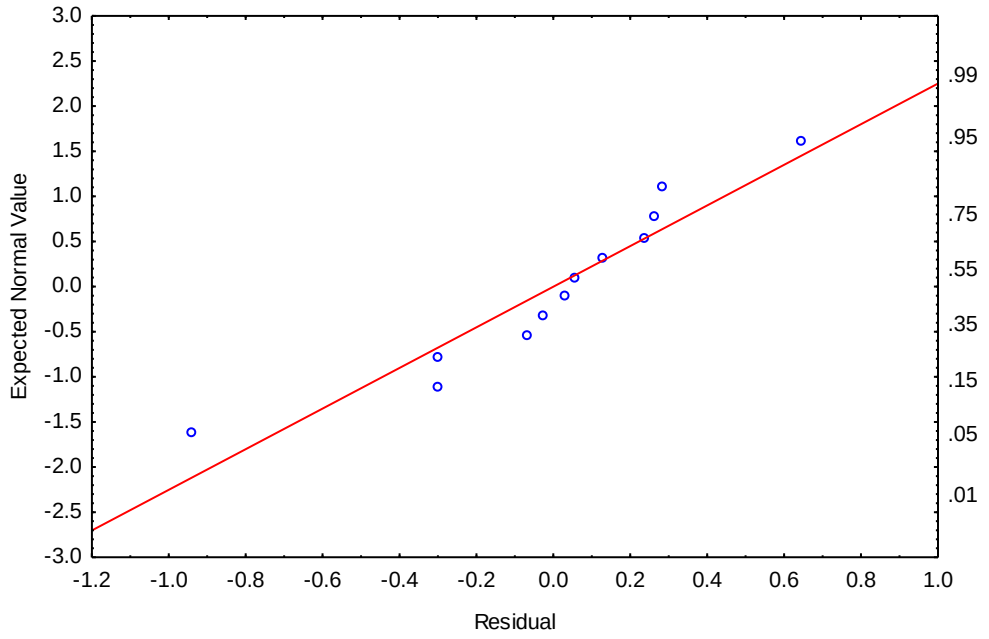


Figure 5.4.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

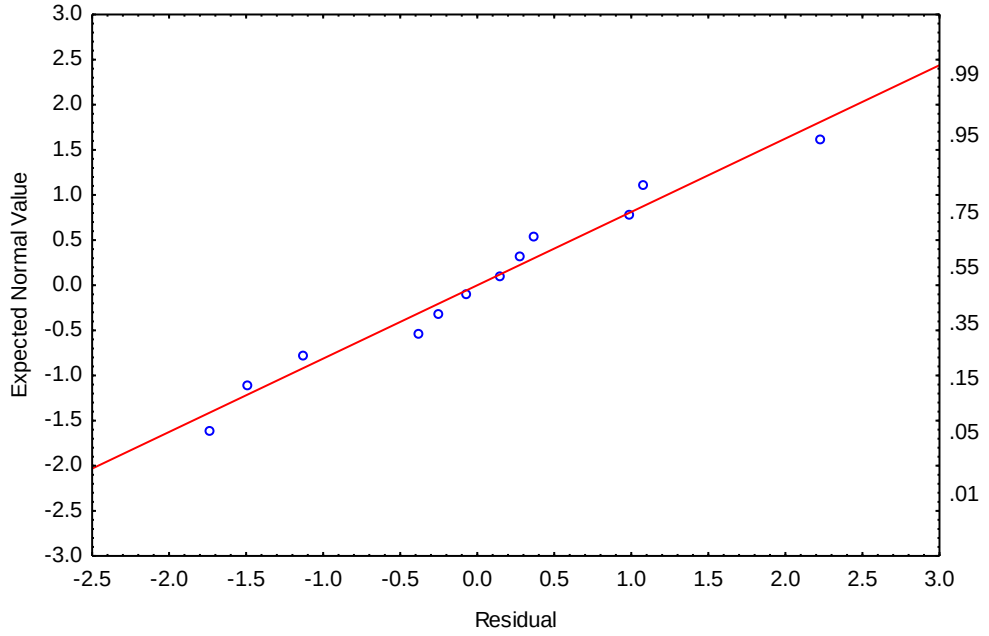
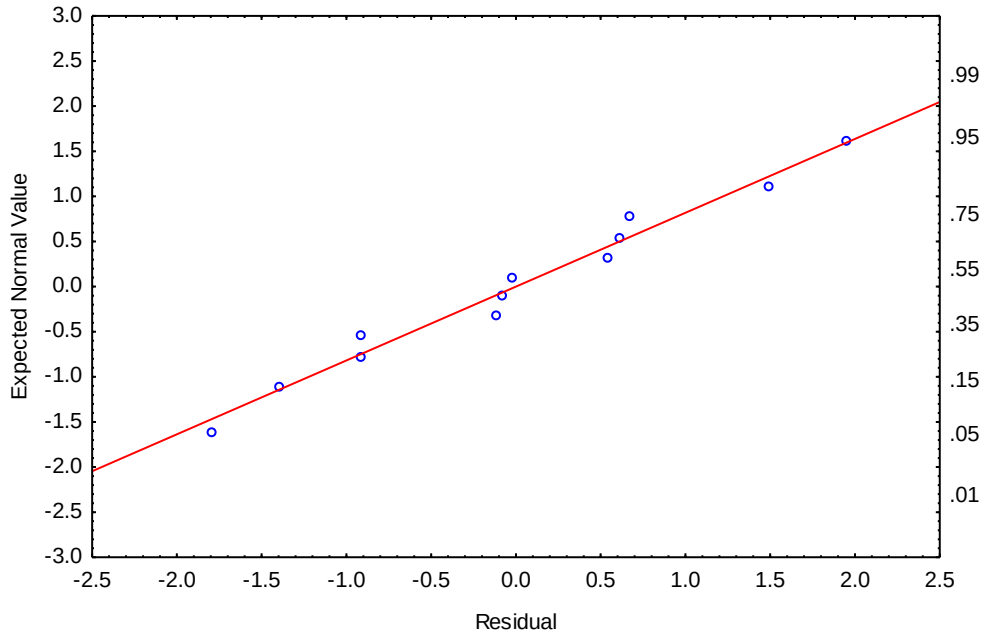


Figure 5.4.5
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent



5.4. Study Four

Figure 5.5.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Supine

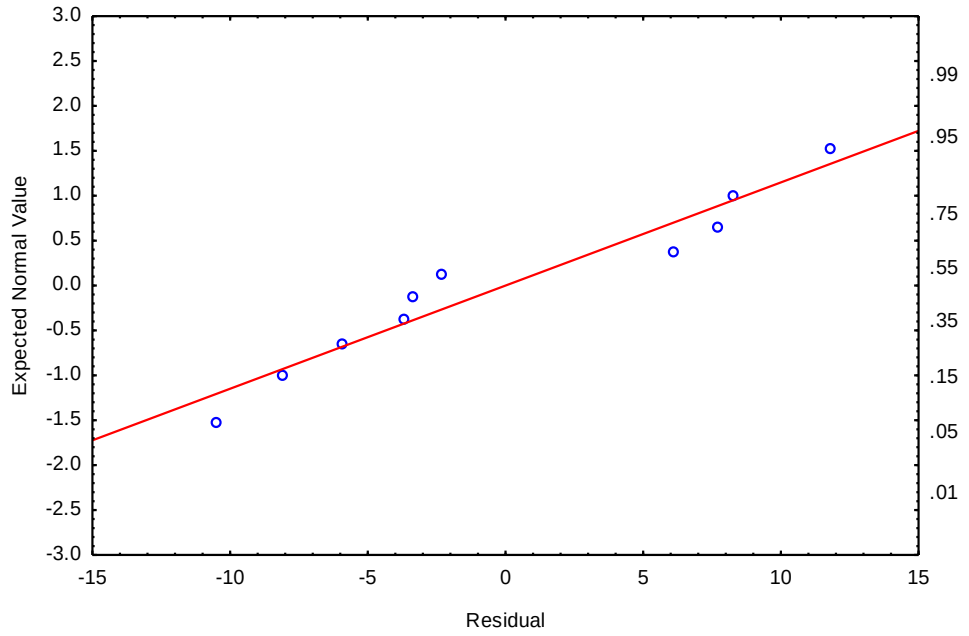


Figure 5.5.2
Normal Prob. Plot; Raw Residuals
Dependent variable: SIde lying - Dependent

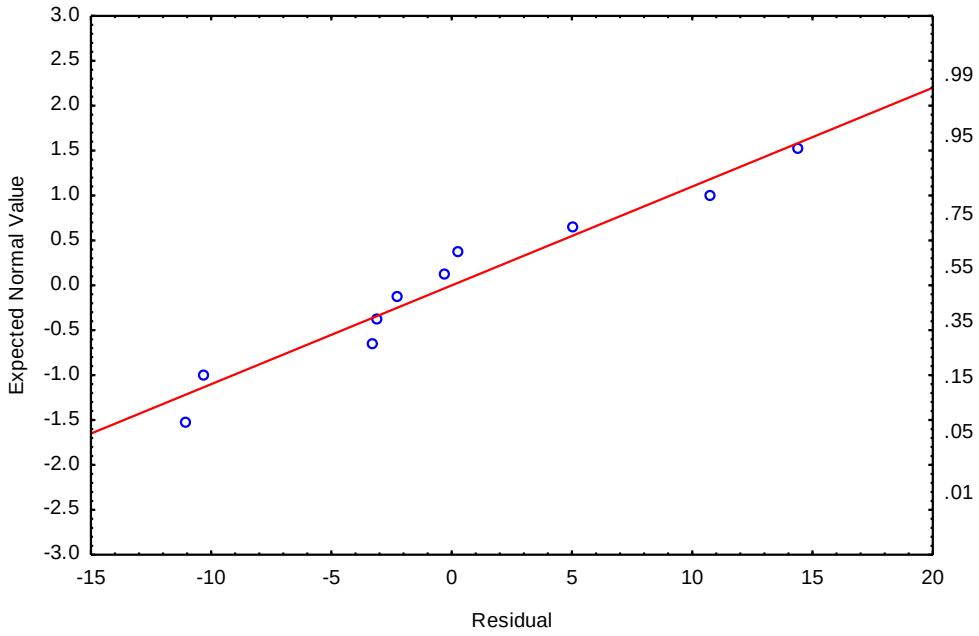


FIgure 5.5.2
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

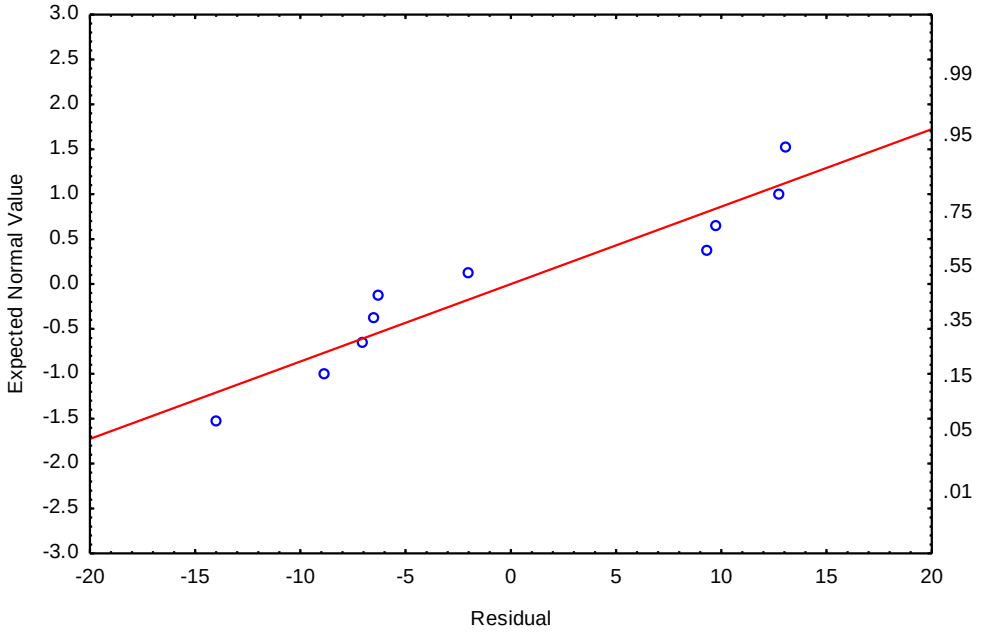


Figure 5.5.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

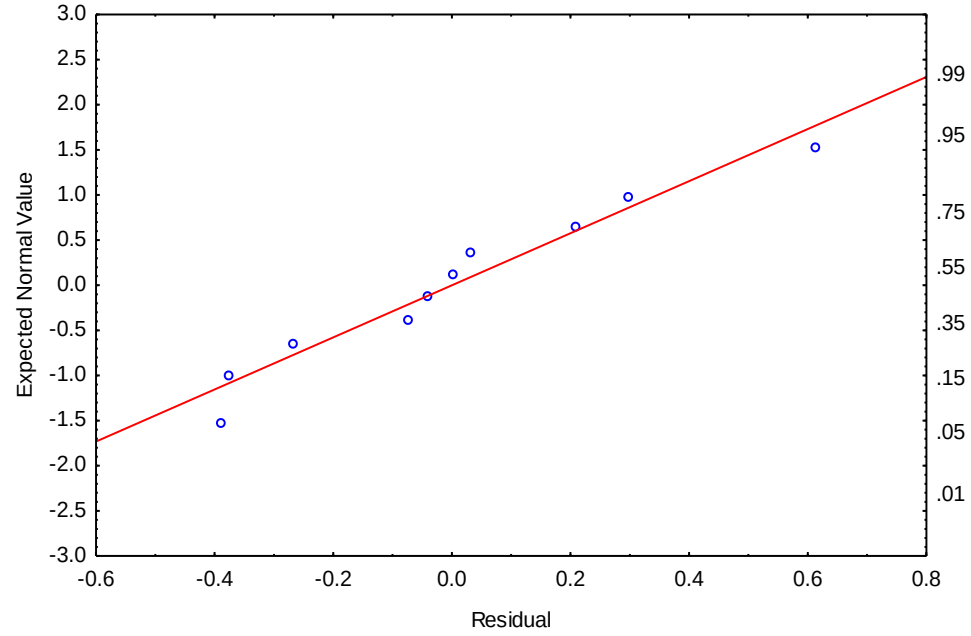


Figure 5.5.3
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent

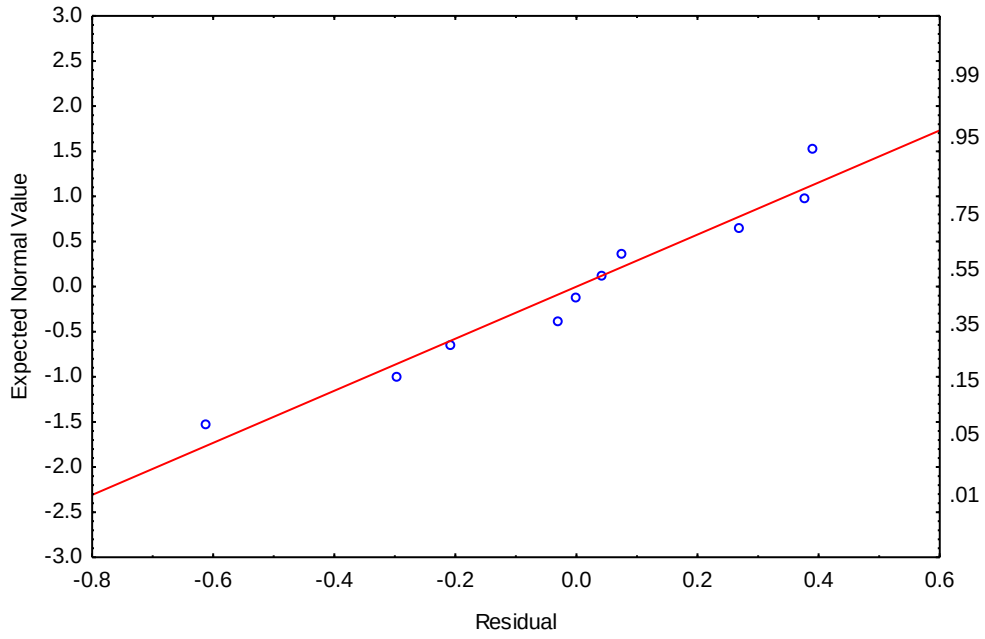


Figure 5.5.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Dependent

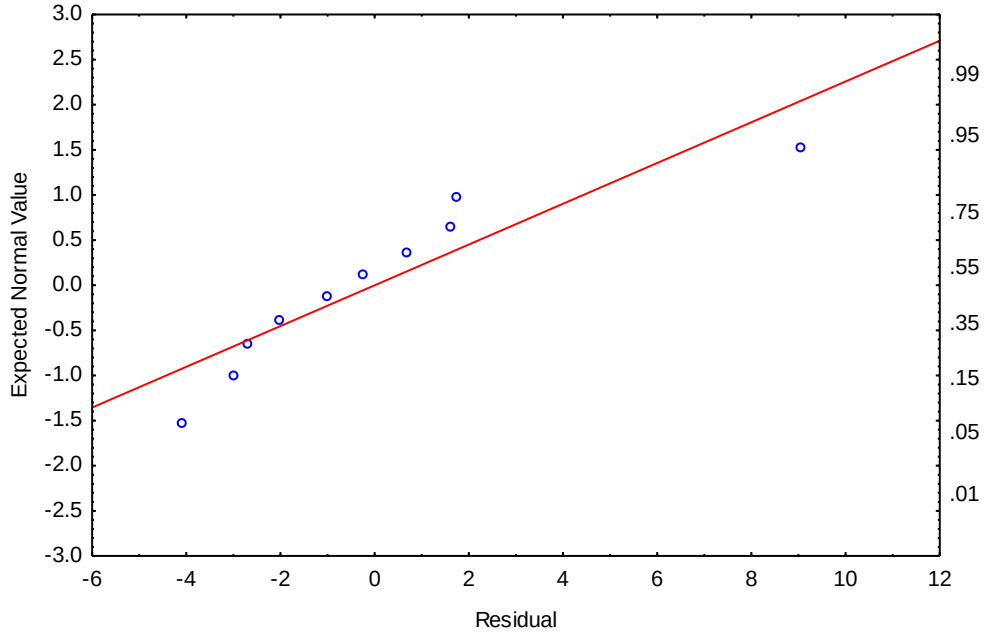
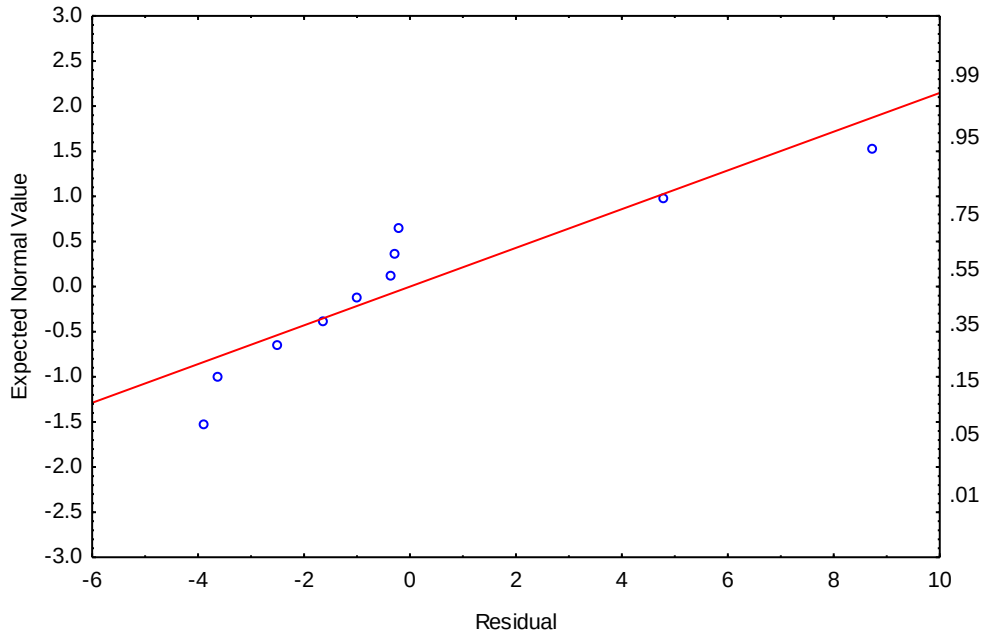


Figure 5.5.4
Normal Prob. Plot; Raw Residuals
Dependent variable: Side lying - Non-dependent



Appendix 6. Additional analysis information – Study 5

6.1. Comparisons between response groups at baseline and 60 minutes

Table A6.1.1 Differences between non-responders and those that showed no change at baseline and 60 minutes after being in the prone position.

	Parameter	Mean		Std Dev.		p - value
		Non-Responder	No change	Non-Responder	No change	
Baseline	HR	124.67	119.40	13.32	31.00	0.79
	MABP	59.67	64.60	14.22	4.16	0.48
	SpO_2	87.67	89.20	5.51	5.54	0.72
	PIP	28.67	18.00	4.16	2.45	<0.01
	PEEP	12.00	5.40	5.29	0.55	0.03
	MAP	17.33	9.80	4.93	0.84	0.01
	Ve_{CORR}	4.76	2.23	3.91	0.38	0.21
	FiO_2	0.53	0.41	0.24	0.10	0.33
	pH	7.29	7.36	0.13	0.03	0.23
	PaO_2	10.51	9.14	2.25	1.53	0.34
	$PaCO_2$	6.90	6.34	1.25	0.92	0.49
	OI	13.70	5.85	11.09	1.32	0.15
	PF	173.24	173.48	98.31	37.21	1.00
	SF	187.49	231.10	81.79	70.09	0.45
60 Minutes	HR	131.00	119.80	10.00	32.71	0.59
	MABP	59.00	60.60	8.89	8.08	0.80
	SpO_2	89.33	93.60	3.21	4.77	0.22
	PIP	32.00	17.80	10.15	2.39	0.02
	PEEP	13.00	5.40	6.08	0.55	0.03
	MAP	19.67	10.40	8.08	0.89	0.04
	Ve_{CORR}	6.43	2.77	6.20	0.30	0.25
	FiO2	0.53	0.38	0.14	0.08	0.09
	pH	7.29	7.35	0.13	0.03	0.31
	PaO_2	7.72	9.16	0.26	2.28	0.33
	$PaCO_2$	6.84	7.02	0.92	1.00	0.80
	OI	19.60	5.84	13.88	1.12	0.06
	PF	113.53	181.98	28.08	29.68	0.02
	SF	175.50	255.53	44.70	58.63	0.09
	% change in OI	5.90	-0.01	3.72	0.29	0.01

Table A6.1.2 Differences between those that showed no change and responders at baseline and 60 minutes after being in the prone position.

	Parameter	Mean		Std Dev.		p - value
		No change	Responder	No change	Responder	
Baseline	HR	119.40	117.00	31.00	38.57	0.92
	MABP	64.60	84.00	4.16	9.38	<0.01
	SpO_2	89.20	97.75	5.54	3.30	0.03
	PIP	18.00	22.50	2.45	5.69	0.15
	PEEP	5.40	6.50	0.55	2.38	0.34
	MAP	9.80	13.25	0.84	3.59	0.07
	Ve_{CORR}	2.77	4.71	0.30	2.54	0.18
	FiO_2	0.41	0.55	0.10	0.20	0.22
	pH	7.36	6.71	0.03	1.36	0.31
	PaO_2	9.14	10.64	1.53	2.76	0.33
	$PaCO_2$	6.34	6.60	0.92	2.33	0.83
	OI	5.85	10.35	1.32	7.51	0.22
	PF	173.48	170.31	37.21	91.56	0.95
	SF	231.10	199.93	70.09	80.05	0.55
60 Minutes	HR	119.80	107.25	32.71	18.50	0.52
	MABP	59.00	73.75	8.89	13.50	0.16
	SpO2	93.60	98.25	4.77	2.36	0.12
	PIP	10.40	12.25	0.89	3.86	0.33
	PEEP	5.40	6.50	0.55	2.38	0.34
	MAP	17.80	20.75	2.39	5.12	0.29
	Ve_{CORR}	2.74	5.32	6.03	2.79	0.13
	FiO_2	0.38	0.44	0.08	0.13	0.42
	pH	7.35	7.36	0.03	0.03	0.67
	PaO_2	9.16	13.62	2.28	2.68	0.03
	$PaCO_2$	7.02	7.22	1.00	1.48	0.82
	OI	5.84	5.24	1.12	1.66	0.54
	PF	181.98	246.75	29.68	80.24	0.13
	SF	255.53	239.86	58.63	72.97	0.73
	% change in OI	-0.01	-5.10	0.29	6.40	0.11

Table A6.1.3 Differences between non-responders and responders at baseline and 60 minutes after being in the prone position.

	Parameter	Mean		Std Dev.		p - value
		Non-responder	Responder	Non-responder	Responder	
Baseline	HR	124.67	117.00	13.32	38.57	0.76
	MABP	59.67	84.00	14.22	9.38	0.04
	SpO_2	87.67	97.75	5.51	3.30	0.03
	PIP	28.67	22.50	4.16	5.69	0.18
	PEEP	12.00	6.50	5.29	2.38	0.12
	MAP	17.33	13.25	4.93	3.59	0.26
	Ve_{CORR}	6.43	4.71	6.19	2.54	0.68
	FiO_2	0.53	0.55	0.24	0.20	0.92
	pH	7.29	6.71	0.13	1.36	0.50
	PaO_2	10.51	10.64	2.25	2.76	0.95
	$PaCO_2$	6.90	6.60	1.25	2.33	0.85
	OI	173.24	170.31	98.31	91.56	0.97
	PF	13.70	10.35	11.09	7.51	0.65
	SF	187.49	199.93	81.79	80.05	0.85
60 Minutes	HR	131.00	107.25	10.00	18.50	0.10
	MABP	59.00	73.75	8.89	13.50	0.16
	SpO2	89.33	98.25	3.21	2.36	0.01
	PIP	32.00	20.75	10.15	5.12	0.11
	PEEP	19.67	12.25	8.08	3.86	0.16
	MAP	13.00	6.50	6.08	2.38	0.10
	Ve_{CORR}	6.43	5.32	6.02	2.79	0.79
	FiO_2	0.53	0.44	0.14	0.13	0.39
	pH	7.29	7.36	0.13	0.03	0.32
	PaO_2	7.72	13.62	0.26	2.68	0.01
	$PaCO_2$	6.84	7.22	0.92	1.48	0.71
	OI	113.53	246.75	28.08	80.24	0.04
	PF	19.60	5.24	13.88	1.66	0.09
	SF	175.50	239.86	44.70	72.97	0.24
	% change in OI	5.90	-5.10	3.72	6.40	0.05

6.2. Corrected Minute Ventilation calculation and analysis

Correct minute ventilation was calculated as described in the Berlin Definition (Force, 2012). The following formula was used in the calculation:

$$Corrected\ Minute\ ventilation = \ Minute\ ventilation\ (Ve) \times \frac{7.5 \times \mathrm{PaCO_2}}{40}$$

Table A6.2.1 Corrected minute ventilation for the different response groups at baseline and 60 minutes after being turned into the prone position

	Baseline	**60 minutes**	**p-value**
Responders	4.74 ± 2.53	5.32 ± 2.79	0.80
Non-responders	6.43 ± 6.20	6.43 ± 6.03	1.00
No change	2.77 ± 0.30	2.74 ± 0.87	0.95