Measuring the effects of chest physiotherapy on respiratory function in mechanically ventilated infants and children

Bronagh McAlinden

BPhty (Hons I)

A thesis submitted in total fulfilment of the requirements of the degree

Master of Philosophy

School of Allied Health
Faculty of Health Sciences
Australian Catholic University
1100 Nudgee Rd, Banyo

Date of Submission: 31/03/2018

1

Statement of Authorship

This thesis contains no material published elsewhere or extracted in whole or in part from a thesis by which I have qualified for or been awarded another degree or diploma.

No parts of this thesis have been submitted towards the award of any other degree or diploma in any other tertiary institution.

No other person's work has been used without due acknowledgment in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

Name: Bronagh McAlinden

Signature:

Date: 26/03/2018

Acknowledgments

This completed thesis has been the product of many people's collective input, knowledge, time and support. I am incredibly grateful for each and every one of these people who have supported me through this process and I know this milestone would not have been achievable without their valuable contributions.

Firstly, a huge thank you to my supervisors, Professor Suzanne Kuys and Dr Judith Hough. I have no doubt that without both of you providing me with your immense expertise, wisdom, patience and guidance this completed thesis would not have eventuated. Both of you have contributed many long hours to discussing, reading and editing this document, particularly over the last 18 months, and your input has been invaluable. Thank you also to Dr George Ntoumenopoulos who also provided me with his time and knowledge as a supervisor during the early part of my MPhil journey. This has certainly been a team effort and I am thankful to you all for having been part of that team.

Secondly, acknowledgement and thank you must be given to Dr Jacqui Jauncey-Cooke and Associate Professor Andreas Schibler for allowing me generous access not only to their data, but their immense knowledge and assistance at many different points along this process. I also must thank the Mater Children's Hospital Golden Casket foundation, funding from which provided the start of this Phil and was an invaluable assistance.

Thank you to my director and the LCCH physiotherapy crew. Kellie, thank you for the constant encouragement and for supporting me to complete this project while working full-time. To my team and colleagues, thank you for always backing me up, supporting me and for putting

iii

up with an often very tired clinical lead. I feel very lucky and grateful to work in a team as amazing as ours and I look forward to sharing the knowledge I have gained throughout this experience with all of you.

And lastly, thank you to my wonderful family and my great friends for the unwavering support you have provided me throughout this process, over the last 5 years, and through all that has happened around it. This process has been far from easy and while it has never been my favourite topic of conversation, I could not have survived through this MPhil journey without the knowledge that you were behind me all the way. Thanks for everything you have done for me, including all the seemingly insignificant day-to-day things. They have always been appreciated and have made getting through this process a whole lot easier. I am so grateful to you and love you lots and lots.

Table of Contents

Grants Awarded and Presentations

Grants Awarded

1. Mater Children's Hospital Golden Casket Seeding Grant, 2011 - $9000.00

Podium Presentations

1. **McAlinden B,** Ntoumenopoulos G, Stanton W, Jauncey-Cooke J, Schibler A, Hough, J. Chest physiotherapy (CPT) results in changes in regional ventilation distribution and gas exchange in ventilated children as measured by Electrical Impedance Tomography. Oral presentation at Australian Physiotherapy Association National Conference, Melbourne 2013

Poster presentations

1. **McAlinden B,** Ntoumenopoulos G, Stanton W, Jauncey-Cooke J, Schibler A, Hough, J. The effect of chest physiotherapy on regional lung volume changes and gas exchange in ventilated children using electrical impedance tomography. Poster presentation at the Australian and New Zealand Intensive Care Society (ANZICS) Conference, Hobart, 2013.

2. **McAlinden B,** Ntoumenopoulos G, Stanton W, Jauncey-Cooke J, Schibler A, Hough, J. The effect of chest physiotherapy on regional lung volume changes and gas exchange in ventilated children using electrical impedance tomography. Poster presentation for 7th World Congress on Pediatric Critical Care, Istanbul Turkey, 2014. Published as Abstract 447: Pediatric Critical Care Medicine 15 (4). P102-103.

List of Figures

List of Tables

Abstract

Chest physiotherapy is well described as a treatment modality in ventilated infants and children with lung pathology and aims to positively affect secretion clearance, ventilation and gas exchange within underinflated regions of lung. Despite widespread use, evidence for the effect of chest physiotherapy in ventilated infants and children is limited. One reason for this is the numerous and varied measurement tools used to evaluate the effects of chest physiotherapy. Valid, reliable and responsive measurement tools are essential in understanding the effects of chest physiotherapy on lung function in ventilated infants and children and to guide safe and effective treatment. Little evidence exists to recommend the use of one measurement tool over another and it is unknown which tool represents the most robust for measuring chest physiotherapy effects in ventilated infants and children. This knowledge gap formed the basis for this research program which aimed to investigate current and novel measurement tools used to measure chest physiotherapy effects in ventilated infants and children to determine the best tools available to physiotherapists working with this population.

Two studies were designed to address the identified knowledge gap forming the basis for this research program. Study 1 comprised a systematic review examining current measurement tools used to assess chest physiotherapy effects and their clinimetric properties in ventilated infants and children. Eight measurement tools were identified that measured chest physiotherapy effects on secretion clearance, respiratory mechanics, gas exchange and radiological appearance of the lung. No tools were identified that were capable of measuring ventilation distribution. From the eight identified tools, four reported clinimetric data although the yield and overall quality of studies was low. The CO_2SMO Plus respiratory mechanics monitor was found to have the most reported clinimetric data though the quality of studies investigating these clinimetric properties was low.

Chest physiotherapy aims to affect the distribution of ventilation to under-ventilated lung regions through the removal of secretions, and tools capable of measuring these changes were identified as potentially more appropriate to measure chest physiotherapy effects. As no tools capable of measuring ventilation distribution were identified in Study 1, novel tools were therefore identified and one such tool, electrical impedance tomography, able to provide real-time, bedside measurement of regional aeration, was the focus of Study 2.

Study 2 comprised a clinical study that aimed to compare effects of chest physiotherapy with routine airway clearance in ventilated infants and children on ventilation distribution using electrical impedance tomography. Study 2 was a secondary analysis of data collected within a larger prospective randomised controlled trial comparing recruitment manoeuvre effects following endotracheal suction in ventilated infants and children. As a result, the opportunity to investigate whether recruitment manoeuvres enhanced chest physiotherapy effects was also undertaken. Electrical impedance tomography-derived measures and measures of gas exchange formed the outcomes of this study. Physiological measures were also collected to monitor any negative effects of chest physiotherapy or routine airway clearance. Chest physiotherapy significantly improved global and regional end expiratory lung volume and geometric centre compared to routine airway clearance. Posterior end expiratory lung volume increased significantly over time, with the largest improvement appearing to occur in the first 30 minutes after suctioning. Chest physiotherapy resulted in a drop in homogeneity of ventilation. However inhomogeneity was higher overall in the group of participants receiving chest physiotherapy which may have reflected that this group had more severe lung disease at baseline. No differences were found for transcutaneous or partial pressure of arterial oxygen or any physiological measurements collected. The use of a recruitment manoeuvre following chest physiotherapy did not appear to enhance ventilation distribution or gas exchange.

Key findings from this research program indicate no single robust measurement tool has been used to measure the effects of chest physiotherapy in ventilated infants and children. Electrical impedance tomography shows promise as a novel tool able to measure the effects of chest physiotherapy on ventilation distribution. Differences between chest physiotherapy and routine airway clearance were identified using electrical impedance tomography that were not identified using other measures of lung function such as gas exchange. Future research addressing high quality clinimetric studies of current chest physiotherapy measurement tools and further larger scale, controlled clinical studies using electrical impedance tomography are required to build upon key findings of this program.

Abbreviations

ABG – Arterial Blood Gas

ANOVA – Analysis of variance

CINAHL - Cumulative Index to Nursing and Allied Health Literature

COSMIN - Consensus-based Standards for the Selection of health Measurement Instruments

CO_2 - Carbon dioxide

CPT – Chest Physiotherapy

CXR – Chest radiograph

EELV – End expiratory lung volume

EIT - Electrical Impedance Tomography

ETT – Endotracheal tube

FiO_2 – Fraction of inspired oxygen

HREC – Human research ethics committee

MeSH - Medical subject headings

MHI – Manual hyperinflation

O_2 – Oxygen

PaO_2 – Partial pressure of arterial oxygen

$PaCO_2$ – Partial pressure of arterial carbon dioxide

PEEP – Positive end expiratory pressure

PF– Partial pressure of arterial oxygen/ fraction of inspired oxygen

PICO – Population, intervention, comparator, outcome

PICU – Paediatric intensive care unit

SpO_2 – Oxygen saturation

1 Introduction

Chest physiotherapy (CPT) is well described as an intervention for mechanically ventilated infants and children with lung disease (McCord et al., 2013). One aim of CPT is to improve the distribution of ventilation and subsequently gas exchange, that is, the delivery of oxygen (O_2) to, and the removal of carbon dioxide (CO_2) from the blood (Main & Denehy, 2016). For the purposes of this thesis, CPT in ventilated infants and children is considered to comprise a combination of manual and assisted breathing techniques and airway suctioning (Main & Denehy, 2016; McCord et al., 2013). Removing secretions with CPT is thought to result in improved distribution of ventilation to lung regions that, as a consequence of airway obstruction by secretions, are poorly or not ventilated, and will thus improve gas exchange (Main & Denehy, 2016). Despite widespread use, high quality clinical trials investigating the effect of CPT on distribution of ventilation and the subsequent effect on gas exchange in ventilated infants and children remain limited and findings inconsistent. The lack of clear evidence makes it difficult for physiotherapists to draw meaningful and robust conclusions on which to base clinical practice (Walsh, Hood, & Merritt, 2011).

One reason for the variability in the findings in the literature may be related to the range of tools, and hence outcome measures, reported and the lack of synthesised information regarding the suitability of these for use in ventilated infants and children (Almeida, Ribeiro, Almeida-Júnior, & Zeferino, 2005; Gregson et al., 2012; Main, Castle, Newham, & Stocks, 2004; Main & Stocks, 2004). To date, no single tool or outcome measure is consistently recommended above another. To understand how CPT affects distribution of ventilation and the impact of this on gas exchange in ventilated infants and children, physiotherapists need tools that are capable of detecting and quantifying these changes. In particular tools that provide information about regional changes in distribution of ventilation in the lungs may be useful to explain CPT effects in ventilated infants and children.

1

Tools previously reported to measure CPT effects in ventilated infants and children include chest radiograph (CXR) (Deakins & Chatburn, 2002), respiratory mechanics monitors (Main, Castle, Newham, & Stocks, 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015) and arterial blood gas (ABG) analysis (Main et al., 2004; Main & Stocks, 2004). While often readily available, it is unclear whether these tools are valid, reliable or responsive, when used in ventilated infants and children to measure the effects of CPT. A systematic review of studies reporting on these tools to measure CPT effects in ventilated infants and children would identify the tools and outcome measures currently being used. The clinimetric properties of these tools could then be established to determine if these tools should continue to be used for measuring CPT effects in ventilated infants and children.

Reported CPT measurement tools may also be inadequate to measure changes in ventilation distribution that may result from CPT in ventilated infants and children (Hough, 2009). A key aim of CPT in ventilated infants and children is to improve distribution of ventilation, and therefore gas exchange, within under-ventilated lung regions as a result of removing secretions obstructing these areas. As such, tools capable of quantifying changes in ventilation distribution, in particular regional changes, may be beneficial for measuring and improving understanding of CPT effects in ventilated infants and children. Commonly used tools such as CXR and ABG may provide insight into lung function but are not capable of measuring ventilation distribution and therefore may not be sensitive enough to effects of CPT on lung function. Physiotherapists working with ventilated infants and children must therefore consider new tools, such as electrical impedance tomography (EIT), that do have the ability to measure immediate and regional changes in ventilation distribution.

EIT is a measurement tool which allows real-time imaging of lung ventilation and perfusion from which measurements of lung function can be derived (Frerichs et al., 2017). EIT has been shown to safely provide non-invasive real-time information about ventilation distribution, within and between

2

different lung regions, in ventilated adult and paediatric populations (Frerichs et al., 2017). To date no evidence exists to describe and support the use of EIT in ventilated infants and children to measure changes in ventilation distribution in response to CPT. However the use of EIT may present a new opportunity to physiotherapists working with ventilated infants and children to gain clinically meaningful regional data regarding if and how CPT directly affects ventilation distribution.

The research program detailed in this thesis was approached with two objectives. The first objective was to determine the breadth and clinimetric properties of tools used to measure the effects of CPT on lung function. Tools measuring lung function were defined in this thesis as including tools of secretion clearance, respiratory mechanics, gas exchange, radiological lung imaging and ventilation distribution. The second objective was to investigate CPT effects on lung function in ventilated infants and children using EIT, a measurement tool previously undescribed to measure CPT effects in this population. EIT has theoretical advantages over existing measurement tools for its ability to measure changes in global and regional ventilation distribution in response to CPT. It is anticipated that the information presented in this thesis may help guide the choice of measurement tools used by physiotherapists clinically, and in future clinical trials, to investigate the effects of CPT in ventilated paediatric populations.

1.1 Objective, Aims and Scope of the Thesis

The aim of this thesis was to investigate current and novel measurements used by physiotherapists working in the Paediatric Intensive Care Unit (PICU) to measure the effects of CPT on lung function in ventilated infants and children.

Two studies comprise this thesis. Study 1 reports on a systematic review to identify the measurement tools used to assess the effects of CPT in ventilated infants and children and to identify the clinimetric properties of these tools. Study 2 aimed to compare the effects of CPT with routine airway clearance, in the form of endotracheal tube (ETT) suctioning, on ventilation distribution, gas exchange and physiological status in ventilated infants and children.

As Study 2 was a secondary analysis of data collected within a larger prospective randomised controlled trial investigating the effects of two different lung recruitment manoeuvres compared to ETT suction alone. CPT does not typically include lung recruitment manoeuvres, therefore this design enabled the investigation of whether lung recruitment manoeuvres as an adjunct to CPT enhanced the effect of CPT on ventilation distribution, gas exchange and physiological state in ventilated infants and children. The use of EIT has not previously been reported in mechanically ventilated infants and children in response to CPT and is presented in this thesis as a novel technique to investigate the effects CPT, and of lung recruitment following CPT, in this population.

1.2   Overview of the Thesis

This thesis consists of six chapters. The first chapter introduces the research program. An outline of the remaining chapters is presented below.

Chapter 2 provides the background to the thesis and introduces the tools used to measure CPT in ventilated infants and children. Existing literature regarding CPT in ventilated infants and children is reviewed. Additionally, EIT as a potential measurement tool in this population is presented. Lung recruitment as an adjunct to CPT is also introduced, including a review of its effects in ventilated infants and children, as well as a discussion of its potential use following CPT.

Chapter 3 details the methodology used to underpin the two studies that make up this thesis. For Study 1 this includes a comprehensive description of the process involved in undertaking the systematic review identifying the measurement tools used and their clinimetric properties to assess CPT effects in ventilated infants and children. Details regarding the design, methodology and ethical considerations of a clinical trial investigating the use of EIT as a novel measurement tool to assess the effect of CPT in the same population are presented for Study 2.

Chapter 4 presents the first study in this thesis, a systematic review of the literature investigating the tools used to measure the effect of CPT in ventilated infants and children. Results are presented as a descriptive analysis of the identified measurement tools followed by a critical evaluation of their clinimetric properties.

Chapter 5 presents the second study in this thesis. This was a secondary analysis of data collected within a larger prospective randomised controlled trial. Data are presented for a cohort of ventilated paediatric participants who underwent CPT during enrolment in the randomised controlled trial. EIT is described as the primary measurement tool in this study as a novel way of measuring CPT effects in ventilated infants and children.

Chapter 6 forms the discussion and conclusion of this thesis. This chapter includes a synthesis of the main findings from both studies included in this research program as well as a comment on the limitations associated with these studies. Clinical implications and future avenues for research are discussed and a concluding remark completes the thesis.

2 Background

This chapter presents a review of the literature of the use of CPT in ventilated infants and children, how CPT is traditionally measured in this population and how the measurement tools used may impact the outcomes reported in clinical trials. This chapter will begin with an overview of some of the challenges faced by physiotherapists managing respiratory issues in ventilated infants and children; specifically challenges due to anatomy and physiology of the paediatric respiratory system and those resulting from intubation and mechanical ventilation.

The second section of this chapter will provide a rationale for the use of CPT in ventilated infants and children and outline CPT techniques used with ventilated infants and children. Lung recruitment is introduced as an adjunct to CPT for its potential benefits in improving the effect of CPT in ventilated infants and children. Known CPT effects in ventilated infants and children are presented, followed by a review of the types of measurement tools that have been used to assess CPT effects. The need for the systematic review including a review of the clinimetric properties of tools currently used to measure CPT effects in ventilated infants and children will be described. This chapter concludes with a discussion of novel measurement tools used to measure CPT effects in ventilated paediatric and adult populations and provides the rationale for the investigation of one of these tools as the basis for the clinical study described in this thesis.

2.1 Challenges to ventilation in infants and children

2.1.1 Impact of anatomy and physiology on paediatric ventilation

Physiotherapists working with ventilated infants and children require a thorough knowledge of paediatric respiratory anatomy and physiology to understand how ventilation is impacted by the use of CPT. Historically adult studies have been used to direct the use of CPT in paediatric settings (Main & Denehy, 2016). However it is now accepted that the paediatric respiratory system differs to that of

6

an adult (Abbas, Singer, Yammine, Casaulta, & Latzin, 2013; Schechter, 2007) and consequently to simply extrapolate findings from studies of adults is inadequate (Main & Denehy, 2016; Walsh et al., 2011).

The immature nature of the paediatric respiratory system uniquely predisposes infants and children to airway collapse which can impair their ability to ventilate effectively (Main & Denehy, 2016). As a result of their developing anatomy and physiology, infants and young children have a more flexible thoracic cage, lower functional residual capacity, reduced lung compliance, smaller calibre airways and fewer and more underdeveloped collateral ventilation channels compared to adults, predisposing them to airway collapse and hypoventilation (Main & Denehy, 2016; Schechter, 2007). Additionally, infants and children also have comparably increased density and size of submucosal glands, producing more acidic and potentially viscous mucus (Walsh et al., 2011), which places them at high risk for obstructive mucus plugging and subsequent collapse and consolidation (Walsh et al., 2011). These normal anatomical factors can be exaggerated in the presence of lung pathology, placing unwell infants and children at high risk for secretion retention, lung damage, ineffective ventilation and suboptimal gas exchange (Main & Denehy, 2016).

2.1.2 Impact of intubation and mechanical ventilation in paediatrics

In the presence of disease, some infants and children will require mechanical ventilation to support their respiratory function and ensure adequate gas exchange until recovery occurs. Mechanical ventilation involves the insertion of an ETT into the child's airway, placed below the level of the vocal cords. The ventilator delivers gas directly to the child's lungs via the ETT, and this is referred to as positive pressure ventilation (Courey & Hyzy, 2017). Positive pressure ventilation often involves the delivery of mandatory breaths, programmed through the ventilator (Courey & Hyzy, 2017). While mechanical ventilation is necessary to support the child's respiratory function during a disease

process, the presence of an ETT (Walsh et al., 2011) and the potential delivery of high pressures or volumes via the ventilator (Dahlem, van Aalderen, Hamaker, Dijkgraaf, & Bos, 2003) can have negative consequences on the child's lung function and ability to manage airway secretions (Main & Denehy, 2016).

Increased mucus production can result from the presence of the ETT in the airway (Walsh et al., 2011) and cough effectiveness is impaired due to the inability of the glottis to close while the ETT is in situ (Krause & Hoehn, 2000; Main & Denehy, 2016; Walsh et al., 2011). These factors can result in secretion retention, infection and secondary lung collapse (Main & Denehy, 2016; Walsh et al., 2011) which may prolong recovery time and possible irreversible lung damage (Peroni & Boner, 2000). The negative consequences of mechanical ventilation can be exaggerated in the presence of primary lung disease, such as pneumonia or lower respiratory tract infection, where secretion volume and viscosity may be increased (Main & Denehy, 2016). In such cases, effective secretion clearance is essential to minimise or avoid lung damage that can result when secretions are retained (Walsh et al., 2011). In ventilated infants and children, secretion clearance is often achieved through CPT (McCord et al., 2013).

Mechanical ventilation itself can also be a potential source of damage to the paediatric lung (Dahlem et al., 2003). Ventilator associated lung injury refers to damage to the lung tissue caused by positive pressure ventilation (Slutsky & Ranieri 2013) and has been associated with poor outcome and survival in ventilated adults (Slutsky & Ranieri 2013) and paediatric patients with acute lung injury (Taussig, Landau, & Souëf, 2008). Ventilator associated lung injury can occur for a number of reasons including over-distention of the alveoli from excessive pressure (barotrauma) (Tremblay & Slutsky, 1998), the release of inflammatory mediators (biotrauma) (Dahlem et al., 2003), prolonged oxygen exposure (hyperoxia) (Cheifetz & Hamel, 2006) and as a result of large volume changes causing

repetitive alveolar shearing (volutrauma) (Tremblay & Slutsky, 1998). While ventilator associated lung injury in paediatrics is still not well described in the literature, careful consideration of the pressures and volumes prescribed during positive pressure ventilation (Jauncey-Cooke, Bogossian, & East, 2009) to ventilated infants and children is considered essential to avoid risk of further damage to the lung and facilitate recovery.

2.2 CPT in ventilated paediatric patients

CPT in ventilated children and infants is traditionally delivered as a combination of techniques which together are used to mobilise peripherally located airway secretions into larger airways and evacuate these secretions through airway suctioning (Main & Denehy, 2016). By clearing these secretions, CPT aims to reduce airflow resistance, improve lung compliance, optimise gas exchange and oxygenation, reduce inflammation caused by retained secretions and facilitate recruitment of previously collapsed regions of lung (Main & Denehy, 2016; Wallis & Prasad, 1999). The combination of CPT techniques used is individually prescribed and varies depending on the presenting pathology, age of the child and primary aim of the CPT intervention (Main & Denehy, 2016).

2.2.1 Indications for CPT in ventilated infants and children

The decision to treat, and which CPT techniques to use, is often determined by the PICU physiotherapist. In practice, physiotherapists may treat children with both primary respiratory pathologies, such as bronchiolitis and atelectasis (Main & Denehy, 2016; McCord et al., 2013), and secondary respiratory problems, such as ventilator associated pneumonia following trauma or surgery (Main & Denehy, 2016; McCord et al., 2013).

CPT is typically instigated when there is evidence of lung collapse or hypoventilation on CXR (McCord et al., 2013), auscultation findings indicative of atelectasis such as decreased breath sounds or adventitious noises (Main & Denehy, 2016; Walsh et al., 2011), and/or clinical signs of secretion

9

retention including changes in respiratory mechanics (Main et al., 2004), increased ventilation parameters (McCord et al., 2013) or deteriorating ABG (Gregson et al., 2012). All of these findings can reflect the presence of secretions obstructing normal airflow and therefore are used by physiotherapists as indicators for CPT intervention (Gregson et al., 2012). For example secretions obstructing distal airways may result in acute lung collapse or hypoventilation on CXR (Main & Denehy, 2016). Similarly, diminished breath sounds or crackles on auscultation may indicate the presence of sputum plugs which can result in reduced airflow to a lung area and/or cause turbulent airflow which may be identified on auscultation (Marques, Bruton, & Barney, 2006). An increased volume or consistency of airways secretions may indicate the presence of lung pathology and a need for CPT (Main & Denehy, 2016). When secretions have obstructed airways and caused distal collapse, an increase in airway resistance or a reduction in lung compliance may result (Main & Denehy, 2016), and in some cases may result in progressive respiratory failure, seen in the need for increased ventilator support and hypoxia and/or hypercarbia on ABG results (Main & Denehy, 2016). While these clinical signs may reflect the need for CPT, the tools used to quantify them are not specific to measuring CPT effects. Therefore clinical practise is often based to some degree on the physiotherapist's experience in interpreting these measures rather than rigorous, evidence-based measures (Walsh et al., 2011).

It is likely that not all children will respond in the same way to CPT and that the underlying type and severity of lung disease may impact the effect of CPT (Walsh et al., 2011). In cases where acute discrete secretion obstruction is the cause of suboptimal ventilation or gas exchange, CPT may have a relatively immediate effect if obstructing secretions can be removed and the distal lung re-inflates (Main & Denehy, 2016). In other cases, ventilated infants and children may have more severe or extensive lung disease, with multiple pathological processes occurring together (Main & Denehy, 2016). For example, ventilated infants and children with acute respiratory distress syndrome may

10

have regions of lung collapse that may respond to CPT, but may also have areas of hyperinflation or oedema which are unlikely to respond to CPT techniques (Main & Denehy, 2016). Furthermore, many children who require intensive care management may have varying co-morbidities, for example neuromuscular, developmental or congenital heart disorders (McCord et al., 2013), that may impact on their cardiopulmonary status and influence the response to CPT (McCord et al., 2013).

These varying presentations make predicting the effects of CPT across the range of patients treated in the PICU difficult and highlights the importance of accurately measuring CPT effects to safely guide treatment progression. Knowledge of the measurements tools available to physiotherapists working in the PICU is therefore essential.

2.2.2. CPT techniques used with ventilated infants and children

There are a number of CPT techniques described for use in ventilated infants and children and the selection of CPT techniques is likely to depend on the indication for CPT and the type and severity of the presenting lung pathology. CPT techniques may be used in isolation or in combination. CPT techniques commonly used to treat ventilated infants and children are described below. While this is not an exhaustive list, the techniques described are commonly used. CPT techniques only used with non-ventilated infants and children are beyond the scope of this research program and will not be discussed. A description of and rationale for each technique are provided in the following sections.

2.2.2.1 Positioning

Positioning is frequently used by physiotherapists treating ventilated infants and children to influence lung physiology, including ventilation and perfusion (Oberwaldner, 2000). Positioning uses gravity to influence the movement of airway secretions from distal to proximal airways (Oberwaldner, 2000; Walsh et al., 2011). Due to the configuration of the airways originating from each lung lobe, placing the ventilated infant or child in specific positions can theoretically encourage

11

secretion drainage from specific lung segments where pathology is identified (Main & Denehy, 2016). Positioning can also be used to influence the distribution of ventilation and to promote preferential ventilation to and thereby recruitment of hypo-ventilated regions of lung (Lupton-Smith, 2017).

<u>2.2.2.2   Manual CPT</u>

Manual CPT broadly refers to the application of techniques delivered directly via the hands of the physiotherapist to the chest wall of the infant or child. Manual techniques typically include percussion and chest wall vibrations but variations on these techniques have also been described in the literature such as the Expiratory Flow Increase Technique (Almeida, Ribeiro, Almeida-Júnior, & Zeferino, 2005), chest shaking or chest clapping (Main & Denehy, 2016). Manual techniques are underpinned by the concept of thixotropy, the property of liquids to become less viscous when subjected to mechanical stressors (McIlwaine, 2006).

2.2.2.2.1   Percussion

Percussion refers to the use of rhythmical cupping over a specific area of collapsed lung to loosen secretions in this area (Main & Denehy, 2016) (Figure 2.1). Percussion is often used in combination with positioning to mobilise secretions from the inside of the peripheral airway wall and facilitate forward movement toward the larger airways using the effects of gravity (Walsh et al., 2011). The ideal frequency for percussion is unknown (Ciesla, 1996) and has been described across a range of frequencies (Blazey, Jenkins, & Smith, 1998; Gallon, 1991). Percussion should not be painful but there are a number of precautions to its use in ventilated infants and children (Main & Denehy, 2016). Percussion should be used with caution in infants and children with bone mineral deficiencies, osteopenia (Main & Denehy, 2016) or coagulopathies (Main & Denehy, 2016). Percussion is also thought to potentially increase airway reactivity and is not advocated for use in infants and children presenting with severe bronchospasm (Main & Denehy, 2016).

12

Figure 2.1   Percussion as it would be performed in a ventilated child

2.2.2.2.2   Chest wall vibrations

Chest wall vibrations refer to the use of compressive, oscillatory forces delivered to the chest wall of the child by the physiotherapist at the beginning of expiration to mobilise loosened secretions and promote movement of these secretions from peripheral to central airways for removal via ETT suctioning (Gregson, 2008; Gregson et al., 2012) (Figure 2.2). Reported frequencies and forces when delivering chest wall vibrations by physiotherapists vary (Gregson et al., 2007; Li & Silva, 2008; Shannon, Stocks, Gregson, Hines, et al., 2015), with some of this variation possibly influenced by individual physiotherapists experience (Shannon, Stocks, Gregson, Hines, et al., 2015).
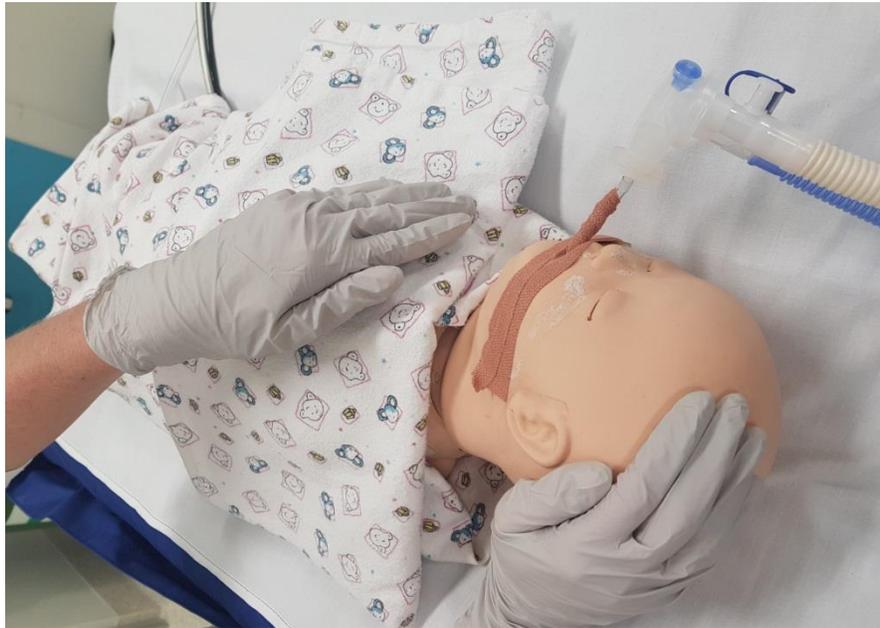
Figure 2.2   Chest wall vibration in a ventilated infant

Chest wall vibrations can be used in combination with manual hyperinflation (MHI) to increase expiratory flow rate, thereby influencing proximal movement and evacuation of secretions (Gregson et al., 2012; Gregson et al., 2007). Chest wall vibrations are considered to have the same precautions as percussion (Main & Denehy, 2016). In non-ventilated infants however, chest wall vibrations are also considered to have a theoretical risk of causing lung collapse if the chest wall is compressed beyond the child's closing volume (volume at which airways collapse as pressure external to the airways exceeds internal airway pressure) (Gregson, 2008). This risk is managed in ventilated infants and children through the use of PEEP to reinstate the pressure in the airway following chest wall compression and manage the risk of airway collapse (Gregson, 2008; Main & Denehy, 2016).

2.2.3 Manual hyperinflation

Manual hyperinflation refers to specific breathing techniques used by physiotherapists to mobilise airway secretions toward the trachea, enhance airflow to areas of lung collapse, and recruit lung units following chest wall compression, ventilator disconnection or following ETT suctioning (Ntoumenopoulos, 2005; Paulus, Binnekade, Vroom, & Schultz, 2012). MHI involves delivering slow inspiratory breaths via a hand held anaesthetic bag at a volume that is larger than the child's tidal volume. MHI is used to encourage the expansion of collapsed lung regions via collateral ventilation channels (Figure 2.3) and encourage air behind obstructing mucus plugs to assist in mobilising the mucous plugs (Denehy, 1999; McCarren & Chow, 1996). Following mobilisation of secretions towards larger airways, a hyperinflation followed by a quick release of the anaesthetic bag creates an increase in expiratory flow and propels mucus toward the trachea where it can be suctioned out (Ntoumenopoulos, 2005).

MHI has been shown to increase expiratory flow rate as well as increasing the expiratory to inspiratory flow bias in ventilated infants and children when paired with chest wall vibrations (Gregson et al., 2012). Increasing the expiratory to inspiratory flow bias has been suggested as the reason why MHI and chest wall vibrations are able to facilitate proximal secretion movement by biasing the direction of airflow, and therefore secretion movement, toward the upper airway (Kim, Iglesias, & Sackner, 1987).

(a)   (b)
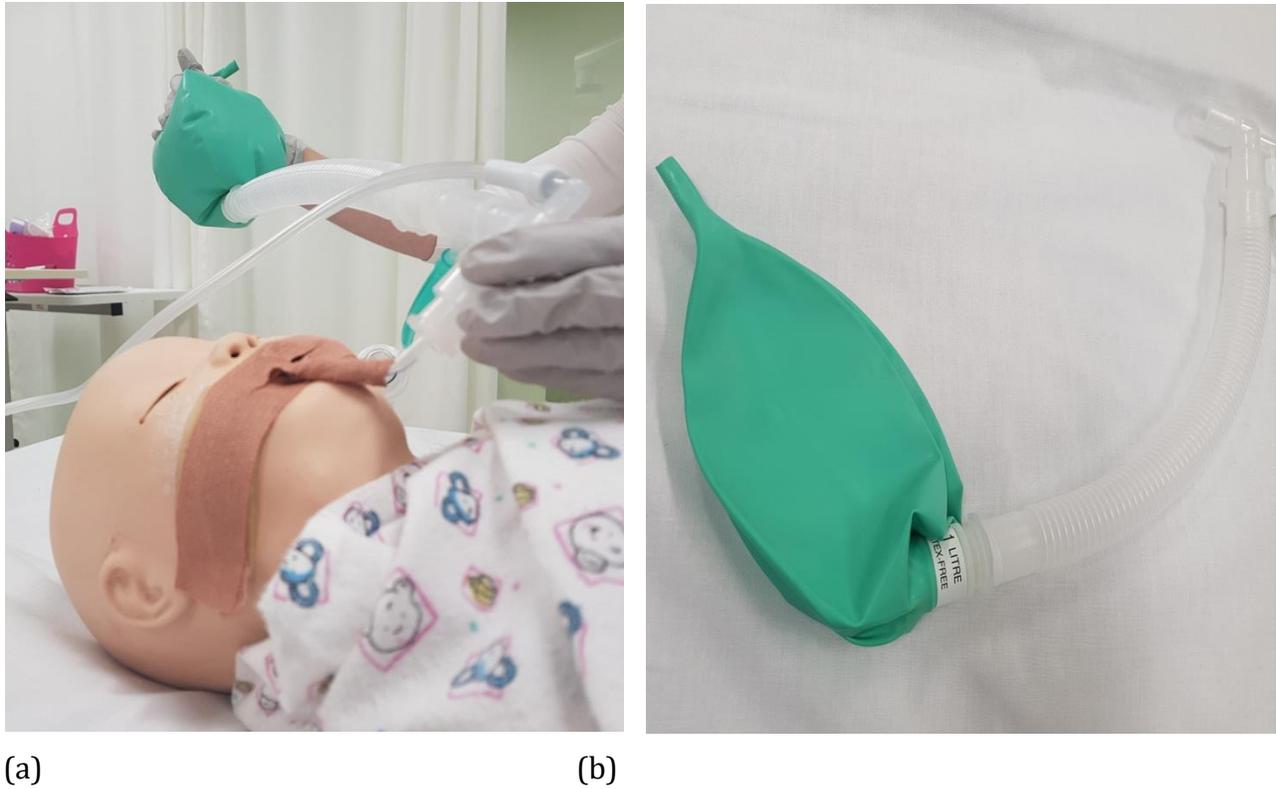
Figure 2.3   **(a) Delivery of manual hyperinflation to a ventilated infant and (b) open-ended anaesthetic bag used to deliver manual hyperinflation**

Despite benefits, there are risks associated with MHI in ventilated infants and children (Argent & Morrow, 2012; Paulus et al., 2012). MHI involves the disconnection of the infant or child from the ventilator which can result in a loss of airway pressure and may lead to lung collapse (Paulus et al., 2012). MHI in ventilated infants and children also commonly involves the use of an open-ended anaesthetic bag that requires the physiotherapist to maintain a minimum level of pressure, referred to as positive end expiratory pressure (PEEP), to avoid loss of pressure in the lung which can also result in lung collapse (Gregson, 2008). Furthermore, undertaking hyperinflation breaths involves delivering larger breaths than those the infant or child is receiving on the ventilator (Main & Denehy,

16

2016). If MHI is not performed appropriately by trained physiotherapists, MHI may not be effective and at worst, may result in lung damage in the form of collapse (through the loss of PEEP), and/or alveolar injury as a result of dangerously high volumes or pressures being delivered (Gregson, 2008). Excessive inspiratory volumes (Anning, Paratz, Wong, & Wilson, 2003) or PEEP (Taussig et al., 2008) can also negatively affect cardiac output by increasing pressure in the thorax relative to the heart, thereby reducing venous return and as a result cardiac output (Anning et al., 2003; Taussig et al., 2008). Therefore MHI must be used with caution in ventilated infants and children with already low cardiac output as a result of cardiovascular instability.

2.2.4   Devices

Specialised therapeutic devices are an alternative to traditionally used CPT techniques such as percussion and chest wall vibrations. Examples of these devices include the intra-pulmonary percussive ventilator (Deakins & Chatburn, 2002; Lineham, Johnson, Madden, Ramdat, & Custer, 2016; Toussaint, 2011; Toussaint, De Win, Steens, & Soudon, 2003; Toussaint, Pernet, Steens, Haan, & Sheers, 2016) and the high frequency chest compression vest (Lee, Button, & Tannenbaum, 2017; Yuan et al., 2010).

The intra-pulmonary percussive ventilator delivers an oscillating pressure directly into the airways of the infant or child via a specially designed machine (Toussaint, 2011). In ventilated infants and children this oscillatory pressure is delivered via the child's ETT and may be used in combination with other techniques such as positioning or endotracheal suctioning (Deakins & Chatburn, 2002). The rationale behind the use of the intra-pulmonary percussive ventilator is that it delivers percussive effects directly into the airway to affect secretion mobilisation (Main & Denehy, 2016). This is in contrast to traditionally delivered percussion which is delivered externally to the chest wall (Main & Denehy, 2016).

17

High frequency chest compression is another device that can be used in infants and children and works by transmitting pulsating airwaves through the child's chest via a specially designed vest (Hansen, Warwick, & Hansen, 1994). The resulting oscillatory effect is applied through the chest wall and is thought to influence secretion mobilisation in a similar way to traditional chest wall percussion (Arens et al., 1994). The high frequency chest compression vest has been shown to positively influence secretion clearance in non-ventilated infants and children with cystic fibrosis (Arens et al., 1994; Hansen et al., 1994) and neuromuscular disease (Panitch, 2006; Yuan et al., 2010). While a small number of studies have investigated the use of the vest in ventilated adults (Chuang, Chou, Lee, & Huang, 2017; Kuyrukluyildiz et al., 2016; Whitman, Van Beusekom, Olson, Worm, & Indihar, 1993), to date no evidence exists to supports its use in ventilated infants and children.

2.2.5 Endotracheal Suctioning

Endotracheal suctioning refers to the application of negative pressure to the ETT via a suction catheter, to remove secretions occluding the airway (Morrow & Argent, 2008) (Figure 2.4). ETT suctioning forms an integral part of CPT as the final technique in the CPT treatment in ventilated infants and children and is often used following other CPT techniques to remove mobilised secretions from the larger airways in the absence of an effective cough mechanism (Main et al., 2004). While considered to be an essential component of airway clearance, and therefore CPT, in ventilated paediatric patients, ETT suctioning is well documented to cause a range of negative physiological effects, including bradycardia, tachycardia, desaturation, and lung de-recruitment (Morrow & Argent, 2008).

Figure 2.4   ETT suctioning in a ventilated infant

2.2.5.1 Negative physiological effects of suctioning

Physiological instability following ETT suctioning has been most commonly described in neonatal and preterm populations (Evans, 1992; Fanconi & Duc, 1987; Skov, Ryding, Pryds, & Greisen, 1992) however a number of studies have also investigated physiological instability in ventilated paediatric cohorts (Kerem, Yatsiv, & Goitein, 1990; Ridling, Martin, & Bratton, 2003; Singh, Kissoon, Frewen, & Tiffin, 1991). Hypoxaemia (Evans, 1992), apnoea (Evans, 1992), bradycardia (Evans, 1992) and other arrhythmias (Simbruner et al., 1981) have been associated with ETT suctioning and as such, a number of recommendations have been suggested to minimise these negative sequelae.

Pre-oxygenation has been suggested as a strategy to minimise hypoxaemia and bradycardia (Evans, 1992; Kerem et al., 1990; Walsh et al., 2011) associated with ETT suctioning. The avoidance of routine ETT suction has also been suggested (Day, Farnell, & Wilson-Barnett, 2002) as well as minimising the use of normal saline instillation during ETT suction (Ridling et al., 2003). The use of closed ETT suctioning technique has been shown to reduce desaturation and bradycardia in preterm infants

19

(Kalyn, Blatz, Feuerstake, Paes, & Bautista, 2003; Restrepo, 2010) and in ventilated paediatric patients to minimise desaturation and loss of lung volume (Choong, Chatrkaw, Frndova, & Cox, 2003).

<u>2.2.5.2   Lung de-recruitment</u>

Apart from the physiological sequelae resulting from ETT suction, lung de-recruitment has become a well-recognised problem in ventilated infants and children (Tingay et al., 2010). Lung de-recruitment refers to the loss of volume in the lung at the end of expiration, beyond that required to maintain open alveoli (Lindgren et al., 2007). This volume loss occurs when the child is disconnected from the ventilator and as a result of negative pressure being applied directly to the lung during ETT suctioning (Lindgren et al., 2007; Maggiore et al., 2003). Maintaining a volume of air within the lungs at the end of expiration is essential for avoiding alveolar collapse (Slutsky & Tremblay, 1998) and the subsequent damaging shear forces that result from repeated opening of these collapsed alveoli (Taskar, John, Evander, Robertson, & Jonson, 1997). This damage can be negated through the use of PEEP and lung recruitment (Jauncey-Cooke et al., 2009; G. Wolf et al., 2012).

2.3   Lung recruitment manoeuvres

Lung recruitment manoeuvres encompass a range of deliberate, transient strategies used to increase the trans-pulmonary pressure within the lungs, above the level achieved during tidal breathing (Hess & Bigatello, 2002). The aim of lung recruitment is to open collapsed alveoli and reinstate functional residual capacity (Hess & Bigatello, 2002). This may be particularly important in the presence of certain pathologies where lung compliance is reduced (Lapinsky & Mehta, 2005). Functional residual capacity refers to the volume of air remaining in the lungs at end expiration and must be maintained to prevent alveolar collapse during expiration (Taussig et al., 2008). The maintenance of functional residual capacity helps optimise oxygenation (Taussig et al., 2008) and to maintain an open lung, thereby avoiding shear forces that can result from repetitive opening of the lung from a collapsed
20

state (Taussig et al., 2008). In ventilated patients, functional residual capacity is maintained by the presence of PEEP (Taussig et al., 2008), a constant pressure delivered by the ventilator sufficient to overcome alveolar opening pressure (Lapinsky, 2002). PEEP has the potential to be rapidly lost in ventilated patients following disconnection from the ventilator and as a result of ETT suctioning (Lindgren et al., 2007) and therefore, potentially after CPT as well. PEEP is particularly important in infants and children where functional residual capacity is lower than in adults, therefore predisposing the airways to collapse (Mansell, Bryan, & Levison, 1972). PEEP is therefore commonly used with lung recruitment manoeuvres in ventilated infants and children (Boriosi et al., 2011; Jauncey-Cooke et al., 2012).

2.3.1 Positive end expiratory pressure (PEEP)

PEEP is thought to improve oxygenation (Lapinsky, 2002), alveolar ventilation (Taussig et al., 2008) and lung compliance (Sivan, Deakers, & Newth, 1991) in ventilated patients. PEEP is appreciated as improving oxygenation and alveolar ventilation by increasing functional residual capacity (Main & Denehy, 2016; Taussig et al., 2008). Optimising functional residual capacity improves the amount of time air is able to interface with the alveolar capillaries and maximises the size of this interface by maintaining open alveoli (Lapinsky, 2002). Both of these effects promote optimum gas exchange in ventilated patients (Main & Denehy, 2016; Taussig et al., 2008). PEEP is also thought to be of particular importance in cases of reduced lung compliance (Taussig et al., 2008), where alveoli are prone to collapse and high recruitment pressures are required (Taussig et al., 2008). Lung compliance is defined as the ability of the lungs to distend and can be considered in terms of the pressure-volume interaction (Main & Denehy, 2016). When lung compliance is reduced, high pressures can be generated in the context of minimal increases in volume (Main & Denehy, 2016). This makes ventilating the lungs with adequate tidal volumes to ensure gas exchange difficult and places alveoli at risk of damage from these high pressures, referred to as barotrauma (Taussig et al.,

21

2008). PEEP can improve lung compliance by opening, and splinting alveoli in the presence of poor lung compliance and/or lung disease (Taussig et al., 2008).

Different types of lung recruitment manoeuvres have been described in the paediatric literature however most can be classified according to two main strategies; sustained pressure delivered via an anaesthetic bag (Duff, Rosychuk, & Joffe, 2007; Marcus, van der Walt, & Pettifer, 2002; Morrow, Futter, & Argent, 2007; Tusman et al., 2003), and through the manipulation of PEEP (Boriosi et al., 2011; Jauncey-Cooke et al., 2012; Kheir et al., 2012; G. Wolf et al., 2012). Sustained inflations refer to the application of a slowly delivered breath to a desired plateau pressure (higher than that achieved during tidal ventilation) that is then held for a sustained period (Jauncey-Cooke et al., 2009). Sustained inflation manoeuvres are typically delivered manually using an anaesthetic bag (Morrow et al., 2007) or using the ventilator (Duff et al., 2007; Marcus et al., 2002). Sustained inflations are thought to recruit the lungs through the combination of the pressure delivered and the time over which it is delivered (Jauncey-Cooke et al., 2009), the latter being required to overcome the physiological resistance to alveolar opening. Sustained inflations have been shown to be safe and efficacious in paediatric patients (Duff et al., 2007). However when delivered manually by the use of an anaesthetic bag, there is a risk of losing the benefit of a sustained inflation manoeuvre due to the need to disconnect the patient from the circuit to return them to the ventilator (Morrow et al., 2007).

Manipulating PEEP involves the increase, and subsequent decrease, in baseline PEEP for a specified period of time to reverse or minimise end-expiratory alveolar collapse (Boriosi et al., 2011; Jauncey-Cooke et al., 2012; Kheir et al., 2012; G. Wolf et al., 2012). Different strategies for manipulating PEEP have been described including a single increase in PEEP to a pre-determined level above baseline (Marcus et al., 2002) or using an incremental approach (Boriosi et al., 2011; Jauncey-Cooke et al., 2012; Kheir et al., 2012; G. Wolf et al., 2012) to more gradually increase PEEP. Double PEEP

22

manoeuvres refer to the doubling of baseline PEEP for a period of time (Jauncey-Cooke, 2012). Comparatively, incremental PEEP manoeuvres involve the use of a stepwise increase and then decrease in PEEP, resulting in a more gradual change in PEEP (Boriosi et al., 2011; Jauncey-Cooke et al., 2012; Kheir et al., 2012; G. Wolf et al., 2012). Clinical studies have been undertaken using sustained inflation manoeuvre (Duff et al., 2007; Morrow et al., 2007), double PEEP (Jauncey-Cooke et al., 2012) and incremental PEEP strategies (Boriosi et al., 2011; Kheir et al., 2012; G. Wolf et al., 2012) in ventilated infants and children however currently one strategy has not been advocated over another in ventilated infants and children (Jauncey-Cooke et al., 2009).

2.3.2 CPT and lung recruitment manoeuvres

One reason for using recruitment manoeuvres in ventilated infants and children following ETT suctioning (Jauncey-Cooke et al., 2009) is to re-instate the pressure required to keep alveoli open after the delivery of negative suction pressure (Lapinsky, 2002). It follows therefore, that recruitment manoeuvres may also be of benefit following CPT, as CPT typically involves ETT suction as a component (Main et al., 2004).

The effect of lung recruitment manoeuvres used after CPT in ventilated infants and children has not previously been investigated. Lung recruitment used after CPT may be advantageous by minimising the same negative sequelae associated with ETT suction when used alone. Yet lung recruitment may have additional benefits when used after CPT to enhance CPT effects on regional ventilation. As CPT aims to remove secretions obstructing distal airways and reinflate previously collapsed lung regions, the addition of a lung recruitment manoeuvre may augment this reinflation, thereby enhancing the CPT effect. This requires further investigation to identify whether lung recruitment used after CPT is beneficial and should therefore be considered for use by physiotherapists working with ventilated infants and children.

23

2.4 Measuring the effects of CPT in the Paediatric Intensive Care Unit

Measuring CPT effects in ventilated infants and children is an essential part of best practice for physiotherapists working in the PICU to identify appropriate patients, guide treatment decisions and evaluate effect (Main & Denehy, 2016). Measuring CPT effects in ventilated infants and children however has some inherent difficulties due to the wide variability in patient age and types of pathology encountered in a PICU (Randolph, 2017; Randolph et al., 2003). The individualised nature of CPT interventions in ventilated infants and children limits standardisation of treatment protocols (McCord et al., 2013) and consequently also the measurement tools used. Most tools used by physiotherapists working with ventilated infants and children are not specifically designed to measure CPT effects, making it unclear whether these tools are suitable to measure the specific effects CPT seeks to achieve.

Numerous tools and outcome measures have been used to measure CPT effects in ventilated infants and children, with no single tool being recommended above another. It is unclear how measurement tools are selected by physiotherapists but it is likely that the desired CPT effect the physiotherapist is aiming to achieve is one consideration (Mokkink, Prinsen, Bouter, de Vet, & Terwee, 2016). CPT effects may result in improvements in secretion clearance, respiratory mechanics, auscultation findings, gas exchange and/or the radiological appearance of the lung. The measurement of each of these effects is considered below. Improving ventilation distribution is also considered to be a desired CPT effect and the measurement of this effect will be discussed separately. Reported outcomes for each CPT effect, and the mentioned inconsistencies in study findings reporting on these effects, are also discussed.

2.4.1   Secretion clearance

Secretion wet weight is frequently considered as an outcome measure of the effect of CPT as it is a tangible clinical measure of secretion clearance. While used commonly in the clinical setting, secretion weight has also been described in the literature to measure CPT effects, though more commonly in studies of non-intubated paediatric cohorts including those with cystic fibrosis and bronchiectasis (Eaton, Young, Zeng, & Kolbe, 2007; Patterson, Bradley, Hewitt, Bradbury, & Elborn, 2005; Zach, Purrer, & Oberwaldner, 1981). Reporting secretion weight in these populations makes sense, as cystic fibrosis and bronchiectasis are characterised by chronic sputum production (Main & Denehy, 2016) and therefore measures of secretion weight may be reasonable to be used.

The use of secretion weight as a measure of the effect of CPT in ventilated paediatric patients is not widely reported. One study (Tannenbaum, Prasad, Dinwiddie, & Main, 2007) included secretion weight as a secondary outcome to measure the effect of CPT, specifically intrapulmonary percussive ventilation, on intubated children with cystic fibrosis (Tannenbaum et al., 2007). However, secretion weight was not quantified in the study results, leaving it unclear whether it represents a useful measurement tool in ventilated infants and children.

Measuring changes in secretion volume, colour and consistency can be used by physiotherapists to monitor clinical progress and identify potential change in clinical presentation (Main & Denehy, 2016). Secretion weight is possibly more useful and sensitive in pathologies associated with high or chronic secretion production such as cystic fibrosis and bronchiectasis (Main & Denehy, 2016) where changes in usual volume might indicate an acute exacerbation of these conditions (Main & Denehy, 2016). The weight of cleared secretions in ventilated infants and children who are acutely unwell is likely to vary depending on the underlying lung pathology, size and age of the child (Main & Denehy, 2016) and therefore as an outcome measure may not provide accurate or useful information about

treatment effect in all patients. It is also possible that the weight of cleared secretions during a CPT treatment may not necessarily reflect whether that treatment was effective or not (Marques et al., 2006). Mobilising and evacuating airway secretions is considered a primary aim of CPT in ventilated infants and children to improve ventilation to previously collapsed lung regions (Main & Stocks, 2004). However measuring secretion weight alone is unlikely to indicate whether a subsequent improvement in ventilation has occurred. Further understanding of the validity, reliability and responsiveness of secretion weight in measuring CPT effects is therefore warranted.

2.4.2 Respiratory mechanics

Respiratory mechanics refer to measures of the mechanical properties of the lung and include measures of pressure and flow as well as derived measures of airway resistance, lung compliance, volumes and dead space (Hess, 2014). Respiratory mechanics can be measured directly on the ventilator or via a standalone monitor inserted into the child's ventilator circuit. Respiratory mechanics monitors have become particularly popular with PICU physiotherapists in the last twenty years as these can be used safely by the bedside (Almeida et al., 2005; Castle, Dunne, Mok, Wade, & Stocks, 2002; Main et al., 2004). Additionally, respiratory mechanic monitors provide immediate information to the clinician regarding airway and lung function potentially resulting from secretion removal and lung re-inflation (Main et al., 2004). Respiratory mechanics measures relevant to physiotherapists managing ventilated infants and children include measures of tidal volume of spontaneous patient breaths, airway resistance, lung compliance and dead space.

2.4.2.1.   Tidal volume measures

Tidal volume, the quantity of gas the ventilator delivers to the lungs during a normal breath (Warner & Patel, 2013), has been used as an outcome measure for CPT in ventilated infants and children (Almeida et al., 2005; Elizabeth, Yoel, Ali, Lubis, & Yanni, 2016; Main et al., 2004; Shannon, Stocks,

26

Gregson, Dunne, et al., 2015). A small number of studies (Almeida et al., 2005; Main et al., 2004; Main & Denehy, 2016; Shannon, Stocks, Gregson, Dunne, et al., 2015) report an increase in tidal volume, though only one (Shannon, Stocks, Gregson, Dunne, et al., 2015) reports this increase as significant. All these studies used a portable respiratory mechanics monitor inserted into the child's ventilator circuit to measure tidal volume. Conversely, no significant change in tidal volume as a result of CPT in ventilated children was reported when tidal volume was measured directly by the child's ventilator (Elizabeth et al., 2016). An increase in tidal volume of spontaneous breaths may be considered to be a positive effect of CPT, as theoretically an improvement in lung inflation, through the removal of obstructing airway secretions, would result in a larger volume of gas being delivered to the lungs and improved opportunity for gas exchange (Main & Denehy, 2016). It is possible that the use of different measurement tools contributed to these mixed findings.

2.4.2.2 Resistance and compliance

Resistance and compliance are measurements of respiratory mechanics used to quantify the effect of CPT in ventilated infants and children. Resistance refers to the impedance to airflow through the airways (Hess, 2014) and is appreciated as being increased by any material obstructing the airways and therefore reducing the airway calibre (Taussig et al., 2008). Airway resistance may increase as a result of excessive airway secretions, lung collapse or when functional residual capacity is reduced (Taussig et al., 2008). Therefore a reduction in resistance has been suggested as a potential positive effect of CPT as a result of improving secretion clearance and re-instating lung expansion and/or functional residual capacity (Main et al., 2004). Resistance has been shown to significantly drop following the combined effect of CPT techniques including manual techniques, manual hyperinflation and ETT suctioning in ventilated paediatric patients (Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015). Conversely, significant increases in airway resistance following CPT have also been reported (Tannenbaum et al., 2007) along with one study reporting no change in airway

27

resistance following CPT in ventilated infants and children (Almeida et al., 2005). These mixed findings make it unclear whether resistance is sensitive to changes caused by CPT in ventilated infants and children and therefore further investigation of resistance as an outcome measure in this population is needed.

Compliance is a reflection of lung tissue elasticity (Hess, 2014). A reduction in compliance has been linked to lung collapse in ventilated paediatric patients (Taussig et al., 2008). Therefore, it has been suggested that lung compliance may be useful for physiotherapists as an indicator of lung collapse (Main et al., 2004). It could be suggested that an increase in lung compliance could reflect reinflation of collapse, while a reduction in lung compliance could reflect worsening of lung collapse (Deakins & Chatburn, 2002; Main et al., 2004). Studies using compliance to evaluate CPT effects in ventilated infants and children have demonstrated variable results, with increases (Shannon, Stocks, Gregson, Dunne, et al., 2015), reductions (Main et al., 2004) or no change (Almeida et al., 2005; Deakins & Chatburn, 2002) in compliance reported. The variable effect of CPT on lung compliance described in these studies similarly suggests that lung compliance measures may not be sensitive enough to adequately explain CPT effects in ventilated infants and children.

2.4.2.3   Dead space measures

Dead space measures are derived from respiratory mechanics and gas exchange measurements (Hess, 2014) and have been used in a small number of studies in ventilated infants and children as a measure of CPT (Almeida et al., 2005; Main & Stocks, 2004). Anatomical dead space refers to the amount of tidal volume that remains in the airways during each breath. As this volume of air does not come into contact with alveoli, it does not participate in gas exchange and is therefore considered dead space (Main & Denehy, 2016; Taussig et al., 2008). Alveolar dead space refers to air that comes into contact with the alveoli but is unable to participate in normal gas exchange (Main & Denehy,

28

2016; Taussig et al., 2008). In normal circumstances, air reaching the alveoli should move across the alveolar membrane and into the adjacent capillaries, however if blood supply is inadequate no gas exchange can occur (Main & Denehy, 2016). Physiological dead space refers to the sum of anatomical and alveolar dead space and equates to the total amount of tidal volume entering the lungs that does participate in gas exchange (Main & Denehy, 2016).

Dead space has been used to evaluate CPT effects in ventilated infants and children on ventilation-perfusion matching (Almeida et al., 2005; Main & Stocks, 2004). Two studies have described changes in dead space in response to CPT in ventilated paediatric cohorts with mixed findings. No change was found in airway or alveolar dead space in infants with obstructive respiratory failure following CPT (Almeida et al., 2005). In contrast, significant increases in airway, alveolar and physiological dead space were reported (Main & Stocks, 2004) following CPT that were not observed after ETT suction alone. The latter study (Main & Stocks, 2004) suggests the significant increase in physiological dead space may represent a mismatch in the ventilation-perfusion balance caused by re-expansion of collapsed regions of lung but a delay in a corresponding increase in perfusion to these areas (Main & Stocks, 2004). This is plausible however the authors were not able to confirm this hypothesis unequivocally based on the measurements described. This raises some doubt over the usefulness of dead space measures to measure CPT in ventilated infants and children and raises the need for further investigation of these measures and their clinimetric properties.

2.4.3   Radiological appearance of the lung

Lung imaging is used by physiotherapists to measure changes in the radiological appearance of the lung as a result of CPT and includes numerous modalities including CXR, ultrasound, computed tomography and magnetic resonance imaging (Ciesla, 1996; Main & Denehy, 2016). CXR is the most commonly used modality in ventilated infants and children to image the lungs and thoracic structures

(Taussig et al., 2008). Ventilated infants and children may undergo regular CXR while in the PICU, often daily, to aid diagnosis (Main & Denehy, 2016) and to monitor the presence, progression or improvement of lung pathology in response to different treatments (Taussig et al., 2008). CPT can be considered one of these treatments and as such, CXRs are used by physiotherapists to assess CPT effects. The presence of lung collapse on CXR is a frequent indication for the use of CPT in ventilated infants and children (McCord et al., 2013), with improvements in the appearance of collapse theoretically lending support to the efficacy of CPT in clearing secretions and facilitating lobar re-expansion (Mackenzie, Shin, & McAslan, 1978).

CXRs have been used as an outcome measure of CPT effectiveness in infants and children (Al-Alaiyan, Dyer, & Khan, 1996; Bloomfield, Teele, Voss, Knight, & Harding, 1998; Deakins & Chatburn, 2002; Galvis, Reyes, & Nelson, 1994). Participants in these studies are often not ventilated (Al-Alaiyan et al., 1996; Bloomfield et al., 1998) and/or are preterm cohorts (Bloomfield et al., 1998; Pandya, Shetye, Nanavati, & Mehta, 2011). The few studies that measured CPT effects in ventilated infants or children using CXR (Deakins & Chatburn, 2002; Galvis et al., 1994) demonstrated improvements in atelectasis (Deakins & Chatburn, 2002) and air bronchograms (Galvis et al., 1994). These findings support the use of CXR as a potential tool to measure the effectiveness of CPT in improving or resolving lung pathology (Walsh et al., 2011). It is not known whether CXR can provide information that is sensitive or specific enough to reliably inform outcomes of CPT in ventilated infants and children.

Despite being a commonly used tool in PICU, there are a number of factors which physiotherapists should consider when using CXR to evaluate CPT effects in ventilated infants and children. Firstly, CXR delivers a radiation dose and therefore use should be limited to avoid exposing children to unnecessarily high radiation doses (Taussig et al., 2008). As a result, in clinical settings, CXRs are taken at most only once a day for routine purposes, though at times more frequent images may be

required in urgent clinical situations. Therefore, it is reasonable to suggest that CXRs are unlikely to be able to detect immediate changes within the lung as a result of CPT and may not be practical for use for continued reassessment associated with the delivery of CPT (Main & Denehy, 2016).

Secondly, the timing of CXRs may also influence the relevance of information able to be yielded by physiotherapists working with ventilated infants and children. Radiological changes on CXR may lag behind the pathological process (Slonim & Pollack, 2006), making it difficult to reliably monitor change as a result of CPT. Furthermore, CXRs may not be taken immediately after CPT, and in some cases may be taken hours after CPT completion, which limit CXRs as a sensitive measurement tool of the effects of CPT.

Thirdly, the accuracy with which CXRs are interpreted can also influence how useful they are as a measurement tool for physiotherapists working with ventilated infants and children (Zach & Oberwaldner, 2008). Valid interpretation of paediatric CXRs involves knowledge of age-related changes in thoracic appearance as well as a sound knowledge of normal and pathological lung appearance (Taussig et al., 2008). Accuracy in interpreting CXRs in children may be improved by the use of standardised scoring methods (De Jong et al., 2011; Ferrero et al., 2008). However these scoring systems still rely on adequate training (Jeffrey, Goddard, Callaway, & Greenwood, 2003) and for optimum accuracy, interpretation should only be undertaken by an experienced radiologist (Deakins & Chatburn, 2002). All of these factors suggest that CXRs may have limitations as a measurement tool for physiotherapists working with ventilated infants and children. However, evidence of the validity, reliability and responsiveness of CXR to CPT effects is required to determine if there is value in using in ventilated infants and children.

2.4.4 Stethoscope

Stethoscopes are used regularly by physiotherapists to measure the absence or presence of breath sounds and adventitious sounds, such as crackles, wheeze or transmitted sounds, through auscultation of the chest wall (Marques et al., 2006). Auscultation is used by physiotherapists to indicate possible pathology or secretions in the airways and can be used as a clinical tool for measuring CPT effects (Marques et al., 2006). A stethoscope is a readily available and relatively inexpensive tool available to physiotherapists working with ventilated infants and children. However interpretation of the findings from auscultation is generally regarded as subjective (Marques et al., 2006) and therefore may not be robust enough to us as a tool to measure CPT effects.

2.4.5 Gas exchange

ABG and transcutaneous oxygen and carbon dioxide monitoring are commonplace in the PICU as tools for monitoring gas exchange and oxygenation in response to medical and nursing interventions (Marik, 2015). ABGs are considered the gold standard tool for measuring gas exchange and acid-base balance (Severinghaus, 1966). ABGs provide values of the partial pressure of oxygen (O_2) and carbon dioxide (CO_2) in arterial blood, saturation of oxygen, as well as measures of the acid-base balance, including pH, bicarbonate and base excess (Taussig et al., 2008). ABGs have been used to measure the effects of CPT on gas exchange in ventilated infants and children but results are conflicting. The partial pressure of arterial oxygenation has been shown to increase after CPT in some studies (Galvis et al., 1994) while others report no change (Almeida et al., 2005; Elizabeth et al., 2016). Small but significant reductions in arterial oxygen saturations, the amount of oxygen dissolved in the blood, have also been described following CPT in ventilated infants and children (Main et al., 2004).

While it could be theorised that the removal of obstructing secretions and the re-inflation of distal lung regions by CPT could improve ventilation to these areas and therefore improve oxygenation

(Main & Denehy, 2016), results from previous studies do not uniformly support this. This may be because the anticipated effect has not been achieved, or it may indicate that CPT effects are not appreciated by measures of arterial oxygenation in ventilated infants and children. Reductions in oxygen saturations may be reflective of the potential negative physiological response to ETT suctioning previously described (Evans, 1992; Kerem et al., 1990; Ridling et al., 2003; Singh et al., 1991), as ETT suction traditionally comprises part of CPT

Changes in carbon dioxide levels in response to CPT are more consistent with three studies reporting no change from baseline following the CPT (Almeida et al., 2005; Elizabeth et al., 2016; Main & Stocks, 2004). However as previously presented, changes in dead space, which are derived in part from carbon dioxide removal (Main & Stocks, 2004), have been reported following CPT compared to ETT suction alone, suggesting that partial pressure of arterial carbon dioxide may lack sensitivity to identify CPT effects in ventilated infants and children.

Despite inconsistent results, ABG and transcutaneous oxygen saturations reflect potentially important measures for physiotherapists to evaluate and monitor changes, both positive and adverse effects, in lung physiology, as a result of affecting ventilation and gas exchange, in ventilated infants and children. The clinimetric properties of the tools used to derive these measures however require further investigation in this population to confirm their value in measuring CPT effects.

2.5   Ventilation distribution

A primary aim of CPT in ventilated infants and children is to improve the distribution of ventilation, and thereby gas exchange, to previously under-ventilated or collapsed lung regions through the removal of airway secretions (Main et al., 2004). As such, measuring changes in ventilation distribution, both globally and regionally, is likely to be necessary to understand CPT effects. Many of the measurement tools described in the preceding sections to assess CPT effects in ventilated

33

infants and children may be considered as measuring aspects of lung function. However these tools do not measure changes in the distribution of ventilation and therefore may not be adequate to explain CPT effects in this population. New measurement tools with the ability to measure ventilation distribution need to be considered by physiotherapists working with ventilated infants and children to better understand if and how CPT affects lung function.

2.5.1   Measures of ventilation distribution

A number of novel measurement tools have recently been described in the literature to measure CPT effects on global and regional ventilation distribution in ventilated adults such as computed tomography (Ides et al., 2012), computerised lung sound monitoring (Ntoumenopoulos & Glickman, 2012) and lung ultrasound (Leech, Bissett, Kot, & Ntoumenopoulos, 2014). All of these tools are able to assess changes in ventilation distribution in response to CPT (Ides et al., 2012; Leech et al., 2014; Ntoumenopoulos & Glickman, 2012) and have been used in combination with clinical measurement tools such as sputum clearance (Ntoumenopoulos & Glickman, 2012) and ABG analysis (Ides et al., 2012) to explain CPT effects.

While computed tomography has the ability to measure global and regional ventilation distribution comprehensively and with most detail (Taussig et al., 2008), several disadvantages limit the clinical utility of this tool including that it is costly, is inaccessible at the bedside and has a relatively high associated radiation dose (Taussig et al., 2008). Computerised lung monitoring and lung ultrasound appear to have higher clinical utility as these tools can be used by the bedside. However both rely on specialised equipment and skills and to date neither have been used or validated in a ventilated paediatric cohort to measure the effects of CPT.

2.5.2   Electrical impedance tomography (EIT)

A tool that can measure real-time changes in global and regional ventilation distribution and is able to be used by the bedside in critically unwell patients is EIT (Frerichs et al., 2017). EIT has been suggested as a novel CPT measurement tool in ventilated infants and children (Main & Denehy, 2016). EIT has been used with ventilated preterm infants (Hough, Flenady, Johnston, & Woodgate, 2010; Hough, Johnston, Brauer, Woodgate, & Schibler, 2013; Hough, Shearman, Liley, Grant, & Schibler, 2014) to provide detailed measurement of both global and regional ventilation. EIT maps the relative changes in bio-impedance of the thorax to create images that measure where and how much gas is delivered to different regions of the lung (Frerichs et al., 2017). EIT has been validated in ventilated adult populations (Richard et al., 2009; Victorino et al., 2004) but has not been used as a measurement tool in studies investigating the effects of CPT in mechanically ventilated infants and children.

EIT is a non-invasive imaging technique capable of providing real-time information about lung function and has been shown to be safe for use with ventilated infants and children (Frerichs et al., 2017). By sending multiple small electrical currents through the chest wall and measuring the relative impedance change between different structures within it, EIT is capable of producing an anatomical map of ventilation distribution within the lungs, representing local and global tidal volume changes (Hinz et al., 2003; Kunst, Vonk Noordegraaf, Hoekstra, Postmus, & de Vries, 1998). EIT has been shown to be able to measure regional lung volume changes in response to different interventions such as ETT tube placement and suctioning (Steinmann, Engehausen, Stiller, & Guttmann, 2013; van Veenendaal et al., 2009) and in the presence of lung pathology such as atelectasis (Frerichs, Hahn, Schiffmann, Berger, & Hellige, 1999; Riedel, Richards, & Schibler, 2005; van der Burg, Miedema, de Jongh, & van Kaam, 2014).

Recent studies have used EIT to assess the effect on global and regional ventilation distribution in response to ETT suctioning and lung recruitment manoeuvres in mechanically ventilated children (G. Wolf et al., 2012) and different body positions in ventilated preterm (Hough et al., 2013) and paediatric cohorts (Lupton-Smith, Argent, Rimensberger, Frerichs, & Morrow, 2017). EIT has been able to show for the first time at the bed side, variability in the response of ventilated preterm and paediatric patients to changes in position with respect to the amount and homogeneity of regional lung filling (Hough et al., 2013; Hough et al., 2014; Lupton-Smith et al., 2017). This variability suggests that air distribution changes among different regions of the lung, even to a change in body position, are likely to be complex.

Therefore, it is also possible that the effect of multi-modal CPT interventions in ventilated infants and children are also complex and that measures of lung function used in previous studies may not be sufficient to appreciate this. EIT provides an opportunity to understand the effect of CPT on regional ventilation distribution and this will be investigated in the clinical component of this thesis. By pairing EIT with ABG analysis, the direct effects of CPT in ventilated infants and children on global measures of gas exchange and regional measures of ventilation distribution may be better explained and the validity of global measures more understood.

2.6   Considerations regarding choice of measurement tool to measure CPT effects

Physiotherapists should consider a number of factors when choosing a measurement tool to evaluate CPT effects in ventilated infants and children, to ensure the best tool is chosen for the desired outcome. These factors include the construct or measurement domain being evaluated, the population of interest that the construct is being measured in, clinimetric properties as well as the

clinical utility, generalisability and burden for both patients and users (Mokkink et al., 2016; Mokkink et al., 2010).

2.6.1 Measurement domain

When selecting a tool to measure the effects of CPT, the desired aim of the CPT treatment should inform the decision-making (Marques et al., 2006). For example, removing secretions from the large airways may positively affect the patency of these airways, but may not result in significant changes to gas exchange or overall lung compliance (Main et al., 2004). Therefore respiratory mechanics measures, such as airway resistance, may be the most appropriate measurement tool (Main et al., 2004) compared to tools that measure global lung changes, such as lung imaging or ABG analysis. Conversely, if CPT aims to achieve the mobilisation and removal of secretions from more distal airways resulting in re-expansion of a previously collapsed region of lung, CXR or measures of gas exchange and lung compliance may reflect more useful and valid options.

2.6.2 Population of interest

The choice of tool to measure CPT effects and interpretation of measurement outcomes may depend on the child's age and disease process (Main & Denehy, 2016). For example, secretion wet weight may provide relevant information about the efficacy of CPT in children with chronic sputum production, such as cystic fibrosis or bronchiectasis (Main & Denehy, 2016; Tannenbaum et al., 2007), however this measure may not be as sensitive to CPT effects in a ventilated infant where secretion load may be small or in pathologies not characterised by high secretion volumes (Walsh et al., 2011).

Similarly tools that have only been used or validated in adult populations may lack sensitivity and specificity in ventilated paediatric populations (Schechter, 2007). Differences in adult and paediatric anatomy and physiology are well documented (Main & Denehy, 2016; Schechter, 2007; Taussig et al.,

37

2008) and similarly tools that measure CPT effects cannot simply be extrapolated from adult studies into paediatric populations (Main & Denehy, 2016; Marques et al., 2006). For example, the use of computerised lung sounds tool has been trialled in ventilated adults to improve measurement of regional change in ventilation and airflow as a result of CPT (Ntoumenopoulos & Glickman, 2012). However in infants and children breath sounds and adventitious sounds may be transmitted differently (Main & Denehy, 2016) making it harder to differentiate between sounds and their cause (Main & Denehy, 2016). This difference may make a tool such as computerised lung sounds inaccurate in ventilated infants and children despite having been used in ventilated adult patients (Ntoumenopoulos & Glickman, 2012).

2.6.3 Clinimetric properties

Most measurement tools used by physiotherapists in the PICU are not specifically designed to measure CPT effects and it is unknown whether the clinimetric properties of these tools are robust enough to identify effects specific to CPT in ventilated infants and children. Understanding the clinimetric properties of measurement tools is essential to ensure that physiotherapists working in the PICU are using tools that are valid, reliable and responsive to change. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) framework has been developed by a multidisciplinary group of researchers as a standardised approach to the selection of outcome measures and reporting and evaluating health outcomes (Mokkink et al., 2016). Three domains of measurement have been agreed upon as relevant for evaluating outcomes; validity, reliability and responsiveness (Mokkink et al., 2010).

Validity refers to the ability of a tool to measure what it is designed to measure (Mokkink et al., 2010). Validity of measurement tools used to evaluate CPT in acutely unwell, ventilated infants and children is particularly important to differentiate the effect of CPT from other interventions that might be

occurring concurrently. Criterion validity and construct validity may be of benefit when evaluating tools used to measure CPT effects in ventilated infants and children. Criterion validity compares a tool to a reasonable gold standard to determine how well that tool measures the construct of interest (Mokkink et al., 2010). Where a gold standard tool does not exist, construct validity, for example in the form of hypothesis testing, may be used. Hypothesis testing refers to how well a tool meets a priori hypotheses regarding the comparison of that tool to a comparator instrument (Mokkink et al., 2010). Criterion or construct validity is necessary to establish in tools used to measure CPT effects in ventilated infants and children to ensure measurements derived from these tools are accurate and trustworthy.

Reliability refers to the ability of a tool to measure a construct without error and to measure true differences within and between patients (Mokkink et al., 2010). Like validity, the reliability of tools used to measure CPT effects in ventilated infants and children is essential to consider when choosing the optimum tool. Clinically, CPT in ventilated infants and children may be delivered many times, over consecutive days and at multiple different times of the day and by a number of different physiotherapists (Main & Denehy, 2016). Tools used to measure CPT effects must therefore be reliable to ensure that effects measured between sessions (test-retest) and between physiotherapists (inter-rater) are consistent and reflect true differences as a result of CPT (Mokkink et al., 2016). A review of the evidence for the reliability of commonly used tools to measure CPT effects in ventilated infants and children is required.

Responsiveness of a tool is also an important consideration for physiotherapists working with ventilated infants and children and refers to the ability of a tool to detect meaningful and valid change over time (Mokkink et al., 2010). Clinically, ventilated patients in PICU are likely to receive more than one CPT technique, often over consecutive days (McCord et al., 2013). If the tool used to measure CPT

39

techniques is not responsive to change, incorrect interpretation of the CPT effects may be made. Furthermore, a lack of change measured in response to CPT in ventilated infants and children may reflect a lack of treatment effect, or it may reflect a lack of responsiveness in the tool being used. Responsiveness of a tool considers similar properties to validity, requiring the tool to be evaluated against an appropriately sensitive, or gold standard comparator instrument (Mokkink et al., 2010). Like validity and reliability, responsiveness is an important clinimetric property to consider when choosing a CPT measurement tool in ventilated infants and children and a review of the evidence regarding responsiveness of commonly used CPT tool is required.

2.6.4 Generalisability and clinical utility

The generalisability of measurement tools to measure CPT effects in ventilated infants and children must also be considered. Generalisability considers how well measurements derived from a tool in one population can be generalised to other populations (Mokkink et al., 2016). Many tools used to measure CPT effects in ventilated infants and children do not reflect tools that have been specifically designed to measure CPT in this population, for example ABG or respiratory mechanics monitors. Therefore the use of these tools must be generalised to this population, making generalisability an important property for physiotherapists to consider when choosing a tool to measure their effect.

Clinical utility may also require consideration by physiotherapists when treating ventilated infants and children and refers to the practicality of a measurement tool for use in the environment and population of interest. The ability for a tool to be used by the bedside with minimal impact on clinical care of the ventilated infant and child is likely to influence how readily that tool is chosen by the physiotherapist to measure their effects. It is likely that the best tools to measure CPT effects, in particular ventilation distribution effects, include specialised imaging techniques including multiple breath gas washout (Schibler et al., 2002), hyperpolarized helium-3 magnetic resonance imaging

(Roos, McAdams, Kaushik, & Driehuys, 2015) and computed tomography (Ides et al., 2012; Simon, 2005). However these tools are not easily used by the bedside, require specific equipment, expertise and cost (Taussig et al., 2008) and therefore are unlikely to be feasible or safe for use with critically unwell infants and children to measure immediate effects of CPT (Main & Denehy, 2016). Clinical utility should be considered when choosing a tool to measure CPT in ventilated infants and children however should not be valued above validity and reliability (Mokkink et al., 2016).

Choosing which tool to use to measure CPT effects in ventilated infants and children is complex and requires a sound understanding of the clinimetric properties of the available measures. At present, there is no clear evidence as to which of the measurement tools described in Section 2.4 best meets the clinimetric properties described above and therefore represents the optimum choice for physiotherapists working with ventilated infants and children. Without this evidence, there is a risk that future CPT studies will use different tools or tools without appropriate clinimetric properties to investigate CPT effects in ventilated infants and children which may lead to results being not comparable, inconsistent and potentially leading to inadequate or incorrect conclusions (Mokkink et al., 2016). New tools such as EIT show promise as an alternative measure of CPT effects to directly measure changes in regional ventilation. However, the use of EIT in ventilated infants and children to measure the effects of CPT on regional ventilation requires investigation.

2.7 Summary

CPT is a commonly used intervention to positively affect lung function in ventilated infants and children. The exact effects of CPT however remain unclear and this likely is related to the lack of evidence-based measurement tools to quantify these effects. Instead, a variety of measurement tools are described in the literature and while most appear useful, the clinimetric rigour of these tools in measuring CPT effects in ventilated infants and children is largely unknown. Many of these

41

measurement tools are also considered to be surrogate measures of lung function and may not be specific or detailed enough to explain the CPT effects on regional ventilation distribution within the lungs. It is therefore important for physiotherapists working with ventilated infants and children to consider new measurement tools to quantify their intervention and EIT provides such an example. The first part of thesis will present information that will attempt to bridge the knowledge gaps presented. This will be achieved through a systematic review investigating the types, and clinimetric properties of measurement tools used to assess CPT effects in ventilated infants and children. The second part of this thesis will present the results of a clinical study investigating the value of EIT to quantify CPT effects in the same population.

2.8   Research Objectives, Aims and Hypotheses

The aim of this thesis was to investigate current and novel measurements tools used by physiotherapists working in the PICU to measure the effects of CPT on lung function in ventilated infants and children.

This was done through two studies. The aims of Study 1 were:

1.   To identify and describe the measurement tools that have been used to measure effects of CPT in mechanically ventilated infants and children, and

2.   To critically evaluate the clinimetric properties of these measurement tools to measure CPT effects in the same population.

From these two aims, it was hypothesised that while there would be a number of measurement tools documented in the literature, few would have robust clinimetric properties to support their use in ventilated infants and children receiving CPT.

The aim of the Study 2 was:

1.   To investigate CPT effects compared to routine airway clearance, on ventilation distribution and gas exchange in ventilated infants and children

This study was opportunistically undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial which compared the effect of two lung recruitment manoeuvres to a control group (Jauncey-Cooke, 2012). Therefore a secondary aim of this study was:

2.   To investigate whether a lung recruitment manoeuvre used immediately after CPT enhances the effect on regional ventilation distribution, gas exchange and physiological state.

The following hypotheses were made for Study 2:

1.   CPT would improve regional ventilation distribution (global ventilation, EELV and global inhomogeneity) and gas exchange compared to routine airway clearance

2.   Using a lung recruitment manoeuvre immediately after CPT in ventilated infants and children would enhance regional ventilation distribution and gas exchange and minimise the physiological sequelae of CPT compared to using no recruitment manoeuvre.

3.   Methodology and Design

In this chapter, the detailed methodological procedures for the two studies making up this thesis are outlined. Study 1 comprised a two-part systematic review to identify the measurement tools used to assess the effects of CPT in ventilated infants and children and explore the clinimetric properties of these tools. For Study 2, details regarding the study design and procedures including data management and analysis will be outlined.

3.1   Study 1

Study 1 of this thesis comprises a systematic review. This methodology was chosen as the primary aim was to identify and critically evaluate tools used to measure CPT effects on secretion clearance, respiratory mechanics, radiological appearance of the lung and gas exchange in ventilated infants and children. A systematic review ensured that all available data meeting the specific inclusion criteria for this thesis program were identified and only measurement tools that met these criteria were assessed for clinimetric properties.

3.1.1   Protocol and registration of systematic review

Prior to undertaking the systematic review, a search of the topic of measuring the effect of CPT in mechanically ventilated infants and children was undertaken to ensure that this topic had not been previously undertaken or was in the process of being completed. No previous or current protocols were identified so a protocol was developed that met the purposes of investigating this topic within the overall scope of this thesis. The protocol was registered with the International Prospective Register for Systematic Reviews (PROSPERO) and accepted for publication on its database on 30th May 2017. This protocol can be viewed online on the PROSPERO register under the registration code CRD42017064443 (Appendix 1).

3.1.2 Eligibility criteria

The eligibility criteria for this systematic review were prospectively identified to ensure that the review was undertaken according to the specific requirements of this type of study. The study question, search strategy, types of studies to be included, condition, population and interventions being studied were all prospectively described as part of the search strategy recorded in the registered protocol prior to undertaking the literature search.

3.1.3 Review question

This systematic review was designed to answer two separate research questions: (i) what measurement tools are used to evaluate CPT effects in ventilated infants and children, and (ii) what are the clinimetric properties of these measurement tools?

The first question was designed to systematically identify the full breadth of measurement tools used by physiotherapists when treating ventilated infants and children. The PICO (Population Intervention Comparator Outcome) question format (Richardson, Wilson, Nishikawa, & Hayward, 1995; van Loveren & Aartman, 2007) was utilised to clearly identify the target population (infants and children 0-16 years receiving mechanical ventilation), intervention (CPT) and outcomes (measurement tools used to assess the effects of CPT, specifically secretion clearance, ventilation and gas exchange) of interest. The primary focus of this question was to describe the measurement tools used to assess CPT effects in ventilated infants and children therefore a comparator was not included in the PICO question.

The second question was designed to critically evaluate the measurement tools identified by the first research question to report on the clinimetric properties of these tools used to measure the effects of CPT in ventilated infants and children. The COSMIN framework was used (Terwee et al., 2012) and will be discussed in further detail below.

45

3.1.4 Search Strategy

Six electronic databases were chosen for their relevance to the review topic and as databases known for publishing medical and allied health related papers. These included Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, Embase, The Cochrane Library, Physiotherapy Evidence Database and Web of Science. Trial registries including the ClinicalTrials.gov and World Health Organisation International Clinical Trials Registry Platforms were also searched to identify planned or ongoing trials using the same key search terms.

The search strategy utilised medical subject heading (MeSH) terms and key text words specific to the databases to improve the likelihood of identifying all relevant papers pertaining to the search terms of this paper. Key search terms included those relating to the primary population, infants and children, mechanical ventilation, intensive care and to CPT as the primary intervention. Terms relating to secretion clearance, ventilation and gas exchange as the key outcome were included. Where available, filters and Boolean operators were also used to limit findings to the target population of infants and children. The search strategy used for CINAHL is presented in Table 3.1 as an example. This search strategy was modified for other databases as required.

Table 3.1   **Search strategy for CINAHL**

Search	Terms
S1	(MH "Chest Physical Therapy") OR "chest physiotherapy" OR "respiratory physiotherapy"
S2	(MH "Respiration, Artificial") OR (MH "Positive Pressure Ventilation") OR (MH "Pulmonary Atelectasis")
S3	(MH "Child") OR (MH "Infant") OR paediatric OR pediatric
S4	(MH "Respiratory Function Tests") OR (MH "Lung Volume Measurements") OR "lung function"
S5	S1 AND S2 AND S3 AND S4

Abbreviations: MH, Mesh Heading.

3.1.5   Inclusion and exclusion criteria

Inclusion criteria for this study were defined a priori to ensure that all eligible papers reporting on measurement tools used to assess CPT effects in ventilated infants and children were identified and to avoid bias in selecting these papers. Exclusion criteria were also prospectively defined to ensure only papers pertaining to the target age range (0-16 years) and intervention (CPT) were included for review. Included studies were required to meet all of the inclusion criteria to be considered eligible for this review.

Inclusion criteria were defined as measurement tools that met the following:

(1) Used in subjects 0-16 years old receiving mechanical ventilation via ETT/ tracheostomy within a PICU,

(2) Where subjects received CPT (defined as any single or combination of techniques including positioning, manual techniques, manual hyperinflation or mechanical airway clearance devices used in combination with ETT suctioning)

(3) Used to measure CPT effects (including secretion clearance, respiratory mechanics, radiological appearance of the lung or gas exchange) during/and or after CPT

Exclusion criteria were defined as studies that described measurement tools that were:

(1) Used in subjects over 16 years old or premature infants < 38 weeks age

(2) Used in subjects not mechanically ventilated via ETT

(3) Used in subjects not receiving CPT or only used prior to CPT

(4) Used to measure another aspect of CPT other than its effect on lung function e.g. mechanistic effect of a CPT technique

3.1.6   Limits

It was hypothesised that the number of eligible studies meeting the inclusion criteria would be low and therefore additional limits placed on study characteristics were kept to a minimum to ensure that all relevant papers were identified. Results were not biased by the language of publication, design or date of publishing. The primary purpose of the systematic review was to identify

measurement tools that had been used in published studies to measure CPT effects in ventilated infants and children, therefore conference abstracts and studies in progress were not included.

3.1.7 Search processes

The initial search of identified databases was undertaken by the candidate using the pre-defined search strategy. The details of these searches, including the date, search strategy, key words and the results yielded from each search were documented in Microsoft Excel 97-2003 for each database and can be seen in Appendix 2. Search results were also downloaded to a citation manager (Endnote X7 Thomson Reuters) and duplicates were removed.

Titles and abstracts of all identified papers were systematically screened by the candidate and a second, independent reviewer (JH) against the inclusion and exclusion criteria to determine eligibility. Online translation services were used for abstracts not published in English so as not to exclude potentially relevant papers. Where eligibility was unclear, the full text article was accessed. Once key articles were identified by both researchers, conflicting viewpoints were discussed until consensus was reached. Where consensus was not able to be reached, a third reviewer (SK) adjudicated to determine inclusion.

3.1.8 Search of clinimetric properties

Following the identification of eligible articles from the initial search, further strategies were employed to ensure that any additional studies that were not initially identified, but met inclusion criteria, were identified and included in the review. This was primarily achieved through manual, targeted reference searches of identified eligible, full-text articles. ClinicalTrials.gov and World Health Organisation International Clinical Trials Registry Platform were also searched using the same key search terms as the initial search strategy to identify any relevant unpublished articles or articles in press.

49

Following the identification of eligible tools from papers retrieved from the first systematic search, a further systematic search was undertaken to retrieve studies investigating the clinimetric properties of the included tools. The specific clinimetric properties reported in this review were based on the COSMIN manual (Terwee et al., 2012) and included validity, reliability and responsiveness.

These properties were chosen as they reflect those properties felt to be most useful for therapists measuring CPT effects in ventilated children. While not considered to be a clinimetric property, generalisability was also reported on using the specified criteria outlined in the COSMIN manual to identify how results could be generalised to ventilated infants and children receiving CPT. Normative data for each tool and the characteristics of the populations in which it has been tested were also collected where available.

It was hypothesised that the yield of studies investigating the clinimetric properties of the included CPT measurement tools in ventilated infants and children would be limited. Therefore the search strategy was designed to reflect targeted search terms using databases most likely to identify relevant studies, as well as a broad search strategy designed to ensure all relevant studies were identified and included.

A targeted search was undertaken of three of the electronic databases used in the original search strategy: CINAHL, PubMed, and Embase. These databases were specifically chosen for the high volume of medical and allied health-related papers published in each and were therefore considered to provide a higher chance of identifying relevant articles compared to smaller databases such as Physiotherapy Evidence Database. Google Scholar was also included in the search strategy for the large number of records available through this database and as a platform for searching broader terms to ensure all relevant studies were identified. This search was limited to clinical studies therefore The Cochrane Library was not included as a database searched during the second search.

50

Web of Science was also not included as it was considered to be less likely to identify relevant articles compared to databases with a stronger medical and allied health bias. Sources such as grey literature and clinical trial registries were not included as they were unlikely to produce results that reflected peer-reviewed clinical trials.

The search strategy utilised MeSH terms and key text words specific to the databases used. Key search terms included the name of the measurement tool, terms related to the population of interest (ventilated infants and children), clinimetric properties (validity, reliability and responsiveness). CPT was not included in the search strategy as the focus was on the measurement tools that had been identified in the initial search used to measure the effects of CPT in ventilated infants and children. Filters and Boolean operators were used to limit findings to the target age range. The search strategy used for CINAHL for CO_2SMO Plus respiratory monitor is presented Table 3.2 as an example. This search strategy was modified for other databases as required. The search strategy used for CINAHL is presented Table 3.2 as an example. This search strategy was modified for other databases as required.

Table 3.2   Search strategy for CINAHL for the CO_2SMO Plus respiratory monitor

Search	Terms
S1	"CO_2SMO Plus" OR "CO_2SMO Plus respiratory monitor"
S2	(Valid* OR validity study) OR (Reliab* OR reliability study) OR (responsive* OR responsiveness study)
S3	(Infant OR child*)
S4	S1 AND S2 AND S3

Details of the search strategy were documented in Microsoft Excel 97-2003 and Endnote X7 (Thomson Reuters) in the same way as the initial search strategy. Identified titles and abstracts were again independently reviewed by the same two researchers and conflicting views managed in the same way as in the initial search.

3.1.9 Data extraction

Data for both searches were extracted for each eligible paper by the research candidate using Microsoft Excel and included the following:

(1) Reference details – including title, authors and details of journal publication

(2) Study design - randomised controlled trial, non-randomised controlled trial, prospective observational study, cohort study

(3) Participant details – number, age and weight of participants, inclusion/ exclusion criteria relating to participant pathology, details of mechanical ventilation used in the study, details of sedation and paralysis used during the study

(4) Intervention details – CPT techniques used, the order of use and details of procedure, details of comparator or control if used

(5) Measurement tools used – name and description of tool, primary CPT effect being measured, the timing of the measurements (before, during and/ or after CPT intervention)

(6) Clinimetric properties – validity, reliability, responsiveness and generalisability

3.1.10 Quality assessment

Quality assessment of the studies retrieved in the first search to identify the measurement tools was not required as this search was aimed at identifying the measurement tools used to measure the effects of CPT in ventilated infants and children.

Quality assessment was undertaken for studies reporting clinimetric properties of the measurement tools. Studies reporting on the clinimetric properties of the identified measurement tools were assessed for quality using the COSMIN checklist, a validated quality assessment tool for use in clinimetric systematic reviews (Terwee et al., 2012). The COSMIN checklist consists of specific criteria related to the key clinimetric properties of a measurement tool, which in this study were identified as validity, reliability and responsiveness. The 4-point COSMIN rating scale was utilised in this study according to the instructions outlined in the COSMIN manual (Terwee et al., 2012). Each identified measurement tool was considered separately and key data were extracted from each study reporting on the clinimetric properties of that tool. Data were extracted against specific rating criteria and scored as excellent, good, fair or poor depending on how well the study met each of these criteria. Scoring was undertaken by the research candidate and checked by an independent reviewer. An overall quality score was derived for each study based on the lowest rating across all criteria for that clinimetric property.

While not considered a clinimetric property, generalisability is considered as an adjunct to the COSMIN checklist and was also scored in this study as a measure of how well the identified studies could be generalised to measuring CPT effects.

3.2 Study 2

Study 2 of this thesis was a clinical study that aimed to investigate EIT as a measurement tool for physiotherapists to measure CPT effects in ventilated infants and children. EIT was investigated as the primary measurement tool for its ability to measure regional ventilation changes. No studies have investigated this measurement tool to evaluate CPT effects in ventilated infants and children and it was hypothesised that EIT could be used to measure changes in regional ventilation distribution in response to CPT in this population. The details of the methodology underpinning this study are discussed in this section.

3.2.1 Study aims

The primary aim of this study was to investigate CPT effects compared to routine airway clearance on ventilation distribution and gas exchange in ventilated infants and children. This study was opportunistically undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial which investigated the effect of recruitment manoeuvres in ventilated infants and children following ETT suctioning (Jauncey-Cooke, 2012). As such this design enabled the investigation of whether lung recruitment manoeuvres enhance the effect of CPT on regional ventilation distribution and gas exchange in ventilated infants and children.

3.2.2 Design

Study 2 of this thesis was a secondary analysis of data collected within a larger prospective randomised controlled trial that compared the effect of two different lung recruitment manoeuvres with no recruitment manoeuvre, on lung function following routine airway clearance, in the form of ETT suction, in ventilated infants and children (Jauncey-Cooke, 2012). During the randomised controlled trial, a proportion of participants in both the lung recruitment and no recruitment groups received CPT in addition to routine airway clearance to optimise airway clearance.

54

CPT was provided as clinically required by an experienced paediatric intensive care physiotherapist to those participants who required more intensive airway clearance than routine airway clearance alone. The remaining participants received routine airway clearance, as per the randomised controlled trial. EIT data were collected in all participants as part of the randomised controlled trial and used opportunistically in this study to firstly compare the effect of CPT to routine airway clearance, and secondly to identify whether a recruitment manoeuvre enhanced the effect of CPT on regional ventilation distribution and gas exchange in ventilated infants.

3.2.3 Participants

Participants in Study 2 were recruited from children receiving critical care treatment within a tertiary PICU at the Mater Children's Hospital in Brisbane, Australia. Participants in Study 2 were initially recruited into the randomised controlled trial (Jauncey-Cooke, 2012). Those participants deemed requiring additional CPT techniques to optimise airway clearance by an experienced respiratory physiotherapist were included as the intervention group in Study 2. CPT was instigated as part of the partcipants' clinical management and therefore no additional consent was required. Participants who did not require additional CPT to optimise airway clearance received routine airway clearance and were considered as the comparison group in Study 2. The inclusion and exclusion criteria for the initial recruitment into the randomised controlled trial is outlined below.

3.2.3.1 Inclusion Criteria

To be elgible for inclusion in the randomised controlled trial, participants had to:

- Be between 0 and 16 years of age
- Have informed verbal and written consent provided by parents or guardians
- Have endotracheal intubation and require mechanical ventilation for longer than 12 hours

55

· Have invasive blood pressure monitoring in situ

3.2.3.2 Exclusion criteria

Potential participants were excluded if they:

- · Were less than 36 weeks gestational age
- · Were experiencing an air leak (pneumothorax, pneumomediastinum, pneumopericardium) confirmed by a medical practitioner
- · Were hemodynamically unstable (shock, hypovolemia, hypotension defined as blood pressure below acceptable level for age) confirmed by a medical practitioner
- · Had chest wounds or dressings prohibiting the use of electrocardiograph electrodes required for the use of EIT
- · Were likely to require significant intervention, or known planned procedures, during the study that would preclude the collection of uninterrupted data for the length of the study

3.2.4 Intervention

The interventions of interest in Study 2 were CPT and routine airway clearance. As this study was undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial comparing two lung recruitment manoeuvres immediately following ETT suction, all participants received ETT suction, either as part of routine airway clearance or as part of CPT. Study 2 is reporting on participants in the randomised control trial who required CPT. CPT was not standardised but was individualised to participants' clinical presentation and delivered by the same experienced physiotherapist throughout the study periods. CPT techniques available for use in this study are described below including indications for use and details regarding implementation in this study. Routine airway clearance was delivered by the bedside nurse to participants who did not

56

receive CPT. All CPT techniques, including ETT suction, were delivered by the same physiotherapist. In all participants, ETT suction was undertaken in accordance with the participating facility suction policy. The ETT suction technique is described below. CPT and routine airway clearance were undertaken in supine and the rationale behind this is discussed in section 3.2.4.3. The two recruitment manoevures used within the randomised controlled trial are detailed in section 3.2.4.4.

3.2.4.1   CPT

CPT formed the primary intervention of interest in this study. CPT is used in ventilated infants and children to mobilise airway secretions from peripheral to central airways for removal via ETT suctioning (Main & Denehy, 2016). In ventilated infants and children CPT is traditionally prescribed when there is evidence of retained secretions which can cause distal lung collapse as a result of secretion-obstructed airways (Main & Denehy, 2016). Indications for the use of CPT in this population can include evidence of lung collapse on CXR, increases in ventilation requirements, adventitious sounds on auscultation and, or the report of tenacious secretions (Main & Denehy, 2016). Participants recruited to the randomised controlled trial who met these indications and for whom additional airway clearance was required received CPT deemed necessary by the treating experienced physiotherapist. These participants were identified and included in Study 2 of this thesis.

CPT interventions were performed by a single experienced intensive care physiotherapist. Treatments were not standardised, instead CPT was individualised to each child based on a thorough clinical assessment (Main & Denehy, 2016). CPT was considered to be any combination of percussions, chest wall vibrations, MHI using an open anaesthetic bag (Fraction of inspired oxygen (FiO$_2$) 1.0) and open ETT suctioning. Normal saline (0.1ml/kg) was used in combination with MHI and chest wall vibrations when secretions were assessed by the physiotherapist as being particularly

57

tenacious (Schults, Mitchell, Cooke, & Schibler, 2018); Mater Children's Hospital Endotracheal Suction Policy) (Appendix 4). A detailed description of each of these CPT techniques is provided in Section 2.2.2.

3.2.4.2   Routine airway clearance

Routine airway clearance suction formed the comparison intervention in this study and refers to pre-oxygenation of participants using hand bagging followed by ETT suction. Routine airway clearance in ventilated infants and children is performed by nursing staff at regular intervals to remove excess airway secretions and maintain patency of the ETT.

In Study 2 of this thesis routine airway clearance was performed by the bedside nurse as part of routine care of the participants and was undertaken according to a standardised procedure specific to the Mater Children's Hospital PICU (Appendix 4). Participants were disconnected from the ventilator and connected to an open-ended anaesthetic bag and MHI using 100% oxygen FiO$_2$ 1.0) (Appendix 4). A suction catheter was passed directly into the ETT using an open technique (Figure 3.1). The size of the suction catheter used was half the diameter of the ETT to ensure effective passage of the catheter (Appendix 4). Suction passes were continued using this procedure until all secretions were deemed to have been removed. On completion of the ETT suctioning, participants were disconnected from the anaesthetic bag and reconnected to the ventilator.

(a)   **(b)**

Figure 3.1   (a) ETT suctioning procedure and (b) suction catheter

3.2.4.3   Supine positioning

Participants were positioned in supine for the delivery of the interventions associated with Study 2. Participant position was standardised in supine throughout the study duration to minimise any effect of position on regional ventilation distribution. Previous studies have reported differences in regional ventilation distribution as a result of body positioning in adults and neonates (Hough et al., 2013; Spaeth, Daume, Goebel, Wirth, & Schumann, 2016). This potential source of bias was mimimised in this study however it may have resulted in a limitation to the optimal benefit of CPT

3.2.4.4   Recruitment manoeuvres

Two recruitment manoeuvres were used in Study 2; double PEEP and incremental PEEP. These recruitment manoeuvres were delivered by a single experienced PICU nurse and were performed immediately following re-connection of the participant to the ventilator following ETT suctioning in both routine airway clearance and CPT groups. The double PEEP manoeuvre involved doubling

59

baseline PEEP for two minutes immediately after the completion of the ETT suction. At the completion of two minutes, PEEP was returned to baseline levels. The incremental PEEP manoeuvre involved sequential increases in PEEP in 4 cmH$_2$O increments up to a maximum of 18 cmH$_2$O, with each increment being held for 60 seconds. PEEP was then incrementally dropped back to baseline PEEP in the same way. Ventilator parameters were kept stable as much as possible and changes were only made if clinically warranted..

3.2.5   Outcome measures

The primary outcome of Study 2 was regional ventilation distribution considered to include measures of tidal ventilation, end expiratory lung volume, global inhomogeneity and geometric centre. Regional ventilation distribution measurements in this study were collected using a Göttingen Goe-MF II EIT system (VIASYS Healthcare, Hochberg, Germany). Details regarding the use of EIT and its application and analysis in this study are discussed in the following sections. Secondary outcomes included gas exchange (ABGs) and physiological measurements (heart rate and respiratory rate) which represent surrogate measures of lung function previously used in ventilated CPT studies. ABG and transcutaneous oxygen saturations were collected concurrently with EIT measures to evaluate CPT effects on both ventilation distribution and gas exchange. Heart rate and respiratory rate were recorded to monitor the physiological sequelae of CPT and routine airway clearance Measures of gas exchange and physiological status used in Study 2 are also discussed in the following sections.

EIT and physiological measurements were taken at baseline and at 30, 60 and 120 minutes after ETT suctioning. ABG measurements were taken at baseline and at 30 and 120 minutes after ETT suctioning. Additional baseline data included demographic data (age and weight), ventilation characteristics (ETT size and presence of cuff, fraction of inspired oxygen, mode of ventilation, respiratory rate, PEEP, peak inspiratory pressure, mean airway pressure), gas exchange parameters

(partial pressure of arterial oxygen (PaO_2), partial pressure of cardbon dioxide ($PaCO_2$) and ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (P/F ratio)) and reason for intubation. All measurements were taken at the same time points in all participants, regardless of whether they received CPT or not.

3.2.5.1   EIT

EIT was chosen as the primary measurement tool in Study 2 for its ability to provide instantaneous, pain-free, radiation-free imaging of the lungs (Frerichs et al., 2017). Images generated by EIT have been validated against computed tomography scans in ventilated adults (Victorino et al., 2004). EIT can be used by the bedside to provide immediate information about changes to regional ventilation distribution (Frerichs et al., 2017). EIT has been successfully and reliably used in ventilated paediatric patients to assess the effect of recruitment manouevres (G. Wolf et al., 2012) and different body positioning (Lupton-Smith et al., 2017) and to monitor atelectasis, pulmonary oedema, pneumonic changes and over-ventilation of the lungs (Frerichs et al., 2017). EIT is promising as a measurement tool as it can potentially show instantaneous changes in regional distribution of ventilation in response to CPT. Regional changes in ventilation resulting from CPT in ventilated infants and children have not been previously described and this information is necessary to accurately explain CPT effects on lung function.

The Goettingen high-performance EIT tomograph (VIASYS Healthcare, Gottingen, Netherlands) was used in Study 2. Cross-sectional lung images were derived from measurements of surface electrical potentials resulting from an excitation with known small electrical currents (5mAmp and 50 kHz). To obtain the EIT measurments, a 16-electrode array of conventional self-adhesive surface electrodes were placed transversely around the circumference of the chest wall of the child at the mid-nipple level (Frerichs et al., 2017) (Figure 3.2).

Figure 3.2 **Circumferential placement of self-adhesive electrodes for EIT measurements**

(Acknowledgement Jacqui Jauncey-Cooke (Jauncey-Cooke, 2012) for photograph and photograph collected with parental consent)

Small injections of electrical current (5mA, 50kHz) were passed between adjacent pairs of electrodes and the resulting voltages measured on the remaining electrodes (Frerichs et al., 2017). The current injections and the voltages detected were used to calculate the regional impedance data (Barber & Brown, 1989). EIT scans were then generated from the collected potential difference and the known excitation currents using weighted back-projection in a 32x32 pixel matrix where a single pixel represents the instantaneous local impedance (Brown, 2003) (Figure 3.3).
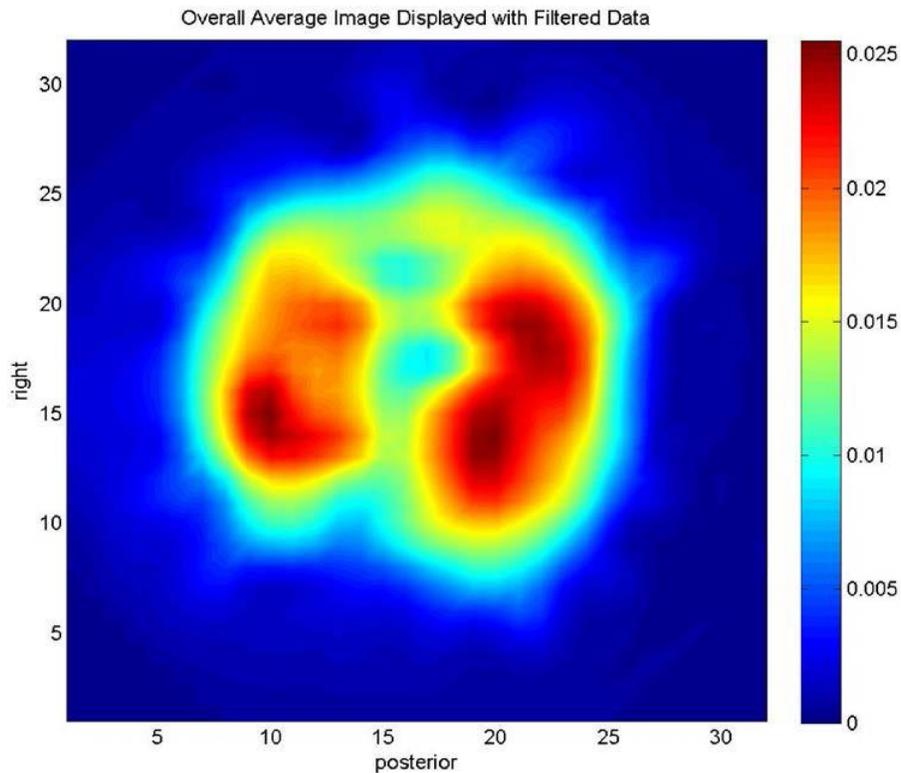
Figure 3.3 A typical EIT image obtained during spontaneous breathing

The fields with red or yellow colours are well-ventilated areas, whereas the blue areas are less well ventilated**.**

EIT has the ability to provide functional images of the lungs showing the distribution of ventilation within the lungs (Figure 3.3, Figure 3.4) however Study 2 primarily reported on quantitative data measurements based on these images. Analysis of EIT used EIT waveforms that were generated from multiple raw EIT images in individual image pixels (Frerichs et al., 2017) (Figure 3.4).
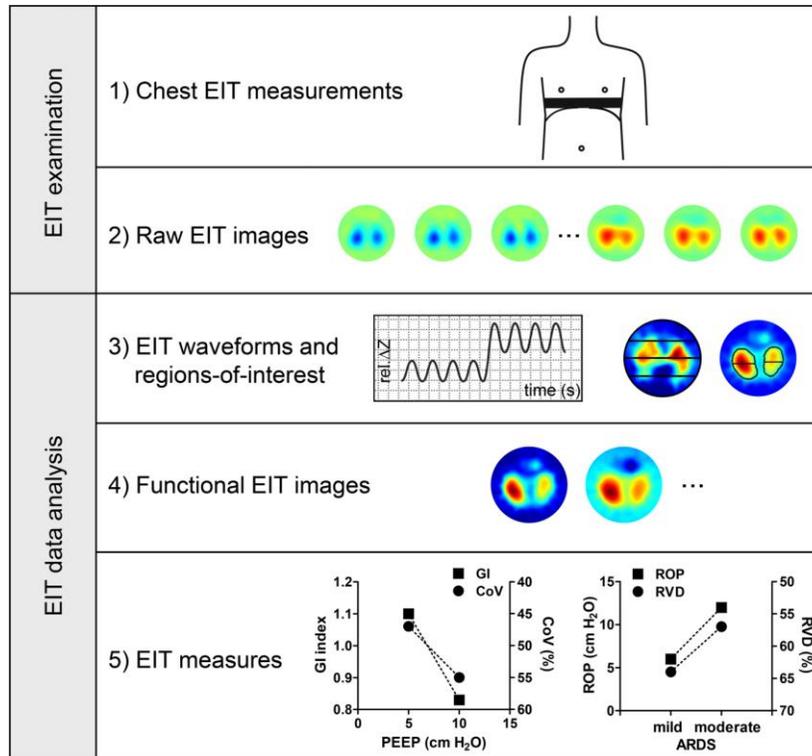
Figure 3.4 **Schematic representation of EIT examination (measurements collected from electrodes placed around the chest and resulting raw images) and, EIT data analysis (EIT waveforms, functional images and resulting measures) (Image from Frerichs et al., 2017)**

Data were band-pass filtered to include the first and second harmonic of the respiratory rate (Dunlop et al., 2006) and cardiac interference was eliminated using a cutoff mask of 20% of the peak impedance signal according to previous studies (Dunlop et al., 2006; Pulletz et al., 2006). Eliminating cardiac interference was important as EIT measures the entire thorax and not just the lungs, therefore it was necessary to ensure that the waveforms analysed were reflective of impedance changes caused by ventilation changes, and not by cardiac interference or interference from body movement or medical devices (Frerichs et al., 2017).

EIT data sections chosen for analysis reflected three to five continuous mandatory ventilator breaths of stable tidal volume and end-expiratory lung volume (Hough et al., 2013). EIT data sections were analysed to obtain specific measurements of regional ventilation: (i) tidal ventilation, (ii) end expiratory lung volume (iii) global inhomogeneity and (iv) geometric centre.

(i) Tidal ventilation measurements were based on impedance amplitude changes, which equalled the average difference across the three to five mandatory ventilator breaths in impedance of each pixel measured at the peak and trough of the tidal breath (Frerichs et al., 2017; Hough et al., 2013). Regional tidal volume changes were described for non-dependent (anterior amplitude) and dependent (posterior amplitude) lung regions and for the lungs as a whole (global impedance amplitude).

(ii) End expiratory lung volume (EELV) reflects the relative electrical impedance measured at the end of expiration (end-expiratory minima) and has been shown to be a comparable measure of functional residual capacity (Hough et al., 2013). Measures of EELV were obtained for the non-dependent (anterior EELV) and dependent (posterior EELV) lung regions and for the lungs as a whole (global EELV) (Hough et al., 2013).

(iii) Global inhomogeneity is derived from the EIT and describes the degree of tidal volume distribution heterogeneity within the lung (Zhao, Moller, Steinmann, Frerichs, & Guttmann, 2009; Zhao, Pulletz, Frerichs, Müller-Lisse, & Möller, 2014). Global inhomogeneity has been validated against hyperpolarised helium-3 magnetic resonance imaging scans in ventilated animal studies (Dunster, Friese, Fraser, Galloway, et al., 2012). Larger global inhomogeneity values indicate greater ventilation inhomogeneity while smaller global inhomogeneity values indicate less ventilation inhomogeneity (Frerichs et al., 2017; Zhao et al., 2009).

Global inhomogeneity measures were calculated from the generated tidal image using the median value of the end-inspiratory to end-expiratory difference (Hough et al., 2013). The sum of the absolute difference between the end-inspiratory to end-expiratory difference for each pixel reflects the tidal volume distribution within the lung and is normalized to the total number of pixels in the tidal image to quantify homogeneity (Hough et al., 2013; Hough et al., 2014).

(iv) Geometric centre is also derived from EIT and is a measure of the distribution of ventilation within different lung regions able to identify areas of lung that are preferentially ventilated (Frerichs et al., 1998). Geometric centre was expressed as a percentage of the anterior to posterior ventilation within the lung, with a higher percentage reflecting a relatively more anterior (non-dependent) centre of ventilation and a smaller percentage reflecting a more posterior (dependent) centre of ventilation (Frerichs et al., 1998). An increase or decrease in the geometric centre as a result of CPT was considered to reflect a respective shift in ventilation anteriorly or posteriorly.

3.2.5.2   Gas exchange

ABG analysis was utilised as the accepted gold standard measurment of gas exchange and acid base balance (Severinghaus, 1968). Previous studies investigating CPT effects in ventilated infants and children have used ABG analysis (Almeida et al., 2005; Elizabeth et al., 2016). ABG values were collected concurrently with EIT measurements taken at baseline, 30 minutes and 120 minutes after ETT suction to describe the concurrent changes in regional ventilation distribution and oxygenation and carbon dioxide clearance.

Arterial blood samples (0.5 ml) were collected in a standardised manner by the bedside nurse using a 1 ml heparinised syringe (Ref. 3100-25, Westmed, Tucson, Arizona) via the arterial line. Blood gas analysis was undertaken within 5 minutes of collection using an ABL-837 arterial blood gas analyser loader with software version 6.10108 (Radiometer Copenhagen, Denmark). Measures recorded included PaO_2, $PaCO_2$ and P/F ratio were manually calculated from the ABG results as an additional reflection of oxygenation in each participant at each time point.

Transcutaneous oxygen saturations were continuously monitored for all participants as part of usual patient care received in the PICU for the duration of the study period. Specific values for SpO_2 were recorded at the same time points as the EIT measurements to investigate concurrent changes in transcutaneous oxygenation measures in response to CPT.

3.2.5.3 Physiological measurements

Physiological measurements are used by physiotherapists working with ventilated infants and children to obtain an overall clinical picture of their patients and to monitor physiological sequelae following CPT and routine airway clearance. Physiological measurements recorded in the study period included heart rate and respiratory rate. These parameters were continuously monitored for all participants as part of usual patient care received in the PICU for the duration of the study period. Specific values for heart rate and respiratory rate were recorded at the same time points as the EIT measurements to investigate concurrent clinical changes in response to CPT.

3.2.6 Statistical analysis

Baseline data were presented using means and 95% confidence intervals, or standard deviation. As the primary objective in Study 2 was to compare CPT effects to routine airway clearance, an independent sample T-test was used to compare participants who received CPT to those who received routine airway clearance, regardless of whether participants received a recruitment
67

manoeuvre. All baseline variables were compared including demographics (age, weight and ETT size), gas exchange measurements (fraction of inspired oxygen, PaO_2, $PaCO_2$ and P/F ratio) and ventilation characteristics (respiratory rate, PEEP, peak inspiratory pressure and mean airway pressure). Significance was considered as p-value <0.05.

To answer the second study aims, a generalized linear mixed model was used to compare participants receiving CPT to those receiving routine airway clearance across the four studied time points (baseline, 30 minutes, 60 minutes and 120 minutes) and across the three recruitment manoeuvre groups (double PEEP, incremental PEEP and no recruitment). This model was chosen over a repeated measures analysis of variance (ANOVA) for its ability to consider both fixed and random effects and because it can accommodate for non-parametric and missing data (McCulloch & Neuhaus, 2001).

Data were presented as means and 95% confidence intervals. Tests of fixed effects were undertaken for EIT variables (global, anterior and posterior amplitudes; global anterior and posterior end expiratory lung volume, global inhomogeneity and geometric centre), ABG (PaO_2, and $PaCO_2$) and physiological variables (heart rate, respiratory rate and SpO_2). Each test compared CPT, recruitment and time effects individually and also considered the interaction of CPT and time effects, CPT and recruitment effects and the interaction of CPT, time and recruitment effects.

Significance was considered as a p-value <0.05. All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Somers, NY).

3.2.7   Ethical Considerations

This study formed part of a larger randomised controlled trial undertaken within the Mater Children's Hospital PICU that received prospective ethical approval through the Mater Health Services Human Research Ethics Committee (Ref No. 660C). The randomised controlled trial

investigated the effect on lung function of different lung recruitment manoeuvres, used after ETT suctioning in ventilated infants and children.

CPT was instigated in a cohort of participants within the randomised controlled trial who were deemed by an intensive care physiotherapist to require intensive airway clearance in addition to ETT suction. CPT was delivered as a part of the participants' clinical treatment and initiated independently of the randomised controlled trial. Ethical approval was obtained to retrospectively utilise data collected as part of the randomised controlled trial to compare participants who received CPT with those who received routine airway clearance. This approval was obtained as a low-negligible risk study through the Mater Health Services Human Research Ethics Committee (HREC/17/MHS/72 (2012-25)) (Appendix 5). Separate consent was also received to use the data collected within the randomised controlled trial from the primary investigators of that study (Appendix 6). As part of the requirements of this thesis, ethical approval was also obtained through the Australian Catholic University Human Research Ethics Committee (2017-153R) (Appendix 5).

Additional specific ethical considerations associated with undertaking a clinical study in ventilated infants and children are discussed in the following sections.

3.2.7.1   Vulnerable subject group

This study involved the enrolment of infants and children, a population considered to be a vulnerable subject group by the World Medical Association Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). Although infants and children are considered to be a vulnerable group, research in this population is required to advance management and optimise outcomes for this population. For the purposes of this study, it was necessary to obtain ethical approval from two human research ethics committees.

Throughout the research process every effort was made to ensure that this study was performed in accordance with Mater Health Services and Australian Catholic University ethical requirements.

To ensure participants were not disadvantaged by their participation in this study, the clinical care of each participant was always prioritised over the study. Informed, written consent was gained from each participant's parent or guardian prior to enrolment in the randomised controlled trial. Parents and/or guardians were provided with the approved study Information Sheet and had an opportunity to ask questions of the investigative team prior to providing written informed consent.

CPT was undertaken when it was deemed safe and clinically indicated by an experienced PICU physiotherapist and only after informed verbal consent from the parent or guardian or the bedside nurse if the participant's parent or guardian were not present. CPT is provided to all ventilated infants and children within Mater Health Services as required and based on the patients' presenting signs and symptoms. CPT provided was individualised to participants' clinical presentation as is typically done in this and other PICUs. CPT provided was also done with consent and in collaboration with the treating medical team of each participant.

Details of the CPT interventions were documented in the participants' electronic medical record in accordance with the medico-legal requirements of Mater Health Services and the Australian Health Practitioner Regulation Agency ("Physiotherapy Board of Australia Code of Conduct," 2014).

3.2.7.2   Consent

Study 2 of this thesis was undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial however the intervention of interest in this study was CPT. CPT was undertaken during the randomised controlled trial study period when it was deemed clinically necessary by an experienced intensive care physiotherapist. Because CPT was delivered as

a clinical intervention, consent was obtained according to the practice standards for informed clinical consent required of Mater Health Service and the Australian Health Practitioner Regulation Agency ("Physiotherapy Board of Australia Code of Conduct," 2014). This involved obtaining verbal consent from the participants' parents or guardian, or bedside nurse if the parent was not present, following an explanation of the rationale for undertaking CPT and the expected composition and outcome of the intervention. This was obtained prior to undertaking the intervention. Informed verbal consent in this manner was reflective of the usual practise undertaken by physiotherapists working within the Mater Children's Hospital PICU.

As Study 2 was a secondary analysis of data collected within a larger prospective randomised controlled trial, the primary data used in this study were collected as part of the larger randomised controlled trial. Participant recruitment for the randomised controlled trial was dependent on the receipt of informed written consent from the parents or guardian ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). This consent was gained separately to Study 2 and was acknowledged by the intensive care physiotherapist prior to undertaking CPT in the current study. Ethical approval to utilise this data in Study 2 of this thesis without further written consent were granted by the Mater Health Services Human Research Ethics Committee.

3.2.7.3   Confidentiality

Maintaining patient confidentiality is an ethical and legal requirement for physiotherapists under the Australian Health Practitioner Regulation Agency ("Physiotherapy Board of Australia Code of Conduct," 2014). It is also a requirement under the World Medical Association Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects," 2013). Documentation of compliance with confidentiality requirements was

71

submitted yearly to the Mater Health Services Human Research Ethics Committee for the duration of the study (2012-2018). This was the minimal reporting standard required of this ethics board. Procedures used during this study to ensure adherence to the confidentiality requirements are detailed below.

(i) Patient information and study data recorded and accessed within this study were managed in accordance with maintaining participant confidentiality requirements. No participant names were recorded as part of this study. Each participant was allocated a specific identification number and all data analysed within this study was referred to by this number. No references to any specific participant condition, presentation or other clinical information that could be potentially identifiable were made in this study.

(ii) Data used in this study were required to be available for analysis between January 2013 and January 2018. During this time data were managed in accordance with Mater Health Services data storage policy. This included original paper copies of the participant records, informed consent documents and paper copies of ABG printouts remained within the Mater Children's Hospital PICU in a locked filing cabinet, in a staff handover room secured location only accessible with swipe card access. Electronic files were stored on a password protected computer and only the research candidate had access to the data for the duration of the study. A back up copy of the electronic files were stored on a hard drive only accessible to the research candidate and when not in use, this hard drive was kept in locked cabinet, within a secure area of the Mater Children's Hospital PICU and subsequently, the Lady Cilento Children's Hospital Clinical Directorate (following the merge of Mater Children's Hospital into the Lady Cilento Children's Hospital in 2014).

(iii) Research data for paediatric (under 18 years) clinical trials is required to be stored for a period of 25 years after the completion of the study according to the Mater Research Institute Ownership, Storage and Retention of Human Research Materials and Data Policy (2014) (Appendix 7). As this study involved data collected from paediatric participants, data will be stored according to this requirement. At the completion of the required storage period, data will be destroyed, and this documented, according to the Destruction of Data requirements outlined in the Mater Research Institute Ownership, Storage and Retention of Human Research Materials and Data Policy (2014). Destruction of data will involve the shredding and disposal of paper documents using the hospital confidential disposal system and electronic files including all copies will be deleted.

3.2.7.4 Risk

The overall risk associated with undertaking Study 2 of this thesis was considered to be low. This was determined based on consideration of the risk associated with undertaking CPT in ventilated infants and children and the risk associated with the use of previously collected data in this study.

CPT formed the only part of Study 2 that was independent to the randomised controlled trial. CPT was delivered during the randomised controlled trial study period as part of the participants' optimal clinical care and the risk associated with its use in this study was considered to be low. While CPT has the potential to cause negative sequelae in highly unstable patients (Main & Denehy, 2016), CPT was only utilised in Study 2 after individualised assessment of participants, in collaboration with the consulting medical officer. CPT techniques were undertaken by an experienced PICU physiotherapist and therefore risk was reflective of the usual risk associated with undertaking CPT in ventilated infants and children. As part of usual clinical practise, any adverse events associated with CPT in this study were recorded in the participant's electronic medical record.

Study 2 reported on data previously collected as part of a randomised controlled trial investigating the use of different lung recruitment manoeuvres following ETT suction in ventilated infants and children (Mater Health Services Human Research Ethics Committee (Ref No. 1010C) (Appendix 6). No new data were collected as part of Study 2 therefore it was considered and approved as a low-negligible risk study by Mater Health Services and Australian Catholic University Human Research Ethics Committees. To ensure accountability around the requirements for a low-negligible risk study, yearly progress reports were submitted to the relevant committees for the duration of the study (2012-2018) including confirmation of how risk was being managed and reporting of any adverse events.

4. Study 1: A systematic review of the clinimetric properties of tools used to measure the effects of chest physiotherapy in mechanically ventilated infants and children aged 0-16 years

This chapter describes Study 1 of this research program; a systematic review conducted in two parts. This systematic review first identified the tools used to measure the effect of CPT on lung function in mechanically ventilated children aged 0-16 years and the second to report on the clinimetric properties of these tools using the COSMIN framework (Terwee et al., 2012).

4.1 Introduction

CPT is a well-accepted adjunct to the intensive care management of children receiving mechanical ventilation. Traditionally CPT comprises a combination of manual and assisted breathing techniques and airway suctioning (Zach & Oberwaldner, 2008). CPT is thought to expedite recovery in children with lung disease, through the removal of obstructing airway secretions resulting in improved ventilation and gas exchange in previously collapsed regions of lung. Despite widespread use, high quality research investigating CPT in ventilated children remains limited and CPT effects in this population are not well understood. Clinical outcomes from studies in this area vary in their findings (Almeida et al., 2005; Galvis et al., 1994; Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015). One reason for this may be due to the variability in outcome measures used. To date, no single measurement tool has been recommended above another for measuring CPT effects in ventilated infants and children. Such variability raises questions about whether the tools used by physiotherapists when treating ventilated infants and children are sufficiently robust to detect meaningful clinical change in response to CPT.

Best practice for physiotherapists working in a PICU can only be observed if CPT effects can be quantified using valid, reliable and responsive measurement tools. Tools currently used include

CXR, ABG analysis and respiratory mechanics measures (Main et al., 2004; Main & Stocks, 2004). However, the clinimetric properties of these measurement tools in ventilated children have yet to be determined.

Previous reviews of CPT in ventilated infants and children have reported on treatment effects (Hough et al., 2010; Krause & Hoehn, 1999, 2000) rather than the measurement tools used to derive these effects. While these reviews provide useful information about treatment outcomes, conclusions drawn must be interpreted with caution without knowledge of the clinimetric properties of the measurement tools used. The lack of reported consensus recommending one tool over another when measuring CPT in ventilated infants and children has prompted the current review. This review sought to systematically identify all reported tools used to measure CPT effects on lung function in mechanically ventilated infants and children 0-16 years and to evaluate the clinimetric properties of these tools.

The following research questions for this systematic review were:

(i) What measurement tools are used to evaluate CPT effects in ventilated infants and children?

(ii) What are the clinimetric properties of these measurement tools?

4.2   Method

4.2.1   Identification and selection of studies

A systematic search of six computerised databases, Pubmed, CINAHL, Embase, The Cochrane Library, Physiotherapy Evidence Database and Web of Science was undertaken. The search strategy included the use of pre-determined MeSH terms and key text words for 'chest physiotherapy', 'mechanical ventilation', 'intensive care' and 'lung function'. These search terms were combined with search filters to limit the findings to the target age groups of infants or children. Manual, targeted reference searches of identified key studies and reviews were

undertaken to identify additional eligible studies not identified by the original searches. ClinicalTrials.gov and World Health Organisation International Clinical Trials Registry Platform were searched to identify planned or ongoing trials, unpublished articles or articles in press using the same key search terms. There were no restrictions placed on study design, language or date of publishing.

Following the initial search and removal of duplicates, resulting titles and abstracts were independently screened by two researchers (BM and JH) against the inclusion and exclusion criteria. Where unclear, the full article was accessed. Key articles were identified, independently reviewed and decision regarding eligibility compared. Conflicting viewpoints were discussed until consensus was reached. Where consensus was not able to be reached, a third reviewer (SK) adjudicated to determine inclusion. Following the identification of included assessment tools and outcome measures, a second search was undertaken to identify studies that addressed the clinimetric properties of these outcome measures in mechanically ventilated infants and children 0-16 years of age.

The following a priori inclusion criteria were used to determine study eligibility (Box 4.1). Studies were included if they described any measurement tool that met *all* of the following criteria:

(i) Used in subjects 0-16 years old receiving mechanical ventilation via an ETT/ tracheostomy within a PICU,

(ii) Where subjects received CPT (defined as any single or combination of techniques including positioning, manual techniques, manual hyperinflation or mechanical airway clearance devices used in combination with ETT suctioning), and

(iii) Used to measure CPT effects including secretion clearance, respiratory mechanics, radiological appearance of the lung or gas exchange during/and or after CPT.

Studies were excluded if the measurement tools were:

(i)   Used in subjects over 16 years old or premature infants < 38 weeks of age

(ii)   Used in subjects not mechanically ventilated via ETT

(iii) Used in subjects not receiving CPT or only used prior to CPT

(iv)   Used to measure the delivery of a CPT technique eg. mechanistic effect of CPT

Box 4.1. Inclusion criteria

Design

- All trials in which the outcome of the intervention of CPT has been measured

Participants

- Children or infants term to 16 years of age

- Participants receiving CPT

Intervention

- Trials that measure lung function during and/ or after CPT

- CPT includes any single or combination of techniques including positioning, manual techniques, manual hyperinflation or mechanical airway clearance devices used in combination with ETT suctioning

Outcome measures

- Tools that measure effects of CPT - secretion clearance, respiratory mechanics, gas exchange, radiological appearance of lung

Comparisons

- All trials will be included regardless of whether there is a comparator or control group

4.2.2   Assessment of characteristics of studies

For each included study, data extracted included study details (author, year, country of origin), population characteristics (number of participants, age, gender, underlying pathology, mode of ventilation) and details of the CPT intervention (techniques used, order of technique delivery and rationale) and measurement tool used. Characteristics of measurement tools extracted included the tool, purpose of use, description and type of measurement.

Further searches were undertaken to identify the clinimetric properties of each included measurement tool. Key search terms used included the name of the measurement tool, the population of interest (infants and children) and the clinimetric properties of interest (validity, reliability and reliability), as outlined in the COSMIN manual (Terwee et al., 2012). For each measurement tool, population characteristics and details regarding validity, reliability and responsiveness were recorded and methodological quality was assessed using the COSMIN checklist. A 4-point rating scale was used to score each tool's clinimetric properties as excellent, good, fair, or poor and determine the overall quality score of each study (Terwee et al., 2012). Overall scores were derived from the lowest rating across all aspects of that property (Terwee et al., 2012).

4.2.3   Data analysis

Descriptive synthesis of the included studies was undertaken. This included detailed descriptions of study design, population characteristics, including age, weight, gender, pathology and ventilation characteristics, type of CPT intervention and control intervention where applicable, and measurement tools used. Descriptive synthesis of the reported properties of validity, reliability, responsiveness and generalizability of the measurement tools identified was undertaken.

4.3 Results

4.3.1 Flow of studies through the review

Initial searches yielded 374 papers (Figure 4.1). A further five titles were identified through searches of clinical trials databases. After screening titles and abstracts and removing duplicates, 323 papers were excluded and 57 full text articles were retrieved for independent review (BM, JH). A further 45 papers were excluded as not meeting the predefined inclusion criteria. Reasons for exclusion are shown in Figure 4.1.

Twelve studies met all inclusion criteria and were included in the review (Almeida et al., 2005; Deakins & Chatburn, 2002; Elizabeth et al., 2016; Galvis et al., 1994; Gregson et al., 2012; Main et al., 2004; Main & Stocks, 2004; Schultz et al., 2005; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015; Soundararajan & Thankappan, 2015; Tannenbaum et al., 2007). Two studies reported on the same participants (Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015) and for the purposes of this systematic review, were considered as duplicate papers. Manual searches of reference lists of relevant review articles identified one additional study (Hussey, Hayward, Andrews, Macrae, & Elliot, 1996) that met inclusion criteria, resulting in thirteen studies being included in the current review.
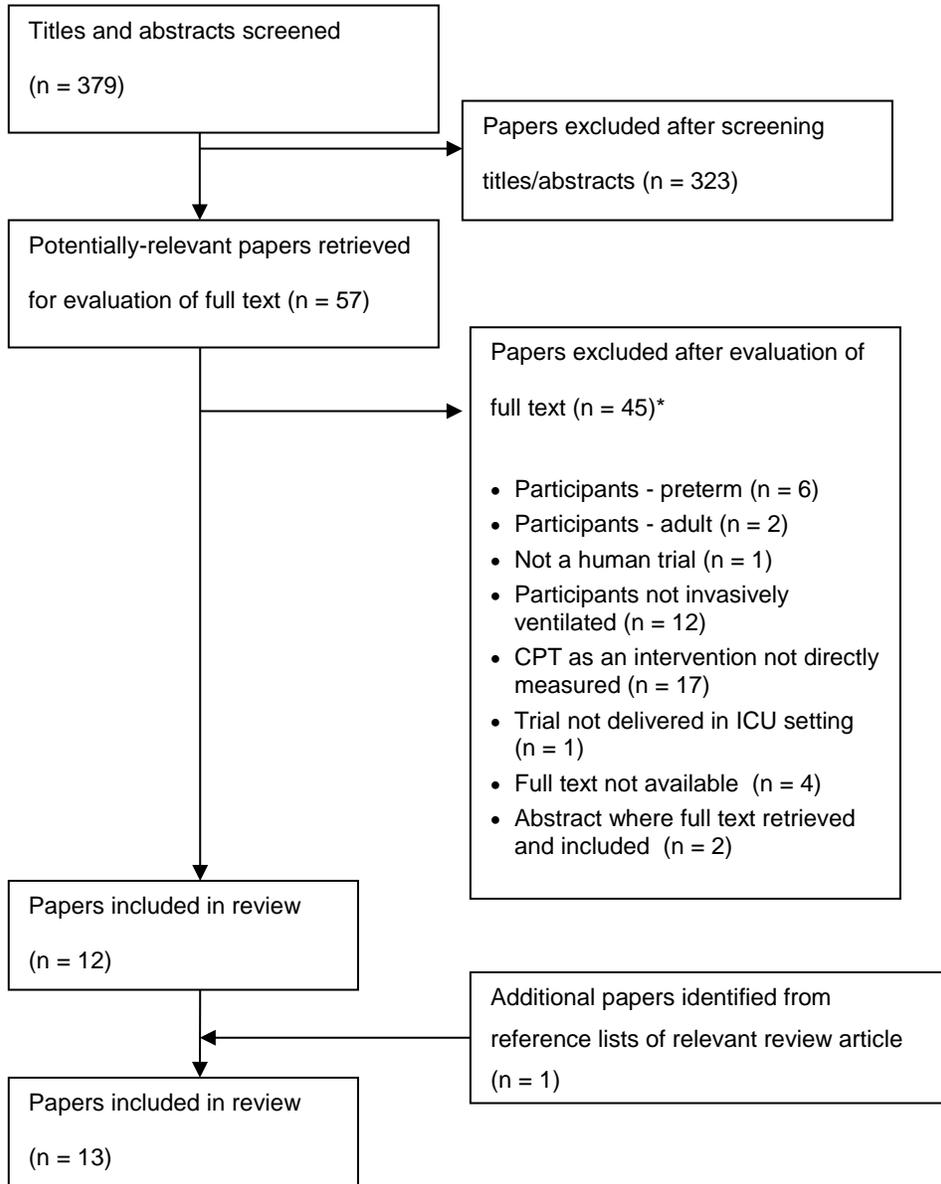
Figure 4.1   Flow of studies through the review

* Papers may have been excluded for failing to meet more than one inclusion criteria.

4.3.2   Characteristics of studies

Study design, participant characteristics and CPT intervention details of the included studies are listed in Table 4.1. Included studies consisted of one randomised controlled trial (Deakins & Chatburn, 2002), seven prospective randomized crossover studies (Deakins & Chatburn, 2002; Main et al., 2004; Main & Stocks, 2004; Schultz et al., 2005; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015; Tannenbaum et al., 2007), four prospective observational studies (Almeida et al., 2005; Gregson et al., 2012; Hussey, Hayward, Andrews, Macrae, & Elliot, 1996; Soundararajan & Thankappan, 2015) and one single-blind clinical trial (Elizabeth et al., 2016). The majority of studies (n = 11, 85%) included participants of varying ages, ranging from neonates to adolescents with two studies only including participants under 12 months of age (Almeida et al., 2005; Galvis et al., 1994).

Eight studies reported mean participant age. Of these, three studies had a mean age less than 12 months (Almeida et al., 2005; Hussey, Hayward, Andrews, Macrae, & Elliot, 1996; Main et al., 2004), four (Elizabeth et al., 2016; Gregson et al., 2012; Main & Stocks, 2004; Soundararajan & Thankappan, 2015) reported mean ages of 12-24 months and one (Schultz et al., 2005) reported a mean age over 2 years.

Table 4.1   Summary of included studies.

Study	Design	Participants	Intervention	Measurement tools and outcome measures
Almeida et al (2005)	Prospective, non-randomized, non-controlled	n = 22 Mean age (month) = 3.1 (range 1-11) Mean weight (Kg) = 5.6 Gender = 18 M, 4 F Mode of ventilation = SIMV Position: Elevated supine Sedation Y, paralysis N Pathology: Obstructive acute RF Exclusion: Paralysis, cardiovascular instability, neuromuscular disease, cardiac disease, post-operative, chronic lung disease, malnutrition, UA disease, significant atelectasis, PEEP > 10cmH$_2$O	CPT = Expiratory Flow Increase Technique x 40 reps and ETT suction Con = no control	Respiratory Rate, CO$_2$SMO Plus (Expired Vt, alveolar Vt, minute ventilation, alveolar ventilation, airway dead space volume, total dead space volume, dead space volume/ tidal volume ratio, dynamic inspiratory resistance, dynamic expiratory resistance, dynamic compliance); ABG analysis
Deakins & Chatburn (2002)	Prospective, RCT	n = 12 (CPT = 7; Con = 5) Mean age (month) = NR (range 2-168) Mean weight (Kg) = (CPT = 7.5; Con = 16.9) Gender = NR Mode of ventilation = SIMV Position = Supine Sedation, paralysis = NR Pathology: Atelectasis Exclusion: Febrile, air leak, pneumonia	CPT = IPV + normal saline instillation, 180-220 cycles/min, 4 hourly Con = Percussion, vibrations and ETT suction, 10-15 mins, 4 hourly	Pulse oximetry (oxygen saturations), BP, Respiratory Rate, Breath sounds, CXR (atelectasis score), CO$_2$SMO Plus (expired end tidal volume, Plateau pressure)
Elizabeth et al (2016)	Single-blind Prospective,	n = 40 (CPT = 24; Con = 16) Mean age (month) = (CPT = 10.5; Con = 14.5)	CPT = "CPT" and ETT suction x 30 mins	ABG analysis (pH, PCO$_2$, PO$_2$, HCO$_3$, BE), Transcutaneous

83

Study	Design	Participants	Intervention	Measurement tools and outcome measures
	non-randomized, non-controlled	(range 1-204) Mean weight (Kg) = (CPT = 7.9; Con = 9.5) Gender = 23 M, 17 F Mode of ventilation = Any mode Position = NR Sedation, paralysis = NR Pathology: Consolidation, atelectasis, effusion Exclusion: Chest trauma, coagulopathy, head injury	Con = Single ETT suction	CO_2 monitor,, Pulse oximetry (oxygen saturations), Ventilator (Vt, PIP, PIF, PEF)
Galvis et al (1994)	Prospective, non-randomised observational study	n = 57 Mean age (month) = NR (range 0-12) Mean weight (Kg) = NR Gender = NR Mode of ventilation = NR Position = NR Sedation Y, paralysis Y Pathology: Atelectasis Exclusion: Pneumonia	CPT = Saline washout-stimulated cough technique (incorporating bagging, saline instillation, MHI, vibes and ETT suctioning; performed multiple times on affected lung and once on unaffected lung Con = No control	ABG analysis, CXR (presence of air bronchograms), Pulse oximetry (oxygen saturations)
Gregson et al (2012)	Prospective, observational study	n = 105 Mean age (month) = 15 (0-198) Mean weight (Kg) = NR Gender = NR Mode of ventilation = NR Position = NR Sedation Y, paralysis Y	CPT = Combination of techniques, inclusive of MHI, compressions-vibrations, saline instillation, ETT suction; intervention based on clinical indication, no restrictions or guidelines around order	CO_2SMO Plus (PEF, PIF, VI, PEF:PIF, PIP)

Study	Design	Participants	Intervention	Measurement tools and outcome measures
		Pathology = Consolidation, atelectasis, reduced breath sounds or added sounds on auscultation, deteriorating ABGs, increased ventilator requirements in preceding 4 hours	Con = No control	
		Exclusion = Coagulopathy, raised ICP, metabolic bone disease, ETT leak > 20%		
Hussey et al (1996)	Prospective, observational study	n = 71 Mean age (month) = 11 (0-47) Mean weight (Kg) = NR Gender = 35 M, 36 F Mode of ventilation = NR Position = Supine, R or L lateral Sedation Y, paralysis N Pathology = Atelectasis, signs of secretion retention Exclusion = cardiovascular instability, clear CXR, no signs of increased secretions	CPT = Bag squeezing (3 tidal breaths:1 hyperinflation), percussion and vibrations, positioning, increased FiO_2 (20% above set amount) and ETT suction Con = No control	Electrocardiograph (HR), Invasive BP, Pulse oximetry (oxygen saturations)
Main et al (2004)	Prospective, randomized crossover study	n = 90 Mean age (month) = 9 (range 0-192) Mean weight (Kg) = 7 Gender = 44 M, 46 F Mode of ventilation = Volume and pressure modes Position = NR Sedation Y, paralysis Y Pathology = Primary and secondary RF Exclusion = ETT leak > 20%	CPT = Flexibly defined, single treatment of combination of pre-oxygenation, saline instillation, manual techniques, MHI and ETT suction Con = Single ETT suction	ABG analysis, CO_2SMO (Expired Vt, resistance, compliance)

85

Study	Design	Participants	Intervention	Measurement tools and outcome measures
Main & Stocks (2004)	Prospective, randomized crossover study	n = 75 Mean age (month) = 2 (range 0-192) with primary cardiac diagnosis = 22 (range 0-192) with primary FR diagnosis Mean weight (Kg) = NR Gender = NR Mode of ventilation = Volume (n= 19) and pressure (n=56) modes Position = NR Sedation Y, paralysis Y Pathology = Primary cardiac diagnosis (n= 43), primary RF (n = 32) Exclusion = ETT leak > 20%	CPT = Flexibly defined, single treatment of combination of pre-oxygenation, saline instillation, chest wall vibrations, percussion and postural drainage, MHI and ETT suction, as many cycles as deemed necessary Con = Flexibly defined, single treatment of combination of pre-oxygenation, saline instillation, MHI and ETT suction, as many cycles as deemed necessary	ABG analysis, CO_2SMO Plus (Physiological dead space, alveolar dead space, expired Vt, CO_2 elimination, $EtCO_2$, mixed expired CO_2, anatomical dead space)
Schultz et al (2005)	Prospective, randomized crossover study	n = 35 Mean age (month) = 32 (range 8-96) Mean weight (Kg) = 13.2 Gender = M, F Mode of ventilation = NR Position = Varied Sedation NR, paralysis NR Pathology = Primary and secondary RF, including cardiac and general ICU patients Exclusion = Extracorporeal Membrane oxygenation with unstable cannulae, High Frequency Oscillation Ventilation, unstable	CPT = Kinetic bed positioning (PediDyne) + bed percussion every 2 hrs for 18 hrs; positioning initiated at 80º arc with pauses in each position Con = 'Standard PT' of manual turning and percussion	ABG analysis ($P(A-a)O_2$)), oxygenation index)

Study	Design	Participants	Intervention	Measurement tools and outcome measures
		spinal cord, persistent uncontrolled ICP, uncontrolled bronchospasm, severe claustrophobia, severe diarrhoea, skeletal traction, within 24 hr of receiving inhaled nitric oxide or surfactant		
Shannon, Stocks, Gregson, Dunne, et al. (2015) Shannon, Stocks, Gregson, Hines, et al.(2015)	Prospective, randomized crossover study	n = 63 Mean age (month) = (range 0-192) Mean weight (Kg) = NR Gender = 32 M, 30 F Mode of ventilation = Volume and pressure modes Position = NR Sedation Y, paralysis Y Pathology = Consolidation or atelectasis on CXR, added or decreased BS on auscultation, increased ventilator requirements Exclusion = ETT tube leak > 20%, coagulopathy, rib fractures	CPT = Combination of positioning, saline or mucolytic instillation, MHI or VHI, manual techniques and ETT suction Con = No control	$NICO_2$ (Compliance, resistance, Vt, PIP, PEEP, PIP, PIF, PEF inspired and expired volumes)
Soundararajan & Thankappan (2015)	Prospective, non-randomised observational study	n = 18 Mean age (month) = 19 Mean weight (Kg) = 5 Gender = 10 M, 8 F Mode of ventilation = NR Position = Elevated supine Sedation NR, paralysis NR Pathology = Cardiac surgery and upper lobe atelectasis	CPT = MHI and chest wall vibrations, 4 x 8 breaths followed by normal saline instillation ETT suction (once/ min for 4 minutes) Con = No control	ABG analysis (PaO_2), CXR

Study	Design	Participants	Intervention	Measurement tools and outcome measures
		Exclusion = Abnormal position of ETT, Acute respiratory distress syndrome, acute pulmonary oedema, cardiovascular instability, undrained tension pneumothorax, PIP > 40cmH$_2$O, FiO$_2$ > 0.7 or PEEP > 10 cmH$_2$O		
Tannenbaum et al (2007)	Prospective, randomized crossover study	n = 18 Mean age (month) = NR (range 33-180) Mean weight (Kg) = NR Gender = NR Mode of ventilation = NR Position = NR Sedation Y, paralysis NR Pathology = Cystic fibrosis undergoing general surgical procedures Exclusion = Subjects requiring thoracic surgery	CPT = Modified postural drainage, saline instillation, MHI, expiratory vibrations, ETT suction; duration and combination of techniques not standardized Con = ETT suction as indicated	CO$_2$SMO Plus (Compliance, PIP, resistance, expired Vt), sputum yield (timing NR)

Abbreviations: ABG - Arterial blood gas , BE - Base excess, BP - Blood pressure, Con - control group, CPT - Chest Physiotherapy group, CXR - Chest X-ray, ETCO$_2$ - End-tidal carbon dioxide, ETT - Endotracheal Tube, HR - Heart rate, ICP - intracranial pressure, IPV - Intrapulmonary percussive ventilator, MHI - Manual Hyperinflation, n – sample size, NR - Not reported, P(A-a)O2 - arterial-alveolar oxygen tension difference, PEEP - Positive end expiratory pressure, PEF - Peak expiratory flow, PIF - Peak inspiratory flow, PIM2 - Pediatric Index of Mortality 2, PIP - Peak inspiratory pressure, RCT - Randomized controlled trial, RF - Respiratory failure, SIMV - Synchronized Intermittent Mandatory Ventilation, UA - Upper airway, VI - Inflation volume, Vt - Tidal volume, Y - Yes (reported)

All reviewed studies measured the effects of at least one CPT intervention. Nine studies described the use of a combination of CPT techniques determined by the treating physiotherapist, including manual or ventilator hyperinflation, chest vibrations, percussion, positioning, saline instillation, ETT suction (Galvis et al., 1994; Gregson et al., 2012; Hussey, Hayward, Andrews, Macrae, & Elliot, 1996) (Main et al., 2004; Main & Stocks, 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015; Soundararajan & Thankappan, 2015; Tannenbaum et al., 2007). One study described the Expiratory Flow Increase Technique as an alternative CPT intervention (Almeida et al., 2005). Control interventions were described in four studies, consisting of varied ETT suction protocols that differed from CPT by the lack of manual techniques performed (Elizabeth et al., 2016; Main et al., 2004; Main & Stocks, 2004; Tannenbaum et al., 2007). Two studies compared two different CPT interventions, each comparing standard CPT, defined as manual techniques, positioning and suctioning, to either intrapulmonary percussive ventilation (Deakins & Chatburn, 2002) and kinetic bed therapy (Schultz et al., 2005).

From the included papers, eight measurement tools measured CPT effects in ventilated children and infants. The eight tools identified were secretion weight, CO_2SMO Plus and $NICO_2$ respiratory monitors, ventilator, stethoscope, ABG, pulse oximetry and CXR. Two studies (Gregson et al., 2012; Shannon, Stocks, Gregson, Hines, et al., 2015) also reported on the Pliance force-sensing mat as a tool to measure the force and pressure generated during chest wall vibrations in ventilated infants and children. This tool was not included in the systematic review as it did not measure an effect of CPT on lung function, rather the effect of chest wall vibrations as a CPT technique.

4.3.3 Measures of CPT effects

<u>4.3.3.1 Secretion clearance</u>

The quantity and appearance of airway secretions have been proposed as an outcome measure for the effectiveness of CPT (Main & Denehy, 2016). Secretion clearance was described in only one study and was reported as sputum volume per kilogram in ventilated children with cystic fibrosis receiving CPT during anaesthesia (Tannenbaum et al., 2007). While reported as an outcome of CPT, secretion clearance was not the primary measure in this study.

<u>4.3.3.2 Respiratory mechanics</u>

In the current review, respiratory mechanics refers to tools that measure the mechanical properties of the lung and airways during mechanical ventilation, including derivatives of volumes, pressures, rates and flows generated throughout the respiratory cycle (Hess, 2014). Respiratory mechanics measurements were described as those directly measured via the ventilator or by a bedside respiratory monitor attached into the ventilator circuit measuring flow at the airway opening. Measures of respiratory mechanics were described in eight studies, with seven (Almeida et al., 2005; Deakins & Chatburn, 2002; Gregson et al., 2012) (Main et al., 2004; Main & Stocks, 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Tannenbaum et al., 2007) reporting results using standalone bedside respiratory monitors (CO_2SMO Plus (n=6) and $NICO_2$ (n=1)) and one study (Elizabeth et al., 2016) reporting changes in ventilator-derived parameters. Reported measures included inspired, expired and alveolar tidal volumes, dead space volumes (anatomical, alveolar and physiological), peak inspiratory pressure and peak inspiratory and expiratory flow rate, inspiratory and expiratory resistance, dynamic compliance, minute ventilation and alveolar ventilation. The type and brand of ventilator used to obtain directly-derived ventilator parameters was not specified (Elizabeth et al., 2016).

4.3.3.3   Lung sounds

Lung sounds are assessed using a stethoscope through auscultation of the chest. Lung sounds refer to the presence or absence of both breath sounds and adventitious sounds (crackles, wheeze, stridor or rub) and can indicate pathology within the lung or airway (Main & Denehy, 2016). One study reported auscultation findings as a secondary outcome measure to assess CPT effects in ventilated paediatric patients with upper lobe collapse (Soundararajan & Thankappan, 2015). A second study (Deakins & Chatburn, 2002) measured breath sounds at baseline in a clinical trial comparing intrapulmonary percussive ventilation and standard manual techniques however outcomes following CPT were not quantified.

4.3.3.4   Radiological appearance of lung

CXR was described as a lung imaging tool to measure CPT effects in three studies. Deakins and Chatburn (2002) and Galvis et al (1994) both described radiologist-derived scoring systems to measure changes in lung appearance following CPT. Deakins and Chatburn (2002) described the use of an atelectasis score, an ordinal rating scale based on the presence of mediastinal shift toward the affected side, elevation of the affected hemi-diaphragm and/or reduction in ipsilateral intercostal spaces. Atelectasis was also specified as partial or complete and bias was controlled by blinding the assigning radiologist to whether study participants received CPT or not (Deakins & Chatburn, 2002). Routinely collected CXRs were used in this analysis but the authors did not specify how long after CPT images were taken (Deakins & Chatburn, 2002).

Galvis et al (1994) describes the use of CXR to measure changes in lung aeration following CPT. CXRs, taken at 6 and 24 hours post CPT, were interpreted by a radiologist to determine the presence or absence of air bronchograms as a measure of atelectasis. Radiologist blinding was not described. Soundararajan & Thankappan (2015) also report on changes in CXR appearance as a secondary

91

outcome, comparing pre and post films, the latter taken 30 minutes after the administration of CPT. A specific scoring system was not used; instead each radiograph was assessed for the presence of atelectasis, pulmonary infiltrates, extra-vascular lung and/ or pleural fluid, or pneumothorax following CPT intervention (Soundararajan & Thankappan, 2015).

<u>4.3.3.5   Gas exchange</u>

Gas exchange in the lungs refers to the exchange of oxygen and carbon dioxide between gas-filled alveoli and adjacent blood vessels (Taussig et al., 2008). For the purposes of this review, gas exchange included measures from transcutaneous monitoring and ABG analysis.

Three studies described the use of transcutaneous oxygen monitoring to measure effects of CPT on oxygenation following CPT intervention (Deakins & Chatburn, 2002; Elizabeth et al., 2016; Hussey, Hayward, Andrews, Macrae, & Elliot, 1996). Deakins & Chatburn (2002) described discrete oxygen saturation measurements, prior to, and after CPT but provided no detail about the type of oximeter utilised. Two studies used continuous transcutaneous oxygen saturation monitoring before (Hussey, Hayward, Andrews, Macrae, & Elliot, 1996) and during (Hussey, Hayward, Andrews, Macrae, & Elliott, 1996;Galvis et al., 1994) CPT. Only Hussey et al (1996) specified the type of oximeter used, the location of the probe and reported on specific timing of measurement. Hussey et al (1996) also described controlling for accuracy of measurements by reporting oxygen saturation values that had a corresponding pulse rate within five beats of the electro-cardiograph derived rate.

ABGs collectively refer to measurements of pH, PaO_2 and $PaCO_2$ from samples of arterial blood, that together can be used to provide information about the adequacy of ventilation, tissue oxygenation and acid-base status (Taussig et al., 2008). ABG analysis was undertaken in seven studies (Almeida et al., 2005; Elizabeth et al., 2016; Galvis et al., 1994; Main et al., 2004; Main & Stocks, 2004; Schultz

92

et al., 2005; Soundararajan & Thankappan, 2015). ABG analysis compared samples taken immediately prior to CPT with at least one sample taken following the intervention. Samples were taken at 30 minutes (Almeida et al., 2005; Elizabeth et al., 2016; Main et al., 2004; Main & Stocks, 2004; Schultz et al., 2005; Soundararajan & Thankappan, 2015), 60 minutes (Elizabeth et al., 2016), 6 hours and 24 hours (Galvis et al., 1994) post CPT, and every 2 hours during CPT in a 36 hour trial comparing standard CPT (percussion and positioning) with kinetic bed therapy (Schultz et al., 2005). The blood gas analyser used was specified in four studies; the Hewlett Packard i-Stat portable clinical analyser in three studies (Main et al., 2004; Main & Stocks, 2004; Schultz et al., 2005) and the Cobas B 121 system in one study (Elizabeth et al., 2016).

The values reported through ABG analysis varied with most studies (n=6) reporting on measures of both oxygenation and CO_2 clearance (Almeida et al., 2005; Elizabeth et al., 2016; Galvis et al., 1994; Main et al., 2004; Schultz et al., 2005; Soundararajan & Thankappan, 2015). Six studies (Almeida et al., 2005; Elizabeth et al., 2016; Galvis et al., 1994; Main et al., 2004; Schultz et al., 2005; Soundararajan & Thankappan, 2015) reported on arterial oxygenation, including direct measures of the PaO_2 and derived measures including alveolar-arterial gradient (Almeida et al., 2005; Schultz et al., 2005), arterial oxygen saturations (Almeida et al., 2005; Main et al., 2004) and oxygenation index (Schultz et al., 2005). One study (Main & Stocks, 2004) used ABG analysis to report on changes in ventilation, measured through changes in carbon dioxide levels directly and as a means of determining dead-space volumes.

4.3.4 Clinimetric properties

Figure 4.2 outlines the flow of studies included in the clinimetric review of the eight identified measurement tools. Fourteen studies reported on the clinimetric properties of validity, reliability and responsiveness of the included measurement tools (Table 4.2). Two studies reported clinimetric data on more than one measurement tool (Cannon et al., 2000; Castle et al., 2002). No studies were identified that evaluated the clinimetric properties of secretion weight, lung sounds or CXR in ventilated infants and children. COSMIN scores for the included clinimetric studies are outlined in Table 4.3 and Appendix 3 and ranged from poor to good. Twelve of the fourteen included studies were scored as having high generalisability according to the COSMIN checklist (Terwee et al., 2012).

<u>4.3.4.1 Respiratory mechanics</u>

Thirteen studies were identified that reported on the clinimetric properties of the CO_2SMO Plus and $NICO_2$ respiratory monitors (n=9) (Cannon et al., 2000; Castle et al., 2002; Gregson et al., 2012; Main et al., 2004; Main, Castle, Stocks, James, & Hatch, 2001; Main & Stocks, 2004; Riou et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015) and ventilator-derived measurements (n=4), (Cannon et al., 2000; Castle et al., 2002; Heulitt, Thurman, Holt, Jo, & Simpson, 2009; Kim, Salazar, Ross, Newth, & Khemani, 2015) with two studies reporting clinimetric properties for both measurement tools (Cannon et al., 2000; Castle et al., 2002).
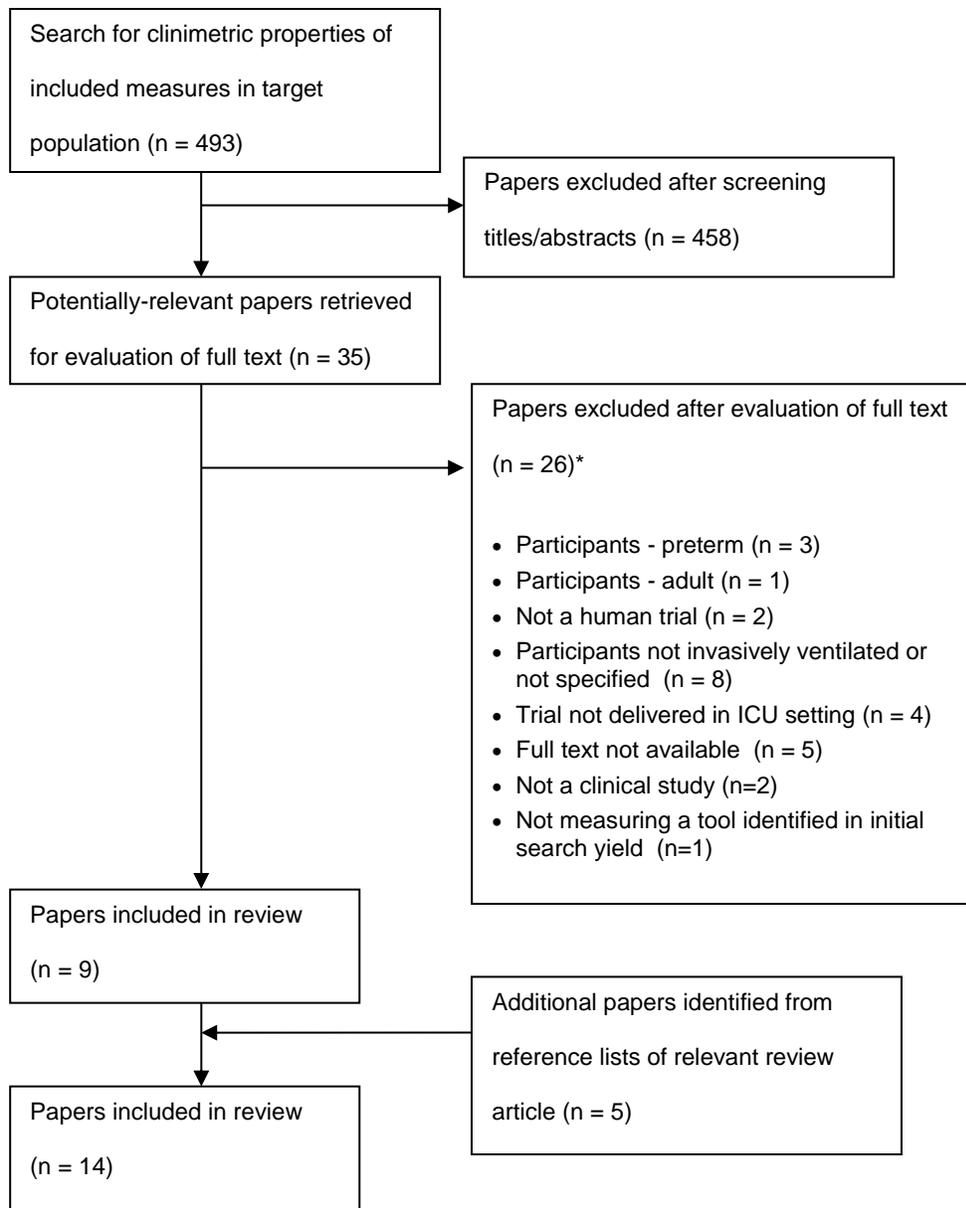
Figure 4.2   Flow of studies in clinimetric review

* Papers may have been excluded for failing to meet more than one inclusion criteria.

Table 4.2   Clinimetric properties of identified tools of CPT effects

CPT effect	Measurement tool	Studies	Measures derived from tool	Clinimetric properties		
				Validity	**Reliability**	**Responsiveness**
Secretion clearance	Sputum weight/ volume		Sputum volume, weight	NR	NR	NR
Respiratory mechanics	CO_2SMO Plus	Cannon et al (2000)	Vt	Poor correlation for expired Vt for infant circuit with effective Vt measured using a bench model (r_2 0.58); paediatric circuit showed no difference between CO_2SMO Plus and bench model (p=0.16) and better correlation (r_2 0.85)	NR	NR
		Castle et al (2002)	Vt	Tidal volume measures accurate within 5% for neonate (0.3 to 20 L/min), paediatric (4 to 80 L/min) and adult (2.5 to 130 L/min) flow sensor	Tidal volume measures repeatable -0.21 mL/kg (-0.53-0.12)	NR
				Pressure measurements between 0 - 70 cm H_2O for neonate, paediatric and adult sensors were accurate within 3% of those recorded by Digitron pressure manometer	PIP measures repeatable 0.17cm H_2O (-0.42-0.76)	

CPT effect	Measurement tool	Studies	Measures derived from tool	Clinimetric properties		
				Validity	Reliability	Responsiveness
		Gregson et al (2012)		NR	NR	Increased PEF, PIP and inspiratory volume with CPT (inflation + vibrations)
		Main & Stocks (2004)	VD_{phys}, VD_{alv}, Vt, $EtCO_2$, $PaCO_2$, $PeCO_2$	NR	NR	VD_{phys}, VD_{alv}, expired Vt, $PeCO_2$ and $ETCO_2$ larger after CPT compared to suction alone
		Main et al (2001)	R_{rs}, C_{rs}, Vt	R_{rs} and C_{rs} overestimated with ETT leaks > 20%, irrespective of volume or pressure-controlled mode	Wide intra and test-retest variability with ETT leak > 20%	NR
		Main et al (2004)	R_{rs}, C_{rs}, Vt	NR	Within epoch measures of expired Vt, C_{rs} and R_{rs} highly reproducible (coefficient of variation 1.1%, 0.9% and 4.2% respectively) Between epoch reproducible with no significant change in expired Vt, C_{rs} and R_{rs}	R_{rs} reduced in infants in response to CPT, significant in VC mode ($p<0.05$), not in PCV mode ($p<0.09$) Significant within-subject differences in expired Vt, C_{rs} and R_{rs} in response to CPT

97

CPT effect	Measurement tool	Studies	Measures derived from tool	Clinimetric properties		
				Validity	Reliability	Responsiveness
		Riou et al (2004)	VD_{Airway}	Mean difference: -0.287± 1.046 ml/kg, or 6.8% mean value (not significant) between dead space values measured by SBT-CO_2 method compared to the Bohr-Enghoff equation	Reproducible airway dead space measurements over 1 hour period using the SBT-CO_2 method (intra-class correlation coefficient: 0.84 to 0.87)	NR
	$NICO_2$	Shannon, Stocks, Gregson, Dunne, et al., (2015); Shannon, Stocks, Gregson, Hines, et al., (2015)		NR	NR	Increased tidal volume and compliance and reduced resistance following CPT; no change in PIP in volume mode
	Ventilator	Cannon et al (2000)	Vt	Servo 300 – Infant circuit, mean Vt overestimated compared to Vt measured at airway opening by pneumotachometer (CO_2SMO Plus) (p<0.0001) and showed poor correlation (r^2 0.54) Paediatric circuit, mean Vt measured at ventilator overestimated Vt (p=0.03), good correlation (r^2 0.84)	NR	NR
		Castle et al (2002)	Vt	Servo 300 - At expired Vt <160 ml mean 32% (SD 20%) error; at expired Vt	Servo 300 - magnitude of error varied within and	NR

CPT effect	Measurement tool	Studies	Measures derived from tool	Clinimetric properties		
				Validity	**Reliability**	**Responsiveness**
				>160 mL mean 18% (SD 6%) error Correcting for gas compression, Servo 300 true expired Vt underestimated up to 64% in smallest infants and overestimated up to 29% in older children	between subjects and was influenced by pressure change during breath, expired Vt and circuit size	
		Heulitt et al (2009)	Vt	Servo-I - Vt measured on ventilator without circuit compensation overestimated true Vt measured by pneumotachometer at airway opening; with circuit compensation, Vt underestimated	PRVC showed a 1 mL /kg difference in Vt with infant circuit compared to VSV which showed < 1-mL/kg difference in Vt for infant and adult circuit, with or without circuit compensation	NR
		Kim et al (2015)	Vt	PCV - Median difference 22% (7.4–34.1%) in Vt measured at proximal flow sensor versus pneumotachometer; Median difference 16.4% (7.1–9.8%) in Vt measured on ventilator versus pneumotachometer No difference between Vt measured on ventilator versus flow sensor; PVC - Ventilator	NR	NR

99

CPT effect	Measurement tool	Studies	Measures derived from tool	Clinimetric properties		
				Validity	Reliability	Responsiveness
				underestimated Vt by mean volume 1.9 mL/kg		
				PRVC - Ventilator underestimated Vt by mean volume of 2.5 mL/kg		
	Stethoscope		Lung sounds	NR	NR	NR
Gas exchange	ABG		pH, PaO_2, PCO_2, $HCO_{3,}$-BE, SaO_2	NR	NR	NR
	Pulse oximeter	Das et al (2010)	Oxygen saturations	Bias (SpO_2-SaO_2) lowest with sole sensor (-0.088), highest in ear sensor (1.572) (p=0.005); sole sensor showed least bias and highest accuracy in both <90% and >90% groups	No sensor location had better reproducibility than another; children with SpO_2 <90% had mean precision 1.013% compared with SpO_2 > 90% mean precision 1.324%	NR
		Khemani et al (2012)	Oxygen saturations	OSI had a strong linear association with OI (regression equation OSI = 2.76 + 0.547*OI)	NR	NR
				SF ALI value 264 had 91% sensitivity and 53% specificity in detecting PF ratio <300; SF ARDS value 221 had 88% sensitivity and 78%		

100

CPT effect	Measurement tool	Studies	Measures derived from tool	Clinimetric properties		
				Validity	Reliability	Responsiveness
				specificity in detecting PF ratio <200		
		Ross et al (2014)	Oxygen saturations	Bias varied through SpO_2 values 65-97%; bias greatest between 81-85% (mean 6.6%; accuracy root mean 9.1%); SpO_2 more accurate between 91-97% (mean 1.5%; accuracy root mean 4.2%)	NR	NR
Radiological appearance	CXR		Atelectasis score\n\nChange in pathology	NR	NR	NR

Abbreviations: ALI - Acute lung injury, ARDS - Acute respiratory distress syndrome, BE - Base excess, CPT - Chest physiotherapy, C_{rs} - Respiratory compliance, $EtCO_2$ - End tidal carbon dioxide, ETT - Endotracheal tube, HCO_3 - Bicarbonate, H_2O - Water, NR - Not reported, OI - Oxygenation index, OSI - Oxygen saturation index, $PaCO_2$ – Partial pressure of arterial carbon dioxide, PaO_2 - Partial pressure of arterial oxygen, PCV - Pressure controlled ventilation, $PeCO_2$ - Mixed expired CO_2 , PEF - Peak Expiratory Flow, PF - Partial pressure of arterial oxygen/ fraction of inspired oxygen, PIP - Peak Inspiratory Flow, PRVC - Pressure regulated volume control, r^2 – correlation coefficient, R_{rs} - Respiratory resistance, SaO_2 - Arterial saturation of oxygen, SBT - Single breath technique, SF - Saturation of oxygen/ fraction of inspired oxygen, SpO_2 - Saturation of oxygen, SD - Standard deviation, VC - Volume control, VSV - Volume support ventilation, Vt - Tidal volume, VD_{alv} - Alveolar dead space, VD_{phy} - Physiological dead space

Table 4.3 **COSMIN scores of included studies reporting clinimetric properties of measures of CPT effects**

Measurement Tool	Study	Validity	Reliability	Responsiveness	Generalisability
CO_2SMO Plus	Cannon et al (2000)*				
	Infants	Fair			Yes
	Paediatrics	Poor			
	Castle et al (2002)*	Fair	Poor		Yes
	Gregson et al (2012)			Poor	
	Main & Stocks (2004)			Poor	Yes
	Main et al (2001)	Fair	Poor		Yes
	Main et al (2004)		Poor	Poor	Yes
	Riou et al 2004	Fair	Fair		Yes
$NICO_2$	Shannon, Stocks, Gregson, Dunne, et al. (2015); Shannon, Stocks, Gregson, Hines, et al., (2015)**			Poor	
Ventilator-derived measurements	Cannon et al (2000)*				
	Infants	Fair			Yes
	Paediatrics	Poor			
	Castle et al (2002)*	Fair	Poor		Yes
	Heulitt et al (2009)	Fair	Fair		Yes
	Kim et al (2015)	Good			Yes
Pulse oximeter	Das et al 2010	Fair	Poor		No
	Ross et al (2014)	Good			Yes
	Khemani (2012)	Good			No

*Studies assessed for quality for more than 1 measurement tool ** Studies considered together as same sample and scored based on Shannon, Stocks, Gregson, Dunne, et al. (2015)

102

4.3.4.1.1   CO$_2$SMO Plus

Clinimetric properties of the CO$_2$SMO Plus were reported in seven studies (Cannon et al., 2000; Castle et al., 2002; Gregson et al., 2012; Main et al., 2004; Main et al., 2001; Main & Stocks, 2004; Riou et al., 2004). Four studies reported on validity (Cannon et al., 2000; Castle et al., 2002; Main et al., 2001; Riou et al., 2004), three on reliability (Castle et al., 2002; Main et al., 2004; Riou et al., 2004) and three on responsiveness (Gregson et al., 2007; Main et al., 2004; Main & Stocks, 2004).

Studies reported validity associated with measuring expired tidal volumes (Cannon et al., 2000; Castle et al., 2002), resistance (Main et al., 2001), compliance (Main et al., 2001) and airway dead space (Riou et al., 2004). Tidal volume measures recorded by the CO$_2$SMO Plus were found to be accurate to within 5% across a range of flows (Castle et al., 2002), but poorly correlated with tidal volumes measured against a bench model when using an infant circuit (Cannon et al., 2000). Peak inspiratory pressure measurements generated from tidal volumes recorded by the CO$_2$SMO Plus were found to be accurate to within 3% of those recorded simultaneously with a pressure manometer across a range of pressures, using neonatal, paediatric and adult flow sensors (Castle et al., 2002). CO$_2$SMO Plus measures of resistance and compliance were accurate with an ETT in situ. In the presence of an ETT leak over 20% of the delivered tidal volume or inspiratory pressure, resistance and compliance measures were overestimated (Main et al., 2001). Similarly, dead space calculations using measurements recorded by the CO$_2$SMO Plus were found to be accurate in ventilated infants and children when ETT leak was minimised (Riou et al., 2004).

Reliability of tidal volume (Castle et al., 2002; Main et al., 2004), resistance (Main et al., 2004), compliance (Main et al., 2004) and dead space measurements (Riou et al., 2004) using the CO$_2$SMO Plus was dependent on minimal ETT leak and minimal alteration of the participants' ventilation parameters (Castle et al., 2002). Three studies found the CO$_2$SMO Plus to be responsive to change as

103

a result of CPT, detecting significant changes in flow, pressure, volume and dead space measurements following CPT intervention in ventilated infants and children (Gregson et al., 2007; Main et al., 2004; Main & Stocks, 2004).

4.3.4.1.2 $NICO_2$

Two studies (Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015) reported responsiveness of the $NICO_2$ respiratory monitor when measuring CPT effects in ventilated infants and children. As both studies reported on the same sample, they were considered together. The $NICO_2$ was responsive to changes in tidal volume, compliance and resistance as a result of CPT in ventilated infants in children. No validity or reliability data for the $NICO_2$ were identified.

4.3.4.1.3 Ventilators

Studies identified in the initial search of this systematic review did not report details of the specific ventilators used to measure respiratory mechanics in ventilated infants and children. Therefore, studies that reported clinimetric properties of commonly used paediatric ventilators were included to evaluate this tool. Four studies were identified that reported on validity and reliability of ventilator-derived measures (Cannon et al., 2000; Castle et al., 2002; Heulitt et al., 2009; Kim et al., 2015). All studies reported on Servo ventilators; two on the Servo 300 model (Cannon et al., 2000; Castle et al., 2002) and two more recently on the Servo-I model (Heulitt et al., 2009; Kim et al., 2015).

The validity of the ventilator to measure tidal volume against a pneumotachometer inserted into the patient circuit at the airway opening was evaluated in all studies (Cannon et al., 2000; Castle et al., 2002; Heulitt et al., 2009; Kim et al., 2015). Differences between the two measurements were consistently shown, with reported variations as much as 64% underestimation of the ventilator-displayed tidal volumes when measured against the pneumotachometer values in ventilated infants (Castle et al., 2002). Within and between subject error was measured and was shown to be influenced

104

by the pressure change during the breath, the magnitude of the tidal breath and the circuit size (Castle et al., 2002).

4.3.4.3 Gas exchange

No studies were identified that reported on the clinimetric properties of ABG analysis in ventilated infants and children, though three reported on the validity of transcutaneous oxygen saturation (SpO_2) (Das, Aggarwal, & Aggarwal, 2010; Khemani et al., 2012; Ross, Khemani, & Newth, 2013). Measurement bias, the difference between oxygen saturations measured through transcutaneous oximetry compared to saturations obtained through ABG analysis, was used to evaluate validity in two studies (Das et al., 2010; Ross et al., 2013). Measurement bias was used to compare the validity of the saturation probe when placed in different locations on ventilated infants, with the highest accuracy reported from measurements taken from the sole of the patient's foot, independent of the saturation range being measured (Das et al., 2010). Higher measurement bias, and therefore lower accuracy, was reported for transcutaneous oxygen saturations measured in ranges less than 85%, in particular being overestimated compared to corresponding arterial saturation values (Ross et al., 2013). Oxygenation index and PaO_2/FiO_2 measurements derived from transcutaneous oxygen saturations were found to be valid compared to those using arterial oxygenation values. Transcutaneous SpO_2 measurements were highly sensitive in estimating PaO_2/FiO_2 measurements to identify acute lung injury and acute respiratory distress syndrome (Khemani et al., 2012).

105

4.4 Discussion

This is the first systematic review to investigate measurement tools used to assess CPT effects in mechanically ventilated infants and children and to evaluate the clinimetric properties of these tools. Eight measurement tools were identified. However few tools were found to have reported clinimetric data and the methodological quality of studies underpinning this data were generally low.

The tools identified in this systematic review measured the effects of CPT on secretion clearance, respiratory mechanics, radiological appearance of the lung and gas exchange in ventilated infants and children. Identified tools included those that required specialised equipment and software, such as portable respiratory monitors, ABG and CXR, as well as more readily available tools such as pulse oximetry and secretion weight. No tools identified in this review were specifically designed to measure CPT effects in ventilated infants and children.

The most commonly described tools in this review measured respiratory mechanics and primarily included portable respiratory monitors such as the CO_2SMO Plus and $NICO_2$. The emergence of these portable respiratory monitors in the 1990's provided physiotherapists with a means of measuring changes in flows, pressures and volumes through the placement of these devices directly into the circuit of the ventilated infant or child during CPT (Hammer & Newth, 1995). The potential of these monitors to provide insight into the effect of CPT on lung function is reflected in the number of studies utilising these tools (Almeida et al., 2005; Deakins & Chatburn, 2002; Gregson et al., 2012; Main et al., 2004; Main & Stocks, 2004; Tannenbaum et al., 2007).

Respiratory monitors provided a range of respiratory mechanics measures including expiratory and inspiratory flow rates (Gregson et al., 2012; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015) as well as derived measurements of airway resistance (Almeida

106

et al., 2005; Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Tannenbaum et al., 2007), lung compliance (Almeida et al., 2005; Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Tannenbaum et al., 2007), tidal volume (Almeida et al., 2005; Deakins & Chatburn, 2002; Gregson et al., 2012; Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Tannenbaum et al., 2007), and anatomical and physiological dead space (Almeida et al., 2005; Main & Stocks, 2004). Latter measurements, such as anatomical and physiological dead space, potentially reflect measures that might be more sensitive to CPT effects in ventilated infants and children compared to measures such as tidal volume (Main & Stocks, 2004). However only a small number of studies to date have investigated dead space measurements in response to CPT, suggesting that these tools remain poorly understood and potentially underutilised (Main & Stocks, 2004).

The number of studies reporting clinimetric properties of validity, reliability and responsiveness for each identified measurement tool varied. Overall the yield and methodological quality of retrieved studies was generally low, with only fourteen relevant studies identified with quality ranging from poor to good. Of the eight measurement tools, only the CO_2SMO Plus respiratory monitor had been investigated for all clinimetric properties of interest in this review; validity, reliabilty and responsiveness. This raises uncertainty around the use of other tools to measure CPT effects in ventilated infants and children suggesting there is a need for further clinimetric investigation to support their use.

Respiratory mechanics measurements, derived from both the CO_2SMO Plus and $NICO_2$ respiratory monitors, and directly from the patient ventilator, yielded the highest number of clinimetric studies; a promising finding considering the popularity of these tools in the identifed CPT studies in ventilated infants and children. Importantly, measures derived directly from the ventilator were found to be inaccurate when compared to measures recorded by the CO_2SMO Plus respiratory monitor.

107

Specifically, tidal volume measures were consistently over or underestimated when measured at the ventilator. This highlights the importance of using a separate respiratory monitor placed at the airway opening to ensure accurate tidal volume measures on which to judge treatment effects (Castle et al., 2002).

The CO_2SMO Plus was valid and reliable for measuring resistance, compliance and dead space in ventilated infants and children (Cannon et al., 2000; Castle et al., 2002; Main et al., 2001; Riou et al., 2004). However, the CO_2SMO Plus was neither valid, nor reliable in the presence of an ETT leak greater than 20% of the prescribed tidal volume or inspiratory pressure (Main et al., 2001). This is an important consideration for physiotherapists working with ventilated infants and children, particularly as most studies were undertaken in fully sedated and paralysed children (Castle et al., 2002; Main et al., 2001; Riou et al., 2004). The use of heavy sedation and/or paralysis may assist in reducing ETT leak but may not necessarily reflect the majority of patients in the PICU (A. Wolf, 2012). No studies were found investigating validity or reliability of the $NICO_2$, although the $NICO_2$ was shown to be responsive to CPT (Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015). This suggests that as a tool to measure CPT effects in ventilated infants and children, the $NICO_2$ should be used with caution until further investigation of clinimetric propertise has been undertaken.

ABGs were well reported in CPT studies in ventilated infants and children (Elizabeth et al., 2016; Galvis et al., 1994; Main et al., 2004; Main & Stocks, 2004; Schultz et al., 2005; Soundararajan & Thankappan, 2015) however no studies were identifed investigating clinimetric properties in ventilated infants and children. ABGs were validated in adults when first developed in the 1950's (Severinghaus, 1966, 1968, 2002; Severinghaus & Astrup, 1986) and for half a century this has guided the use of ABGs as the main method of quantifying gas exchange (Severinghaus, 2002). ABGs are

considered a valid tool for measuring gas exchange (Severinghaus, 2002) and have been used to measure changes in gas exchange thought to result from improvements in ventilation distribution following CPT. However, the lack of paediatric validation and reliability identifies a need to evaluate these tools if they are to be used by physiotherapists to evaluate CPT effects in ventilated infants and children. Measurement of transcutaneous oxygenation through pulse oximetry may be an alternative to ABG. Pulse oximetry was found to be valid in studies with good methodological quality (Khemani et al., 2012; Ross et al., 2013) and is used by physiotherapists clinically to monitor immediate changes in oxygenation in response to CPT in ventilated children. It is reasonable to suggest that both ABGs and pulse oximetry may have a place measuring CPT effects in ventilated infants and children, however further clinimetric data in this population is essential to ensure these tools are robust.

Interestingly tools commonly available in clinical settings were infrequently used in ventilated paediatric cohorts and had little clinimetric investigation. CXR (Deakins & Chatburn, 2002; Galvis et al., 1994) and secretion weight (Tannenbaum et al., 2007) for example, were only reported in a small number of studies despite being used clinically by physiotherapists as an indicator for CPT intervention and to monitor CPT effect (Marques et al., 2006). However objectively measuring secretion volume or weight in this population is difficult. Secretion wet and dry weight have been successfully used in paediatric cystic fibrosis (Konstan, Stern, & Doershuk, 1994; Thomas, Cook, & Brooks, 1995; Varekojis et al., 2003) and ventilated adult cohorts (Berney & Denehy, 2002; Berney, Denehy, & Pretto, 2004; Dennis, Jacob, & Budgeon, 2012) where secretion load is typically high. However secretion volume encountered in ventilated infants and children may not be as large and may vary significantly depending on the child's age, size and underlying pathology (Marques et al., 2006; Walsh et al., 2011). Similarly, the stethoscope was infrequently reported as a tool to measure

109

CPT effects in ventilated infants and children. While used readily in clinical settings, the accuracy of auscultation findings are influenced by the quality of the stethoscope, the age and size of the child, the underlying lung pathology and the experience and perception of the physiotherapist (Marques et al., 2006) making it a potentially subjective, unreliable and insensitive measure of CPT effect.

No single measurement tool was identified that had clinimetric rigour and the ability to measure CPT effects on the distribution of ventilation in ventilated infants and children. Tools measuring respiratory mechanics measures, such as CO_2SMO Plus and $NICO_2$, show some promise in informing physiotherapists about the effect of CPT on lung function (Gregson et al., 2012; Main et al., 2004; Main & Denehy, 2016; Main & Stocks, 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015). However measures of respiratory mechanics are unable to explain the underlying physiological processes responsible for the mechanical changes measured by these tools. To understand these physiological effects, tools that can measure distribution of ventilation may be beneficial in explaining CPT effects in ventilated infants and children (Frerichs et al., 2017).

To better understand how CPT may affect ventilation distribution in ventilated infants and children, tools are required that can measure changes in global and regional lung aeration. Lung ultrasound (Leech et al., 2014) and computerised lung sound monitoring (Ntoumenopoulos & Glickman, 2012) have been described in ventilated adults cohorts to measure CPT effects but have yet to be investigated in ventilated infants and children. An alternative tool that has been used successfully in ventilated infants and children is EIT, which is emerging as a potential new tool to measure real time changes in regional ventilation distribution (Hough, Flenady, Johnston, & Woodgate, 2008; Main & Denehy, 2016). Electrical impedance tomography may provide specific information about CPT effects on global and regional ventilation distribution in ventilated infants and children however

further research investigating its use as a tool to measure the effects of CPT in this population is required.

4.4.1 Limitations

One limitation of this review was the decision not to include unpublished studies or studies in progress. This decision was made to ensure studies included for review were peer-reviewed. However it is possible that additional or novel tools for measuring CPT effects in ventilated infants and children may have been missed as a result of not considering these studies. The decision to only include tools in this review that measured CPT effects on aspects of lung function, specifically secretion clearance, ventilation and gas exchange, may have also limited our findings. This review chose not to include tools that measured the technique of delivery of specific CPT techniques, for example chest wall vibrations. The force and pressure delivered during chest wall vibrations has been measured and paired with respiratory mechanics monitors such as the CO_2SMO Plus (Gregson et al., 2011; Gregson et al., 2007). This review did not include such tools as when considered alone, CPT effects on lung function were not measured, which was the primary aim of this study.

The included age range in this review and the definition of CPT were kept broad in the inclusion criteria for this review to reflect clinical reality of delivering CPT to ventilated infants and children. It was also expected that there would be a small yeild of eligible studies and broad inclusion criteria potentially allowed more studies to be considered for inclusion in this review. Broadly defining the age range and CPT definition however may have limited the generalisability of results from this review. Future systematic reviews using more specific inclusion criteria may be beneficial to identify whether specific tools are more appropriate for different ages or to measure more specific CPT techniques.

111

4.5   Conclusion

Measurement tools used by physiotherapists working with ventilated infants and children are used to evaluate effects of CPT on secretion clearance, respiratory mechanics, radiological appearance of the lung and gas exchange. The majority of identified tools lack high quality evidence of validity, reliability and responsiveness, making it difficult to recommend one tool over another. When choosing a measurement tool, physiotherapists working in PICU must consider the aim of the intervention being delivered, the underlying pathology being treated and importantly, the tool's clinimetric properties, not just availability or convenience. The CO_2SMO Plus respiratory monitor is the tool most supported by clinimetric data however only provides measures of respiratory mechanics and cannot appreciate regional ventilation changes resulting from CPT. New tools such as EIT may provide such information, however further research is required to support their use in ventilated infants and children in response to CPT.

5. Study 2: The effects of chest physiotherapy on regional lung volume changes in ventilated children using Electrical Impedance Tomography

This chapter describes Study 2 of this two-part research program. Study 1 of this research program did not identify a tool that demonstrated robust clinimetric properties capable of measuring changes in ventilation distribution as a result of CPT in ventilated infants and children. Electrical impedance tomography is emerging as a potential new measurement tool able to measure real time changes in ventilation distribution by the bedside. As a measurement tool for physiotherapists, EIT may be able to provide new and more specific information about the effects of CPT in ventilated infants and children by quantifying changes in ventilation distribution in response to CPT. EIT was selected as the measurement tool of choice in Study 2 to compare the effects of CPT and routine airway clearance on ventilation distribution in ventilated infants and children.

5.1 Introduction

CPT is a well-accepted adjunct to the intensive care management of children receiving mechanical ventilation that aims to improve secretion clearance, and subsequently ventilation and gas exchange, beyond that achieved through routine airway clearance alone (Main et al., 2004). However despite widespread use, high quality research of CPT effects in ventilated children remains limited (Argent & Morrow, 2004; Krause & Hoehn, 2000). This is in part due to the difficulty in studying a critically unwell population and as a result of variations in study design, patient characteristics and measurement tools used (Almeida et al., 2005; Gregson et al., 2012; Main et al., 2004; Main & Stocks, 2004). As a result, discrepencies exist in the reported effects of CPT on ventilation (Almeida et al., 2005; Main et al., 2004) and gas exchange (Almeida et al., 2005; Hussey, Hayward, Andrews, Macrae,

& Elliot, 1996; Main et al., 2004), making it difficult to draw meaningful and robust conclusions on which to base clinical practice (Johnston et al., 2012; Walsh et al., 2011).

CPT effects are often measured using ABG analysis (Galvis et al., 1994; Hussey, Hayward, Andrews, Macrae, & Elliot, 1996; Main et al., 2004; Main & Stocks, 2004; Marques et al., 2006; Schultz et al., 2005), respiratory function measures (Main et al., 2004; Main & Stocks, 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015), radiological changes (Marques et al., 2006) and changes in physiological parameters such as respiratory rate and heart rate (Almeida et al., 2005; Deakins & Chatburn, 2002; Main & Denehy, 2016). While providing insight into the effect of CPT on lung function, these measures do not provide information on the distribution of ventilation within the lung resulting from CPT. Therefore, a tool is needed that can quantify changes in regional ventilation distribution in response to CPT to better understand CPT effects in ventilated infants and children. One tool that shows promise is EIT.

EIT is a measurement tool which allows real-time imaging of lung ventilation and perfusion from which measurements of ventilation distribution can be derived (Frerichs et al., 2017). EIT can safely and non-invasively examine global and regional changes in lung physiology in ventilated infants and children (Frerichs et al., 2017) including information about tidal ventilation (Frerichs et al., 2017), end expiratory lung volume (Frerichs et al., 2017) and the distribution of ventilation within different regions of the lung (Dunster, Friese, Fraser, Cowin, & Schibler, 2012; Zhao et al., 2009; Zhao et al., 2014). EIT has been previously validated against computed tomography (Gunnar et al., 2013; Victorino et al., 2004) and positron emission tomography (Richard et al., 2009) in ventilated adult (Victorino et al., 2004) and animal studies (Gunnar et al., 2013; Richard et al., 2009), against CXR in a small number of preterm infant studies (Miedema, Frerichs, de Jongh, van Veenendaal, & van Kaam,

2011; van der Burg et al., 2014) and shown to be reliable in ventilated animal studies (Frerichs et al., 2007).

EIT is able to provide information regarding regional ventilation distribution at the bedside, making it a potentially valuable tool for investigating how CPT affects lung function in ventilated infants and children. It is important to differentiate effects between CPT and routine airway clearance. Differences between CPT and ETT suction have been described with respect to respiratory mechanics and gas exchange (Main et al., 2004) but it is unclear if there are different effects on ventilation distribution. CPT aims to improve regional distribution of ventilation, and thereby gas exchange, to under-ventilated lung regions through the mobilisation and removal of airway secretions from small and larger airways (Main et al., 2004). In contrast, ETT suction is primarily used to clear secretions from the trachea and therefore is not considered to affect the distribution of ventilation within the lungs (Main et al., 2004). EIT has previously been used in mechanically ventilated infants and children to measure the effects of ETT suctioning (Hough et al., 2014; Jauncey-Cooke et al., 2012; van Veenendaal et al., 2009) and components of CPT such as body positioning (Hough et al., 2013; Lupton-Smith et al., 2017) on regional ventilation distribution. However, to date no study has used EIT to investigate the effect of CPT on regional ventilation distribution in ventilated infants and children or compared these effects to those of ETT suction alone.

The aim of this study was therefore to compare the effects of CPT with routine airway clearance on ventilation distribution and gas exchange in ventilated infants and children. A secondary aim was to investigate whether lung recruitment manoeuvres enhance the effect of CPT on ventilation distribution and gas exchange in ventilated infants and children.

5.2 Method

5.2.1 Design

This was a secondary anaylsis of data collected within a prospective randomised controlled trial investigating the effect of recruitment manoeuvres on ventilated children following ETT suctioning using EIT (Jauncey-Cooke, 2012). A subgroup of study participants from both recruitment manoeuvre groups received CPT for intensive airway clearance during the study period. Data were opportunistically collected before and after CPT to measure CPT effects on ventilation distribuition. Ethical approval was obtained to retrospectively utilise data collected as part of the randomised controlled trial through the Mater Health Services Human Research Ethics Committee (HREC/17/MHS/72 (2012-25)) (Appendix 5) and through the Australian Catholic University Human Research Ethics Committee (2017-153R) (Appendix 5). Separate consent was also received to use the data collected within the randomised controlled trial from the primary investigators of that study (Appendix 6).

5.2.2 Participants

Children receiving treatment within a tertiary PICU at the Mater Children's Hospital, Brisbane were considered eligible for this study. Eligibility criteria included any infant or child aged from birth to sixteen years who required mechanical ventilation for longer than 12 hours and had an arterial line in situ. Preterm infants < 36 weeks gestational age were excluded as were children who had evidence of an air leak on CXR (pneumothorax, pneumomediastinum or pneumopericardium), were deemed haemodynamically unstable (shock, hypovolemia, hypotension defined as blood pressure below acceptable level for age), had chest wounds or dressings prohibiting the use of electrocardiograph electrodes or who had planned interventions that precluded the collection of uninterrupted data collection for the duration of the study period (140 minutes).

Following enrolment, participants were randomised into one of three groups; to receive a recruitment manoeuvre, either double PEEP or incremental PEEP, or to receive no recruitment manoeuvre. Randomisation was undertaken using sequentially numbered sealed opaque envelopes, concealed until the study period had commenced. CPT was performed if clinically indicated in all groups.

5.2.3 Intervention

CPT was instigated in participants when it was deemed to be clinically necessary by the same experienced clinical intensive care physiotherapist blinded to the recruitment manoeuvre group allocation. Indications for CPT included evidence of atelectasis on CXR, evidence of retained secretions including adventitious sounds on ausculation, increase in ventilatory requirements or clinical evidence of retained secretions (Main & Denehy, 2016). CPT was defined as any combination of percussion, manual hyperinflation with chest wall vibrations followed by open ETT suctioning (Main & Denehy, 2016). Normal saline installation was used as required when secretions were determined by the treating physiotherapist to be overly tenacious. All CPT interventions were undertaken by the same treating physiotherapist and were individualised based on clinical assessment. Assessment and treatment decisions reflected clinical practice in the unit where the study took place and usual safety practices were observed.

Immediately following ETT suction participants received either a double PEEP, incremental PEEP or no recruitment manoeuvre. The double PEEP manoeuvre involved doubling the baseline PEEP for two minutes. The incremental PEEP manoeuvre involved sequential increases in PEEP in 4 cmH_2O increments up to a maximum of 18 cmH_2O, with each increment being held for 60 seconds. The

physiotherapist undertaking the CPT intervention was blinded to whether participants received the double PEEP, incremental PEEP or no recruitment manoeuvre.

For this secondary analysis CPT study, participants receiving CPT were considered the experimental group. Those not requiring CPT underwent routine airway clearance and were considered the control group. Due to this study being a secondary analysis of data collected within a larger prospective randomised controlled trial, participants in the current study were classified into one of six groups:

    (1) CPT + double PEEP manoeuvre (CPT-double),

    (2) CPT + incremental PEEP manoeuvre (CPT-incremental),

    (3) CPT with no recuitment manoeuvre (CPT-only),

    (4) Routine airway clearance + double PEEP manoeuvre (control-double),

    (5) Routine airway clearance + incremental PEEP manoeuvre (control-incremental) and

    (6) Routine airway clearance with no recruitment manoeuvre (control-only).

5.2.4 Outcome measures

The primary measures of interest were those of ventilation distribution, measured using EIT. Secondary measures were measures of gas exchange, obtained using both ABG and pulse oximetry, and physiological state, measured using transcutaneous electrocardiograph and respiratory monitoring.

EIT is a non-invasive, radiation-free bedside imaging tool that uses the resistivity of different tissues in the thorax to electrical current to generate a map of ventilation distribution within the lungs (Frerichs et al., 2017). Cross-sectional lung images are derived from measurements of surface electrical potentials resulting from an excitation with known small electrical currents (5mAmp and 50 kHz) (Barber & Brown, 1989). Voltage measurements and current injections occur between pairs of conventional self-adhesive surface electrodes of a 16-electrode array placed around the circumference of the chest wall (Barber & Brown, 1989). Images are then generated from the collected potential difference and the known excitation currents using weighted back-projection in a 32x32 pixel matrix (Brown, 2003). Each single pixel within the matrix represents the instantaneous local impedance. Tidal impedance changes can be measured for each individual pixel or averaged across the whole lung matrix to estimate regional tidal volume changes (Frerichs et al., 2017).

EIT measures ventilation distribution and this study specifically considered measures of tidal ventilation, EELV and ventilation distribution measures of global inhomogeneity and geometric centre. All EIT measurements in this study were collected using a Göttingen Goe-MF II EIT system (VIASYS Healthcare, Hochberg, Germany) by a nurse trained in the use of the equipment. Software provided with the equipment was used for data acquisition and reconstruction of functional relative EIT images. Data were further analysed off-line using Matlab 7.7 (R2008b: TheMathWorks, Natick, MA) by the candidate who was blind to group allocation and recruitment intervention. EIT data were band-pass filtered to include the first and second harmonic of the respiratory rate (Dunlop et al., 2006) and cardiac interference was eliminated using a cut-off mask of 20% of the peak impedance signal (Dunlop et al., 2006; Pulletz et al., 2006). To ensure good quality data, sections for analysis

were chosen using predetermined criteria of data reflecting three to five continuous mandatory breaths with stable tidal volume and end-expiratory lung volume (Hough et al., 2013).

5.2.4.1.1   Tidal Ventilation

Tidal ventilation changes were evaluated using EIT through the measurement of regional impedance amplitudes. Impedance amplitudes reflect the magnitude of regional tidal volume change within a subject over time. Tidal ventilation changes were referred to as impedance amplitudes changes and were calculated for the lung as a whole (global impedance amplitude) by averaging differences in impedance between end-expiration and end-inspiration for individual pixels. To account for the unequal number of pixels analysed in each region of interest, the average amplitude for each region of interest is reported (Hough et al., 2013). Global amplitudes were calculated for all participants at baseline and at 30, 60 and 120 minute intervals following ETT suction by a nurse trained in the use of the equipment.

5.2.4.1.2   End Expiratory Lung Volume

End expiratory lung volume reflects the relative impedance measured at end-expiration and can be considered comparable to functional residual capacity (Hough et al., 2013). EELV was calculated for the whole lung (global) and for anterior (non-dependent) and posterior (dependent) lung regions and data were collected for all participants at baseline and at 30, 60 and 120 minute intervals following ETT suction by a nurse trained in the use of the equipment.

5.2.4.1.3   Global inhomogeneity and Geometric centre

Global inhomogeneity and geometric centre are measures derived from EIT describing the distribution of ventilation within different lung regions (Zhao et al., 2009). Measures of global inhomogeneity and geometric centre have been shown to have a high level of agreement with

hyperpolarised helium-3 magnetic resonance imaging scans in ventilated animal studies (Dunster, Friese, Fraser, Galloway, et al., 2012).

Global inhomogeneity describes the heterogeneity of ventilation distribution within the lung (Zhao et al., 2009). Larger global inhomogeneity indices indicate greater ventilation inhomogeneity (Hough et al., 2013). Global inhomogeneity indices allow for comparison of ventilation distribution homgeneity between individual subjects and within subjects in response to interventions and are independent of body position (Zhao et al., 2009). Reliability (Zhao et al., 2014) and inter-patient comparability (Zhao et al., 2009) have been previously demonstrated for global inhomogeneity in ventilated and healthy adult populations. Global inhomogeneity indices were calculated from the lung image using the median value of the end-inspiratory to end-expiratory difference for that image (Zhao et al., 2009). The sum of the absolute difference between these values and each pixel reflects the tidal volume distribution within the lung and this was normalized to the total number of pixels in the tidal image to quantify homogeneity (Hough et al., 2013; Hough et al., 2014).

Geometric centre is a measure of ventilation distribution that quantifies the location of the centre of ventilation in the anterior-posterior plane of the lung (Dunster, Friese, Fraser, Galloway, et al., 2012; Frerichs, Dargaville, van Genderingen, Morel, & Rimensberger, 2006; Frerichs et al., 1998). Geometric centre was expressed as a percentage of the anterior to posterior ventilation within the lung, with a higher percentage reflecting a relatively more anterior (non-dependent) centre of ventilation and a smaller percentage reflecting a more posterior (dependent) centre of ventilation (Dunster, Friese, Fraser, Galloway, et al., 2012; Frerichs et al., 2006; Frerichs et al., 1998). An increase or decrease in the geometric centre as a result of CPT was considered to reflect a respective shift in preferential ventilation anteriorly or posteriorly.

121

Measures of global inhomogeneity and geometric centre were collected for all participants at baseline and at 30, 60 and 120 minute intervals following ETT suction by a nurse trained in the use of the equipment.

5.2.4.2 Gas exchange

CPT aims to improve oxygenation and CO_2 removal by improving ventilation to under-ventilated regions of lung (Oberwaldner, 2000). Gas exchange measures were recorded in Study 2 to identify whether hypothesized changes in regional ventilation distribution measured by EIT were reflected by concurrent changes in gas exchange.

Arterial blood samples (0.5 ml) were collected by the clinical nursing staff using a 1 ml heparinised syringe (Ref. 3100-25, Westmed, Tucson, Arizona) via the arterial line at baseline and at 30 minutes and 120 minutes intervals. ABG analysis was undertaken within 5 minutes of collection using an ABL-837 arterial blood gas analyser loader with software version 6.10108 (Radiometer Copenhagen, Denmark). PaO_2/FiO_2 (P/F) ratios were manually calculated from the ABG results. Transcutaneous oxygen saturations measurements were continuously recorded throughout the duration of the study as part of routine clinical care of participants with discrete measurement recorded at baseline and at 30, 60 and 120 minute intervals by study personnel not directly involved in the clinical care of the participant.

5.2.4.3 Physiological measurements

Measurements of heart rate and respiratory rate were recorded during the study to monitor for physiological sequelae of CPT and ETT suction. Heart rate and respiratory rate were continuously recorded throughout the duration of the study as part of routine clinical care of participants. Discrete measurements were recorded at baseline and at 30, 60 and 120 minute intervals by study personnel

not directly involved in the clinical care of the participant. Changes to baseline mode of ventilation and fraction of inspired oxygen during the study period were also recorded by study personnel.

5.2.5 Procedure

The primary investigator of the randomised controlled trial undertook all participant screening, enrolling and consenting. Following enrolment, participants were randomised by the primary investigator using sequentially numbered sealed opaque envelopes to receive one of two lung recruitment manoeuvre or no recruitment manoeuvre following ETT suctioning. All participants were pharmacologically sedated and positioned in supine. Where possible, ventilator parameters were kept stable and changes only made if clinically warranted.

Demographic and clinical data were recorded for all participants by the primary investigator of the randomised controlled trial. Demographic data recorded included participant age and weight. Clinical data included ETT size and presence of cuff, baseline ventilation characteristics (mode, respiratory rate, peak inspiratory pressure, mean airway pressures and PEEP), baseline gas exchange parameters (fraction of inspired oxygen (FiO_2), PaO_2 and $PaCO_2$). Reason for ETT intubation was classified according to primary respiratory pathology (bronchiolitis or pneumonia) or non-respiratory pathology (involving any other pathology, injury or organ dysfunction).

At baseline, EIT recordings (duration 60s at 13Hz), ABG, transcutaneous oxygen saturations and physiological measures were taken for all participants. Following this, CPT participant groups (CPT-double, CPT-incremental and CPT-only) received CPT as required, followed by ETT suctioning. Those who did not receive CPT (control-double, control-incremental and control-only) received routine airway clearance according to the Mater Children's Hospital Tracheal Suctioning Protocol Policy (Appendix 3). Following ETT suctioning and reconnection to the ventilator, participants in the CPT-double, CPT-incremental, routine airway clearance-double and routine airway clearance-

incremental groups received a lung recruitment manoeuvre. Participants in CPT-only and routine airway clearance-only groups were reconnected to the ventilator with no changes made to baseline ventilation parameters.

Further EIT measurements (duration 60 second at 44Hz), ABG samples, transcutaneous oxygen measures and physiological parameters were collected at 30, 60 and 120 minutes post ETT suctioning in all groups by the primary investigator of the randomised controlled trial

5.2.6 Statistical analysis

EIT data were downloaded by the primary investigator of the randomised controlled trial using a Dell laptop connected to the Göttingen Goe-MF 11 EIT tomography and using software provided with the EIT equipment (Science EIT Software, University of Göttingen v1.02). EIT data were stored on a Maxtor hard drive by the primary investigator of the randomised controlled trial and EIT, ABG and ventilation data files were generated for each participant using a standardised naming convention. Data were checked for entry errors and then analysed off-line using Matlab 7.7 (R2008b: TheMathWorks, Natick, MA) by the candidate who was blind to group allocation and recruitment intervention. Missing data were managed through the use of the chosen statistical analysis, the linear mixed model (Krueger & Tian, 2004).

Results are presented as means and confidence intervals or standard deviation for the demographic data and for all baseline clinical data. For the whole sample, baseline data were checked for normality using Kolmogorov-Smirnov statistic and differences between the experimental (those who received CPT) and control (those who received routine airway clearance) groups were determined using an independent samples T-test or non-parametric equivalent.

To determine differences between the experimental and control groups over time (baseline, 30min,

124

60min, 120min) on regional ventilation distribution, gas exchange and physiological state in ventilated infants and children a linear mixed model was used to determine differences and interactions between; those who did and didn't receive CPT; over the four time periods (baseline, 30min, 60min, 120min) for each dependent variable (amplitude, EELV, global inhomogeneity, geometric centre, PaO_2, $PaCO_2$, FiO_2, PF, SpO_2, SpO_2/FiO_2, respiratory rate and heart rate).

To determine whether lung recruitment manoeuvres enhanced the effect of CPT on regional ventilation distribution, gas exchange and physiological state in ventilated infants a linear mixed model was used to determine differences and interactions between the six treatment groups (CPT-double, CPT- incremental, CPT-only, control-double, control-incremental and control only) for each dependent variable (amplitude, EELV, global inhomogeneity, geometric centre percentage PaO_2, $PaCO_2$, FiO_2, PF, SpO_2, SpO_2/FiO_2, respiratory rate and heart rate).

Significance for all statistical analyses was considered as p-value<0.05. All statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Somers, New York) in consultation with a statistician.

5.3   Results

5.3.1   Flow of participants through the study

Sixty children (33 male, 55%) were enrolled and participated in the randomised controlled trial. Seventeen participants (28%) received CPT and forty-three participants (72%) received no CPT across the three participant groups (double PEEP, incremental PEEP and no recruitment manouevre). Figure 5.1 illustrates participant numbers and secondary analysis study within the randomised controlled trial. All participants were ventilated using either Drager Evita 4 or Evita XL ventilator (Dragerwerk AG & Co. Lubeck, Germany).

```
┌─────────────────────────────────────────┐
│   Mechanically ventilated participants   │
│          randomised (n = 60)             │
└─────────────────────────────────────────┘
```

Double PEEP (n = 20)	Incremental PEEP (n = 20)	No recruitment manoeuvre (n = 20)

CPT (n = 6)	Routine airway clearance (n = 14)	CPT (n = 4)	Routine airway clearance (n = 16)	CPT (n = 7)	Routine airway clearance (n = 13)
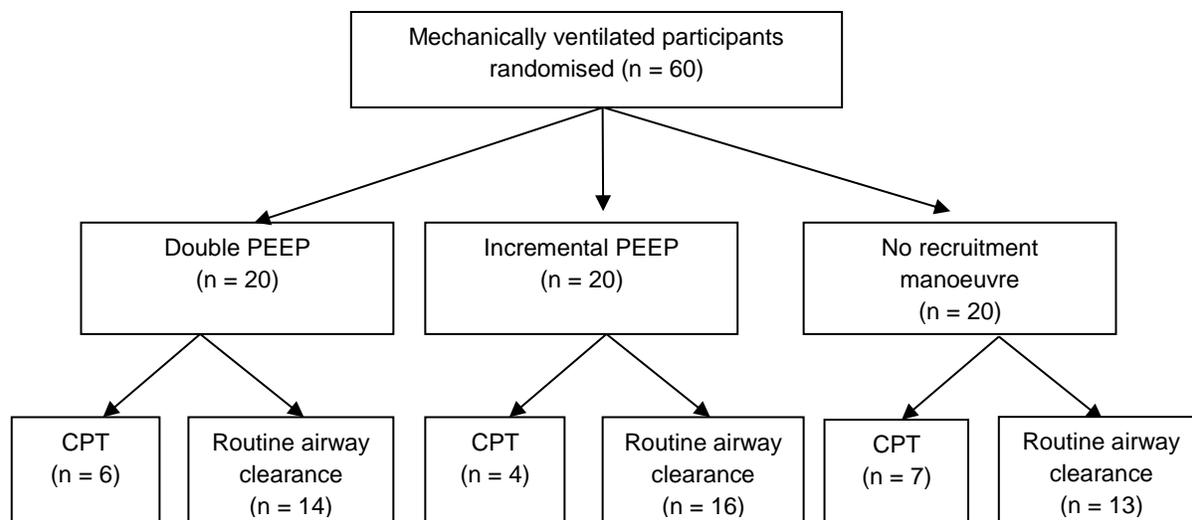
Figure 5.1   Diagram of secondary analysis CPT study within randomised controlled study design

5.3.2   Participant characteristics

Participant demographics, baseline ventilation and oxygenation characteristics and primary reason for intubation for the CPT and routine airway clearance groups are reported in **Error! Reference source not found.**. No differences were found at baseline between participants who received CPT and those who received routine airway clearance in all parameters except $PaCO_2$, which was significantly higher in the CPT group compared to the routine airway clearance group (p=0.003).

Table 5.1   **Participant characteristics at baseline**

Characteristic	CPT	Routine airway clearance	Sig (p-value)
	(n=17)	(n=43)	
Age *(months)*, mean (SD)	28.7 (49.3)	47.8 (55.8)	0.221
Age range *(months)*	(0.75-156)	(0.25-180)	
Weight *(kg)*, mean (SD)	11.1 (11.4)	16.6 (14.2)	0.163
ETT size (Fg)	4.2 (1.1)	4.5 (1.2)	0.328
Baseline FiO_2, mean (SD)	0.4 (0.1)	0.4 (0.1)	0.834
Baseline PaO_2, *(mmHg)* mean (SD)	89.4 (30.2)	96.4 (29.6)	0.411
Baseline $PaCO_2$, *mmHg)* mean (SD)	58.7 (11.1)	48.6 (11.5)	0.003
Baseline P/F ratio, mean (SD)	282.3 (165.9)	286.9 (109.6)	0.901
Baseline RR (*breaths/ min*), mean (SD)	34.7 (17.5)	28.7 (11.2)	0.121
Baseline PEEP (*cmH_2O*), mean (SD)	7.0 (2.4)	7.8 (2.2)	0.239
Baseline PIP (*cmH_2O*, mean (SD)	21.1 (7.0)	21.2 (4.3)	0.932
Baseline MAP (*cmH_2O*), mean (SD)	11.0 (3.6)	11.0 (3.0)	0.939
Ventilation mode, n (%)			
SIMV	16 (94%)	39 (91%)	0.424
PCV	0	1 (2.3%)	
PSV	1 (6%)	2 (4.7%)	-
CPAP	0	1 (2.3%)	-
Reason for intubation (n)*			-
Primary respiratory pathology	10	21	0.226
Secondary respiratory pathology	7	22	-

Abbreviations: CPAP-Continuous positive airway pressure, CPT-Chest physiotherapy, ETT-Endotracheal tube, FiO_2-Fraction of inspired oxygen, MAP-Mean airway pressure, PaO_2-Partial pressure of arterial oxygen, PCV-Pressure controlled ventilation, PEEP-Positive end expiratory pressure, PIP-Peak inspiratory pressure, PSV-Pressure support ventilation, RR-Respiratory rate, SD-Standard deviation, SIMV-Synchronized intermittent mandatory ventilation
*Primary respiratory pathology = bronchiolitis and pneumonia; Secondary respiratory pathology = airway management, sepsis, immersion injury, seizure management, tick paralysis, gastrointestinal bleeding, trauma, neurological injury, Guillain Barre Syndrome, ingestion and renal failure.

5.3.3 CPT effects on tidal ventilation, EELV and ventilation distribution

Mean (SE) tidal ventilation, EELV (global, anterior and posterior) and ventilation distribution (global inhomogeneity, geometric centre) across the four time points (baseline, 30 min, 60 min, 120 min) for intervention groups (CPT, no CPT) are presented in Table 5.2.

5.3.3.1   CPT effects on EIT-derived measures of tidal ventilation, EELV and ventilation distribution

Tidal ventilation was measured using the EIT-derived measure of global amplitude. No differences in global amplitude were found between participants who received CPT compared to routine airway clearance (p=0.745) and no significant interaction effects were observed for CPT over time (p=0.115) (Table 5.2) (Table 5.3).

Global (p=0.00) (Figure 5.2), anterior (p=0.003) (Figure 5.3) and posterior (p=0.00) (Figure 5.4) EELV was significantly greater in participants who received CPT compared to routine airway clearance. An interaction effect was found in the CPT group over time for global EELV (p=0.001) which appeared to increase between the baseline and 30 minute time points (Figure 5.2). There was no interaction between CPT and time for anterior (p=0.072) or posterior (p=0.175) regions.

Table 5.2   Mean (SE) ventilation distribution, gas exchange and physiological measures for experimental (CPT) and control (routine airway clearance) intervention groups across time points (baseline, 30 min, 60 min and 120 min post baseline)

Outcome	Intervention							
	Baseline		30 minutes		60 minutes		120 minutes	
	CPT (n = 17)	Routine airway clearance (n = 43)	CPT (n = 17)	Routine airway clearance (n = 43)	CPT (n = 17)	Routine airway clearance (n = 43)	CPT (n = 17)	Routine airway clearance (n = 43)
Ventilation distribution (relative impedance Δ)								
Global amplitude	0.089	0.058	0.043	0.061	0.050	0.063	0.046	0.061
	(0.015)	(0.10)	(0.016)	(0.10)	(0.016)	(0.10)	(0.015)	(0.10)
Global EELV	-0.007	-0.022	0.104	-0.003	0.107	0.005	0.119	0.008
	(0.021)	(0.013)	(0.022)	(0.013)	(0.021)	(0.013)	(0.021)	(0.013)
Anterior EELV	-0.017	-0.033	0.057	-0.010	0.051	-0.001	0.045	-0.008
	(0.017)	(0.011)	(0.018)	(0.011)	(0.017)	(0.011)	(0.017)	(0.011)
Posterior EELV	0.026	-0.020	0.117	0.010	0.150	0.010	0.164	0.031
	(0.031)	(0.020)	(0.032)	(0.020)	(0.032)	(0.020)	(0.032)	(0.019)
Global inhomogeneity index	0.554	0.503	0.496	0.441	0.459	0.425	0.514	0.483
	(0.025)	(0.016)	(0.026)	(0.016)	(0.027)	(0.016)	(0.026)	(0.016)
Geometric centre (%)	50.49	52.61	49.69	51.84	47.13	50.84	45.80	52.29
	(1.53)	(0.97)	(1.59)	(0.99)	(1.61)	(0.98)	(1.56)	(0.97)
Gas exchange								
PaO_2 (mmHg)	80.56	89.75	87.05	88.69	-	-	82.39	95.15
	(6.47)	(4.03)	(6.54)	(4.06)			(6.47)	(4.06)

Outcome	Intervention							
	Baseline		30 minutes		60 minutes		120 minutes	
	CPT (n = 17)	Routine airway clearance (n = 43)	CPT (n = 17)	Routine airway clearance (n = 43)	CPT (n = 17)	Routine airway clearance (n = 43)	CPT (n = 17)	Routine airway clearance (n = 43)
$PaCO_2$ (mmHg)	59.73 (3.57)	48.60 (2.22)	58.67 (3.65)	53.28 (2.24)	-	-	61.67 (3.57)	49.33 (2.24)
PF ratio	226.15 (30.78)	290.60 (19.28)	245.62 (30.94)	282.82 (19.35)	-	-	241.08 (30.78)	309.42 (19.39)
FiO_2	0.38 (0.03)	0.34 (0.02)	0.38 (0.03)	0.34 (0.02)	0.37 (0.03)	0.34 (0.02)	0.37 (0.04)	0.34 (0.02)
SpO_2 (%)	97.01 (0.85)	97.00 (0.54)	97.45 (0.86)	97.48 (0.54)	98.12 (0.88)	97.60 (0.54)	95.80 (0.91)	97.00 (0.55)
SpO_2/FiO_2	270.47 (18.39)	306.71 (11.63)	272.72 (18.40)	306.63 (11.63)	276.57 (18.14)	306.95 (11.63)	273.15 (18.45)	306.89 (11.64)
Physiological measures								
Respiratory rate *(breaths/ minute)*	32.37 (3.34)	30.71 (2.11)	37.11 (3.38)	31.88 (2.11)	36.49 (3.46)	30.21 (2.11)	39.47 (3.40)	29.08 (2.15)
Heart rate *(beats/minute)*	131.90 (6.31)	125.38 (3.99)	127.25 (6.33)	125.81 (3.99)	128.52 (6.37	123.73 (3.99)	129.86 (6.36)	123.13 (4.02)

Abbreviations: CPT – Chest physiotherapy, EELV – End expiratory level volume, FiO_2 – Fraction of inspired oxygen, HR – Heart rate, n – sample size, PaO_2 – Partial pressure of arterial oxygen, $PaCO_2$ – Partial pressure of arterial carbon dioxide, PF – PaO_2/FiO_2, SE – Standard error, SpO_2 – oxygen saturation, Δ - change

Table 5.3   Mean difference, standard error (SE), significance and 95% confidence intervals (CI) for all outcome measures between CPT and routine airway clearance

	CPT minus Routine airway clearance			
	Difference	SE	Significance	95% CI
Ventilation distribution (relative impedance Δ)				
Global Amp	0.004	0.012	0.745	-0.020 - 0.027
Global EELV	-0.084	0.018	0.000	-0.121 - -0.047
Anterior EELV	-0.047	0.015	0.003	-0.078 - -0.017
Posterior EELV	-0.107	0.027	0.000	-0.160 - -0.053
Global inhomogeneity index	-0.043	0.018	0.017	-0.078 - -0.008
Geometric centre (%)	3.613	1.241	0.005	1.129 – 6.097
Gas exchange				
PaO_2 (mmHg)	7.861	6.186	0.209	-4.521 – 20.243
$PaCO_2$ (mmHg)	-9.615	3.013	0.002	-15.620 - -3.610
PF ratio	56.663	32.220	0.084	-7.885 – 121.210
FiO_2	-0.040	0.024	0.106	-0.089 – 0.009
SpO_2	0.175	0.790	0.825	-1.412 – 1.763
SpO_2/FiO_2	33.565	21.584	0.126	-9.703 – 76.832
Physiological state				
Respiratory rate *(breaths/ minute)*	-5.886	3.190	0.070	-12.267 – 0.495
Heart rate (*beats/minute*)	-4.869	7.021	0.491	-18.940 – 9.202

Abbreviations: Amp – Amplitude, CI – Confidence interval, CPT – Chest physiotherapy, EELV – End expiratory level volume, FiO_2 – Fraction of inspired oxygen, HR – Heart rate, PaO_2 – Partial pressure of arterial oxygen, $PaCO_2$ – Partial pressure of arterial carbon dioxide, PF – PaO_2/FiO_2, SE – Standard error, SpO_2 – oxygen saturation, Δ - change
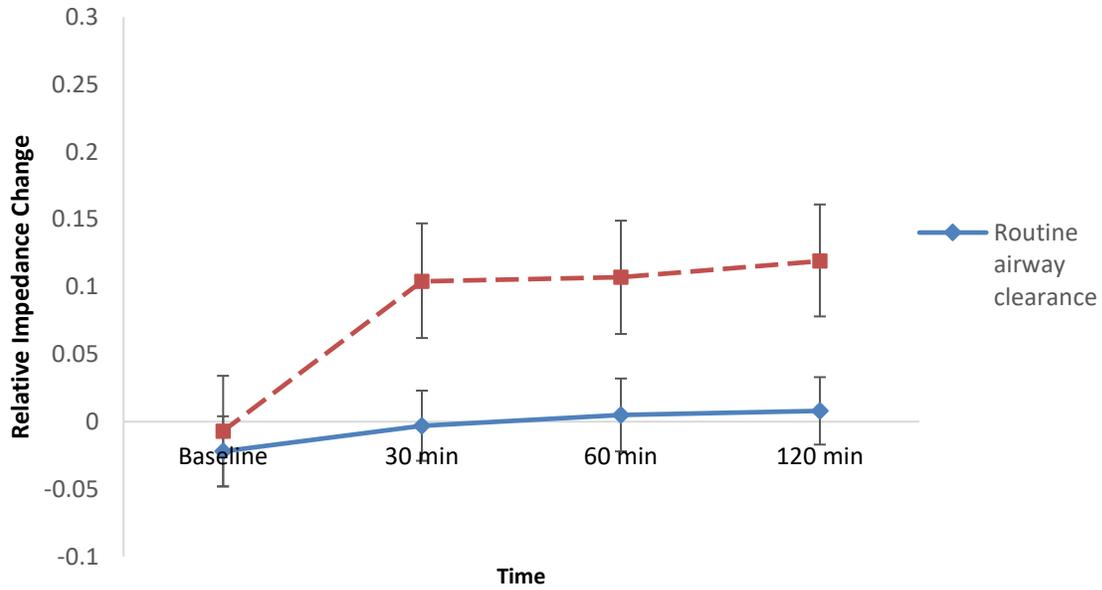
Figure 5.2   Mean (95% confidence interval) global EELV values

Abbreviations: CPT – Chest physiotherapy, EELV – End expiratory level volume
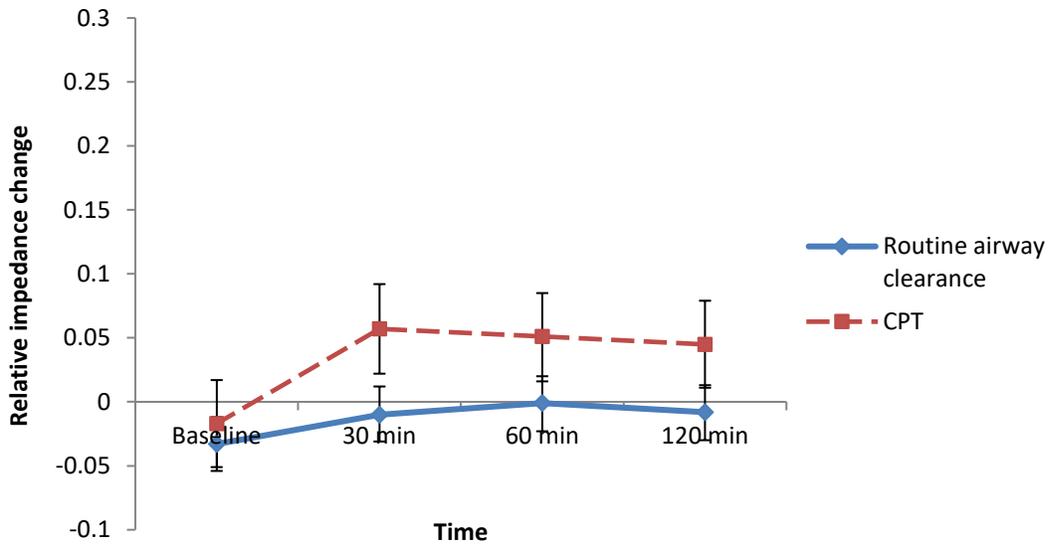
Figure 5.3   Mean (95% confidence interval) anterior EELV values

Abbreviations: CPT – Chest physiotherapy, EELV – End expiratory level volume
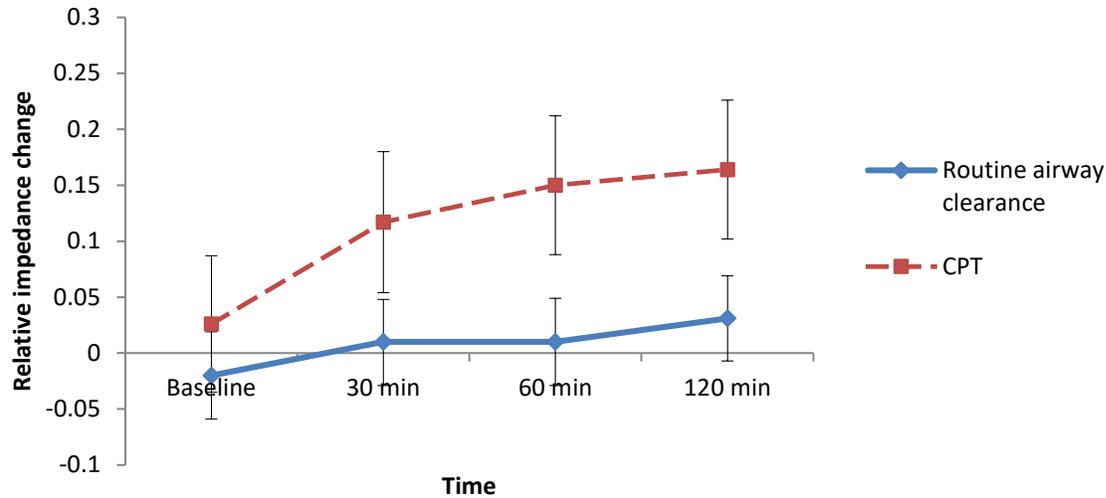
Figure 5.4   Mean (95% confidence interval) posterior EELV values

Abbreviations: CPT – Chest physiotherapy, EELV – End expiratory level volume

Analysis of the ventilation distribution data showed a significantly higher global inhomogeneity index overall in participants receiving CPT compared to those receiving routine airway clearance (p=0.017), signifying more inhomogenous ventilation in the CPT group overall when considering all time points (Figure 5.5). CPT also resulted in an overall significantly lower geometric centre percentage (p=0.005) compared to routine airway suctioning, indicative of a posterior shift in preferential ventilation distribution with CPT (Figure 5.6). There was no significant time effect on geometric centre (p=0.133) however there was a significant change in global inhomogeneity over time (p<0.01) with a significant drop from baseline to 30 minutes (p=0.02), and from baseline to 60 minutes (p<0.01), and a significant increase from 60 to 120 minutes (p=0.006) (Figure 5.5).
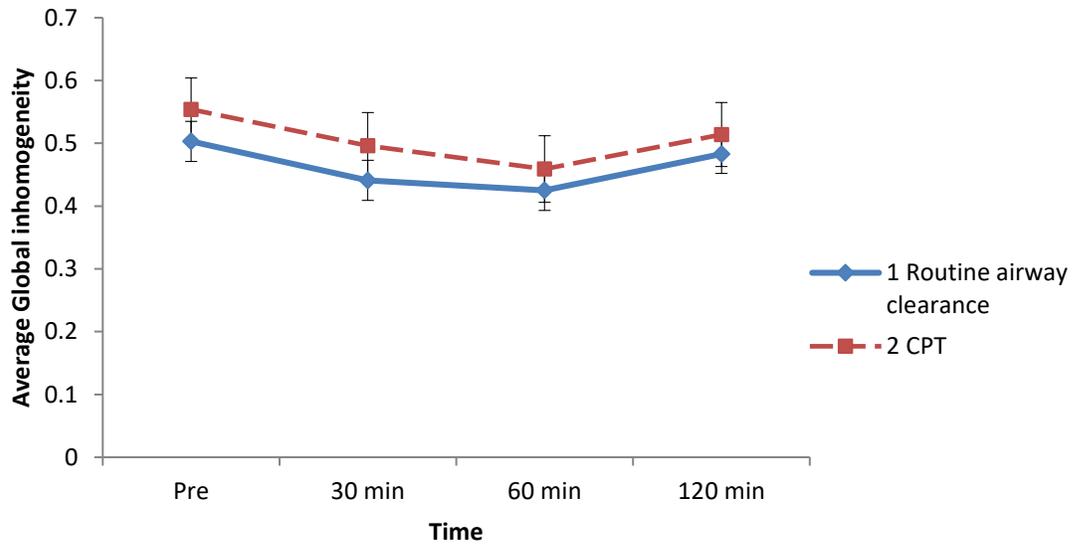
Figure 5.5   Mean (95% confidence interval) global inhomogeneity index

Abbreviations: CPT – Chest physiotherapy
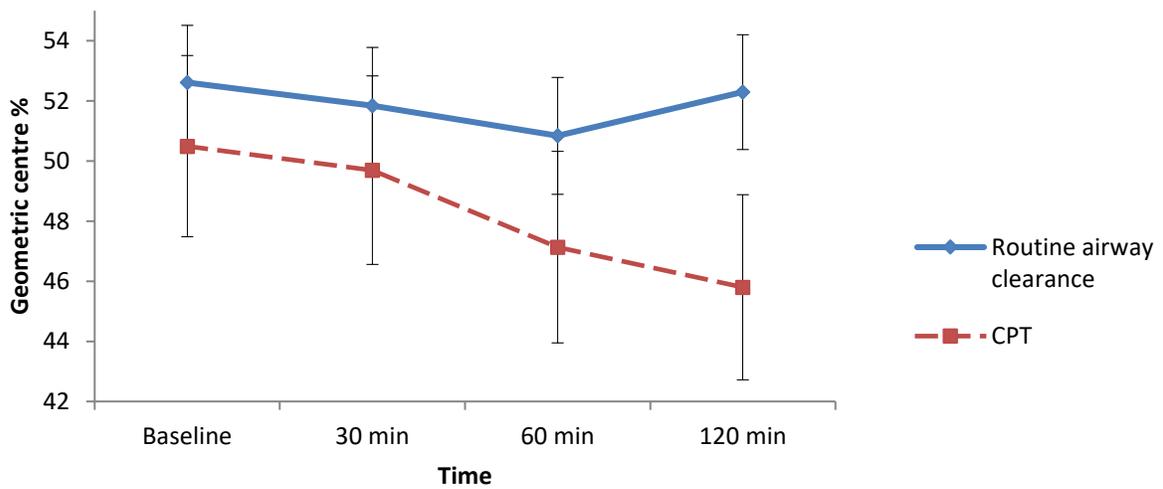
Figure 5.6   Mean (95% confidence interval) geometric centre (%)

Abbreviations: CPT – Chest physiotherapy

134

5.3.3.2   CPT effects on gas exchange

There were no differences in PaO_2 (p=0.209), FiO_2 (p=0.106) or PaO_2/FiO_2 (p=0.084) for participants receiving CPT compared to routine airway clearance. $PaCO_2$ was found to be significantly higher for participants receiving CPT compared to routine airway clearance (p=0.002) however there was a difference between groups at baseline (p=0.003). There were no between-group differences over time for PaO_2 (p=0.682), $PaCO_2$ (p=0.761), FiO_2 (p=0.176), or PaO_2/FiO_2 (p=0.352). No between-group differences or time effects were observed for SpO_2 (p>0.348) or SpO_2/FiO_2 (p>0.126).

5.3.3.3   CPT effects on physiological measurements

There were no between-group differences for the physiological measurements of heart rate (p=0.491) or respiratory rate (p=0.070) (Table 5.3) nor any interaction effects identified between CPT and time for heart rate or respiratory rate (Table 5.4a) (Table 5.4b).

Table 5.4a **Within-group mean differences (95% confidence interval), SE and significance between baseline and 30 min, 60 min and 120 min post baseline time points for participants receiving CPT**

	Baseline minus 30 minute			Baseline minus 60 minute			Baseline minus 120 minute		
	Difference	SE	Sig	Difference	SE	Sig	Difference	SE	Sig
Ventilation distribution (relative impedance Δ)									
Global Amp	0.022	0.011	0.047	0.017	0.012	0.155	0.020	0.012	0.110
	(0.000 - 0.043)			(-0.007 - 0.041)			(-0.005 - 0.045)		
Global EELV	-0.065	0.012	0.000	-0.071	0.015	0.000	-0.078	0.016	0.000
	(-0.089 - -0.042)			(-0.100 - -0.042)			(-0.109 - -0.047)		
Anterior EELV	-0.049	0.010	0.000	-0.050	0.012	0.000	-0.043	0.013	0.001
	(-0.068 - -0.030)			(-0.073 - -0.026)			(-0.069 - -0.018)		
Posterior EELV	-0.060	0.018	0.001	-0.077	0.022	0.001	-0.094	0.024	0.000
	(-0.096 - -0.024)			(-0.120 - -0.034)			(-0.141 - -0.047)		
Global inhomogeneity index	0.060	0.020	0.003	0.087	0.021	0.000	0.031	0.021	0.153
	(0.021 – 0.099)			(0.044 – 0.129)			(-0.011 – 0.073)		
Geometric centre (%)	0.783	1.005	0.437	2.565	1.194	0.033	2.504	1.240	0.045
	(-1.204 – 2.771)			(0.210 – 4.920)			(0.058 – 4.950)		
Gas exchange									
PaO_2 (mmHg)	-2.715	3.595	0.452	-	-	-	-3.614	4.432	0.416

136

	Baseline minus 30 minute			Baseline minus 60 minute			Baseline minus 120 minute		
	Difference	SE	Sig	Difference	SE	Sig	Difference	SE	Sig
	(-9.850 – 9.850)						(-12.378 – 6.255)		
$PaCO_2$ (mmHg)	-1.806	2.454	0.464	-	-	-	-1.341	2.799	0.633
	(-6.671 – 3.060)						(-6.871 – 4.190)		
PF ratio	-5.847	13.215	0.659	-	-	-	-16.876	17.162	0.327
	(-32.067 – 20.373)						(-50.844 – 17.093)		
SpO_2	-0.456	0.447	0.310	-0.850	0.574	0.140	0.608	0.644	0.347
	(-1.339 – 0.428)			(-1.982 – 0.282)			(-0.663 – 1.878)		
FiO_2	0.002	0.002	0.244	0.004	0.002	0.075	0.006	0.003	0.027
	(-0.001 – 0.005)			(0.000 – 0.008)			(0.001 – 0.011)		
SpO_2/FiO_2	-1.087	1.804	0.548	-3.171	2.565	0.218	-1.428	3.167	0.653
	(-4.651 – 2.477)			(-8.239 – 1.897)			(-7.684 – 4.828)		
Physiological state									
Respiratory rate *(breaths/ minute)*	-2.952	1.646	0.075	-1.809	2.143	0.400	-2.731	2.385	0.253
	(-6.203 – 0.300)			(-6.037 – 2.420)			(-7.432 – 1.970)		
Heart rate *(beats/minute)*	2.113	1.683	0.211	2.512	2.340	0.285	2.146	2.780	0.441
	(-1.212 – 5.438)			(-2.109 – 7.132)			(-3.339 – 7.631)		

Abbreviations: Amp – Amplitude, CPT – Chest physiotherapy, EELV – End expiratory level volume, FiO_2 – Fraction of inspired oxygen, HR – Heart rate, PaO_2 – Partial pressure of arterial oxygen, $PaCO_2$ – Partial pressure of arterial carbon dioxide, PF – PaO_2/FiO_2, SE – Standard error, SpO_2 – oxygen saturation, Δ - change

137

Table 5.4b Within-group mean differences (95% confidence interval), SE and significance between time points (30 min, 60 min, 120 min post baseline) for participants receiving CPT

	30 minutes minus 60 minutes			30 minutes minus 120 minutes			60 minutes minus 120 minutes		
	Difference	SE	Sig	Difference	SE	Sig	Difference	SE	Sig
Ventilation distribution (relative impedance Δ)									
Global Amp	-0.004	0.011	0.701	-0.001	0.012	0.903	0.003	0.011	0.801
	(-0.026 – 0.017)			(-0.026 – 0.017)			(-0.018 – 0.024)		
Global EELV	-0.005	0.012	0.653	-0.013	0.015	0.388	-0.007	0.012	0.540
	(-0.029 – 0.018)			(-0.029 – 0.018)			(-0.031 – 0.016)		
Anterior EELV	-0.001	0.010	0.927	0.005	0.012	0.657	0.006	0.010	0.520
	(-0.020 – 0.019)			(-0.018 – 0.029)			(-0.013 – 0.025)		
Posterior EELV	-0.017	0.018	0.364	-0.034	0.022	0.130	-0.017	0.018	0.346
	(-0.053 – 0.020)			(-0.078 – 0.010)			(-0.054 – 0.053)		
Global inhomogeneity index	0.027	0.020	0.186	-0.029	0.021	0.173	-0.056	0.020	0.006
	(-0.013 – 0.067)			(-0.071 – 0.013)			(-0.095 - -0.017)		
Geometric centre (%)	1.781	1.035	0.088	1.721	1.196	0.152	-0.061	1.018	0.953
	(-0.267 – 3.829)			(-0.638 – 4.079)			(-2.075 – 1.954)		
Gas exchange									
PaO$_2$ (mmHg)	-	-	-	-0.899	3.605	0.804	-	-	-

	30 minutes minus 60 minutes			30 minutes minus 120 minutes			60 minutes minus 120 minutes		
	Difference	SE	Sig	Difference	SE	Sig	Difference	SE	Sig
				(-8.052 – 6.255)					
$PaCO_2$ (mmHg)	-	-	-	0.465	2.460	0.850	-	-	-
				(-4.411 – 5.341)					
PF ratio	-	-	-	-11.028	13.255	0.407	-	-	-
				(-37.326 – 15.269)					
SpO_2	-0.394	0.458	0.932	1.063	0.588	0.072	1.457	0.480	0.003
	(-1.301 – 0.513)			(-0.097 – 2.224)			(0.508 – 2.406)		
FiO_2	0.002	0.002	0.179	0.004	0.002	0.062	0.002	0.002	0.208
	(-0.001 – 0.005)			(0.000 – 0.008)			(-0.001 – 0.005)		
SpO_2/FiO_2	-2.084	1.854	0.263	-0.341	2.645	0.898	1.743	1.961	0.375
	(-5.747 – 4.651)			(-5.567 – 4.885)			(-2.131 – 5.616)		
Physiological state									
Respiratory rate *(breaths/ minute)*	1.143	1.688	0.500	0.221	2.143	0.918	-0.922	1.700	0.588
	(-2.193 – 4.479)			(-4.006 – 4.448)			(-4.280 – 2.436)		
Heart rate *(beats/minute)*	0.399	1.727	0.818	0.033	2.354	0.989	-0.365	1.744	0.834
	(-3.013 – 3.810)			(-4.614 – 4.681)			(-3.812 – 3.081)		

Abbreviations: Amp – Amplitude, CPT – Chest physiotherapy, EELV – End expiratory level volume, FiO_2 – Fraction of inspired oxygen, HR – Heart rate, PaO_2 – Partial pressure of arterial oxygen, PCO_2 – Partial pressure of arterial carbon dioxide, PF – PaO_2/FiO_2, SE – Standard error, SpO_2 – oxygen saturation, Δ - change

139

5.3.4 Effect of lung recruitment on CPT effects

To investigate whether lung recruitment manoeuvres enhance the effect of CPT on ventilation distribution and gas exchange in ventilated infants and children, the interaction between CPT and lung recruitment was examined.

There was no interaction identified between CPT and recruitment manoeuvres in global amplitude (p=0.479), global EELV (p=0.293), anterior EELV (p=0.931) posterior EELV (p=0.402), global inhomogeneity (p=0.230), geometric centre (p=0.833), or for PaO_2 (p=0.217), $PaCO_2$ (p=0.110), FiO_2 (p=0.279), or PaO_2/FiO_2 (p=0.250), SpO_2 (p=0.095), or SpO_2/ FiO_2 (p=0.195) (Table 5.5).

A significant interaction between CPT and recruitment manoeuvres was found for both respiratory rate (p=0.001) (Figure 5.7) and heart rate (p=0.048) (Figure 5.8). Respiratory rate was higher in participants receiving CPT and both the incremental and double PEEP recruitment manoeuvres compared to CPT and no recruitment groups (Figure 5.7) (Table 5.5). Similarly, heart rate was higher in participants who received CPT and a recruitment manoeuvre, regardless of whether it was the double or incremental PEEP manoeuvres compared to CPT (Figure 5.8) (Table 5.5).

Table 5.5   **Mean, standard error (SE), 95% confidence interval and significance of interaction effects for total outcome measures between CPT and lung recruitment groups**

	CPT-no recruitment		Routine airway clearance-no recruitment		CPT-Double		Routine airway clearance-Double		CPT-Incremental		Routine airway clearance-Incremental		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Sig
Ventilation distribution (relative impedance Δ)													
Global amplitude	0.062	0.015	0.063	0.011	0.070	0.016	0.057	0.011	0.039	0.020	0.062	0.011	0.479
	(0.031-0.092)		(0.042-0.085)		(0.038-0.101)		(0.035-0.078)		(-0.001-0.079)		(0.040-0.084)		
Global EELV	0.114	0.024	-0.09	0.017	0.076	0.025	0.008	0.017	0.053	0.032	-0.008	0.017	0.293
	(0.066-0.163)		(-0.043-0.024)		(0.027-0.125)		(-0.026-0.042)		(-0.011-0.116)		(-0.042-0.026)		
Anterior EELV	0.027	0.020	-0.023	0.014	0.041	0.020	0.002	0.014	0.034	0.026	-0.018	0.014	0.931
	(-0.013-0.067)		(-0.051-0.005)		(0.001-0.082)		(-0.026-0.030)		(-0.019-0.086)		(-0.047-0.010)		
Posterior EELV	0.151	0.035	-0.001	0.025	0.127	0.036	0.018	0.025	0.065	0.046	0.006	0.025	0.402
	(0.080-0.221)		(-0.050-0.049)		(0.055-0.200)		(-0.032-0.068)		(-0.028-0.157)		(-0.044-0.056)		
Global inhomogeneity	0.518	0.023	0.468	0.016	0.484	0.024	0.482	0.016	0.515	0.030	0.439	0.016	0.230
	(0.472-0.564)		(0.437-0.500)		(0.436-0.532)		(0.450-0.513)		(0.456-0.575)		(0.407-0.471)		
Geometric centre (%)	47.898	1.645	52.225	1.136	50.158	1.672	52.809	1.131	46.783	2.117	50.644	1.149	0.833
	(44.607-51.188)		(49.951-54.498)		(46.820-53.496)		(50.542-55.075)		(42.543-51.022)		(48.345-52.943)		
Gas exchange													
	85.583	8.188	88.182	5.709	92.744	8.173	89.774	5.685	71.675	10.635	95.628	5.703	0.217

	CPT-no recruitment		Routine airway clearance-no recruitment		CPT-Double		Routine airway clearance-Double		CPT-Incremental		Routine airway clearance-Incremental		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Sig
PaO$_2$ (mmHg)	(69.204-101.160)		(76.751-99.614)		(76.398-109.090)		(78.388-101.160)		(50.374-92.976)		(84.209-107.047)		
PaCO$_2$ (mmHg)	60.502	4.013	45.829	2.772	51.751	4.021	50.748	2.752	67.800	5.148	54.631	2.769	0.110
	(52.509-68.495)		(40.303-51.355)		(43.744-59.757)		(45.260-56.236)		(57.533-78.067)		(49.109-60.152)		
PF ratio	235.127	42.454	302.561	29.787	303.548	42.355	288.476	29.717	174.167	55.595	291.793	29.762	0.250
	(150.118-320.137)		(242.879-362.242)		(218.733-388.364)		(228.924-348.029)		(62.754-285.579)		(232.160-351.427)		
SpO$_2$	96.493	1.042	97.733	0.727	99.698	1.042	97.482	0.723	95.087	1.367	96.589	0.723	0.095
	(94.399-98.586)		(96.271-99.194)		(97.606-101.791)		(96.028-98.936)		(92.340-97.834)		(95.135-98.044)		
SpO$_2$/FiO$_2$	272.174	28.270	333.377	19.979	322.480	28.261	302.560	19.976	225.029	37.382	284.438	19.976	0.195
	(215.504-328.844)		(293.325-373.430)		(265.826-379.133)		(262.514-342.607)		(150.090-299.967)		(244.392-324.485)		
FiO$_2$	0.366	0.032	0.308	0.023	0.323	0.032	0.336	0.023	0.444	0.042	0.368	0.023	0.279
	(0.302-0.430)		(0.263-0.353)		(0.259-0.387)		(0.291-0.382)		(0.359-0.528)		(0.323-0.413)		
Physiological state													
Respiratory rate *(breaths/ min)*	24.957	4.219	35.397	2.947	38.803	4.215	29.518	2.933	45.313	5.488	26.500	2.933	0.001
	(16.520-33.393)		(29.501-41.293)		(30.378-47.228)		23.647-35.389)		34.329-56.296)		(20.629-32.371)		
Heart rate *(beats/ min)*	113.546	9.223	132.713	6.496	137.045	9.206	126.107	6.488	137.563	12.139	114.726	6.492	0.048
	(95.066-132.026)		(110.694-145.733)		(118.597-155.494)		(113.101-139.113)		(113.230-161.895)		(101.714-127.738)		

Abbreviations: Amp – Amplitude, CPT – Chest physiotherapy, EELV – End expiratory level volume, FiO$_2$ – Fraction of inspired oxygen, HR – Heart rate, PaO$_2$ – Partial pressure of arterial oxygen, PaCO$_2$ – Partial pressure of arterial carbon dioxide, PF – PaO$_2$/ FiO$_2$, SE – Standard error, SpO$_2$ – oxygen saturation, Δ - change

142
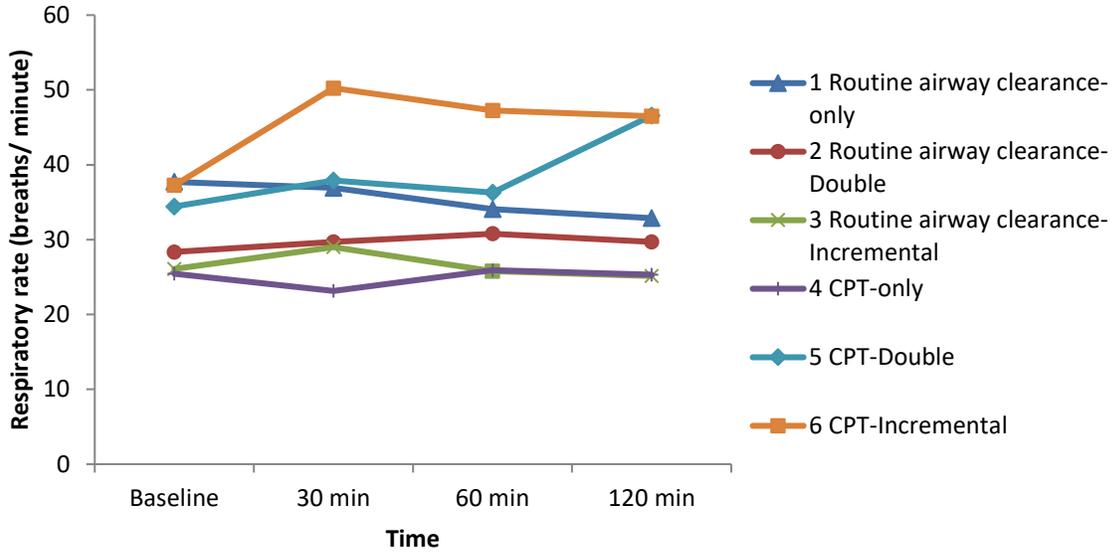
Figure 5.7   Mean respiratory rate comparing effects of lung recruitment

Abbreviations: CPT – Chest physiotherapy
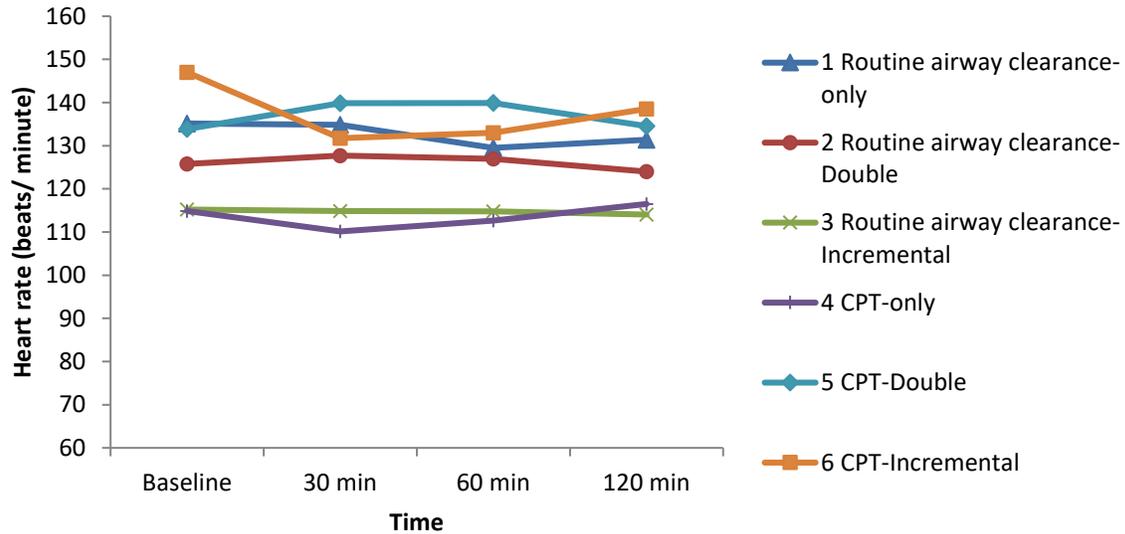
Figure 5.8   Mean heart rate comparing effects of lung recruitment

Abbreviations: CPT – Chest physiotherapy

143

5.4 Discussion

To our knowledge this is the first study to explore the use of EIT as a measurement tool to evaluate CPT effects in ventilated infants and children. CPT demonstrated improvement in ventilation distribution compared with routine airway clearance but no differences were demonstrated for gas exchange and physiological measures. A lung recruitment manoeuvre delivered immediately after CPT did not enhance ventilation distribution or gas exchange however changes in heart rate and respiratory rate were identified in participants who received CPT and a recruitment manoeuvre.

5.4.1 Using EIT to measure CPT effects

No differences in global amplitude, an indicator of tidal volume, were found between participants who received CPT and those who received routine airway clearance. No change in ventilator-derived measures of tidal volume as a result of CPT have previously been demonstrated (Elizabeth et al., 2016). In contrast, improvements in tidal volume as a result of CPT have been reported using respiratory mechanics measures (Almeida et al., 2005; Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015) though only one study reported a significant improvement (Shannon, Stocks, Gregson, Dunne, et al., 2015). It is perhaps unsurprising that this study failed to find a difference in global amplitude as this reflects a measure of tidal ventilation as a whole. Furthermore, the majority of participants in Study 2 were fully ventilated and therefore were receiving a set tidal volume during the study period. Possibly, tidal volume or global amplitude are less likely to be significantly changed following CPT because CPT likely results in regional effects rather than affecting the lung globally. This may mean measures of tidal volume or global amplitude may not be sensitive enough to measure CPT effects and measures of regional ventilation may be more adequate.

EELV increased globally and regionally, in both the anterior and posterior regions of the lung following CPT. One reason for this increase may be the different effects on secretion clearance

144

between CPT and routine airway clearance. CPT is thought to mobilise and remove secretions from peripheral airways of the lung through a combination of manual techniques, MHI and ETT suction (Main & Denehy, 2016). It is within these peripheral lung airways that secretions are likely to cause obstruction, suboptimal ventilation and/or collapse of distal alveoli (Main & Denehy, 2016). Conversely, routine airway clearance likely has minimal effect on peripheral secretion clearance, instead only removing secretions from the ETT and proximal airways (Main et al., 2004). As a result, it is unlikely that routine airway clearance alone would result in the same increases in ventilation as CPT. Differences between CPT and routine airway clearance alone have been previously demonstrated, but only with respiratory mechanics measures such as tidal volume (Main et al., 2004), airway resistance (Almeida et al., 2005; Main et al., 2004) and dead space (Main & Stocks, 2004). This current study provides the first direct evidence of differences in the effects of CPT and routine airway clearance on ventilation at a physiological level. Furthermore, these increases occur in both dependent and non-dependent lung regions, suggestive of changes occurring throughout the lung. It is recognised that an increase in EELV following CPT may not exclusively indicate an improvement in lung recruitment and thereby lung function. An alternative explanation may be that hyperinflation of already open alveoli occurred, potentially as a result of the use of MHI. Corresponding improvements in arterial oxygenation may be expected in the CPT group if the increase in EELV was associated with lung recruitment. While this study did not identify a significant increase in PaO_2 in the CPT group, the small sample size may have limited the ability to definitively explain this finding. Interestingly, both the CPT and routine airway clearance groups received recruitment manoeuvres, which may be considered to be more likely to result in alveolar over-distension than MHI. However the routine airway clearance group did not show the same increases in EELV as the CPT group. Further investigation is required to confirm the increase in EELV and associated clinical benefits.

145

Changes in regional ventilation occurred in the dependent lung and within the first 30 minutes following CPT. This is possibly due to secretions being more likely to collect in the dependent lung (Gamsu, Singer, Vincent, Berry, & Nadel, 1976), resulting in regional lung collapse. The removal of secretions from the dependent lung is likely to result in more notable improvements in ventilation to the dependent lung compared to the non-dependent lung. As participants were positioned in supine in this study, it is possible that secretions tended to collect more posteriorly, as a result of gravity on the airways within the dependent lung and a lower functional residual capacity in this position (Gamsu et al., 1976). The effect of CPT therefore would likely be greater in the posterior lung regions. This theory was supported by the identified redistribution of the centre of ventilation posteriorly, toward the dependent lung in the CPT group, reflected by the reduction in the geometric centre percentage. Additionally, changes in both EELV and geometric centre occurred as early as 30 minutes after CPT suggesting that by facilitating secretion clearance, CPT may result in fairly immediate changes in ventilation distribution and these changes are identifiable using EIT.

Global inhomogeneity was noted to be higher in the CPT group overall compared to the routine airway clearance group reflecting greater inhomogeneity of ventilation within the lungs in the participants who received CPT. Global inhomogeneity reflects the amount of variation in ventilation when the lung is considered as a whole. An increase in global inhomogeneity has been reported in ventilated adult patients with severe lung disease when atelectasis is present (Zhao et al., 2014) and has been shown to remain high even after these collapsed areas have been recruited if residual atelectasis persists (Zhao et al., 2014). It is plausible that participants who required CPT may have had more severe or extensive lung disease compared to participants who did not, as CPT is generally instigated in the presence of worsening lung function (Main et al., 2004; McCord et al., 2013). Due to the small sample size and the lack of severity scores, such as Paediatric Infant Mortality score (Slater, Shann, & Pearson, 2003) used in this study, it is difficult to confirm whether there was a difference

146

between groups in the severity of lung disease. Of note, while global inhomogeneity was higher overall in the CPT group, the trend of change for global inhomogeneity was similar in both the CPT and routine airway clearance groups. In both groups, global inhomogeneity dropped following intervention and then increased again over time. It would be reasonable to expect that ventilation would become more homogenous as ventilation in the lung is improved following CPT (Zhao et al., 2014), which may explain the initial drop in both groups. It appears that the drop in global inhomogeneity may have been more marked in the CPT group compared to routine airway clearance, however this did not reach significance. Further investigation is required.

5.4.2 ABG and physiological measurements

Overall, there was little difference in ABG, SpO_2, heart rate or respiratory rate between CPT and routine airway clearance, indicative of both interventions having a similar effect on gas exchange and physiological state. The only difference found was for $PaCO_2$ which was higher in participants who received CPT from baseline and throughout all time points. Previous studies (Almeida et al., 2005; Elizabeth et al., 2016; Main et al., 2004) have shown no change in $PaCO_2$ as a result of CPT in ventilated infants and children, though one study reported an increase in physiological and alveolar dead space which were derived in-part from carbon dioxide levels (Main & Stocks, 2004). It is possible that participants requiring CPT had more severe or extensive lung disease, hence higher $PaCO_2$, at baseline (Epstein & Singh, 2001) and therefore were more likely to require additional airway clearance through CPT than routine ETT suction alone. It could be suggested that the identified improvements in regional ventilation following CPT in this study may have resulted in a subsequent reduction in $PaCO_2$, as a result of improved ventilation and therefore CO_2 clearance. Instead, $PaCO_2$ appeared to change minimally in the CPT group over time, mirroring previous studies in the field (Almeida et al., 2005; Main et al., 2004). While further studies with similar baseline data are needed to better understand the relationship between changes in regional ventilation
147

distribution and $PaCO_2$, it is possible that ABG may lack sufficient sensitivity to appreciate the effects of CPT on regional ventilation distribution (Main & Stocks, 2004). ABGs are often available to physiotherapists however results of this study raise question over the ability of these tools to reflect changes in regional ventilation distribution and therefore the validity of ABG to measure CPT effects in ventilated infants and children.

5.4.3 Effect of lung recruitment on CPT effects

As the current study was undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial investigating the effect of two different lung recruitment manoeuvres following ETT suction, the impact of these recruitment manoeuvres on CPT effects were also considered. No additional effect of a recruitment manoeuvre on CPT effects was found for global amplitude, EELV (global, anterior or posterior), geometric centre or global inhomogeneity. The absence of significant interaction effects may represent a lack of benefit for recruitment manoeuvres to be used immediately post CPT. However, these findings were likely underpowered, as are based on small participant numbers. Further investigation is required to determine if either a double PEEP or incremental PEEP recruitment manoeuvre enhances the effect of CPT on regional ventilation.

Heart rate and respiratory rate were higher following CPT and recruitment manoeuvres, most notably in respiratory rate following both the incremental and double PEEP manoeuvres. These findings are based on small participant numbers and therefore are difficult to interpret. Despite being elevated following CPT and recruitment, the respiratory rate and heart rate values recorded did not necessarily reflect values that would be unexpected for the age of the participants investigated (Main & Denehy, 2016; Taussig et al., 2008). Another possible explanation for the differences seen in respiratory rate and heart rate in participants who received CPT and the incremental PEEP manoeuvre is a possible change in the participants' level of arousal. Higher respiratory and heart

148

rates are observed in infants and children when awake compared to when sedated (Taussig et al., 2008) and this may have been a factor in the current study. Details of participant level of arousal was not available so cannot be discounted when considering this result. It is also plausible that the combination of CPT and a recruitment manoeuvre in ventilated infants and children may result in greater physiological instability however without larger participant numbers and accounting for age and level of sedation, this is difficult to conclude. Further investigation with larger samples is required.

5.4.4 Limitations of study

There were a number of limitations associated with this study, primarily related to its design as a secondary analysis of data collected within a larger prospective randomised controlled trial, which meant that the study was not specifically designed to investigate the effects of CPT on ventilated infants and children. CPT data were obtained opportunistically and only delivered in participants when deemed clinically advantageous. This resulted in a small number of participants making up the experimental intervention arm of this study. The delivery of CPT also lacked standardisation, making it difficult to determine whether one combination of techniques was more advantageous compared to another or what the ideal CPT prescription may be. However standardising CPT to patients does not reflect usual clinical practice (Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015; Shannon, Stocks, Gregson, Hines, et al., 2015) and therefore this is a consideration that must be accepted in CPT studies in ventilated infants and children. Furthermore, it is acknowledged that the protocol for this study allowed for manipulation of ventilation settings during the study period to respond to individual participants' clinical needs, this may have influenced results.

 It is likely that the current study was underpowered as a result of the small sample size used in this study. Small numbers of participants received CPT due to the pragmatic nature of the intervention

149

delivery. Additionally, when participants were separated according to the presence and type of recruitment manoeuvre used in the randomised controlled trial, numbers in each participant group were reduced further. It is possible that multiple comparisons across multiple variables in the context of small sample size limits the statistical validity of the data however linear mixed model analyses, which has the ability to consider both fixed and random effects, were used to account for this (Krueger & Tian, 2004; McCulloch & Neuhaus, 2001).

Despite the sample size, a number of significant and plausible findings were identified including for the first time some suggestion that there were changes in regional ventilation following CPT. These findings provide a basis for determining sample sizes for future studies to investigate CPT effects in ventilated infants and children using EIT. Using the University of British Columbia sample size calculator (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html) comparing means of two independent samples, a sample size of 63 participants per group was calculated to be sufficient to find a between group difference (CPT versus routine airway clearance) for EIT measures at 30 minutes following CPT at two-tailed significance of 0.05 level with 80% power.

Lastly, differences in baseline values may also have presented in part due to the lack of randomisation in this study and may have contributed to some selection bias influencing the findings. Baseline differences in $PaCO_2$ have potentially limited interpretation of $PaCO_2$ changes associated with CPT and the improvements found in regional ventilation distribution. Baseline differences in global inhomogeneity may also have been present and although these differences failed to reach statistical significance, a larger sample size may have identified this difference. Future studies with larger samples designed to ensure all baseline values are similar are required to further explore the effect of CPT on $PaCO_2$ and global inhomogeneity. A crossover design could also be considered to help

manage any potential differences between children who require CPT and those who require routine airway clearance alone.

5.5   Conclusion

EIT is a measurement tool that can detect regional changes in lung function as a result of CPT in ventilated infants and children. CPT appears to have different effects on lung function compared to routine airway clearance, especially for increasing ventilation distribution in the dependent lung, in the first 30 mins following CPT. The addition of a recruitment manoeuvre following CPT did not appear to enhance the effect of CPT in this group of ventilated infants and children. Further larger studies using EIT are needed to build on findings described in this study to better understand the effect CPT has in ventilated infants and children.

6　Discussion and Conclusion

This chapter presents an overview of the main findings of the two studies making up this research program and will expand upon the discussion presented with Chapters 4 and 5. The findings of Study 1 (systematic review) will be presented first followed by those from Study 2 (clinical EIT study). The clinical implications from the research program will be discussed, followed by an overview of the main limitations of the research program. Broader clinical implications and directions for future research will be discussed and a final summation and conclusion will complete this chapter.

6.1　Overview of significant findings of the thesis

6.1.1　Key findings from Study 1

Study 1 consisted of a systematic review of the existing literature that sought to achieve two aims. Firstly to identify the measurements tools used to assess CPT effects in ventilated infants and children and secondly to investigate the clinimetric properties of these tools, to determine which tools have the best clinimetric rigour for measuring the effects of CPT in ventilated infants and children. It was hypothesised that there would be a variety of measurement tools available to physiotherapists to measure the effects of CPT in ventilated infants and children however few would have robust, clinimetric properties to support their use in ventilated infants and children receiving CPT.

6.1.1.1　Identified measurement tools

Eight measurement tools were identified from 13 retrieved studies that met the a-priori criteria for inclusion in the review. Identified tools included secretion weight, CO_2SMO Plus and $NICO_2$ respiratory monitors, ventilator, stethoscope, ABG, pulse oximetry and CXR.

The CO$_2$SMO Plus and NICO$_2$ were most commonly described and provided comprehensive data regarding respiratory mechanics compared to the other tools such as ventilator or auscultation. Two tools were identified that measured gas exchange and one tool was identified that each measured CPT effects on secretion clearance and radiological appearance of the lung. No tools were identified in Study 1 that represented tools specifically designed specifically for measuring CPT effects.

No tools were identified in Study 1 that were capable of measuring ventilation distribution. A primary outcome of CPT is considered to be an improvement in the distribution of ventilation, often to specific under-ventilated lung regions (Wallis & Prasad, 1999). As such, to truly appreciate the effects of CPT on ventilation, and therefore gas exchange, tools that can measure changes in regional ventilation distribution may be more beneficial (Hough, 2009). The tools identified to measure CPT effects in ventilated infants and children may still provide clinically useful information, however may lack sensitivity and specificity when measuring CPT effects on ventilation distribution. An evaluation of the clinimetric rigor of the tools identified in Study 1 was therefore deemed necessary to investigate validity, reliability and responsiveness of these tools for measuring CPT effects in ventilated infants and children.

6.1.1.2   Clinimetric properties of identified measurement tools

The second part of Study 1 sought to investigate the clinimetric properties of the CPT measurement tools identified in the initial systematic search. Clinimetric properties must be considered when choosing tools to measure CPT effects in ventilated infants and children to ensure measurements derived from these tools are valid, reliable and responsive to the intervention being delivered. Overall the yield of studies investigating the clinimetric properties of the identified tools was low. Only four tools, the CO$_2$SMO Plus and NICO$_2$ respiratory monitors, ventilators and pulse oximeter, had reported clinimetric data in ventilated infants and children. The CO$_2$SMO Plus yielded the highest

number of clinimetric studies in ventilated infants and children and was the only tool to have reported data for all three properties of validity, reliability and responsiveness (Cannon et al., 2000; Castle et al., 2002; Gregson et al., 2007; Main et al., 2004; Main et al., 2001; Main & Stocks, 2004; Riou et al., 2004).

The CO_2SMO Plus was found to be a valid, reliable and responsive tool when measuring tidal volume (Castle et al., 2002), airway resistance (Main et al., 2004), lung compliance (Main et al., 2004) and dead space measurements (Main & Stocks, 2004; Riou et al., 2004) in ventilated infants and children. However, these properties were only demonstrated when there was minimal air leak around the child's ETT (Main et al., 2001). Similar measures derived directly from ventilators (Servo 300 and Servo-I) were not valid (Cannon et al., 2000; Castle et al., 2002; Heulitt et al., 2009; Kim et al., 2015) or reliable (Castle et al., 2002; Heulitt et al., 2009) in ventilated infants and children, with measurements influenced by factors including the ventilation mode and size of the ventilator circuit.

The validity and reliability of transcutaneous pulse oximetry was evaluated in a small number of ventilated paediatric studies (Das et al., 2010; Khemani et al., 2012; Ross et al., 2013) and were influenced by the location of the oximetry probe (Das et al., 2010), the severity of the underlying lung disease (Khemani et al., 2012) and the saturation range being measured (Ross et al., 2013). Validity of pulse oximetry, measured against arterial oxygen saturations, was greatest when used on the sole of the infants' foot (Das et al., 2010), in the presence of less severe lung disease (Khemani et al., 2012) and when measuring saturations greater than 90% (Das et al., 2010; Ross et al., 2013). In ventilated infants and children with more severe lung disease (Khemani et al., 2012) or saturation levels below 90% (Ross et al., 2013), the accuracy of pulse oximetry was reduced. Reliability was investigated in only one study (Das et al., 2010), with most reliable measurements gained when saturations were measured on the sole of the infants' foot (Das et al., 2010).

A number of tools commonly used by physiotherapists clinically, such as auscultation, ABG, CXR and secretion weight were under-reported with respect to clinimetric properties in ventilated infants and children. No studies presenting clinimetric data for these tools were identified, suggesting these tools should be used with caution until the clinimetric properties of these tools in this population can be established.

6.1.1.3   Methodological quality of studies reporting on clinimetric properties

Studies reporting clinimetric properties of validity, reliability and responsiveness for each of the identified CPT measurement tools were rated for methodological quality using the COSMIN checklist (Terwee et al., 2012). Overall the quality of the included studies ranged from good to poor with the majority of identified studies scored as poor according to the COSMIN rating scale. Studies reporting validity data for pulse oximetry demonstrated the highest quality ratings, with two of the three studies (Khemani et al., 2012; Ross et al., 2013) scored as good on the COSMIN tool. However, both of these studies (Khemani et al., 2012; Ross et al., 2013) had the lowest generalisability rating using the COSMIN checklist suggesting care should be taken when extrapolating these findings to ventilated infants and children receiving CPT.

Despite having the highest number of studies reporting clinimetric data, the CO_2SMO Plus and the reported ventilators had some of the lowest quality scores. Failing to adequately report on the quantity and management of missing data was consistently observed as the reason these studies scored as fair or poor for validity and reliability on the COSMIN checklist (Appendix 3). All studies reporting responsiveness of the CO_2SMO Plus scored as poor, most commonly as a result of failing to adequately describe a comparator measurement tool against which the CO_2SMO Plus was measured (Appendix 3). Positively, most studies reporting clinimetric properties of tools used to measure CPT

effects in ventilated infants and children scored well on the COSMIN checklist for sample size, statistical analyses and general methodological design.

No single measurement tool was identified in Study 1 that was able to measure effects of CPT on regional ventilation and/or gas exchange and had high quality clinimetric rigor. The CO_2SMO Plus showed some promise in valid and reliable measurement of the effect of CPT on respiratory mechanics (Cannon et al., 2000; Castle et al., 2002; Main et al., 2001; Riou et al., 2004) however clinimetric studies were of fair to poor quality. Furthermore, no tool was identified that could provide valid and reliable measurement of regional ventilation distribution, which may be necessary to understand how the effects of CPT on ventilation, and therefore gas exchange. It was therefore concluded from Study 1 that physiotherapists providing CPT to ventilated infants and children currently have limited tools available to assess the effect of CPT on regional ventilation and gas exchange and future research is required.

6.1.2   Key findings from clinical EIT study

No tools were identified for physiotherapists to assess the effect of CPT on regional ventilation. Due to the focus of chest physiotherapy to improve ventilation and gas exchange, a tool capable of measuring such changes is needed. EIT, a relatively new measurement tool, appears to have the ability to measure ventilation distribution in critically unwell patients (Frerichs et al., 2017). EIT has been suggested as a novel CPT measurement tool in ventilated infants and children (Main & Denehy, 2016) and has been used with ventilated preterm infants (Hough, Flenady, Johnston, & Woodgate, 2010; Hough, Johnston, Brauer, Woodgate, & Schibler, 2013; Hough, Shearman, Liley, Grant, & Schibler, 2014) to provide detailed measurement of both global and regional ventilation.

Study 2 of this research program investigated the use of EIT as a novel tool to compare the effects of CPT and routine airway clearance on regional ventilation distribution in ventilated infants and

children. Study 2 also opportunistically investigated whether the use of lung recruitment manoeuvres could enhance the effect of CPT in ventilated infants and children. Key findings from this study are presented below.

<u>6.1.2.1   CPT effects on regional ventilation distribution, gas exchange and physiological measures</u>

Significant improvements in global and regional EELV were demonstrated in participants who received CPT compared to routine airway clearance. The largest regional increases in EELV occurred in the posterior region of the lung, which represented the dependent lung in the supine positioned participants. This is an important finding demonstrating that CPT can influence regional ventilation in ventilated infants and children.

Ventilation was found to be preferentially redistributed toward the dependent lung in participants who received CPT compared to routine airway clearance alone, as demonstrated by a significantly lower geometric centre of ventilation in the CPT group. Geometric centre represents the central location of ventilation within the lungs. As participants in Study 2 were positioned in supine, a higher geometric centre percentage reflects ventilation more preferentially directed to the anterior, or non-dependent lung, compared to a lower percentage, which indicates preferential ventilation toward the dependent regions of the lung (Dunster, Friese, Fraser, Galloway, et al., 2012; Frerichs et al., 2006). In combination with the improved EELV, particularly in the posterior lung, CPT was found to improve ventilation within dependent lung regions. Both findings suggest an overall positive effect of CPT on regional ventilation distribution in ventilated infants and children and suggest there may be differences between CPT effects compared to routine airway clearance alone.

No differences were found for arterial oxygenation, respiratory rate, heart rate or transcutaneous oxygen saturations between those who received CPT or routine airway clearance. These measures

157

are not capable of measuring regional ventilation distribution and therefore it is not surprising that no differences between the two groups were found for these measures as a result of CPT.

<u>6.1.2.2   Effect of lung recruitment</u>

The use of a lung recruitment manoeuvre after CPT was opportunistically investigated to determine whether lung recruitment would enhance the effects of CPT on ventilation distribution and gas exchange in ventilated infants and children. This investigation was possible due to the design of Study 2 being undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial comparing two different lung recruitment manoeuvres. It was hypothesized that a lung recruitment manoeuvre used immediately after CPT may enhance the effect of CPT as a result of a two-fold effect. Firstly, that a lung recruitment manoeuvre would negate the loss of airway pressure (Hess & Bigatello, 2002; Lindgren et al., 2007) that can result from disconnection from the ventilator prior to, and after ETT suction and/or following any loss of PEEP during MHI. Secondly, that a lung recruitment manoeuvre may augment the regional re-expansion of hypo-ventilated lung regions following the removal of any secretions from these areas by CPT. Study 2 also provided an opportunity to investigate the effect of two different recruitment manoeuvres, a double PEEP and an incremental PEEP manoeuvre, to identify whether one strategy enhanced CPT effects more than the other.

No significant benefits to ventilation distribution or arterial gas exchange were identified following the use of either a double or incremental PEEP manoeuvre after CPT. Significant interaction effects were identified however between CPT and the use of a recruitment manoeuvre, in respiratory rate and heart rate, which appeared most notable in participants who received CPT or the incremental PEEP manoeuvre. This suggests that CPT in combination with an incremental recruitment manoeuvre may contribute to a more variable physiological state. However this finding, and its

158

clinical implications, needs confirmation through further investigation with larger sample sizes. Overall, the results of Study 2 were not enough to recommend the use of routine lung recruitment manoeuvres after CPT. Further investigation is required to determine the role of lung recruitment in certain populations and to identify responders from non-responders using large scale, stratified studies.

6.2   Clinical Implications

A number of clinical implications can be derived from the findings of this research program. Clinical implications are discussed regarding reported measurement tools used by physiotherapists working in the PICU to assess CPT effects as well as the use of EIT as a novel measurement tool of CTP effects.

6.2.1   Current tools of CPT effect

No single measurement tool was identified that could adequately assess CPT effects in ventilated infants and children. Instead, a range of tools were identified, making it important for physiotherapists to choose tools that reflect aspects of lung function targeted by treatment aims. Few tools identified had robust clinimetric data to support their use in ventilated infants and children and some of the most commonly used tools have little or no clinimetric data to support their use. Lastly, no tools were identified that could measure regional ventilation distribution in response to CPT and therefore new tools may be required. Each clinical implication is expanded upon in the following sections.

6.2.1.1   Measurement tool selection

Tools available to measure CPT effects can be categorised according to the measurements provided. Understanding what measures can be derived from available tools is important for physiotherapists to assist in guiding their selection of tool according to the desired aim of the CPT provided to ventilated infants and children.

159

Of the tools reported in the literature to measure CPT effects in ventilated infants and children, all were able to measure CPT effects on one aspect of lung function such as secretion clearance, respiratory mechanics, radiological appearance of the lung or gas exchange. Therefore, it appears that a combination of tools is required if physiotherapists wish to assess CPT effects in ventilated infants and children across multiple domains. Where possible, tools with evidence of clinimetric rigour such as the CO_2SMO Plus should be considered. However there may also be a place for readily available tools, such as secretion clearance and auscultation, to provide supporting information to physiotherapists, if clinimetric rigour can be demonstrated. Designing and trialling new tools that can measure multiple CPT effects presents an avenue for further investigation.

6.2.1.2 <u>Tools used to measure CPT effects in ventilated infants and children have limited clinimetric</u>
<u>properties</u>

The majority of tools used to measure the effects of CPT in ventilated infants and children have limited investigation into their clinimetric properties. Tools measuring respiratory mechanics and gas exchange, specifically the CO_2SMO Plus and pulse oximetry, have some evidence demonstrating validity, reliability and responsiveness in ventilated infants and children. Despite this, there are limitations associated with the use of these tools in clinical practice.

Valid and reliable respiratory mechanics measures, for example, can only be obtained from portable respiratory monitors such as the CO_2SMO Plus when there is little or no air leak from the ETT (Main et al., 2001). To achieve a minimal ETT leak, studies described subjects as being heavily sedated and paralysed (Main et al., 2004; Main & Stocks, 2004). Although patients are at times paralysed and sedated in paediatric intensive care units, this will not always be possible and may not be reflective of current clinical practise in PICU (A. Wolf, 2012).

Similarly, valid and reliable pulse oximetry readings were only reported when measurements were recorded on the sole of the foot (Das et al., 2010), in infants and children with less severe lung disease (Khemani et al., 2012) and when measuring saturations greater than 90% (Das et al., 2010; Ross et al., 2013). These parameters are not necessarily reflective of every infant or child who will be managed by physiotherapists within a PICU, potentially limiting the generalisability of the use of pulse oximetry as a tool to measure CPT in this population.

6.2.1.3 Commonly used tools for measuring CPT effects in ventilated infants and children lack evidence for validity, reliability and responsiveness

Many of the measurement tools commonly used to assess CPT effects in ventilated infants and children, such as secretion weight, auscultation, ABG and CXR lack clinimetric support. These tools are described regularly in the literature and are often readily available, and therefore utilised, in a clinical setting to measure CPT effects in ventilated infants and children (Marques et al., 2006). While these tools may represent feasible options for physiotherapists working with critically unwell infants and children, caution must be exercised using these tools until clinimetric data becomes available.

One potential problem with using tools based on availability is the inability to control the timing of the measure. For example, a CXR may be taken many hours after CPT is delivered. This is likely to make it difficult to associate any effect of CPT with the measurement outcome (Marques et al., 2006). Furthermore the presence of lung pathology on CXR may lag behind the clinical picture or may be exaggerated or underestimated (Marques et al., 2006), making CXR a potentially insensitive tool for measuring changes in lung function following CPT. Similarly, ABG data collected following CPT may be able to provide some information about treatment effects (Elizabeth et al., 2016; Main et al., 2004; Main & Stocks, 2004; Soundararajan & Thankappan, 2015). However, ABG results may also be influenced by simultaneous changes in ventilation, body positioning or medication (Taussig et al.,

161

2008), which may limit the validity of ABG in detecting CPT effects. Furthermore, both CXR and ABG are associated with risks to the ventilated infant and child. CXR necessitates a radiation dose and ABG, an invasive procedure that can reduce blood volume. These factors make CXR and ABG unsuitable as routine measure of CPT effects.

Auscultation and secretion clearance are used by the bedside to comment on CPT effects (Main & Denehy, 2016) however, neither tool has been validated for use with ventilated infants and children. Auscultation has been shown to have fair to poor inter-rater reliability amongst physiotherapists (Brooks & Thomas, 1995) assessing breath sounds in adults and it would be reasonable to suggest a similar finding is likely when used with ventilated infants and children. Similarly, clinimetric properties associated with the assessment of secretion volume appears to have had little investigation in ventilated infants and children and may not be sensitive enough to indicate meaningful physiological changes that result from CPT. While readily available, the lack of clinimetric data supporting the use of auscultation and secretion weight should be carefully considered when measuring CPT effects in ventilated infants and children.

6.2.1.4   Ventilators should not be used for measuring CPT effects

Paediatric ventilators have the ability to provide breath by breath respiratory mechanics measures in ventilated infants and children. This could be useful as ventilators are readily available in PICUs. However, the lack of validity and reliability of measures recorded using ventilators (Cannon et al., 2000; Castle et al., 2002; Heulitt et al., 2005; Kim et al., 2015) suggests that ventilators are an unlikely measurement tool for measuring CPT effects in this population. The lack of validity was particularly noted when measuring tidal volumes at places other than the airway opening and when tidal volumes generated were below 150 millilitres (Castle et al., 2002) such as in smaller ventilated infants and children.

162

Of note, some ventilator models with poor validity and reliability have been superseded (Cannon et al., 2000; Castle et al., 2002). It is possible that with newer ventilators may have better accuracy and reliability than older ventilators previously studied. Further studies are required to ascertain this.

<u>6.2.1.5   No tools measure regional ventilation distribution</u>

None of tools identified measured the immediate and longer term effects of CPT on regional lung physiology and ventilation distribution.

Tools that can measure changes in ventilation distribution may be able to provide specific information regarding the regional effect of CPT. Measuring regional ventilation distribution is likely to be important if CPT is used to treat focal pathologies, rather than the lung as a whole. Examples of clinical tools that can provide direct measurement of changes in lung physiology include tools such as computed tomography, lung ultrasound (Leech et al., 2014), computerised lung sound monitoring (Ntoumenopoulos & Glickman, 2012) and EIT (Frerichs et al., 2017; Frerichs et al., 2006; Frerichs et al., 1998). However many of these tools may not be suitable for use in ventilated infants and children and more importantly, may not be feasible for use by the bedside.

Computed tomography represents one of the most detailed tools when it comes to measuring lung physiology (Simon, 2005). Computed tomography is not a feasible option for physiotherapists as specialised equipment and training are required (Simon, 2005). Additionally, the patient needs to be moved from the PICU, which is associated with an element of risk in critically unwell infants and children (Simon, 2005). Lung ultrasound can be used by the bedside to image regions of the lung to differentiate between pathologies (Leech et al., 2014). It is feasible that lung ultrasound may be able to guide CPT treatment selection and delivery. Lung ultrasound requires specialised training and has been used as a measurement tool in ventilated adults (Leech et al., 2014). Similarly, a novel computerised lung monitoring tool has been described in ventilated adults to measure CPT effects

163

(Ntoumenopoulos & Glickman, 2012). However, this too relies on specialised equipment that is not yet commonplace in the PICU setting. None of these tools capable of providing direct measures of changes in lung physiology and aeration have been investigated for use in ventilated infants and children.

EIT represents a potentially useful option for measuring CPT effects in ventilated infants and children as it can be used by the bedside and has been shown to be able to directly measure different aspects of lung physiology in response to CPT in ventilated preterm infants (Hough et al., 2008). Furthermore EIT is becoming increasingly available and affordable as the evidence supporting its use increases (Frerichs et al., 2017). Measurement tools such as EIT may therefore represent a new option for physiotherapists working in the PICU.

6.2.2 EIT can be used to measure regional ventilation distribution in ventilated infants and children

Study 2 provides the first evidence for the use of EIT to measure CPT effects in ventilated infants and children supporting the use of EIT as a feasible bedside tool by physiotherapists working in the PICU context. The clinical implications for the use of EIT to measure CPT effects in ventilated infants and children are discussed below.

There are clinical benefits associated with how the EIT measures are taken. EIT measures are taken through a series of adhesive disposable electrodes placed directly around the thoracic cage (Frerichs et al., 2017). Few difficulties were identified by the treating physiotherapist in providing CPT over the electrodes in Study 2, nor were EIT measurements disrupted during the delivery of CPT techniques such as chest percussion or chest wall vibrations. EIT measurements appear to be less likely to be affected by factors such as ETT leak, which have been shown to potentially reduce validity and reliability of tools such as ventilators or respiratory monitors to measure CPT effects in

164

ventilated infants and children (Castle et al., 2002; Main et al., 2004). Additionally, EIT does not rely on the sedation or paralysis of a child in order to record measurements.

Study 2 has demonstrated that EIT can be used by the bedside, an important consideration for physiotherapists when choosing a measurement tool to measure CPT effects in an acutely unwell patient cohort. EIT is a small, portable machine able to be wheeled to the bedside. This differentiates EIT from other lung imaging techniques that provide information regarding regional ventilation distribution, such as computed tomography or helium-3 magnetic resonance imaging (Dunster, Friese, Fraser, Galloway, et al., 2012). Although these imaging tools have the potential to provide detailed information about lung physiology they cannot be delivered by the bedside and consequently carry the increased risk of having to remove patients from the PICU for extended periods of time (Frerichs et al., 2017). EIT can provide comparable lung physiological data (Frerichs et al., 2017) by the bedside with little or no interruption to essential patient care and therefore has benefits over other complex lung imaging techniques.

Lastly, EIT reflects a tool that it is becoming increasingly available, affordable and is investigated in PICUs around the world (Frerichs et al., 2017). A recently published consensus statement for the use of EIT (Frerichs et al., 2017) provides important clarity around the terminology and uses of EIT, improving its clinical utility and potential as a clinical and research tool in ventilated infants and children. This increasing availability, interest and evidence for the use of EIT in the PICU setting makes it a potentially promising option compared to other novel tools used to measure CPT effects (Frerichs et al., 2017).

6.2.3   CPT influences regional ventilation

Study 2 demonstrated that regional ventilation improved in all areas of the lung with the most notable increase occurring in the posterior (dependent) region of the lung. One possible reason for

165

the increased regional ventilation in the dependent lung regions may be due to airway secretions being mobilised. Airway secretions are likely to collect in dependent regions of the lung due to the effect of gravity and the orientation of the airways (Gamsu et al., 1976). If CPT mobilised these secretions towards proximal or central airways for removal via suction it is possible that areas of collapsed or under-ventilated lung would re-expand thus improving regional ventilation.

Although ETT suctioning is a component of CPT, differences between CPT and ETT suction (Main et al., 2004) effects have previously been identified. Findings from this research program have added to the scientific literature providing evidence for the first time about how CPT and routine airway clearance differ in their effect at a physiological level. Significant improvements in EELV and geometric centre were observed in response to CPT that were not observed following routine airway clearance. This may reflect that routine airway clearance likely results in clearance of secretions from larger, upper airways, making it an important clinical intervention to maintain ETT patency but not to re-expand collapsed lung regions. CPT techniques are often directed to specific lung regions or areas of collapse with the aim to improve ventilation and subsequently gas exchange (Oberwaldner, 2000), an important distinction compared with routine airway clearance.

Results of Study 2 provides further support to the suggestion that CPT effects in ventilated infants and children may be more subtle and complex than previously thought (Main & Stocks, 2004). Acute lung pathology does not affect the lung in a homogenous way (Frerichs et al., 2017). Therefore, CPT interventions may be targeted towards specific areas of the lung affected by acute lung pathology, rather than the lung as a whole. It appears that CPT is also unlikely to affect the lung in a uniform way. A greater global inhomogeneity in aeration was found in participants receiving CPT compared to routine airway clearance which may have reflected the presence of more severe lung disease in participants who required CPT. Future studies stratifying severity of lung disease and/or quantifying

166

severity of illness, such as Paediatric Index of Mortality score (Slater et al., 2003), may help to confirm this finding.

6.2.4 Lack of sensitivity of other tools used to measure CPT effects

Traditional measures of lung function, such as ABG and transcutaneous oxygen saturations, appear to not be sensitive to measure changes in lung aeration in response to CPT. Despite a significant improvement in EELV as a result of CPT, no difference in arterial or transcutaneous oxygenation and $PaCO_2$ was found between those ventilated infants and children receiving CPT compared to routine airway clearance. ABG and pulse oximetry represent tools that provide broad measures of lung function which do not provide information about regional changes in the lung. It is also possible that while CPT affects regional ventilation distribution, these changes may not always be significant, or necessarily result in, clinical improvements in gas exchange. It is possible that these more subtle, regional changes were not enough to influence global gas exchange and therefore be identified using ABG analysis or pulse oximetry.

6.2.5 Recruitment manoeuvres do not enhance CPT effects

The use of lung recruitment after CPT in ventilated infants and children has received little investigation and is not routinely recommended (Morrow et al., 2007). Clinically, recruitment manoeuvres may be considered beneficial following CPT to augment improvements in regional ventilation facilitated by secretion removal, and/or to compensate for the negative effects resulting from loss of PEEP, through ventilator disconnection, ETT suction and MHI (Lindgren et al., 2007; Maggiore et al., 2003). It was hypothesized that through secretion removal, regional ventilation distribution to previously under-ventilated lung regions could be facilitated by the application of a recruitment manoeuvre, hence improving the CPT effect. The use of lung recruitment after CPT was

also hypothesized to minimize potential negative effect on ventilation, gas exchange and physiological state caused by disconnection from a ventilator.

No clear benefit was identified from the addition of recruitment manoeuvres following CPT compared to routine airway clearance. This suggests that despite theoretical benefits, recruitment manoeuvres undertaken following CPT in this sample did not provide any additional benefit to improving regional ventilation or gas exchange. Perhaps this is not surprising when the aim of recruitment manoeuvres is to compensate for the loss of PEEP, a different aim than CPT. Small but significant increases in heart rate and respiratory rate were identified in participants who received a recruitment manoeuvre and CPT compared to routine airway clearance and recruitment. These findings may reflect a difference in physiological stability following the combination of CPT and a recruitment manoeuvre, however small participant numbers make this difficult to confirm and a larger study is needed to investigate further.

6.3   Limitations of the research

Several limitations must be acknowledged when considering the findings of this research program. The following section presents the key limitations for both studies.

6.3.1   Low yield and quality of studies included in the systematic review

Few studies were identified for inclusion in the systematic review, both for identifying the tools used to measure CPT effects in ventilated infants and children and investigation of clinimetric properties of the identified tools.

It is possible that only including completed trials in the systematic review may have limited the yield. This decision was made to ensure that measurement tools identified and assessed for clinimetric rigor had been subject to peer-review and therefore studies in progress were discounted in the final study yield. It is possible that novel measurement tools or tools not previously reported in the

literature to assess CPT effects on ventilation and gas exchange in ventilated infants and children were missed. While this is a possible limitation, the results of Study 1 represent an accurate representation of the measurement tools described in the literature at the time the review was undertaken and can be interpreted within this context until studies of novel meausrement tools are completed.

Restricting the systematic review to only include studies investigating CPT effects may have also limited the yield. For example, the Pliance force-sensing mat (Gregson et al., 2012; Gregson et al., 2007) was not included in the systematic review. The force-sensing mat quantifies pressures applied by physiotherapists during the delivery of percussion and chest vibrations. Although these are CPT techniques, the mat does not specifically measure the effects of CPT and therefore was excluded. Future studies combining tools such as the mat with those identified in this thesis that can measure regional ventilation may be useful for further investigation of the effect of CPT treatment techniques on ventilation.

There was a low yield of studies investigating clinimetric properties for the identified measurement tools. The same search strategy was used to identify studies reporting clinimetric properties of the identified measurement tools. This limited the yield to studies investigating clinimetric properties of the tools in ventilated infants and children. It is possible that this approach limited findings as studies investigating clinimetric properties of validity, reliability and/or responsiveness of the identified tools in other populations such as adults or in non-ventilated infants and children were not included. Using clinimetric data from other populations is not considered rigorous (Mokkink et al., 2016) and tools should be validated for use in the population of interest. Therefore, it was important to limit the search to ventilated infants and children.

Methodological quality of included clinimetric studies were determined using the validated COSMIN scoring system which is specifically designed to rate the methodological quality of clinimetric studies (Terwee et al., 2012). COSMIN uses a four point rating system to rank methodological design aspects, with the lowest score determining the overall level of quality for the study (Terwee et al., 2012). Two questions pertaining to each clinimetric property relates to missing data. The lack of reporting about missing data, even if no data were missing, was one reason for the overall low quality rating of the included studies. Ensuring that COSMIN relevant information is reported in future studies measuring CPT effects in ventilated infants and children may improve the quality of studies in future systematic reviews.

6.3.2   EIT study design

The clinical EIT study was undertaken as a secondary analysis of data collected within a larger prospective randomised controlled trial investigating the effect of two different recruitment manoeuvres in ventilated infants and children. The design allowed the opportunistic investigation of CPT compared to routine airway clearance, as well as the exploration of whether a recruitment manoeuvre following CPT would improve its outcome. Study 2 was not purposefully designed to answer the research questions posed in this research program which may limit the findings. Specifically, participants were not randomly allocated to intervention groups, assessors were not necessarily blinded to all treatments received and data have been analysed to answer a different research question from that posed in the original research. All data analyses were conducted by the candidate who was blind to group allocation and recruitment intervention. Additionally, all analyses were chosen and conducted in consultation with a statistician to support the available data.

6.3.3 Sample size

The design of Study 2 resulted in a limited, and potentially underpowered, sample due to the opportunistic enrolment of participants from the randomised controlled trial. The primary intervention in Study 2, CPT, was instigated as per clinical need and was therefore limited to those participants needing additional assistance with secretion clearance. Consequently, CPT was only delivered in seventeen of the sixty participants enrolled in the randomised controlled trial. The remaining forty-three participants who received routine airway clearance were the comparison group. The small size of the experimental and control groups potentially represented an inadequate sample size to investigate the study aims.

The small sample size in Study 2 also likely limits the interpretation of whether recruitment manoeuvres enhanced the effect of CPT on regional aeration, gas exchange and physiological parameters. In the CPT group, only six participants received the double PEEP manoeuvre, four received the incremental PEEP manoeuvre and seven received no recruitment manoeuvre. With such small numbers in each group, it is difficult to draw confident conclusions about the ability of the double PEEP and incremental PEEP recruitment manoeuvres to alter the effect of CPT in ventilated infants and children. Interestingly, there were significant interaction effects between CPT and the use of a recruitment manoeuvre in physiological parameters of heart rate and respiratory rate. These differences may indicate greater physiological instability when a recruitment manoeuvre is used after CPT however careful consideration is needed in interpreting these results in the context of a small sample. Further studies are needed to investigate any benefits associated with using recruitment manoeuvres after CPT.

To account for the small sample size, a linear mixed model analysis was chosen to enable the statistical comparison of data from all participants who received CPT with participants who received

171

routine airway clearance, regardless of the recruitment manoeuvre used (Krueger & Tian, 2004). This maximised the sample size available and enabled results to be interpreted with more confidence. Notably, even with small numbers a significant difference was found for end expiratory lung volume following CPT. This study provides a basis for power calculations for future studies (see Section 6.4.2).

6.3.4 Differences between CPT and routine airway clearance groups

It is possible that clinically important differences were present at baseline between the CPT and routine airway clearance groups. Only PCO_2 was found to be significantly different between the two groups at baseline, however differences were noted in other variables at baseline, despite not reaching statistical significance. Overall the participants receiving CPT were younger, smaller, had worse oxygenation and more inhomogeneity of ventilation compared to the routine airway clearance group. This is plausible as CPT is generally instigated in ventilated infants and children with lung disease, with the aim of improving oxygenation and removal of CO_2. While not statistically significant, differences in the baseline characteristics of the CPT and routine airway clearance groups may have influenced the results obtained in Study 2 and may help to explain why greater changes were identified in EELV in participants receiving CPT, compared to following suction alone. It is possible that a larger sample size may have resulted in significant differences in participant characteristics, oxygenation and ventilation inhomogeneity being identified at baseline and therefore care needs to be taken with the interpretation of Study 2. Further research is required.

6.3.5 Data collection

As data used in Study 2 were previously collected as part of the larger randomised controlled trial the research candidate was not directly involved in the data collection associated with this study. Therefore, assumptions had to be made regarding data collection procedures and that all possible

confounding factors were included in the study record and available to the research candidate when undertaking data analysis. While these factors may limit the confidence with which data can be interpreted, the research candidate undertook steps prior to data analysis to minimise this risk including accessing the randomised controlled trial protocol and checking all retrieved data to ensure all data were collated consistently and accurately. All data used in Study 2 underwent statistical analyses independent of that performed as part of the randomised controlled trial.

6.3.6   Lack of standardised CPT delivery

The delivery of the CPT intervention was not standardised across all participants, making interpretation of results potentially less clear. The CPT interventions in Study 2 were delivered as part of each individual participant's clinical management as required. The only standardised component of the CPT intervention was participant position with all participants positioned in supine. All other aspects of the CPT treatment package had the potential to vary. For example, while all participants underwent a combination of manual techniques, MHI and ETT suction, the duration of treatment and the number of ETT suction passes likely differed, as treatment was undertaken in response to the needs of the patient. A lack of standardisation of CPT may limit the generalisability of results obtained in Study 2. However standardising CPT treatments in ventilated infants and children does not reflect real world clinical practice (McCord et al., 2013) and providing standardised CPT delivery in clinical studies may result in results that are not clinically meaningful (Gregson et al., 2007; Main et al., 2004). One method used to minimise bias associated with non-standardised CPT interventions was through the use of a single physiotherapist delivering all CPT interventions during the study period.

6.4 Future Directions

A number of important directions for future research have emerged from this research program. The lack of sound clinimetric properties found in Study 1 for many of the tools commonly used to evaluate CPT effects in ventilated infants and children highlights the need for further investigation in this area. Results from Study 2 show important differences between the effects of CPT and routine airway clearance in ventilated infants and children despite small participant numbers and support the need for further larger scale studies to build on these findings. Future directions identified from both studies are discussed.

6.4.1 Robust clinimetric studies

The overall lack of clinimetric evidence supporting readily used CPT measurement tools in ventilated infants and children highlights an important direction for further research. A number of tools such as CXR and ABGs, were found to have no supporting clinimetric data yet these tools are used clinically by physiotherapists working with ventilated infants and children. The tool with the most clinimetric data, the CO_2SMO Plus, had some investigation for validity, reliability and responsiveness however overall quality of studies was low. Furthermore, the CO_2SMO Plus isn't routinely used to measure CPT effects in ventilated infants and children. Further research is needed to investigate the clinimetric properties of all available tools, particularly those routinely used to measure CPT effects in ventilated infants and children. Strong clinimetric data supporting these tools will allow physiotherapists working with ventilated infants and children more confidence in interpreting the effects of their intervention.

Investigation of more recent ventilator and respiratory monitors to measure CPT effects in ventilated infants and children is required. A number of studies, particularly those reporting on the CO_2SMO Plus (Cannon et al., 2000; Castle et al., 2002; Main et al., 2001; Main & Stocks, 2004) and ventilators

174

(Cannon et al., 2000; Castle et al., 2002) are dated and in some cases were undertaken over a decade ago. The clinical relevance of these studies may be questioned, considering that many of the ventilators and respiratory monitors investigated in these studies have since been superseded by newer models that may be more accurate or reliable compared to those used in the original studies. Future studies of recent and current tools are needed to investigate the clinimetric properties and measure the effects of CPT in ventilated infants and children.

Future clinimetric studies need to have high methodological quality. Therefore, the COSMIN checklist or a similar clinimetric quality measure should be considered when designing such studies. In particular, many of the identified clinimetric studies scored fair to poor on the COSMIN checklist as a result of not adequately reporting missing items, failing to formulate clear priori hypotheses (Castle et al., 2002; Heulitt et al., 2009; Riou et al., 2004), small sample size (Cannon et al., 2000; Riou et al., 2004), failing to adequately describe comparator instruments (Gregson et al., 2012; Shannon, Stocks, Gregson, Dunne, et al., 2015) and inadequate statistical methods (Castle et al., 2002; Main et al., 2004; Shannon, Stocks, Gregson, Dunne, et al., 2015). Therefore, these factors must be considered when designing future clinimetric studies to ensure high quality results on which to base the choice of CPT measurement tools in ventilated infants and children.

6.4.2 Clinical use of EIT in ventilated infants and children

Studies investigating the use of EIT in ventilated infants and children are limited compared to studies with adults and preterm infants (Frerichs et al., 2017), with most paediatric studies designed to improve understanding of lung physiology and how it is impacted by disease (Frerichs et al., 2017), rather than to measure the effects of interventions. The successful use of EIT in Study 2 in measuring the effect of CPT compared to routine airway clearance in ventilated infants and children opens up

avenues for future studies in this area to supports its use as a clinical measurement tool for physiotherapists in PICU.

6.4.3   Methodological considerations when investigating CPT effects with EIT

Further research is needed to explore EIT as a measurement tool of CPT effects in ventilated in ventilated infants and children. Methodological issues identified in the current study should be considered and strategies included to eliminate or minimise; issues such as larger participant cohorts, ideally using a randomised controlled design.

Findings from Study 2 of this thesis have provided data regarding the between group differences in EIT measures of end expiratory lung volume and ventilation distribution; globally, anterior and for posterior lung regions. Using the University of British Columbia sample size calculator (https://www.stat.ubc.ca/~rollin/stats/ssize/n2.html) comparing means of two independent samples a sample size of 63 participants per group would be sufficient to find a between group difference (CPT versus routine airway clearance) for all EIT measures at 30 minutes following CPT at two-tailed significance of 0.05 level with 80% power.

A larger sample may also make it possible to identify factors that influence which ventilated infants and children are likely to respond to CPT. Previous study findings (Main et al., 2004) and clinical experience suggest that some ventilated infants and children are likely to be more responsive to CPT than others. Study 2 was unable to explore responders from non-responders due to the study design and sample size. Age (Main & Denehy, 2016) and lung pathology (Main et al., 2004; Oberwaldner, 2000) may influence response to CPT. Therefore, a larger sample size with stratification of participants based on factors that may influence response to CPT should be considered. This could improve understanding about the type of patients most likely to benefit from CPT and importantly help guide PICU physiotherapists with respect to patient selection.

176

Future EIT studies evaluating CPT effects in ventilated infants and children may consider collecting simultaneous respiratory mechanics data, for example using the CO_2SMO Plus, to observe concurrent changes in respiratory mechanics and regional aeration. This comparison has not been investigated and may improve understanding of results found in previous studies using respiratory mechanics measures to explain CPT effects in ventilated infants and children. Combining direct measures of lung physiology using EIT with previously used measures such as CO_2SMO Plus may provide an opportunity to understand what is happening at both a global and regional level in the lungs in response to CPT in ventilated infants and children.

6.4.4   Effect of body position

Future studies investigating CPT effects in ventilated infants and children may also consider the effect of body positioning, as a component of CPT, on regional ventilation changes. All participants in Study 2 underwent CPT in supine to minimise positional effects on regional ventilation distribution, EELV and airflow inhomogeneity. Body position has been previously shown to influence these measures in spontaneously breathing newborn and adult cohorts (Schibler et al, 2009). Positioning is a common part of CPT in ventilated infants and children (Schultz et al., 2005), especially in the presence of unilateral or lobar disease (Main & Denehy, 2016), to encourage gravity-assisted secretions drainage and optimise ventilation-perfusion matching (Main & Denehy, 2016). Therefore, to achieve a better understanding of CPT effects in ventilated infants and children, further studies are required that investigate all possible components of CPT treatment.

6.5   Conclusion

The findings from Study 1 and Study 2 have successfully achieved the objectives set out within this research program. This research program identified the breadth and clinimetric properties of measurement tools used to evaluate CPT effects in ventilated infants and children and, used a novel measurement tool, EIT, to investigate CPT effects on regional aeration compared to routine airway clearance.

The results of both studies demonstrate that there is a lack of measurement tools with strong clinimetric rigour with which to measure CPT effects in ventilated infants and children. Furthermore, even tools that do have clinimetric data represent are unable to measure regional aeration in response to CPT.

EIT represents a feasible option for measuring CPT effects in ventilated infants and children and results of this research program demonstrate significant differences CPT and routine airway clearance on EELV and ventilation distribution. The findings of this research program will assist physiotherapists working with ventilated infants and children in their choice of measurement tools and direct future studies using EIT to better understand the complex effect of CPT in this population.

7 Research Portfolio Appendices

7.1 Appendix 1. PROSPERO registration for Study 1 systematic review

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

UNIVERSITY *of York*
Centre for Reviews and Dissemination

Systematic review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon to see guidance on completing each section.

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.
A systematic review of the clinometric properties of tools used to measure the effects of chest physiotherapy in mechanically ventilated infants and children aged 0-16 years

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.
03/07/2017

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.
30/01/2018

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review.

179

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes
Risk of bias (quality) assessment	No	Yes
Data analysis	No	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Miss Bronagh McAlinden

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic mail address of the named contact.
bronagh.mcalinden@health.qld.gov.au

8. Named contact address

Give the full postal address for the named contact.
Physiotherapy Department
Lady Cilento Children's Hospital
South Brisbane
Queensland, 4101
Australia

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
+61730681791

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.
School of Physiotherapy, Australian Catholic University

Organisation web address:
http://www.acu.edu.au/

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Miss Bronagh McAlinden. Australian Catholic University

Professor Suzanne Kuys. Australian Catholic University
Dr Judith Hough. Australian Catholic University

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.
Australian Catholic University

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.
What measurement tools are used to evaluate chest physiotherapy effects in ventilated infants and children?
What are the clinometric properties of these measurement tools?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
The following electronic databases will be searched: PubMed, CINAHL, Embase, The Cochrane Library, PEDro and Web of Science.
The search strategy will include the use of pre-determined medical subject heading (MeSH) terms and key text words relating to the key population and intervention. Where available search filters will be used to limit the findings to the target age groups of infants, children and adolescents.
Manual targeted reference searches of included studies will be undertaken to identify additional eligible studies. ClinicalTrials.gov and WHO ICTRP will be searched to identify planned or ongoing trials, unpublished articles or articles in press using the same key search terms.
There will be no restrictions on study design, language or date of publishing.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Infants and children 0-16 years who are mechanically ventilated and receiving chest physiotherapy.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion:
Measurement tools were included if they met all of the following criteria:
(i) Used in subjects 0-16 years old receiving mechanical ventilation via an endotracheal tube/ tracheostomy within a paediatric intensive care unit, and
(ii) Where subjects received chest physiotherapy (defined as any single or combination of techniques including positioning, manual techniques, manual hyperinflation or mechanical airway clearance devices used in combination with endotracheal suctioning) and,
(iii) Used to measure chest physiotherapy effects including secretion clearance, respiratory mechanics, radiological appearance of the lung or gas exchange during and/or after chest physiotherapy
Exclusion:
Measurement tools were:
(i) Used in subjects over 16 years old or premature infants 38 weeks of age
(ii) Used in subjects not mechanically ventilated via an endotracheal tube
(iii) Used in subjects not receiving chest physiotherapy or only used prior to chest physiotherapy
(iv) Used to measure the delivery of a chest physiotherapy technique eg. the mechanistic effect of CPT

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
Inclusion:
All studies that described tools measuring lung function during/and or after chest physiotherapy, where chest physiotherapy includes any single or combination of techniques including positioning, manual techniques, manual hyperinflation or mechanical airway clearance devices used in combination with endotracheal suctioning
Exclusion:
Studies that describe measures of lung function that are:
i) Used to measure an intervention other than chest physiotherapy
ii) Only used prior to a chest physiotherapy intervention
iii) Used in spontaneously breathing subjects or subjects receiving non-invasive ventilation

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
All studies will be included regardless of whether there is a comparator or control group.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.
All studies in which the outcome of the intervention of chest physiotherapy has been measured.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Ventilated infants and children.

24. * Primary outcome(s).

7. 2 Appendix 2. Search results and data collection tables for (i) Included studies and (ii) excluded studies

(i) Included studies

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
Almeida, C, Ribeiro, J, Almeida Junior, A, Zeferino, A Physiotherapy Research International, 2005:10 (4); pp 213-221	Effect of expiratory flow increase technique on pulmonary function of infants on mechanical ventilation	Prospective, non-randomized, non-controlled	**Subjects:** 22 infants 28 days - 12 months (mean age 3.1 months), mean weight 5.64 kg) **Exclusion:** Paralysed, haemodynamic instability, neuromuscular disease, cardiac disease, post-op, chronic pneumopathies, severe malnutrition or acute respiratory failure 2° upper airway disease, atelectasis > 1/3 lung on CXR, PEEP > 10cmH$_2$O **Pathology:** Obstructive acute respiratory failure (wheezing and coughing; diffuse wheeze or prolonged expiration during auscultation, CXR with air trapping) **Ventilation characteristics:** Intubated & ventilated; mean parameters (PIP 27.8cmH$_2$O, PEEP 4 cmH$_2$O, 24bpm, inspiration time 0.56 seconds, FiO$_2$ 0.4); non-cuffed tube (3.5-4.5 mm); time-cycled, pressure-limited ventilator using SIMV Positioned supine at 30° elevation	Data collected after patient had been ventilated 24-72 hour and at least 12 hours after the last CPT session Suctioned, sedated with midazolam and diazepam, measurements taken immediately before and 30 minutes after expiratory flow increase technique	CPT - expiratory flow increase technique Passive expiration performed using the increase in expiratory flow to remove peripheral secretions from bronchial tree toward trachea Manoeuvre repeated 40 times and followed by ETT suction	Respiratory rate CO$_2$SMO Plus: Expired Vt. Alveolar Vt Minute ventilation Alveolar ventilation Airway dead space volume Alveolar dead space volume Total dead space volume Dead space volume/ tidal volume ratio Dynamic inspiratory resistance Dynamic expiratory resistance Dynamic compliance PaO$_2$ PaCO$_2$ SpO$_2$ PaO$_2$/ FiO$_2$

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
						$P(A-a)O_2$/ PaO_2 PaO_2/ PAO_2
Deakins, K, Chatburn, R Respiratory Care, 2002: 47 (10); pp 11620-1167	A comparison of intrapulmonary percussive ventilation and conventional chest physiotherapy for the treatment of atelectasis in the paediatric patient	Prospective, randomized, controlled trial	**Subjects:** 12 subjects (CPT group = 5; IPV group = 7); 7 weeks - 14years **Exclusion:** Febrile patients, cultures +ve for bacteria, air leak, pulmonary disease with infiltrates **Pathology:** Atelectasis diagnosed on CXR **Ventilation characteristics:** Intubated and ventilated in PICU, Evidence of atelectasis on CXR, minimum weight for inclusion 3Kg; SERVO 900C, SIMV VC, PEEP 5 cmH_2O, Vt 6-10ml/kg, rate determined by age and underlying condition; ETT 3.0-7.0 mm (4.0mm most common)	Subjects randomised Baseline data collected Treatment continued until atelectasis resolved or patient extubated	Conventional treatment group: 10-15 minutes percussion, clapping, vibration over areas of atelectasis, Every 4 hours, Suctioned at end of treatment IPV group: Every 4 hours Removed from vent, attached to IPV, settings equal to peak pressures observed during routine ventilation (15-$30cmH_2O$); frequency 180-220 cycles/ minute Given with 6 ml 0.9% NaCl Intervals lasted 20 second followed by 5-10 second pause; Treatment lasted 10 minutes	Pulse oximeter Respiratory rate Stethoscope (Breath sounds) CXR 'Atelectasis score' (taken daily) Exhaled end tidal volumes Plateau pressure
Elizabeth, M, Yoel, C, Ali, M, Lubis, M, Yanni, G Paediatrica Indonesiana, 2016: 56 (5); pp 285-290	Comparison of ventilation parameters and blood gas analysis in mechanically-ventilated children who received CPT and suctioning versus suctioning alone	Single-blind, clinical trial	**Subjects:** 40 subjects (CPT group = 24; Suction alone = 16); mean weight (CPT group = 7.9kg; Suction alone = 9.5kg), median age (CPT = 10.5month; suction = 14.5 months) **Exclusion:** Chest trauma, clotting dysfunction **Pathology:** Any lung pathology including consolidation, atelectasis/ effusion as diagnosed on CXR **Ventilation characteristics:** Any mode or settings	Subjects randomized into CPT or suctioning alone group	CPT group: 30mins CPT and suctioningComparator: Suction alone	ABG: pH, PCO_2, PO_2, HCO_3, TCO_2, BE, SpO_2 Ventilator: Vt, PIP, PIF, PEF, Peak Expiratory flow rate, Peak Inspiratory flow rate

184

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
Galvis, A, Reyes, G, Nelson, W Pediatr Pulmonol, 1994: 17 (5); pp 326-330	Bedside management of lung collapse in children on mechanical ventilation: saline lavage--simulated cough technique proves simple, effective		**Subjects:** 57 children < 1year (8 < 1month; 49 between 1month and 1 year) **Exclusion:** Not specified **Pathology:** Persistent unilateral lung collapse or 2 or more atelectatic lobes but no suggestion of infection **Ventilation characteristics:** Not specified	Subjects sedated and given short-acting neuromuscular blockade before technique started	Saline washout-stimulated cough Hyper-oxygenation by bag 100% O_2 Saline instillation to desired main stem bronchus Deep ventilation-simulated glottic closure-forced exhalation (MHI) - large volume breaths, forced exhalation with vibes, ETT Suctioning	CXR (presence of air bronchogram) Pulse oximetry: SpO_2 ABG
Gregson, R, Shannon, H, Stocks, J, Cole, T, Peters, M, Main, E Pediatr Crit Care Med, 2012Volume 13 (2); pp e97-3102	The unique contribution of manual chest compression-vibrations to airflow during physiotherapy in sedated, fully ventilated children	Prospective observational study	**Subjects:** 105 (5 excluded as below) sedated, fully ventilated children 0-16 years; Median age 1.3years deemed after PT assessment to require CPT; paralysed and/ or deeply sedated (could not cough or breathe spontaneously); cardio-vascularly stable (no signs of instability within 2 hrs of starting PT) **Exclusion:** At risk of haemorrhage, increased intracranial pressure, metabolic bone disease, tracheal tube leak > 20% **Pathology:** lung consolidation or atelectasis on CXR, added or reduced BS on auscultation, increased vent requirements within last 4 hours and/ or deteriorating ABGs; included primary and	Baseline measurements taken for 10minutes before CPT using the CO_2SMO Tracheal tube leak measured before and after PT	CPT - Selected treatment techniques based on clinical indications (inclusive of combinations of manual lung inflations/ MHI, compressions-vibrations, saline instillation, ETT suction No limitations around the order or use of any components; determined by clinical judgement of the PT	CO_2SMO Plus: Respiratory data (flow, pressure and volume) during mandatory tidal breaths Inflation volume PIP PEF

185

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
			secondary lung pathology, cardiac conditions and post-surgery			
Hussey, J, Hayward, L, Andrews, M, Macrae, Elliot, M

Physiotherapy Theory and Practice, 1996 : 12 (2); pp 77-85 | Chest physiotherapy following paediatric cardiac surgery: The influence of mode of treatment on oxygen saturation and haemodynamic stability | Prospective clinical observational study | **Subjects:** 71 (74 eligible) children up to 4 years (median age 11 months) underwent 101 treatments following corrective cardiac surgery; on mechanical ventilation, with 'clinical indications for CPT
Pathology: Secretion retention and atelectasis due to mucus plugging
Exclusion: If child started moving, were withdrawn due to inaccuracy of SpO_2 reading; extremely cardiovascular instability | CPT determined based on assessment Treatment techniques based on auscultation, CXR findings and nurses report of secretions Recordings of SpO_2, heart rate and blood pressure taken every 60 seconds for at least 5 mins before and throughout CPT | CPT - bag squeezing, percussion and vibes, positioning, increased O_2, suctioning- Standard bag squeezing=3 tidal breaths and 1 hyperinflation- Standard positioning involved supine, right or left side lying- Increasing O_2 involved increase of 20% FiO_2 on ventilator | Pulse oximeter (only recorded when pulse rate on oximeter was within 5 beats of ECG derived heart rate) |
| Main, E, Castle, R, Newham, D, Stocks, J

Intensive Care Medicine, 2004 Volume 30 (6); pp 1144-1151 | Respiratory physiotherapy vs. suction: The effects on respiratory function in ventilated infants and children | Randomised crossover study | **Subjects:** 100 children (7 excluded for tracheal tube leak); paired measurements for 90 subjects;
Pathology: majority had a primary cardiac diagnosis and had undergone surgery, some with delayed sternal closure
Other diagnoses included primary RF, PHT, cardiac transplant, HI, major abdominal surgery, BMT, asthma, inhalation injury, tracheal reconstruction
Exclusion: Tube leak > 20% | Subjects randomly assigned to CPT or suction in morning and alternative in afternoon; minimum interval between sessions 90 minutes Ventilator settings constant during measurements, recorded (mode, OI, tube size, flow sensor size, age, weight | CPT and suction – Any combination of pre-oxygenation, saline instillation, MHI and suction, any number of cycles

CPT - Any combination of above + manual techniques" | CO_2SMO Plus: Expired Vt Resistance Compliance ABG |

186

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
Main, E & Stocks, J Intensive Care Medicine, 2004 Volume 30 (6); pp 1152-1159	The influence of physiotherapy and suction on respiratory dead space in ventilated children	Randomised crossover study	**Subjects:** 87 fully ventilated children requiring CPT ; paired measurements in 81 (6 excluded for tube leak > 20%)' paralysed Pressure pre-set ventilation modes used in 56 children, 19 received volume pre-set modalities; majority had a primary cardiac diagnosis and had undergone surgery, some with delayed sternal closure (6 infants had nitric oxide) Other diagnoses included primary respiratory failure, pulmonary hypertension, cardiac transplant, head injury, major abdominal surgery, BMT, asthma, inhalation injury, tracheal reconstruction **Exclusion:** Tube leak > 20%, no art line	Portable respiratory monitor used to measure respiratory volumes and $EtCO_2$ before and after CPT and suction in same children, measured pressure, flow and CO_2 concentration continuously via disposable, fixed-orifice, differential flow sensor with incorporated mainstream infrared absorption capnography inserted at airway opening between ETT and ventilator circuit Subjects randomly assigned to CPT or suction in morning and alternative in afternoon; minimum 90 minute interval between sessions	CPT and suction procedures delivered as deemed appropriate for the individual patients; both procedures involved any combination of pre-oxygenation, saline instillation, manual hyperinflation and suction, with as many or few cycles as necessary. CPT was distinguishable from suction by the addition of chest wall vibrations, percussion orcompression and postural drainage	CO_2SMO Plus:- Physiological dead space/ Kg Alveolar dead space/ kg Physiological dead space/ Vt Expired tidal volume/ kg CO_2 elimination $EtCO_2$ Mixed expired CO_2 Anatomical dead space ABG
Soundararajan, L & Thankappan, S	Effect of manual hyperinflation on arterial oxygenation in paediatric		**Subjects:** Convenience sample of 18 paediatric in-patients (10 males) who had cardiac surgery and had upper lobe collapse (Right side-17 and Left side-1) in the post-op	Subjects positioned half-lying/ sitting with head of bed slightly elevated and undisturbed for 15	CPT - MHI + vibes + suction MHI - 100% oxygen, rate 15 Litres/min 4 x sets of 8 breaths rate of 10 breaths per minute) delivered during each MHI;	CXR ABG

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
European Journal of General Medicine, 2015: 12 (4); pp 313-318	patients with upper lobe collapse after cardiac surgery		period requiring mechanical ventilation **Excluded:** Abnormal positioning of the ETT, acute respiratory distress syndrome, acute pulmonary oedema, unstable blood pressure, untreated tension pneumothorax, and those with peak inspiratory pressures higher than 40 cmH$_2$O or requiring high respiratory support FiO$_2$>0.7 and PEEP>10 cmH$_2$O)	minutes prior to data collection FiO$_2$ maintained at 100% during the manual hyperinflation and suction and returned back to the pre-set value after intervention	used peak airway pressure of 40 cmH$_2$O followed by a 2 second inspiratory pause and then quick release, PEEP valve included in circuit if patient was ventilated with PEEP Suctioning - Normal saline (1 ml) instilled before hyperinflation and duration of suctioning was 15s; 1 ml of normal saline in the tracheal tube, followed by suctioning, once per minute, for 4 minutes.	
Tannenbaum, E, Prasad, S, Dinwiddie, R., Main, E Pediatric Pulmonology, 2007: 42 (12); pp 1152-1158	Chest physiotherapy during anaesthesia for children with cystic fibrosis: Effects on respiratory function	Prospective, randomized crossover study	**Subjects:** 9 (+ 9 control) children with confirmed CF requiring elective general surgery; cuffed tube to minimise tracheal leak; median age 12y (2.8-15y); median length of anaesthesia 100 min in the CPT group **Exclusion:** Subjects requiring thoracic surgery **Pathology:** Cystic fibrosis; general surgical procedures	Patients randomised into two groups with stratification for FEV1, age and sex. Lung function technicians blinded to treatment group allocation CPT Treatment group received treatment under anaesthesia before surgical procedure Ventilator settings kept constant before and after CPT	CPT Treatment group – modified PD, saline instillation, MHI (1.0 FiO$_2$) with expiratory vibes and tracheal suctioning Duration and types of techniques not standardized to represent normal PT practice; Control group - standard support from anaesthetist, suctioning undertaken by anaesthetist at their discretion	CO$_2$SMO Plus: Compliance, PIP, Resistance, Expired Vt, Sputum yield (ml/kg)

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
Shannon, Harriet, S, Stocks, J, Gregson, R, Dunne, C, Peters, M, Main, E Physiotherapy, 2015: 101 (4); pp 349-356	Clinical effects of specialist and on-call respiratory physiotherapy treatments in mechanically ventilated children: A randomised crossover trial	Prospective randomised crossover trial	**Subjects:** 93 children (aged 3 days - 16 y) receiving mechanical ventilation requiring 2 CPT treatments per day; aged 0-6y, with stable ventilation requirements; deeply sedated and/ or paralysed; most patients naso-tracheally intubated with un-cuffed tubes **Exclusion:** Patients with ETT tube leak > 20%, at risk of haemorrhage, rib fracture or if had "other contraindications to receiving manual techniques" **Pathology:** Consolidation or atelectasis on CXR, added or decreased breath sounds on auscultation, increased ventilator requirements Subjects had primary cardiac diagnosis (n=25); 8 of these had delayed sternal closure; primary respiratory diagnosis (n=19), tracheal surgery (n=14), traumatic brain injury (n=3), 'other medical reasons' (n=2), nitric oxide during treatment (n=12)	Non-respiratory on-call physiotherapist and specialist respiratory physiotherapist recruited to the study Physiotherapists were randomly assigned to allocated sequence (which PT treated first) Research recruited all participants (patients and physiotherapists); no masking; random sample patient data was dually analysed by 2nd blinded independent researcher Patients had 2 CPT treatments in a day, one by each type of physiotherapists	CPT - Clinical indicators were assessed by senior respiratory physiotherapist CPT consisted of a combination of postural changes, instillation of saline or mucolytic, manual or ventilator lung inflations, ETT suction and manual techniques including chest wall vibrations	NICO$_2$: Compliance, resistance, Expired Vt or PIP (depending on the mode of ventilation)

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
Shannon, H, Stocks, J, Gregson, R, Hines, S, Peters, M, Main, E Physiotherapy, 2015: 101 (4); pp 357-363	Differences in delivery of respiratory treatments by on-call physiotherapists in mechanically ventilated children: a randomised crossover trial	Prospective randomised crossover trial	**Subjects:** 93 children (aged 3 days - 16 y) receiving mechanical ventilation requiring 2 CPT treatments per day; aged 0-6yr, with stable MV requirements; deeply sedated and/ or paralysed; most patients naso-tracheally intubated with un-cuffed tubes **Exclusion:** Patients with ETT tube leak > 20%, at risk of haemorrhage, rib fracture or if had "other contraindications to receiving manual techniques" **Pathology:** Consolidation or atelectasis on CXR, added or decreased BS on auscultation, increased ventilator requirements Subjects had primary cardiac diagnosis (n=25); 8 of these had delayed sternal closure; primary respiratory diagnosis (n=19), tracheal surgery (n=14), TBI (n=3), 'other medical reasons' (n=2)N=12 had nitric oxide during CPT	No instructions given concerning use or order of specific treatment components, the physiotherapists applied treatments according to their own clinical judgement As required, patients had 2 CPT treatments in a day, one by each type of physiotherapists	CPT - All treatments for the recruited patients consisted of combinations of saline instillation, manual lung inflations, chest wall vibrations and endotracheal suction.	$NICO_2$: Compliance, Resistance, PIP, PEF, PIF, inspired and expired volumes

Reference details	Title	Study design	Study Population (demographics, baseline characteristics, underlying pathology)	Procedure	CPT characteristics (techniques used, order, rationale)	Measurement Tool characteristics
Schultz, T, Lin, R, Francis, B, Hales, R, Colborn, S, Napoli, L, Helfaer, M Pediatr Crit Care Med, 2005: 6 (4); pp 428-34	Kinetic therapy improves oxygenation in critically ill pediatric patients	Prospective randomised crossover trial	**Subjects:** 50 children requiring positive pressure mechanical ventilation and invasive blood pressure monitoring (via existing arterialcatheters); mean age 32 months, range 8–96 months, mean weight 13.2 kg, range of 8–25.6 kg; 35 children had complete data **Exclusion:** "when the potential risk of kinetic therapy was believed to outweighthe potential benefit" Eg. if on ECMO and unstable cannulae, if on rigid HFOV circuits; unstable spinal cord, persistent uncontrolled intracranial hypertension, uncontrolled bronchospasm, severe uncontrolled claustrophobia, severe uncontrolled diarrhoea, or a requirement for skeletal traction; within 24hr of receiving nitric oxide or surfactant **Pathology:** Included both respiratory and non-respiratory conditions from a cardiac and general PICU	Patients randomised on inclusion to study, immediately placed on PediDyne bed Standard group - Turned and percussed every 2 hours over 18-hour period Intervention group - Kinetic bed positioning + bed percussion every 2 hours over 18 hours During study phase, ventilator variables adjusted according to patient needs, regardless of where in the study, Administration of nitric oxide, when used, continued throughout 36 hour evaluation phase	Control/ Standard PT - manual turning and percussion Intervention group - kinetic therapy with percussion Kinetic therapy initiated at an 80° arc (40° to each side with 7-second pauses at right,left, and centre) for 18 hours, with automatic CPT as available on the bed every 2 hours During both conditions,CPT and ABG done every 2 hours, alternating so that they were both not done at the same hour	ABG (at the onset of evaluation and once every other hour for the 36-hour evaluation phase, 18 hours each condition (I-stat) *alternate hour to when physio given) Oxygenation index, $P(A-a)O_2$ Any change 20% of baseline OI and/or$P(A-a)O_2$ (improvement or deterioration) wasconsidered to be clinically significant

Abbreviations: ABG - Arterial blood gas , BE - Base excess, CO_2 – Carbon dioxide, CPT - Chest Physiotherapy group, CXR - Chest X-ray, ECG – Electroencephalograph, ECMO – Extracorporeal membrane oxygenation, $ETCO_2$ - End-tidal carbon dioxide, ETT - Endotracheal Tube, FiO_2 – Fraction inspired oxygen, IPV – Intrapulmonary percussive ventilator, H_2O – Water, Kg = kilogram, HCO_3 – Bicarbonate, HFOV – high frequency oscillation ventilation, MHI - Manual Hyperinflation, ml – millilitres, mm – millimetres, n- sample size, NaCl – Saline, O_2 – Oxygen, OI – oxygenation index, P(A-a)O2 - arterial-alveolar oxygen tension difference PaO_2 – Partial pressure of arterial oxygen, $PaCO_2$ – Partial pressure of arterial carbon dioxide, PaO_2/ FiO_2 - Partial pressure of arterial oxygen/ fraction inspired oxygen, PEEP - Positive end expiratory pressure, PEF - Peak expiratory flow, PICU – paediatric intensive care unit, PIF - Peak inspiratory flow, PIP - Peak inspiratory pressure, RCT - Randomized controlled trial, RR – Respiratory rate, SIMV - Synchronized Intermittent Mandatory Ventilation, SpO_2 = oxygen saturations, TCO_2 – transcutaneous carbon dioxide, Vt - Tidal volume, > - greater than

(ii) Excluded studies

Authors	Title	Source	Reason/s for Exclusion
Diwate, A	Effectiveness of cardiopulmonary physiotherapy versus prone positioning on respiratory functions in ventilated neonates – A randomized trial	Clinicaltrials.gov	No full text available
McKinnon, C	A pilot study comparing inhaled hypertonic to normal saline on the respiratory function of children with neurological impairment and acute lower respiratory tract infection	Australia and New Zealand Clinical trials Registry	No full text, not all participants ventilated
Moerman, D	Influences of techniques of chest physiotherapy in the pediatric intensive care	World Health Organisation International Clinical Trials Platform (clinical trials.gov)	No full text available
Holloway, R, Adams, E Desai, S, Thambiran, A	Effect of chest physiotherapy on blood gases of neonates treated by intermittent positive pressure respiration	Thorax, 1969:24 (4); pp 421	Preterm population
Bernard-Narbonne, F Daoud, P, Castaing, H Rousset, A	Effectiveness of chest physiotherapy in ventilated children with acute bronchiolitis	Archives de Pediatrie, 2003:10 (12); pp 1043-1047	Preterm population
Demont, B, Vincon, C, Bailleux, S, Cambas, C Dehan, M, Lacaze-Masmonteil, T	Chest physiotherapy using the expiratory flow increase procedure in ventilated newborns: a pilot study	Physiotherapy, 2007:93 (1) pp:12-16	Preterm population
Flenady, V, Gray, P	Chest physiotherapy for preventing morbidity in babies being extubated from mechanical ventilation	Cochrane Database of Systematic Reviews, issue 2	Preterm population
Makic, F, Rauen, M, Jones, C, Fisk, K, Anna	Continuing to Challenge Practice to Be Evidence Based	Critical Care Nursing, 2015:35 (2); pp 39-50	Review article, no described measurements of CPT intervention

Authors	Title	Source	Reason/s for Exclusion
Gajdos, V, Katsahian, S, Beydon, N, Abadie, V de Pontual, L, Larrar, S Epaud, R, Chevallier, B Bailleux, S, Mollet-Boudjemline, A, Bouyer, J Chevret, S, Labrune, P	Effectiveness of Chest Physiotherapy in Infants Hospitalized with Acute Bronchiolitis: A Multicenter, Randomized, Controlled Trial	Plos Medicine, 2010:7 (9); pp	Not mechanically ventilated
Gilgoff, I, Barras, D Sellers Jones, M, Adkins, H	Neck breathing: A form of voluntary respiration for the spine-injured ventilator-dependent quadriplegic child	Pediatrics, 1988:82 (5); pp 741-745	Not in the ICU/ acute setting
Gregson, R, Shannon, H, Stocks, J, Cole, T, Peters, M, Main, E	The unique contribution of manual chest wall vibrations to airflow during physiotherapy in mechanically ventilated children	Physiotherapy, 2011:97; pp eS431-eS432	Abstract (full text article retrieved above)
Gregson, R, Stocks, J Petley, G, Shannon, H Warner, J, Jagannathan, R Main, E	Simultaneous measurement of force and respiratory profiles during chest physiotherapy in ventilated children	Physiological Measures, 2007:28 (9); pp 1017-28	Not measuring CPT intervention
Hawkins, E, Jones, A	What is the role of the physiotherapist in paediatric intensive care units? A systematic review of the evidence for respiratory and rehabilitation interventions for mechanically ventilated patients	Physiotherapy, 2015:101 (4); pp 303-309	Review article, no described measurements of CPT intervention
Hough, J, Flenady, V Johnston, L, Woodgate, P	Chest physiotherapy for reducing respiratory morbidity in infants requiring ventilatory support	Cochrane Database of Systematic Reviews, 2008 Issue 3	Preterm population
Ko Noordin, A, Ross Weller, L	Effectiveness of manual hyperinflation in mechanically ventilated patients: A literature review and implications for use of manual hyperinflation in the paediatric population	Proceedings of Singapore Healthcare, 2012:21; pp S261	Review article, no described measurements of CPT intervention
Krause, M, Hoehn, T	Chest physiotherapy in mechanically ventilated children: A review	Critical Care Medicine, 2000:28 (5); pp 1648-1651	Review article, no described measurements of CPT intervention

Authors	Title	Source	Reason/s for Exclusion
MacLean, D, Drummond, G, Macpherson, C, McLaren, G Prescott, R	Maximum expiratory airflow during chest physiotherapy on ventilated patients before and after the application of an abdominal binder	Intensive Care Medicine, 1989:15 (6); pp 396-399	Adult population
Main, E, Castle, R, Stocks, J James, I, Hatch, D	The influence of endotracheal tube leak on the assessment of respiratory function in ventilated children	Intensive Care Medicine, 2001:27 (11); pp 1788-97	Not measuring effects of CPT intervention
Main, E, Elliott, M, Schindler, M, Stocks, J	Effect of delayed sternal closure after cardiac surgery on respiratory function in ventilated infants	Critical Care Medicine, 2001:29 (9); pp 1798-802	Not measuring effects of CPT intervention
Martin, R, Chatburn, R	Respiratory care of infants and children: Conference summary	Respiratory Care, 1991:36(7); pp 757-760	conference summary
Moerman, D, Houtekie, L	Early Mobilization in the Pediatric Intensive Care Unit	Reanimation, 2016:25(5); pp 542-548	Review article, no described measurements of CPT intervention
Morrow, B, Futter, M Argent, A	A recruitment manoeuvre performed after endotracheal suction does not increase dynamic compliance in ventilated paediatric patients: a randomised controlled trial	Australian Journal of Physiotherapy, 2007:53(3); pp 163-169	Not measuring CPT intervention
Morrow, B, Argent, A	A comprehensive review of pediatric endotracheal suctioning: Effects, indications, and clinical practice	Pediatric Critical Care Medicine, 2008:9 (5); pp 465-477	Not measuring CPT intervention
Niranjan, V	Noninvasive management of pediatric neuromuscular ventilatory failure	Critical Care Medicine, 1998:26 (12); pp 2061-2065	Not measuring CPT intervention
Nicholas, K, Dhouieb, M Marshall, T, Edmunds, A Grant, M	An evaluation of chest physiotherapy in the management of acute bronchiolitis: changing clinical practice [with consumer summary]	Physiotherapy, 1999:85 (12); pp 669-674	Not mechanically ventilated
Oberwaldner, B	Physiotherapy for airway clearance in paediatrics	European Respiratory Journal, 2000:15(1); pp 196-204	Review article, no described measurements of CPT intervention

Authors	Title	Source	Reason/s for Exclusion
Oberwaldner, B, Zach, M	Paediatric chest physiotherapy for mucus clearance	Schweizerische Medizinische Wochenschrift, 2000:130(19); pp 711-719	Review article, no described measurements of CPT intervention
Paludo, C, Zhang, L, Lincho, C S, Lemos, D, Real, G Bergamin, J	Chest physical therapy for children hospitalised with acute pneumonia: a randomised controlled trial	Thorax, 2008:63(9); pp 791-794	Not mechanically ventilated
Panitch, H	Airway clearance in children with neuromuscular weakness	Current Opinion in Pediatrics, 2006: 18 (3); pp 277-281	Not mechanically ventilated
Paperny, D, Ng, K, Light, M	An effective neonatal endotracheal lavage-suctioning technique	Clinical Pediatrics, 1982:21 (4); pp 231-232	Not mechanically ventilated
Postiaux, G, Ladha, K Gillard, C, Charlier, J Lens, E	Chest physiotherapy for young infants (<24 months) guided by lung sounds	Revue Francaise D Allergologie Et D Immunologie Clinique, 1997:37 (2); pp 206-222	Not mechanically ventilated
Reines, H, Sade, R Bradford, B, Marshall, J	Chest physiotherapy fails to prevent postoperative atelectasis in children after cardiac surgery	Annals of Surgery, 1982:195 (4); pp451-455	Not mechanically ventilated
Rose, L, Adhikari N, Leasa, D, Fergusson D, McKim, D	Cough augmentation techniques for extubation or weaning critically ill patients from mechanical ventilation	Cochrane Database of Systematic Reviews, 2017 Issue 1	Review, Not mechanically ventilated with respect to paediatric info
Shannon, H, Gregson, R Dunne, C, Stocks, J, Main, E	The safety and effectiveness of on-call paediatric respiratory physiotherapy in intensive care	Physiotherapy, 2011:97; pp eS1127-eS1128	Not full text (full text article retrieved above)
Shannon, H, Gregson, R Dunne, C, Stocks, J, Main, E	Differences in selection and application of respiratory physiotherapy techniques between respiratory and on-call physiotherapists for mechanically ventilated children	Physiotherapy, 2011:97; pp eS1128	Not measuring CPT intervention
Shannon, H, Stiger, R Gregson, R, Stocks, J Main, E	Effect of chest wall vibration timing on peak expiratory flow and inspiratory pressure in a mechanically ventilated lung model	Physiotherapy, 2010:96 (4); pp 344-349	Not human/ bench-top model

Authors	Title	Source	Reason/s for Exclusion
Toussaint, M, De Win, H Steens, M, Soudon, P	Effect of intrapulmonary percussive ventilation on mucus clearance in Duchenne muscular dystrophy patients: a preliminary report	Respiratory Care, 2003:48(10); pp 940-947	Adult population
Tudehope, D, Bagley, C	Techniques of physiotherapy in intubated babies with the respiratory distress syndrome	Australian Paediatric Journal, 1980:16(4); pp 226-228	Preterm population
Van Ginderdeuren, F, Vandenplas, Y, Deneyer, M Vanlaethem, S, Buyl, R Kerckhofs, E	Effectiveness of airway clearance techniques in children hospitalized with acute bronchiolitis	Pediatric Pulmonology, 2017:52(2); pp 225-231	Not mechanically ventilated
Vianello, ., Corrado, A Arcaro, G, Gallan, F Ori, C, Minuzzo, ., Bevilacqua, M	Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections	American Journal of Physical Medicine & Rehabilitation, 2005:84 (2); pp 83-91	Not mechanically ventilated
Viviano, G, Reale, A Iannelli, M.	Validity and limitations of respiratory physiotherapy in children	La Pediatria medica e chirurgica : Medical and surgical pediatrics, 1990:12(2);pp 155-156	Not mechanically ventilated; in Italian and unable to get full text translated; appears to be a review article as well
Walsh, B, Hood, K Merritt, G	Pediatric Airway Maintenance and Clearance in the Acute Care Setting: How To Stay Out of Trouble	Respiratory Care, 2011 :56(9); pp 1424-1440	Review article, no described measurements of CPT intervention
Webb, M, Martin, J Cartlidge, P. H., Ng, Y Wright, N	Chest physiotherapy in acute bronchiolitis	Archives of Disease in Childhood, 1985:60(11); pp 1078-1079	Review article, no described measurements of CPT intervention
Yuan, N, Kane, P, Shelton, K Matel, J, Becker, B Moss, R	Safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial	Journal of Child Neurology, 2010:25(7); pp 815-821	Not mechanically ventilated
Lineham, D; Johnson, P Madden, M; Ramdat, E; Custer, J	Intrapulmonary percussive ventilation assist in weaning pediatric patients from extracorporeal membrane oxygenation	Respiratory Care, 2016:61(10); pp OF43-OF43	Case study (2) Abstract - No full text available

7.3   Appendix 3. COSMIN scores for validity, reliability and responsiveness

COSMIN item scoring for construct validity (Hypothesis Testing validity)

Tool	Study	Score	1	2	3	4	5	6	7	8	9	10
CO₂SMO Plus	Cannon et al, 2000											
	Infants	Fair	Good	Fair	Good	Excellent	Good	Good	Excellent	Good	Excellent	Excellent
	Paediatrics	Poor	Good	Fair	Poor	Excellent	Good	Good	Excellent	Good	Excellent	Excellent
	Castle et al, 2002	Fair	Good	Fair	Good	Fair	Excellent	Good	Excellent	Excellent	Excellent	Excellent
	Main et al, 2001	Fair	Good	Fair	Good	Good	Excellent	Good	Excellent	Excellent	Excellent	Excellent
	Riou et al, 2004	Fair	Good	Fair	Fair	Fair	good	Good	Excellent	Excellent	Excellent	Excellent
Ventilator	Cannon et al, 2000											
	Infants	Fair	Good	Fair	Good	Excellent	Good	Good	Excellent	Good	Excellent	Excellent
	Paediatrics	Poor	Good	Fair	Poor	Excellent	Good	Good	Excellent	Good	Excellent	Excellent
	Castle et al, 2002	Fair	Good	Fair	Good	Fair	Excellent	Good	Excellent	Excellent	Excellent	Excellent
	Heulitt et al, 2009	Fair	Good	Fair	Good	Fair	Good	Good	Excellent	Excellent	Excellent	Excellent
	Kim et al, 2015	Good	Excellent	Excellent	Good	Excellent	Excellent	Good	Excellent	Excellent	Excellent	Excellent

197

COSMIN item scoring for validity criterion validity

Tool	Study	Score	1	2	3	4	5	6	7
Pulse Oximetry	Das et al, 2010	Fair	Good	Fair	Good	Good	Excellent	-	-
	Khemani et al, 2012	Good	Excellent	Excellent	Excellent	Good	Excellent	Excellent	Excellent
	Ross et al, 2014	Good	Good	Excellent	Excellent	Good	Excellent	-	-

COSMIN item scoring for reliability

Tool	Study	Score	1	2	3	4	5	6	7	8	9	10	11*
CO_2SMO Plus	Main et al, 2001	Poor	Good	Fair	Poor	Excellent	Good	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
	Main et al, 2004	Poor	Excellent	Excellent	Fair	Excellent	Good	Excellent	Excellent	Excellent	Good	Excellent	Poor
	Riou et al, 2004	Fair	Good	Fair	Fair	Excellent	Good	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Ventilator	Castle et al, 2002	Poor	Good	Fair	Poor	Excellent	Good	Excellent	Good	Excellent	Good	Excellent	Poor
	Heulitt et al (2009)	Fair	Good	Fair	Good	Excellent	Good	Excellent	Good	Fair	Good	Excellent	Excellent
Pulse Oximetry	Das et al, 2010	Poor	Good	Fair	Good	Poor	Good	Excellent	Good	Poor	N/A	Poor	N/A

* Items 12-14 not included in table as non-applicable

COSMIN item scoring for responsiveness (Items 1-9)

Tool	Study	Score	1	2	3	4	5	6	7	8	9
CO_2SMO Plus	Gregson et al, 2012	Poor	Excellent	Excellent	Excellent	Excellent	Excellent	Good	Excellent	Fair	Good
	Main & Stocks, 2004	Poor	Excellent	Excellent	Good	Excellent	Excellent	Excellent	Excellent	Fair	Excellent
	Main et al, 2004	Poor	Excellent	Excellent	Good	Excellent	Excellent	Excellent	Excellent	Fair	Good
$NICO_2$	Shannon, Stocks, Gregson, Dunne, et al., 2015;	Poor	Excellent	Good	Good	Excellent	Excellent	Good	Excellent	Excellent	Excellent

COSMIN item scoring for responsiveness (Items 10-18)

Tool	Study	Score	10	11	12	13	14	15	16	17	18
CO_2SMO Plus	Gregson et al, 2012	Poor	Good	Poor	Poor	Excellent	Excellent	N/A	N/A	Excellent	N/A
	Main & Stocks, 2004	Poor	Good	Excellent	Good	Excellent	Excellent	N/A	N/A	Poor	N/A
	Main et al, 2004	Poor	Good	Excellent	Good	Excellent	Excellent	N/A	N/A	Poor	N/A
$NICO_2$	Shannon, Stocks, Gregson, Dunne, et al., 2015;	Poor	Good	Poor	Poor	Excellent	Excellent	N/A	N/A	Poor	N/A

200

7.4 Appendix 4. Mater Children's Hospital ETT suction policy

Mater
Exceptional People. Exceptional Care.

Mater Children's Hospital
PICU

Policy Name: Tracheal Suctioning
Policy No: MHS-WCH-C-015

PRINCIPLE:
Patients with endotracheal or tracheostomy tubes require tracheal suctioning to remove secretions from the airways and maintain airways and maintain airway patency.

POLICY
1. Two persons are required to perform this procedure
2. Tracheal suctioning is to be performed as required and not routinely
3. Standard precautions are to be observed during tracheal suctioning
4. Disposable non sterile gloves are used for the procedure
5. Each attempt at suctioning must take no longer than 5 seconds

PROCEDURE/GUIDELINES
1. Ensure alarm limits are set at appropriate range and turned on

2. Ensure adequate lighting so the child's colour can be observed during the procedure

3. Wash hands apply non sterile gloves

4. Pre-oxygenate by hand bagging. Manometers are used in PICU to reduce the risk of administering excessive pressures.

5. Instil 0.5ml 0.9% sodium chloride to thin/loosen secretions

6. Use appropriate size suction catheter that is not more than half the inside diameter of the endotracheal tube (ETT size x 2)

7. Insert suction catheter to pre-measured length i.e. 0.5 to 1cm beyond the tip of the endotracheal/tracheostomy tube) and apply continuous negative pressure for no longer than 5 seconds as the catheter is withdrawn.

8. The suction source must be regulated to provide a negative pressure appropriate to age of child.

Policy Name: Tracheal Suctioning
Policy No: MHS-WCH-C-015

GUIDE for pressure settings:

Infant < 1year 45 - 65 mmHg
Child 1 - 6 year 65 - 80 mmHg
Older child 80 - 100 mmHg
Adolescent 100 - 120 mmHg

9. Hand ventilate to oxygenate and reinflate any areas collapsed by the suctioning. Observe manometer to monitor and regulate pressures. Maintain PEEP as per written ventilation orders and increase the PIP by 1 -2cmH20.

10. Assess child for need to repeat suctioning. Suction catheter passes should generally be restricted to 2 -3 per session. If not effectively clearing secretions, chest percussions and 'vibes' may assist to loosed secretions and move them along the larger airways so they can be cleared with suctioning.

11. Return child to ventilator, auscultate chest to check air entry, observe chest wall movement, and note that the child's vital signs return to her/his usual range.

12. Suction naso/oro pharynx.

13. Notify team co-ordinator of any concerns such as no clinical improvement in child despite suctioning, decreased lung compliance noted when hand ventilating or difficulty in passing suction catheter.

<u>IMPORTANT</u>
If you are unable to clear a blocked tube and there is no doctor immediately available, remove the endotracheal tube and ventilate with bag and mask. This has been authorised by the PICU director.

<u>Special considerations:</u>
1. In patients with raised intracranial pressure, coughing SHOULD NOT be allowed to occur during suctioning. Administer muscle relaxant as per written order prior to suctioning and allow sufficient time for it to be effective. Lignocaine may also be ordered pre-suctioning. Both coughing and suctioning can cause marked increase in ICP.

2. Children with pulmonary oedema should not be disconnected from ventilator for suctioning, but a suction port adaptor should be incorporated into the ventilator circuit. Minimal suctioning should be performed on these patients.

202

3. For intubated but non-ventilated patients, provide pre/post-oxygenation and PEEP, but do not routinely hand ventilate when hand bagging, as this may result in a period of apnoea when the child is reconnected to the ventilator.

4. If child is on a support mode of ventilation, do not over ventilate when hand bagging, as this may result in a period of apnoea when the child is reconnected to the ventilator.

5. When hand ventilating a non-drug paralysed patient, attempt to synchronise with the child's own breaths as this is more comfortable for them and more effective, especially if the child is crying.

6. Adequate humidification reduces the thickness of secretions and the risk of tube obstruction, thus reducing the need for too frequent suctioning

REFERENCES:

Printed on 29 Aug 2007. This policy is valid for 24 hours after date of printing only.   Page 3 of 3

203

7.5 Appendix 5. Mater HREC and Australian Catholic University HREC Approval and Amendments

Mater

Exceptional People. Exceptional Care.

MATER HEALTH SERVICES HUMAN RESEARCH ETHICS COMMITTEE

4th May 2012

Ms Bronagh McAlinden
Pysiotherapist
Queensland Paediatric Cardiac Service
Mater Children's Hospital

Dear Ms McAlinden

Re: Protocol *Ref №. 2012-25* **The effects of chest physiotherapy on regional lung volume changes in ventilated children using Electrical Impedance Tomography**

I write to advise that the Mater Health Services Human Research Ethics Committee has reviewed this research project and recognises that the project meets the requirement for Low and Negligible Risk Research as set out in the National Statement (Section 5.1.18 – 5.1.21) and has granted ethical approval for your research project.

Documents reviewed and approved:

- LNR Ethics application form Version 1, dated 10th April 2012
- Study Budget
- Protocol Version 1, dated 10th April 2012
- Mandatory cover sheet dated 11th April 2012
- Consent letter for use of previously collected data
- Approval letter for seeding grant
- Protocol Appendix (Tracheal Suctioning Guidelines)

This approval is valid until 4th May 2015. Please note the following conditions of approval.

- The Principal Investigator has responsibility for ensuring that the project is conducted in accordance with the National Statement, with relevant legislation and with Mater Health Services and responsibility for monitoring compliance rests with your Head of Department.
- Any departure from the protocol detailed in your proposal must be reported immediately to the Human Research Ethics Committee.
- When you propose a change to an approved protocol, which you consider to be minor, you are required to submit a written request for approval to the Chairperson, through the Research Ethics and Governance Office. Such requests will be considered on a case by case basis and interim approval may be granted subject to ratification at the next meeting of the Human Research Ethics Committee.
- Where substantial changes to any approved protocol are proposed, you are required to submit a full, new proposal for consideration by the Human Research Ethics Committee.

)621
/07

204

- Under the *NHMRC National Statement on Ethical Conduct in Research Involving Humans*, research ethics committees are responsible for monitoring approved research to ensure continued compliance with ethical standards, and to determine the method of monitoring appropriate to each project. You are required to provide written reports on the progress of the approved project annually (if your project's duration is greater than 1 year), and finally on completion of the project. Please inform the Committee of publications, presentations at Conferences, education and quality improvement outcomes from this study.
- Please provide written confirmation of the date of project commencement.
- You are required to advise the Research Ethics Coordinator immediately of any complaints made, or expressions of concern raised, in relation to the study, or if any serious or unexpected adverse events occur.
- To access medical records, for the purpose of this study, please provide a copy of this approval letter to the Health Information Services and Privacy Office (if applicable).
- The Research Ethics and Governance Office may choose to conduct an interim audit of your research project.
- Please be aware that all study procedures including follow-up of participants and data analysis should be completed within the approval time frame or an extension should be requested

You are reminded that this letter constitutes ethical approval only. You must not commence this research project until authorisation from the Research Governance Office has been obtained.

Please accept our very best wishes for the success of this research project. *In all future correspondence with the Research Ethics and Governance Office please quote the Mater reference number.*

Yours sincerely

A/Prof Andrew Crowden

Chairperson

Mater Health Services Human Research Ethics Committee

11 August 2017

Ms Bronagh McAlinden
PO BOX 3474
Qld 4101

Dear Ms McAlinden

Re: HREC Ref #: HREC/17/MHS/72
        **Project title: The effects of chest physiotherapy on regional lung volume changes in ventilated
        children using Electrical Impedance Tomography**

I refer to your correspondence dated 5 July 2017 requesting an extension to the above study.

I write to advise that on behalf of the Mater Misericordiae Ltd Human Research Ethics Committee (MML
HREC) (EC00332), I reviewed and approved this request for an extension for a further 3 years from the
date of expiry of previous HREC approval and this will be noted by the Committee at its 19 September
2017 meeting.

The approval expiry date has been extended to **4 May 2018.**

**This letter constitutes ethical approval only. Please liaise with your Research Governance office in
regard to any additional requirements. At Mater Misericordiae Ltd please contact the Research
Governance Office on 07 3163 3769.**

It should be noted that all requirements of the original approval still apply. Please provide a progress
report at your soonest convenience and continue to provide at least annual progress reports until the
study has been completed.

Please accept our best wishes for the remainder of the study and should you have any queries, please do
not hesitate to contact the Research Ethics Office on 3163 1585.

Yours sincerely

Dr Conor Brophy MBBS; MD; MBioethics; FRCP; AFRACMA
Chairperson
Mater Misericordiae Ltd Human Research Ethics Committee

*This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on
Ethical Conduct in Human Research (2007), updated in 2015. The processes used by this HREC to review multi-centre research proposals have been
certified by the National Health and Medical Research Council.*

Mater Research HREC Office
Room 294 Level 2 Aubigny Place   Ph: 07 3163 1585 Fax: 07 3163 1588   Email: research.ethics@mmri.mater.org.au

Mater Misericordiae Health Services Brisbane Limited
ACN 096 708 922

Raymond Terrace,
South Brisbane,
Queensland 4101 Australia
Phone + 61 7 3163 8111
www.mater.org.au

206

From:	Pratigya Pozniak on behalf of Res Ethics
To:	Judith Hough
Cc:	Res Ethics; bbmcal001@myacu.edu.au
Subject:	2017-153R Registration of External Ethics Approval
Date:	Wednesday, 11 October 2017 10:55:29 AM

Dear Judith,

Principal Investigator: Dr Judy Hough
Student Researcher: Bronagh McAlinden [HDR Student]
Ethics Register Number: 2017-153R
Project Title: The effects of chest physiotherapy on regional lung volume changes in ventilated children using Electrical Impedance Tomography.
Risk Level: Multi Site
Date Approved: 11/10/2017
Ethics Clearance End Date: 04/05/2018

The Australian Catholic University Human Research Ethics Committee has considered your application for registration of an externally approved ethics protocol and notes that this application has received ethics approval from Mater [Reference: HREC/17/MHS/72].

The ACU HREC accepts the ethics approval with no additional requirements, save that ACU HREC is informed of any modifications of the research proposal and that copies of all progress reports and any other documents be forwarded to it. Any complaints involving ACU staff must also be notified to ACU HREC (National Statement 5.3.3)

We wish you well in this research project.

Regards,

Kylie Pashley
on behalf of ACU HREC Chair, Dr Nadia Crittenden Ethics Officer | Research Services Office of the Deputy Vice Chancellor (Research) res.ethics@acu.edu.au

7.6 Appendix 6. Consent from authors of Randomised Controlled Trial (Jauncey-Cooke, 2012) to use study data in Study 2

8th August, 2011

PICU
Mater Children's Hospital

To whom it may concern,

We have happily given Bronagh McAlinden full access to the data yielded from Human Lung Recruitment Study HREC #1010C. The parent's of participants in this study each provided informed consent. The data Bronagh plans to use includes children that underwent clinically appropriate chest physiotherapy during the study period.

Regards,

Andreas Schibler   Jacqui Jauncey-Cooke

7.7 Appendix 7. Mater Research Institute Ownership, Storage and Retention of Human Research Materials and Data Policy

Policy

Document Title:	**Ownership, Storage and Retention of Human Research Materials and Data Policy**
Document ID:	PY-RSH-300300
Document Name:	Ownership, Storage and Retention of Human Research Materials and Data Policy
Version Number:	1
Revision Date:	12/11/2014 10:38:00 AM
Key Words	research, data, retention, ownership, storage, medical records

Internal Use Only: The Material within this document has been developed solely for the internal business purposes of Mater Research. Disclosure of information of this classification may result in a breach of statutory or regulatory obligations by the Mater.

Notice of Currency: If viewing a printed copy of this document, NEVER assume that the printed copy being viewed is current. Always check the online Mater Research Handbook to confirm you are viewing the current version of this framework.

Our Mission	**Our Vision**	**Our Values**
As Mater Research, together with our partners, we conduct, enable and translate exceptional clinically relevant health research.	Achieving better health for all through exceptional research.	Mercy Dignity Care Commitment Quality

Affirmation

This governance document is consistent with the Mater Values and supports the Mater Research Mission and Vision by establishing and mandating appropriate controls to support the delivery of health care services.

Table of Contents

2	Hospital and Health Boards Act, 2011
3	Privacy Act, 1988 Guidelines approved under Section 95 of the Privacy Act, 1988 Guidelines approved under Section 95A of the Privacy Act, 1988 Guidelines approved under Section 95AA of the Privacy Act, 1988 (Cth) Australian Privacy Principles
4	Public Health Act, 2005
5	Australian Code for the Responsible Conduct of Research, 2007
6	National Statement on Ethical Conduct in Human Research, National Health & Medical Research Council (NHMRC), 2007 (Updated in March 2014) (herein referred to as the *National Statement*)
7	Catholic Health Australia Code of Ethical Standards for Catholic Health and Aged Care Services in Australia, 2001
8	Values and Ethics: Guidelines for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research, 2003
9	Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) – Annotated with TGA Comments. Therapeutic Goods Administration, 2000

2 Introduction

2.1 Purpose

The purpose of this policy is to assist researchers to fulfil their responsibilities with respect to ownership of human research materials and data, their entry, storage, use, disclosure, retention beyond the end of the project, destruction, and appropriate access to the research materials and data by the research community. Information previously collected for a purpose other than research is also within the scope this policy.

2.2 Scope and Context

This policy describes the roles and responsibilities of Mater Health Services (MHS) and Mater Research (MR) researchers and others using MHS resources to ensure that the management of all human research material complies with the "National Statement on Ethical Conduct in Human Research" (2007) (the *National Statement*), the "Australian Code for the Responsible Conduct of Research" (2007) (*the Code*) and the "Notes For Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments" (2000) (GCP).

This policy applies to all MHS and MR employees (permanent, temporary and casual) and students, non-MHS research collaborators, MR honorary appointees, sponsors and agents (including Visiting Medical Officers, visiting health professionals, contractors, consultants and volunteers) who propose to undertake research involving patients, staff and resources of MHS and MR.

2.3 Definitions

Term	Definition
Certified HREC	An HREC which has had its processes assessed and certified under the National Health and Medical Research Council (NHMRC) National Certification Scheme. NHMRC certification lasts for three years. • To access information on the NHMRC Certification Scheme: http://hrep.nhmrc.gov.au/ • To find a certified HREC: http://www.nhmrc.gov.au/_files_nhmrc/file/health_ethics/homer/Certified%20ethical%20review%20process%20v0_11.pdf
The Australian Code for the Responsible conduct of Research (The Code)	The *Australian Code for the Responsible Conduct of Research (2007)* (The Code). This guides institutions and researchers in responsible research practices and promotes integrity in research. It shows how to manage breaches of The Code and allegations of research misconduct, how to manage research data and materials, how to publish and disseminate research findings, including proper attribution of authorship, how to conduct effective peer review and how to manage conflicts of interest. It also explains the responsibilities and rights of researchers if they witness research misconduct.
Co-ordinating Investigator	The lead investigator who takes overall responsibility for the conduct of the research project at all study sites. This individual submits the project for ethical and scientific review. They are responsible for ongoing communication with the HREC and passing on any outcomes from this to the Principal Investigators. For single centre research, Coordinating Investigator and Principal Investigator are synonymous.
Databank	Collection of personal information that may be used for the purposes of research.

Good Clinical Practice (GCP)	An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. May also be referred to as ICH GCP (International Conference on Harmonisation). http://ichgcp.net/
Human Research	Research conducted with or about people, or their data or tissue as described in the *National Statement*.
Human Research Ethics Committee (HREC)	Human Research Ethics Committees (HRECs) review research proposals that involve humans or their tissue or data research involves humans. HRECs are established by organisations which register their HREC with the NHMRC. It may also be referred to as the Reviewing HREC in multi-centre research studies.
Mater Health Services (MHS)	"MHS" means Mater Misericordiae Health Services Brisbane Ltd ACN 096708922 owner and operator of the Mater Hospitals South Brisbane, Redland and other sites notified to the HREC
Mater Research (MR)	"MR" means Mater Medical Research Institute Ltd ACN 109834719 owner and operator of Mater Research and Mater Medical Research Institute
The National Statement (NS)	The *National Statement on Ethical Conduct in Human Research (2007) Revised 2014 (and subsequent revisions)*. A guidance document developed by the NHMRC, the Australian Research Council and the Australian Vice-Chancellors' Committee to provide guidelines for researchers, HRECs and others conducting ethical review of research. It also states institutions' responsibilities for the quality, safety and ethical acceptability of research that they sponsor or permit to be carried out under their auspices. http://www.nhmrc.gov.au/guidelines/publications/e72
Principal Investigator	The individual who takes responsibility for the overall conduct, management, monitoring and reporting of research conducted at a site. They are responsible for submission of the research project for site authorisation and for study-specific communication with the Research Governance Office.
Project Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a research study.
Research	Original investigation undertaken to gain knowledge, understanding and insight as described in the Australian Code for the Responsible Conduct for Research (2007).
Research Governance	Those matters concerning the quality, safety, privacy, risk management, financial management and ethical acceptability of research.

2.4   Legislative Compliance

This policy mandates compliance with laws, regulations, guidelines and codes of practice governing

    a) the conduct of research in Australia; and
    b) privacy, including the Privacy Act (1988) (including the Australian Privacy Principles), Hospital & Health Boards Act (2011) and Public Health Act (2005).

Common law obligations also arise from the relationships between institutions, researchers and participants, while contractual arrangements may impose further obligations.

2.5 Industry Standards

- The Australian Council on Healthcare Standards (ACHS) EQuIP National Guidelines Standard 15. Sydney Australia; ACHS; 2012
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) – Annotated with TGA Comments. Therapeutic Goods Administration, 2000

3   Principles

The following set of principles describes the objectives and outcomes of the policy:

3.1   Principle 1: Responsibilities of the Institution

Mater Health Services and MR have a continuing role in the management of research material and data and are responsible for:

- providing facilities for the safe and secure storage of research data and for maintaining records of where research data are stored;
- identifying ownership of research materials and data during and following the term of the research project; and
- the ownership of, and access to, databases and archives that is consistent with confidentiality requirements, legislation, privacy rules and other guidelines (*the Code* 2.1 – 2.4).

3.2   Principle 2: Responsibilities of Heads of Departments

Heads of Departments are responsible for:

- ensuring that staff and students under their supervision who are conducting research are aware of their responsibilities; and
- ensuring that databanks within their department are kept according to this policy and keeping a register of databanks that are held in their department .

3.3   Principle 3: Responsibilities of Researchers

Researchers are responsible for:

- taking into account the professional standards, legal requirements and contractual arrangements for the retention of research data and primary materials;
- managing research data and primary materials in accordance with this policy;
- ensuring that research data are accurate, complete, authentic, reliable and recorded in a form that is adequate for verification of research results; and
- maintaining the confidentiality of any confidential information to which they have been given access (*the Code* 2.5 – 2.7).

4 Policy Requirements

The following are the specific requirements of this policy.

4.1 Management of Research Data

All research that proposes to collect, use or disclose data for human research at MHS or MR must be submitted for review by an NHMRC certified Human Research Ethics Committee (HREC) and the MHS Research Governance Office. Research to be conducted at MHS and/or MR only is to be submitted to the MHS HREC (see PY-RSH-300305 Human Research Ethics Review Policy).

4.2 Confidentiality of Research Data

All researchers must comply with all provisions relating to the confidentiality of health information (see PY-IID-100016 Information Privacy Policy) and should include in their protocol a plan for the protection of participants' privacy.

To access, for research, identifiable or potentially identifiable health information held by Queensland Health (QH), where a researcher is unable to obtain participant consent, or in situations where it may be inappropriate or extremely difficult to obtain participant consent, a researcher needs to meet the requirements of s282 of the Queensland Public Health Act (PHA). An application will need to be made to the Director-General QH after first obtaining HREC approval.

Primary materials and confidential research must be kept in secure storage. Confidential information must only be used in ways agreed with those who provided it. Particular care must be exercised when confidential data are made available for discussion (*the Code 2.7*).

A breach in confidentiality in regard to information used in research may constitute research misconduct (see PY-RSH-300310 Research Misconduct Policy).

4.3 Ownership and Security of Research Data and Record Keeping

The materials and data created and retained during the conduct of a research study may be the property of the sponsor of the research, the property of the institution where the research was conducted or may be retained in a central repository under a supervising committee. The ownership may also be influenced by the funding arrangements for the project *(the Code 2.3)*. For all research projects involving institutions external to the Mater, an agreement should be developed at the outset covering the ownership and storage of research data and primary materials. (*the Code 2.2*).

Agreements covering ownership and storage of research data should be reviewed whenever there is movement or departure of research staff (*the Code 2.2.1*). Permission from the Head of Department where the principal researcher was primarily employed at time of the research should be obtained before moving stored documents.

Facilities must be provided by MHS and MR for the safe and secure storage of research data and for maintaining records of where research data are stored. Wherever possible and appropriate, research data should be held in the researcher's department or other appropriate institutional repository, although researchers should be permitted, in a secure manner, to hold copies of the research data for their own use. Arrangements for material held in other locations should be documented. Research data and primary materials must be stored in the safe and secure storage provided (*the Code 2.2*).

All researchers must be aware of relevant confidentiality agreements and restrictions on the use of research data (*the Code 2.4.2*).

Computing systems must be secure, and information technology personnel must understand their responsibilities for network security and access control (*the Code* 2.4.3).

Those holding primary material, including electronic material, must understand their responsibilities for security and access (*the Code* 2.4.4).

4.4   Retention of Research Data and Primary Materials

In general, the minimum recommended period for retention of human research data is five (5) years from the date of publication. However, this differs for specific types of research; for example:

- For short-term projects that are for assessment purposes only, such as research projects completed by students, retaining research data for 12 months after the completion of the project may be sufficient.
- For clinical trials data must be retained for a minimum of 15 years for adult studies (persons ≥ 18 years) or 25 years for paediatric studies (persons < 18 years) after formal notification is received that all study procedures are completed and the study is closed.
- For areas such as gene therapy, research data must be retained according to legislation or the code whichever is the greater (e.g. patient records).
- If the work has community or heritage value, research data should be kept permanently, preferably within a national collection.
- For legal reasons, sites may consider indefinite archiving periods.

The Therapeutics Goods Administration position on document retention states:

> *"The TGA requires records to be retained by the sponsor for 15 years following the completion of a clinical trial. However, in Australia the overriding consideration for sponsors with respect to record retention is the issue of product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond, the life of a product in the event of a claim against the sponsor as a result of an adverse outcome associated with the use of the product".*

ICH-GCP requirements for record retention state:

> *"Ensure that essential documents are retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor".*

When considering how long research data and primary materials are to be retained, the researcher must take account of professional standards, legal requirements and contractual arrangements (*the Code* 2.5).

Researchers should retain research data and primary materials for sufficient time to allow reference to them by other researchers and interested parties. For published research data, this may be as long as interest and discussion persist following publication. Research data should be made available for use by other researchers unless this is prevented by ethical, privacy or confidentiality matters. If the results from the research are challenged, all relevant data and materials must be retained until the matter is resolved. Research records that may be relevant to allegations of research misconduct must not be destroyed (*the Code* 2.5).

4.5   Destruction of Data

When the specified period of retention has finished all research data and primary materials should be disposed of securely and safely. The destruction of research data and records should be authorised by the Head of Department on recommendation of the researcher. Destruction of data must be documented.

4.6   Databanks

Most data are collected, aggregated and stored for a single purpose or activity. However, the following activities may occur:

- permission may sometimes be sought from participants to 'bank' their data for possible use in future research projects;
- 'banked' data may be deposited in a warehouse, similar to an archive or library, and aggregated over time; and/or
- archived non-identifiable data may be made available for secondary analysis, unless access is constrained by restrictions imposed by the depositor/s (the *National Statement* 3.2).

All researchers wanting to establish or access data from a databank must refer to Chapter 3.2 of the *National Statement*.

4.7   Consent

Unless a waiver of consent has been granted by the approving HREC, data must only be used for the purpose/s declared to the participants in the participant information sheet and/or consent form. Similarly, disclosure of data must only be made to other people and/or organisations as declared in the participant information and consent form.

Disclosure of data is defined as allowing persons, other than those who have access to the data for the purpose of the approved research study for which it was collected, access to the data. Those who would be expected to have access to the data would include the Principal Investigator, Co-investigators, Study Co-ordinators and associated administrative staff and research support staff for the particular study for which the data was collected. Data collected for a study, cannot then be accessed or used for another study without further approval from the HREC, unless the participant has given authorisation for the data to be used in future research..

In studies where an approving HREC has waived the requirement for consent or an opt-out approach has been granted, data may only be used for the purposes stated to the approving HREC in the study submission.

8.   References

Abbas, C., Singer, F., Yammine, S., Casaulta, C., & Latzin, P. (2013). Treatment response of airway clearance assessed by single-breath washout in children with cystic fibrosis. *Journal of Cystic Fibrosis, 12*(6), 567-574.

Al-Alaiyan, S., Dyer, D., & Khan, B. (1996). Chest physiotherapy and post-extubation atelectasis in infants. *Pediatric Pulmonology, 21*(4), 227-230.

Almeida, C., Ribeiro, J., Almeida-Júnior, A., & Zeferino, A. (2005). Effect of expiratory flow increase technique on pulmonary function of infants on mechanical ventilation. *Physiotherapy Research International, 10*(4), 213-221.

Anning, L., Paratz, J., Wong, W. P., & Wilson, K. (2003). Effect of manual hyperinflation on haemodynamics in an animal model. *Physiotherapy Research International, 8*(3), 155-163.

Arens, R., Gozal, D., Omlin, K., Vega, J., Boyd, K., Keens, T., & Woo, M. (1994). Comparison of high frequency chest compression and conventional chest physiotherapy in hospitalized patients with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine, 150*(4), 1154-1157.

Argent, A., & Morrow, B. (2004). What does chest physiotherapy do to sick infants and children? *Intensive Care Medicine, 30*(6), 1014-1016.

Argent, A., & Morrow, B. (2012). Chest physiotherapy: How does it work (if it does)? *Pediatric Critical Care Medicine, 13*(2), 238-239.

Barber, D. C., & Brown, B. H. (1989). Applied potential tomography. *Journal of the British Interplanetary Society, 42*(7), 391-393.

Berney, S., & Denehy, L. (2002). A comparison of the effects of manual and ventilator hyperinflation on static lung compliance and sputum production in intubated and ventilated intensive care patients. *Physiotherapy Research International, 7*(2), 100-108.

Berney, S., Denehy, L., & Pretto, J. (2004). Head-down tilt and manual hyperinflation enhance sputum clearance in patients who are intubated and ventilated. *Australian Journal of Physiotherapy, 50*(1), 9-14.

Blazey, S., Jenkins, S., & Smith, R. (1998). Rate and force of application of manual chest percussion by physiotherapists. *Australian Journal of Physiotherapy, 44*(4), 257-264.

Bloomfield, F. H., Teele, R. L., Voss, M., Knight, D. B., & Harding, J. E. (1998). The role of neonatal chest physiotherapy in preventing postextubation atelectasis. *Journal of Pediatrics, 133*(2), 269-271.

Boriosi, J. P., Sapru, A., Hanson, J. H., Asselin, J., Gildengorin, G., Newman, V., . . . Flori, H. R. (2011). Efficacy and safety of lung recruitment in pediatric patients with acute lung injury. *Pediatric Critical Care Medicine, 12*(4), 431-436.

Brooks, D., & Thomas, J. (1995). Interrater reliability of auscultation of breath sounds among physical therapists. *Physical Therapy, 75*(12), 1082-1088.

Brown, B. H. (2003). Electrical impedance tomography (EIT): a review. *Journal of Medical Engineering & Technology, 27*(3), 97-108.

Cannon, M. L., Cornell, J., Tripp-Hamel, D. S., Gentile, M. A., Hubble, C. L., Meliones, J. N., & Cheifetz, I. M. (2000). Tidal volumes for ventilated infants should be determined with a pneumotachometer placed at the endotracheal tube. *American Journal of Respiratory and Critical Care Medicine, 162*(6), 2109-2112.

Castle, R. A., Dunne, C. J., Mok, Q., Wade, A. M., & Stocks, J. (2002). Accuracy of displayed values of tidal volume in the pediatric intensive care unit. *Critical Care Medicine, 30*(11), 2566-2574.

Cheifetz, I. M., & Hamel, D. S. (2006). Is permissive hypoxemia a beneficial strategy for pediatric acute lung injury? *Respiratory Care Clinics of North America, 12*(3), 359-369.

Choong, K., Chatrkaw, P., Frndova, H., & Cox, P. N. (2003). Comparison of loss in lung volume with open versus in-line catheter endotracheal suctioning. *Pediatric Critical Care Medicine, 4*(1), 69-73.

Chuang, M.-L., Chou, Y.-L., Lee, C.-Y., & Huang, S.-F. (2017). Instantaneous responses to high-frequency chest wall oscillation in patients with acute pneumonic respiratory failure receiving mechanical ventilation: A randomized controlled study. *Medicine, 96*(9), e5912.

Ciesla, N. D. (1996). Chest physical therapy for patients in the intensive care unit. *Physical Therapy, 76*(6), 609-625.

Courey, A. J., & Hyzy, R. C. (2017). Overview of mechanical ventilation. Up To Date database.

Dahlem, P., van Aalderen, W. M. C., Hamaker, M. E., Dijkgraaf, M. G. W., & Bos, A. P. (2003). Incidence and short-term outcome of acute lung injury in mechanically ventilated children. *European Respiratory Journal, 22*(6), 980.

Das, J., Aggarwal, A., & Aggarwal, N. K. (2010). Pulse oximeter accuracy and precision at five different sensor locations in infants and children with cyanotic heart disease. *Indian Journal of Anaesthesia, 54*(6), 531-534.

Day, T., Farnell, S., & Wilson-Barnett, J. (2002). Suctioning: a review of current research recommendations. *Intensive Critical Care Nursing, 18*(2), 79-89.

De Jong, P. A., Achterberg, J. A., Kessels, O. A. M., Van Ginneken, B., Hogeweg, L., Beek, F. J., & Terheggen-Lagro, S. W. J. (2011). Modified Chrispin-Norman chest radiography score for cystic fibrosis: Observer agreement and correlation with lung function. *European Radiology, 21*(4), 722-729.

Deakins, K., & Chatburn, R. L. (2002). A comparison of intrapulmonary percussive ventilation and conventional chest physiotherapy for the treatment of atelectasis in the pediatric patient. *Respiratory Care, 47*(10), 1162-1167.

Denehy, L. (1999). The use of manual hyperinflation in airway clearance. *European Respiratory Journal, 14*(4), 958-965.

Dennis, D., Jacob, W., & Budgeon, C. (2012). Ventilator versus manual hyperinflation in clearing sputum in ventilated intensive care unit patients. *Anaesthesia and Intensive Care, 40*(1), 142.

Duff, J. P., Rosychuk, R. J., & Joffe, A. R. (2007). The safety and efficacy of sustained inflations as a lung recruitment maneuver in pediatric intensive care unit patients. *Intensive Care Medicine, 33*(10), 1778-1786.

Dunlop, S., Hough, J., Riedel, T., Fraser, J., Dunster, K., & Schibler, A. (2006). Electrical impedance tomography in extremely prematurely born infants and during high frequency oscillatory ventilation analyzed in the frequency domain. *Physiological Measurement, 27*(11), 1151.

Dunster, K., Friese, M., Fraser, J., Cowin, G., & Schibler, A. (2012). Ventilation distribution in rats: Part I - The effect of gas composition as measured with electrical impedance tomography. *Biomedical Engineering Online, 11*.

Dunster, K., Friese, M., Fraser, J., Galloway, G., Cowin, G., & Schibler, A. (2012). Ventilation distribution in rats: Part 2 – A comparison of electrical impedance tomography and hyperpolarised helium magnetic resonance imaging. *Biomedical Engineering Online, 11*(1), 68.

Eaton, T., Young, P., Zeng, I., & Kolbe, J. (2007). A randomized evaluation of the acute efficacy, acceptability and tolerability of flutter and active cycle of breathing with and without postural drainage in non-cystic fibrosis bronchiectasis. *Chronic Respiratory Disease, 4*(1), 23-30.

Elizabeth, M., Yoel, C., Ali, M., Lubis, M., & Yanni, G. N. (2016). Comparison of ventilation parameters and blood gas analysis in mechanically-ventilated children who received chest physiotherapy and suctioning vs. suctioning alone. *Paediatrica Indonesiana, 56*(5), 285-290.

Epstein, S., & Singh, N. (2001). Respiratory acidosis. *Respiratory Care, 46*(4), 366-383.

Evans, J. C. (1992). Reducing the hypoxemia, bradycardia, and apnea associated with suctioning in low birthweight infants. *Journal of Perinatology, 12*(2), 137-142.

Fanconi, S., & Duc, G. (1987). Intratracheal suctioning in sick preterm infants: prevention of intracranial hypertension and cerebral hypoperfusion by muscle paralysis. *Pediatrics, 79*(4), 538-543.

Ferrero, F., Torres, F., Noguerol, E., González, N., Lonegro, L., Chiolo, M. J., . . . Benguigui, Y. (2008). Evaluation of two standarized methods for chest radiographs interpretation in children with pneumonia. *Archivos Argentinos de Pediatria, 106*(6), 510-514.

Frerichs, I., Amato, M., van Kaam, A., Tingay, D., Zhao, Z., Grychtol, B., . . . Adler, A. (2017). Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the TRanslational EIT developmeNt stuDy group. *Thorax, 72*(1), 83-93.

Frerichs, I., Dargaville, P., van Genderingen, H., Morel, D., & Rimensberger, P. (2006). Lung volume recruitment after surfactant administration modifies spatial distribution of ventilation. *American Journal of Respiratory and Critical Care Medicine, 174*(7), 772-779.

Frerichs, I., Hahn, G., Golisch, W., Kurpitz, M., Burchardi, H., & Hellige, G. (1998). Monitoring perioperative changes in distribution of pulmonary ventilation by functional electrical impedance tomography. *Acta Anaesthesiologica Scandinavica, 42*(6), 721-726.

Frerichs, I., Hahn, G., Schiffmann, H., Berger, C., & Hellige, G. (1999). Monitoring Regional Lung Ventilation by Functional Electrical Impedance Tomography during Assisted Ventilationa. *Annals of the New York Academy of Sciences, 873*(1), 493-505.

Frerichs, I., Schmitz, G., Pulletz, S., Schädler, D., Zick, G., Scholz, J., & Weiler, N. (2007). Reproducibility of regional lung ventilation distribution determined by electrical impedance tomography during mechanical ventilation. *Physiological Measurement, 28*(7), S261.

Gallon, A. (1991). Evaluation of chest percussion in the treatment of patients with copious sputum production. *Respiratory Medicine, 85*(1), 45-51.

Galvis, A. G., Reyes, G., & Nelson, W. B. (1994). Bedside management of lung collapse in children on mechanical ventilation: saline lavage--simulated cough technique proves simple, effective. *Pediatric Pulmonology, 17*(5), 326-330.

Gamsu, G., Singer, M., Vincent, H., Berry, S., & Nadel, J. (1976). Postoperative impairment of mucous transport in the lung. *The American Review of Respiratory Disease, 114*(4), 673-679.

Gregson, R. (2008). *Characterisation of manual chest physiotherapy and respiratory response in mechanically ventilated children.* (Doctoral), University of Southampton.

Gregson, R., Shannon, H., Stocks, J., Cole, T., Peters, M., & Main, E. (2011). The unique contribution of manual chest wall vibrations to airflow during physiotherapy in mechanically ventilated children. *Physiotherapy, 97*, eS431-eS432.

Gregson, R., Shannon, H., Stocks, J., Cole, T. J., Peters, M. J., & Main, E. (2012). The unique contribution of manual chest compression-vibrations to airflow during physiotherapy in sedated, fully ventilated children. *Pediatric Critical Care Medicine, 13*(2), e97-e102.

Gregson, R., Stocks, J., Petley, G., Shannon, H., Warner, J., Jagannathan, R., & Main, E. (2007). Simultaneous measurement of force and respiratory profiles during chest physiotherapy in ventilated children. *Physiological Measurement, 28*(9), 1017-1028.

Gunnar, E., Matthew, K., Ahmed, F., Bartłomiej, G., Norbert, W., Eric, A., & Inéz, F. (2013). Quantification of ventilation distribution in regional lung injury by electrical impedance tomography and xenon computed tomography. *Physiological Measurement, 34*(10), 1303.

Hammer, J., & Newth, C. J. (1995). Infant lung function testing in the intensive care unit. *Intensive Care Medicine, 21*(9), 744-752.

Hansen, L. G., Warwick, W. J., & Hansen, K. L. (1994). Mucus transport mechanisms in relation to the effect of high frequency chest compression (HFCC) on mucus clearance. *Pediatric Pulmonology, 17*(2), 113-118.

Hess, D. (2014). Respiratory Mechanics in Mechanically Ventilated Patients. *Respiratory Care, 59*(11), 1773.

Hess, D., & Bigatello, L. (2002). Lung recruitment: the role of recruitment maneuvers. *Respiratory Care, 47*(3), 308-317.

Heulitt, M. J., Holt, S. J., Thurman, T. L., Hall, R. A., Jo, C. H., & Simpson, P. (2005). Reliability of measured tidal volume in mechanically ventilated young pigs with normal lungs. *Intensive Care Medicine, 31*(9), 1255-1261.

Heulitt, M. J., Thurman, T. L., Holt, S. J., Jo, C. H., & Simpson, P. (2009). Reliability of displayed tidal volume in infants and children during dual-controlled ventilation. *Pediatric Critical Care Medicine, 10*(6), 661-667.

Hinz, J., Neumann, P., Dudykevych, T., Andersson, L. G., Wrigge, H., Burchardi, H., & Hedenstierna, G. (2003). Regional Ventilation by Electrical Impedance Tomography*A Comparison With Ventilation Scintigraphy in Pigs. *CHEST Journal, 124*(1), 314-322.

Hough, J. (2009). *Effect of chest physiotherapy on lung function in preterm infants.* (PhD Doctor of Philosophy), University of Queensalnd.

Hough, J., Flenady, V., Johnston, L., & Woodgate, P. (2008). Chest physiotherapy for reducing respiratory morbidity in infants requiring ventilatory support. *Cochrane Database of Systematic Reviews*, *16(3)*, CD006445 .

Hough, J., Flenady, V., Johnston, L., & Woodgate, P. (2010). Chest physiotherapy for reducing respiratory morbidity in infants requiring ventilatory support. *Evidence-Based Child Health: A Cochrane Review Journal, 5*(1), 54-79.

Hough, J., Johnston, L., Brauer, S., Woodgate, P., & Schibler, A. (2013). Effect of Body Position on Ventilation Distribution in Ventilated Preterm Infants. *Pediatric Critical Care Medicine, 14*(2), 171-177.

Hough, J., Shearman, A., Liley, H., Grant, C., & Schibler, A. (2014). Lung recruitment and endotracheal suction in ventilated preterm infants measured with electrical impedance tomography. *Journal of Paediatrics and Child Health*, *50*(11), 884-889.

Hussey, J., Hayward, L., Andrews, M., Macrae, D., & Elliot, M. (1996). Chest physiotherapy following paediatric cardiac surgery: The influence of mode of treatment on oxygen saturation and haemodynamic stability. *Physiotherapy Theory and Practice, 12*(2), 77-85.

Ides, K., Vos, W., De Backer, L., Vissers, D., Claes, R., Leemans, G., . . . De Backer, W. (2012). Acute effects of intrapulmonary percussive ventilation in COPD patients assessed by using conventional outcome parameters and a novel computational fluid dynamics technique. *International Journal of Chronic Obstructive Pulmonary Disease, 7*, 667-671.

Jauncey-Cooke, J. (2012). *Optimising Paediatric Ventilation.* (PhD), University of Queensland.

Jauncey-Cooke, J., Bogossian, F., & East, C. (2009). Lung recruitment---a guide for clinicians. *Australian Critical Care, 22*(4), 155-162.

Jauncey-Cooke, J., Pham, J., Grant, C., Bogossian, F., East, C., & Schibler, A. (2012). Lung recruitment by manipulating peep following endotracheal suction improves end expiratory lung volume and oxygenation. *Australian Critical Care, 25*(2), 127-127.

Jeffrey, D. R., Goddard, P. R., Callaway, M. P., & Greenwood, R. (2003). Chest radiograph interpretation by medical students. *Clinical Radiology, 58*(6), 478-481.

Johnston, C., Zanetti, N. M., Comaru, T., Ribeiro, S. N. d. S., Andrade, L. B. d., & Santos, S. L. L. d. (2012). I Recomendação brasileira de fisioterapia respiratória em unidade de terapia intensiva pediátrica e neonatal. *Revista Brasileira De Terapia Intensiva, 24*, 119-129.

Kalyn, A., Blatz, S., Feuerstake, S., Paes, B., & Bautista, C. (2003). Closed suctioning of intubated neonates maintains better physiologic stability: a randomized trial. *Journal of Perinatology, 23*(3), 218-222.

Kerem, E., Yatsiv, I., & Goitein, K. J. (1990). Effect of endotracheal suctioning on arterial blood gases in children. *Intensive Care Medicine, 16*(2), 95-99.

Kheir, J., Walsh, B., Smallwood, C., Rettig, J., Thompson, J., Gómez-Laberge, C., . . . Arnold, J. (2012). Comparison of Two Lung Recruitment Strategies in Children with Acute Lung. *Respiratory Care*, *58*(8), 1280-90.

Khemani, R., Thomas, N., Venkatachalam, V., Scimeme, J., Berutti, T., Schneider, J., . . . Newth, C. (2012). Comparison of SpO2 to PaO2 based markers of lung disease severity for children with acute lung injury. *Critical Care Medicine, 40*(4), 1309-1316.

Kim, C., Iglesias, A., & Sackner, M. (1987). Mucus clearance by two-phase gas-liquid flow mechanism: asymmetric periodic flow model. *Journal of Applied Physiology, 62*(3), 959-971.

Kim, P., Salazar, A., Ross, P., Newth, C., & Khemani, R. (2015). Comparison of Tidal Volumes at the Endotracheal Tube and at the Ventilator. *Pediatric Critical Care Medicine, 16*(9), e324-331.

Konstan, M. W., Stern, R. C., & Doershuk, C. F. (1994). Efficacy of the Flutter device for airway mucus clearance in patients with cystic fibrosis. *The Journal of Pediatrics, 124*(5), 689-693.

Krause, M. F., & Hoehn, T. (1999). Efficiency and risks of chest physiotherapy in the newborn - A review. *Klinische Padiatrie, 211*(1), 11-17.

Krause, M. F., & Hoehn, T. (2000). Chest physiotherapy in mechanically ventilated children: A review. *Critical Care Medicine, 28*(5), 1648-1651.

Krueger, C., & Tian, L. (2004). A Comparison of the General Linear Mixed Model and Repeated Measures ANOVA Using a Dataset with Multiple Missing Data Points. *Biological Research For Nursing, 6*(2), 151-157.

Kunst, P., Vonk Noordegraaf, A., Hoekstra, O., Postmus, P., & de Vries, P. (1998). Ventilation and perfusion imaging by electrical impedance tomography: a comparison with radionuclide scanning. *Physiological Measurement, 19*(4), 481-490.

Kuyrukluyildiz, U., Binici, O., Kupeli, l., Erturk, N., Gulhan, B., Akyol, F., . . . Karabakan, G. (2016). What is the best pulmonary physiotherapy method in ICU? *Canadian Respiratory Journal, 2016*, Article ID 4752467.

223

Lapinsky, S. (2003). Recruitment and retention of lung volume. *Critical Care, 7*(1), 9-10.

Lapinsky, S., & Mehta, S. (2005). Bench-to-bedside review: Recruitment and recruiting maneuvers. *Crit Care, 9*(1), 60-65.

Lee, A. L., Button, B. M., & Tannenbaum, E.-L. (2017). Airway-clearance techniques in children and adolescents with chronic suppurative lung disease and bronchiectasis. *Frontiers in Pediatrics, 5*, 2.

Leech, M., Bissett, B., Kot, M., & Ntoumenopoulos, G. (2014). Lung ultrasound for critical care physiotherapists: A narrative review. *Physiotherapy Research International*, *20*(2), 69-76.

Li, S. K., & Silva, Y. R. (2008). Investigation of the frequency and force of chest vibration performed by physiotherapists. *Physiotherapy Canada, 60*(4), 341-348.

Lindgren, S., Odenstedt, H., Olegård, C., Söndergaard, S., Lundin, S., & Stenqvist, O. (2007). Regional lung derecruitment after endotracheal suction during volume-or pressure-controlled ventilation: a study using electric impedance tomography. *Intensive Care Medicine, 33*(1), 172-180.

Lineham, D., Johnson, P., Madden, M., Ramdat, E., & Custer, J. (2016). Intrapulmonary percussive ventilation assist in weaning pediatric patients from extracorporeal membrane oxygenation. *Respiratory Care, 61*(10), OF43-OF43.

Lupton-Smith, A., Argent, A., Rimensberger, P., Frerichs, I., & Morrow, B. (2017). Prone Positioning Improves Ventilation Homogeneity in Children With Acute Respiratory Distress Syndrome. *Pediatric Critical Care Medicine, 18*(5), e229-e234.

Mackenzie, C., Shin, B., & McAslan, T. (1978). Chest physiotherapy: the effect on arterial oxygenation. *Anesthesia and Analgesia, 57*(1), 28-30.

Maggiore, S. M., Lellouche, F., Pigeot, J., Taille, S., Deye, N., Durrmeyer, X., . . . Brochard, L. (2003). Prevention of endotracheal suctioning-induced alveolar derecruitment in acute lung injury. *American Journal of Respiratory and Critical Care Medicine, 167*(9), 1215-1224.

Main, E., Castle, R., Newham, D., & Stocks, J. (2004). Respiratory physiotherapy vs. suction: The effects on respiratory function in ventilated infants and children. *Intensive Care Medicine, 30*(6), 1144-1151.

Main, E., Castle, R., Stocks, J., James, I., & Hatch, D. (2001). The influence of endotracheal tube leak on the assessment of respiratory function in ventilated children. *Intensive Care Medicine, 27*(11), 1788-1797.

Main, E., & Denehy, L. (2016). *Cardiorespiratory Physiotherapy: Adults and Paediatrics E-Book: formerly Physiotherapy for Respiratory and Cardiac Problems*: Elsevier Health Sciences.

Main, E., & Stocks, J. (2004). The influence of physiotherapy and suction on respiratory deadspace in ventilated children. *Intensive Care Medicine, 30*(6), 1152-1159.

Mansell, A., Bryan, C., & Levison, H. (1972). Airway closure in children. *Journal of Applied Physiology, 33*(6), 711-714.

Marcus, R. J., van der Walt, J. H., & Pettifer, R. J. (2002). Pulmonary volume recruitment restores pulmonary compliance and resistance in anaesthetized young children. *Paediatric Anaesthesia, 12*(7), 579-584.

Marik, P. E. (2015). Arterial Blood Gas Analysis *Evidence-Based Critical Care* (pp. 329-347). Cham: Springer International Publishing.

Marques, A., Bruton, A., & Barney, A. (2006). Clinically useful outcome measures for physiotherapy airway clearance techniques: a review. *Physical Therapy Reviews, 11*(4), 299-307.

McCarren, B., & Chow, C. (1996). Manual hyperinflation: a description of the technique. *Journal of Physiotherapy, 42*(3), 203-208.

McCord, J., Krull, N., Kraiker, J., Ryan, R., Duczeminski, E., Hassall, A., . . . Mathur, S. (2013). Cardiopulmonary physical therapy practice in the paediatric intensive care unit. *Physiotherapy Canada, 65*(4), 374-377.

McCulloch, C. E., & Neuhaus, J. M. (2001). *Generalized linear mixed models*: Wiley Online Library.

McIlwaine, M. (2006). Physiotherapy and airway clearance techniques and devices. *Paediatric Respiratory Reviews, 7*, S220-S222.

Miedema, M., Frerichs, I., de Jongh, F., van Veenendaal, M., & van Kaam, A. (2011). Pneumothorax in a preterm infant monitored by electrical impedance tomography: A case report. *Neonatology, 99*(1), 10-13.

Mokkink, L. B., Prinsen, C. A., Bouter, L. M., de Vet, H. C., & Terwee, C. B. (2016). The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) and how to select an outcome measurement instrument. *Brazilian Journal of Physical Therapy, 20*(2), 105-113.

Mokkink, L. B., Terwee, C. B., Patrick, D. L., Alonso, J., Stratford, P. W., Knol, D. L., . . . de Vet, H. C. (2010). The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *Journal Of Clinical Epidemiology, 63*(7), 737-745.

Morrow, B., & Argent, A. (2008). A comprehensive review of pediatric endotracheal suctioning: Effects, indications, and clinical practice. *Pediatric Critical Care Medicine, 9*(5), 465-477.

Morrow, B., Futter, M., & Argent, A. (2007). A recruitment manoeuvre performed after endotracheal suction does not increase dynamic compliance in ventilated paediatric patients: a randomised controlled trial. *Australian Journal of Physiotherapy, 53*(3), 163-169.

Ntoumenopoulos, G. (2005). Indications for manual lung hyperinflation (MHI) in the mechanically ventilated patient with chronic obstructivepulmonary disease. *Chronic Respiratory Disease, 2*(4), 199-207.

Ntoumenopoulos, G., & Glickman, Y. (2012). Computerised lung sound monitoring to assess effectiveness of chest physiotherapy and secretion removal: a feasibility study. *Physiotherapy, 98*(3), 250-255.

Oberwaldner, B. (2000). Physiotherapy for airway clearance in paediatrics. *European Respiratory Journal, 15*(1), 196-204.

Pandya, Y. S., Shetye, J., Nanavati, R., & Mehta, A. (2011). Resolution of lung collapse in a preterm neonate following chest physiotherapy. *Indian Journal of Pediatrics, 78*(9), 1148-1150.

Panitch, H. B. (2006). Airway clearance in children with neuromuscular weakness. *Current Opinion in Pediatrics, 18*(3), 277-281.

Patterson, J. E., Bradley, J. M., Hewitt, O., Bradbury, I., & Elborn, J. S. (2005). Airway clearance in bronchiectasis: a randomized crossover trial of active cycle of breathing techniques versus Acapella. *Respiration, 72*(3), 239-242.

Paulus, F., Binnekade, J. M., Vroom, M. B., & Schultz, M. J. (2012). Benefits and risks of manual hyperinflation in intubated and mechanically ventilated intensive care unit patients: a systematic review. *Critical Care, 16*(4), R145-R145.

Peroni, D. G., & Boner, A. L. (2000). Atelectasis: mechanisms, diagnosis and management. *Paediatric Respiratory Reviews, 1*(3), 274-278.

Physiotherapy Board of Australia Code of Conduct. (2014). *Australian Health Practitioner Regulation Agency* (pp. 25). Australia: Australian Health Practitioner Regulation Agency.

Pulletz, S., van Genderingen, H., Schmitz, G., Zick, G., Sch dler, D., Scholz, J., . . . Frerichs. (2006). Comparison of different methods to define regions of interest for evaluation of regional lung ventilation by EIT. *Physiological Measurement, 27*(5), S115.

Randolph, A. G. (2017). Why so few randomized trials in pediatric critical care medicine? Ask the trialists. *Pediatric Critical Care Medicine, 18*(5), 486-487.

Randolph, A. G., Meert, K. L., O'Neil, M. E., Hanson, J. H., Luckett, P. M., Arnold, J. H., . . . Cheifetz, I. M. (2003). The feasibility of conducting clinical trials in infants and children with acute respiratory failure. *Am J Respir Crit Care Med, 167*(10), 1334-1340.

Restrepo, R. D. (2010). Endotracheal suctioning of mechanically ventilated patients with artificial airways *Respiratory Care, 55*(6), 758-764.

Richard, J., Pouzot, C., Gros, A., Tourevieille, C., Lebars, D., Lavenne, F., . . . Guerin, C. (2009). Electrical impedance tomography compared to positron emission tomography for the measurement of regional lung ventilation: an experimental study. *Critical Care, 13*(3), R82.

Richardson, W. S., Wilson, M. C., Nishikawa, J., & Hayward, R. S. (1995). The well-built clinical question: a key to evidence-based decisions. *ACP Journal Club, 123*(3), A12-13.

Ridling, D. A., Martin, L. D., & Bratton, S. L. (2003). Endotracheal suctioning with or without instillation of isotonic sodium chloride solution in critically ill children. *American Journal of Critical Care, 12*(3), 212-219.

Riedel, T., Richards, T., & Schibler, A. (2005). The value of electrical impedance tomography in assessing the effect of body position and positive airway pressures on regional lung ventilation in spontaneously breathing subjects. *Intensive Care Medicine, 31*(11), 1522-1528.

Riou, Y., Leclerc, F., Neve, V., Dupuy, L., Noizet, O., Leteurtre, S., & Sadik, A. (2004). Reproducibility of the respiratory dead space measurements in mechanically ventilated children using the CO2SMO monitor. *Intensive Care Medicine, 30*(7), 1461-1467.

Roos, J. E., McAdams, H. P., Kaushik, S. S., & Driehuys, B. (2015). Hyperpolarized Gas MRI: Technique and Applications. *Magnetic Resonance Imaging Clinics of North America, 23*(2), 217-229.

Ross, P., Khemani, R., & Newth, C. (2013). The accuracy of Spo2 measurements in pediatric patients in the range of 65 to 87%. *American Journal of Respiratory and Critical Care Medicine, 187*.

Schechter, M. S. (2007). Airway clearance applications in infants and children. *Respiratory Care, 52*(10), 1382-1391.

Schibler, A., Hall, G., Businger, F., Reinmann, B., Wildhaber, J., Cernelc, M., & Frey, U. (2002). Measurement of lung volume and ventilation distribution with an ultrasonic flow meter in healthy infants. *European Respiratory Journal, 20*(4), 912-918.

Schults, J., Mitchell, M., Cooke, M., & Schibler, A. (2018). Efficacy and safety of normal saline instillation and paediatric endotracheal suction: An integrative review. *Australian Critical Care, 31*(1), 3-9.

Schultz, T. R., Lin, R., Francis, B. A., Hales, R. L., Colborn, S., Napoli, L. A., & Helfaer, M. A. (2005). Kinetic therapy improves oxygenation in critically ill pediatric patients. *Pediatric Critical Care Medicine, 6*(4), 428-434.

Severinghaus, J. (1966). Blood gas calculator. *Journal of Applied Physiology, 21*(3), 1108.

Severinghaus, J. (1968). Measurements of blood gases: Po2 and Pco2*. *Annals of the New York Academy of Sciences, 148*(1), 115-132.

Severinghaus, J. (2002). The invention and development of blood gas analysis apparatus. *Anesthesiology, 97*(1), 253-256.

Severinghaus, J., & Astrup, P. (1986). History of blood gas analysis. VI. Oximetry. *Journal of Clinical Monitoring, 2*(4), 270-288.

Shannon, H., Stocks, J., Gregson, R., Dunne, C., Peters, M., & Main, E. (2015). Clinical effects of specialist and on-call respiratory physiotherapy treatments in mechanically ventilated children: A randomised crossover trial. *Physiotherapy, 101*(4), 349-356.

Shannon, H., Stocks, J., Gregson, R., Hines, S., Peters, M., & Main, E. (2015). Differences in delivery of respiratory treatments by on-call physiotherapists in mechanically ventilated children: a randomised crossover trial. *Physiotherapy, 101*(4), 357-363.

Simbruner, G., Coradello, H., Fodor, M., Havelec, L., Lubec, G., & Pollak, A. (1981). Effect of tracheal suction on oxygenation, circulation, and lung mechanics in newborn infants. *Archives of Disease in Childhood, 56*(5), 326-330.

Simon, B. A. (2005). Regional ventilation and lung mechanics using X-Ray CT. *Academic Radiology, 12*(11), 1414-1422.

Singh, N. C., Kissoon, N., Frewen, T., & Tiffin, N. (1991). Physiological responses to endotracheal and oral suctioning in paediatric patients: the influence of endotracheal tube sizes and suction pressures. *Clinical Intensive Care, 2*(6), 345-350.

Sivan, Y., Deakers, T., & Newth, C. (1991). Effect of positive end‐expiratory pressure on respiratory compliance in children with acute respiratory failure. *Pediatric Pulmonology, 11*(2), 103-107.

Skov, L., Ryding, J., Pryds, O., & Greisen, G. (1992). Changes in cerebral oxygenation and cerebral blood volume during endotracheal suctioning in ventilated neonates. *Acta Paediatrica, 81*(5), 389-393.

Slater, A., Shann, F., & Pearson, G. (2003). PIM2: a revised version of the Paediatric Index of Mortality. *Intensive Care Medicine, 29*(2), 278-285.

Slonim, A. D., & Pollack, M. M. (2006). *Pediatric critical care medicine*: Lippincott Williams & Wilkins.

Slutsky , A. S., & Ranieri , V. M. (2013). Ventilator-Induced Lung Injury. *New England Journal of Medicine, 369*(22), 2126-2136.

Slutsky, A. S., & Tremblay, L. N. (1998). Multiple system organ failure. Is mechanical ventilation a contributing factor? *American Journal of Respiratory and Critical Care Medicine, 157*, 1721 - 1725.

Soundararajan, L. R. A., & Thankappan, S. M. (2015). Effect of manual hyperinflation on arterial oxygenation in paediatric patients with upper lobe collapse after cardiac surgery. *European Journal of General Medicine, 12*(4), 313-318.

Spaeth, J., Daume, K., Goebel, U., Wirth, S., & Schumann, S. (2016). Increasing positive end-expiratory pressure (re-)improves intraoperative respiratory mechanics and lung ventilation after prone positioning. *British Journal of Anaesthesia, 116*(6), 838-846.

Steinmann, D., Engehausen, M., Stiller, B., & Guttmann, J. (2013). Electrical impedance tomography for verification of correct endotracheal tube placement in paediatric patients: a feasibility study. *Acta Anaesthesiologica Scandinavica, 57*(7), 881-887.

Tannenbaum, E., Prasad, S. A., Dinwiddie, R., & Main, E. (2007). Chest physiotherapy during anesthesia for children with cystic fibrosis: Effects on respiratory function. *Pediatric Pulmonology, 42*(12), 1152-1158.

227

Taskar, V., John, J., Evander, E., Robertson, B., & Jonson, B. (1997). Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. *American Journal of Respiratory and Critical Care Medicine, 155*(1), 313-320.

Taussig, L. M., Landau, L. I., & Souëf, P. N. L. (2008). *Pediatric Respiratory Medicine*: *2nd Edition*, Mosby/Elsevier.

Terwee, C. B., Mokkink, L. B., Knol, D. L., Ostelo, R. W., Bouter, L. M., & de Vet, H. C. (2012). Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. *Quality of Life Research, 21*(4), 651-657.

Thomas, J., Cook, D. J., & Brooks, D. (1995). Chest physical therapy management of patients with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine, 151*, 846-850.

Tingay, D., Copnell, B., Grant, C., Dargaville, P., Dunster, K., & Schibler, A. (2010). The effect of endotracheal suction on regional tidal ventilation and end-expiratory lung volume. *Intensive Care Medicine, 36*(5), 888-896.

Toussaint, M. (2011). The use of mechanical insufflation-exsufflation via artificial airways. *Respiratory Care, 56*(8), 1217-1219.

Toussaint, M., De Win, H., Steens, M., & Soudon, P. (2003). Effect of intrapulmonary percussive ventilation on mucus clearance in Duchenne muscular dystrophy patients: a preliminary report. *Respiratory Care, 48*(10), 940-947.

Toussaint, M., Pernet, K., Steens, M., Haan, J., & Sheers, N. (2016). Cough Augmentation in Subjects With Duchenne Muscular Dystrophy: Comparison of Air Stacking via a Resuscitator Bag Versus Mechanical Ventilation. *Respiratory Care, 61*(1), 61-67.

Tremblay, L. N., & Slutsky, A. S. (1998). Ventilator-induced injury: from barotrauma to biotrauma. *Proceedings of the Association of American Physicians, 110*(6), 482-488.

Tusman, G., Bohm, S., Tempra, A., Melkun, F., Garcia, E., Turchetto, E., . . . Lachmann, B. (2003). Effects of Recruitment Maneuver on Atelectasis in Anesthetized Children. *Anesthesiology, 98*(1), 14-22.

van der Burg, P. S., Miedema, M., de Jongh, F. H., & van Kaam, A. H. (2014). Unilateral atelectasis in a preterm infant monitored with electrical impedance tomography: a case report. *European Journal of Pediatrics, 173*(12), 1715-1717.

van Loveren, C., & Aartman, I. H. (2007). [The PICO (Patient-Intervention-Comparison-Outcome) question]. *Nederlands Tijdschrift Voor Tandheelkunde, 114*(4), 172-178.

van Veenendaal, M., Miedema, M., de Jongh, F., van der Lee, J., Frerichs, I., & van Kaam, A. (2009). Effect of closed endotracheal suction in high-frequency ventilated premature infants measured with electrical impedance tomography. *Intensive Care Medicine, 35*(12), 2130-2134.

Varekojis, S., Douce, F., Flucke, R., Filbrun, D., Tice, J., McCoy, K., & Castile, R. (2003). A comparison of the therapeutic effectiveness of and preference for postural drainage and percussion, intrapulmonary percussive ventilation, and high-frequency chest wall compression in hospitalized cystic fibrosis patients. *Respiratory Care 48*(1):24-28.

Victorino, J., Borges, J., Okamoto, V., Matos, G., Tucci, M., Caramez, M., . . . Amato, M. (2004). Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *American Journal of Respiratory and Critical Care Medicine, 169*(7), 791-800.

Wallis, C., & Prasad, A. (1999). Who needs chest physiotherapy? Moving from anecdote to evidence. *Archives of Disease in Childhood, 80*(4), 393-397.

Walsh, B., Hood, K., & Merritt, G. (2011). Pediatric Airway Maintenance and Clearance in the Acute Care Setting: How To Stay Out of Trouble. *Respiratory Care, 56*(9), 1424-1440.

Warner, M. A., & Patel, B. (2013). Chapter 48 - Mechanical Ventilation A2 - Hagberg, Carin A *Benumof and Hagberg's Airway Management (Third Edition)* (pp. 981-997.e983). Philadelphia: W.B. Saunders.

Whitman, J., Van Beusekom, R., Olson, S., Worm, M., & Indihar, F. (1993). Preliminary evaluation of high-frequency chest compression for secretion clearance in mechanically ventilated patients. *Respiratory Care, 38*(10), 1081-1087.

Wolf, A. (2012). Analgesia and sedation in paediatric intensive care. *Southern African Journal of Anaesthesia and Analgesia, 18*(5).

Wolf, G., Gomez-Laberge, C., Kheir, J., Zurakowski, D., Walsh, B., Adler, A., & Arnold, J. (2012). Reversal of dependent lung collapse predicts response to lung recruitment in children with early acute lung injury. *Pediatric Critical Care Medicine, 13*(5), 509-515.

World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. (2013). *The Journal of the American Medical Association, 310*(20), 2191-2194.

Yuan, N., Kane, P., Shelton, K., Matel, J., Becker, B. C., & Moss, R. B. (2010). Safety, tolerability, and efficacy of high-frequency chest wall oscillation in pediatric patients with cerebral palsy and neuromuscular diseases: an exploratory randomized controlled trial. *Journal of Child Neurology, 25*(7):815-821.

Zach, M. S., & Oberwaldner, B. (2008). Chapter 18 - Chest Physiotherapy. In M. T. Lynn, Md, & A. O. M. D. D. L. F. Louis I. Landau (Eds.), *Pediatric Respiratory Medicine (Second Edition)* (pp. 241-251). Philadelphia: Mosby.

Zach, M. S., Purrer, B., & Oberwaldner, B. (1981). Effect of swimming on forced expiration and sputum clearance in cystic fibrosis. *The Lancet, 318*(8257), 1201-1203.

Zhao, Z., Moller, K., Steinmann, D., Frerichs, I., & Guttmann, J. (2009). Evaluation of an electrical impedance tomography-based Global Inhomogeneity Index for pulmonary ventilation distribution. *Intensive Care Medicine, 35*(11), 1900-1906.

Zhao, Z., Pulletz, S., Frerichs, I., Müller-Lisse, U., & Möller, K. (2014). The EIT-based global inhomogeneity index is highly correlated with regional lung opening in patients with acute respiratory distress syndrome. *BMC Research Notes, 7*, 82-82.