Recruitment manoeuvres for patients with acute respiratory distress syndrome.

Carol Lynette Hodgson

B. App. Sc. (Physio), P.G. Dip (Cardio), M (Research), FACP.

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Department of Physiotherapy

School of Primary Health Care

Faculty of Medicine, Nursing and Health Sciences

Monash University

Victoria,

Australia, 3199

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List of Abbreviations used in this Thesis

AAA = abdominal aortic aneurysm

ALI = acute lung injury

AML=acute myeloid leukaemia

ARDS = acute respiratory distress syndrome

BP = blood pressure

BPM = beats per minute

CI = confidence interval

Cstat = static lung compliance

CVC = central venous catheter

CVP = central venous pressure

CXR = chest X-ray

F = female

FiO_2 = fraction of inspired oxygen

HR = heart rate

Hrs = hours

ICC = intraclass correlation coefficient

ICU = intensive care unit

ICU LOS = intensive care length of stay

IL-1ß = plasma interleukin 1-beta

IL-6 = plasma interleukin 6

L = left

LISS = lung injury severity score

LOS = length of stay

LOV = length of ventilation

M= male

MAP = mean arterial pressure

MD = mean difference

MDC_{90} = clinical change required for 90% confidence

Min = minutes

ml/cm_2 = millilitres per centimetre of water

N= the number of patients

NOK = next of kin

PEEP = positive end expiratory pressure

PA = pulmonary artery

PaO_2/FIO_2 = partial pressure of oxygen to inspired fraction of oxygen ratio

$PaCO_2$ = partial pressure of carbon dioxide

PCV = pressure control ventilation

Pplateau = plateau pressure

PR = person responsible

Qs/Qt = shunt fraction

R = right

RCT = randomised controlled trial

RM = recruitment manoeuvre

RR = respiratory rate

SaO_2 = oxyhaemoglobin saturation measured in arterial blood

Sa-cvO2 = arterial-venous oxygen saturation difference

$ScvO_2$ = venous oxygen saturation measured from a central line

SD = standard deviation

SDdiff = standard deviation of the difference score

SE = standard error

SEM = standard error of the measurement

SIMV = synchronised intermittent mandatory ventilation

SMD =standardised mean difference

SpO2 = oxyhaemoglobin saturation measured by pulse oximetry

SOFA= sequential organ failure assessment score

SRM = staircase recruitment manoeuvre

Vd/Vt% = alveolar dead space

X-ray = radiograph

V_T= tidal volume

Summary of Thesis

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are inflammatory conditions resulting from direct or indirect lung injury that affects over 11,000 people annually in Australia[1-2]. Mortality associated with ARDS is high (30-41%)[1,3]. Ninety percent of people affected by ARDS require mechanical ventilation to maintain gas exchange during the critical phase of the condition. A protective mechanical ventilation strategy characterized by low tidal volume and limitation of plateau airway pressure (Pplat) is now widely accepted[4-8]. However, this strategy may fail to expand the most dependent lung regions and inadequately reduce cyclic opening and closing of atelectatic alveoli. Both of these effects may contribute to the progression of lung injury. Recruitment manoeuvres (RMs) may have an important role in the management of ventilated patients with ARDS and ALI by opening collapsed alveoli during low tidal volume ventilation[9-11]. Recruitment manoeuvres used with PEEP may recruit dependent lung regions with prolonged collapse and reduce alveolar derecruitment and shear forces across the alveoli, resulting in reduced barotrauma, atelectrauma and biotrauma[12]. However, little information is available regarding the most effective type of RM to use for patients with ARDS. The aim of the research detailed in this thesis was to investigate the safety and short-term effectiveness of a new staircase RM in patients mechanically ventilated with ARDS and to establish the longer term effects of a staircase RM on patients with ARDS compared to current best practice.

A Cochrane review of the effects of RMs, that identified seven relevant randomised trials, concluded that RMs transiently improved oxygenation in patients with ALI without adverse effects of barotrauma or hypotension. There was substantial heterogeneity in methods used to deliver RMs, including peak pressure, time at maximum pressure, concurrent ventilatory strategies and end PEEP levels. The most common RM used in protective ventilatory strategies was a static RM of 40 cm H_2O pressure for 40 seconds. There was no long term benefit to patients with ALI of a static RM in a protective ventilation strategy, perhaps because the static RM

was not performed for an adequate time or with adequate pressure to open collapsed alveoli in patients with ALI.

The staircase recruitment manoeuver (SRM) was examined in an observational study of 20 patients with ARDS to evaluate the safety of the SRM[13]. Eighty percent of participants responded to the SRM with improved shunt fraction (36.3 ± 10% at baseline to 26.4 ± 14% after the SRM, $P<0.01$). In addition, desaturation during the SRM, a marker previously thought to imply non-response, did not indicate a failure to respond at the end of the SRM or one hour later.

Two investigations were undertaken to facilitate selection of outcome measures for assessing response to the new SRM. The accuracy of oxyhaemoglobin saturation using a finger probe was compared to a forehead probe in patients with ARDS who may have compromised peripheral circulation that could affect accurate reading of oxyhaemoglobin saturation (SpO_2) from a finger probe[14]. Oxygen saturation measured using a forehead probe was less reliable that finger probe during periods of low oxygen saturation and high positive end expiratory pressure (PEEP). Finger probes were employed in subsequent experiments in favour of forehead probes. In a second study, the reliability and validity of digital chest X-rays as an objective measure of lung area and radiolucency in intensive care was assessed. If digital chest X-rays were informative, they would provide a safe and cost-effective method for monitoring lung recruitment compared to the current best practice of using a CT scan to measure lung volume. The lung area score was found to be adequately reliable and valid while the radiolucency score was determined to be useful as an adjunctive but not for the primary assessment of patients with ARDS.

Finally a randomised controlled trial was conducted to assess the effects of the SRM in a protective ventilation strategy. Twenty patients with ARDS were randomised to conventional “best practice” ARDS ventilation according to the ARDSnet[15] recommendations or to PHARLAP ventilation (permissive hypercapnia, alveolar recruitment and low airway pressure)[16].

Lung compliance and oxygenation were significantly better and inflammatory cytokines reduced in the PHARLAP group compared to the comparison group across a 7 day period. Those receiving the PHARLAP strategy had, on average, reduced time on mechanical ventilation, in ICU and in hospital, however this did not reach statistical significance.

The SRM appears to be safe and can be effectively incorporated into a protective ventilation strategy in patients ventilated in intensive care with ARDS. The effects of the PHARLAP strategy on important outcomes such as length of mechanical ventilation and hospital stay warrant further investigation in larger trials.

PART A: General Declaration

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

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

This thesis includes 3 original papers published in peer reviewed journals and 2 unpublished, submitted publications. The core theme of the thesis is recruitment manoeuvres in patients with acute respiratory distress syndrome. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Faculty of Medicine, Nursing and Health Sciences under the supervision of Professor Jenny Keating.

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

In the case of Chapters 2,3,4,5 and 6 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
2	A systematic review of recruitment manoeuvres for adults receiving mechanical ventilation with acute lung injury.	Published	70% Search strategies, abstract review, quality review, data extraction and analysis, writing the manuscript, liaison with Cochrane Organisation.
3	Comparison of forehead MAX-FAST pulse oximetry sensor with finger sensor at high PEEP in adult patients with ARDS	Published	70% Consent, screening, data collection, data synthesis and analysis, writing the manuscript
4	Oxygen desaturation during a recruitment manoeuvre and PEEP titration does not indicate failure to respond in patients with ALI	In Press	70% Consent, screening, data collection, data synthesis and analysis, writing the manuscript
5	The reliability and validity of digital portable chest radiographs in intensive	Submitted	80% Consent, screening, data collection, data synthesis and analysis, writing the

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
	care.		manuscript
6	A randomised controlled pilot trial of permissive hypercapnia, alveolar staircase recruitment manoeuvres, PEEP titration and low airway pressure (PHARLAP) in patients with ARDS.	Submitted	50% Consent, screening, data collection, data synthesis and analysis, writing the manuscript
Appendix 11	Lung recruitment: who, when and how	In press	50% Writing the manuscript

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ……

Date: ……26/07/10……

Acknowledgments

'Being 'educated' means knowing how little I really know' Carol T Lloyd.

I have truly enjoyed the journey of my PhD. I have been fortunate to have amazing support and encouragement from my family, supervisors, colleagues and the families of the critically ill participants. It has been measured by life milestones – our sea change, the twins starting kindergarten and school, my wonderful, boisterous Dad passing away.

Firstly I would like to thank my family, especially my husband Mike for his enduring love and support. In our 26 years together I have been fortunate to share another rewarding part of my life with you. To my beautiful children, Sam, Bella, Alex and Nick who have grown from toddlers to tall, articulate children, thank-you for your loving patience and encouragement. I hope *'We should turn out people who love learning so much and learn so well that they will be able to learn whatever needs to be learned.*' (*John Holt)* To my Mum, Pam Taylor, and my sister, Pauline Newton, I would like to say thank-you for being a constant source of love and support.

I would like to thank my three supervisors, all different, inspiring and immensely talented. Your brilliance and wealth of knowledge never cease to amaze me. Thank-you to Professor Jenny Keating, Head of Physiotherapy, School of Primary Health Care, Faculty of Medicine, Nursing and Health Sciences Monash University, who was my principal supervisor. Jenny is a gifted mentor, teacher and role model. I am privileged that she spent time guiding and supervising my work and I have learnt a great deal about rigorous research methods and professional excellence. Thank-you to Associate Professor David Tuxen, who was my clinical supervisor. Tux is enthusiastic and truly inspirational in his work in intensive care. He has been extremely generous with his time, energy and advice. He has been a champion for my work in ICU and it has been a pleasure to work with you. I hope I will continue to do so for a long time. Thank-you finally to Associate Professor Anne Holland who has strongly supported my research at The Alfred. Her unique combination of clinical expertise and excellence in research has provided a balance that has

been very much appreciated throughout the entire period of my candidature and her friendship is valued highly. She is insightful, clever and has an amazing life balance that will inspire me in the years ahead.

I am grateful to the patients in intensive care and their families who were supportive and encouraging of the work we were doing in their time of uncertainty and grief. *'In order for the brain to comprehend the heart must first listen.' (David Perkins)* It is an area of research I feel very passionately about.

I would like to thank those bodies that have supported me financially throughout the period of my candidature. Firstly, the National Health and Research Medical Council provided me with a Dora Lush Scholarship and a wonderful opportunity to treat my time studying as a pleasant job. The inaugural Jeff Richards Scholarship at Monash University supported me for the first year of my candidature and was in memory of an inspiring academic. Monash University, The Alfred Intensive Care and Physiotherapy Departments have supported my travel to present the results of our work in the USA at the American Thoracic Society Conferences in 2009 and 2010. This was one of the most interesting and rewarding parts of my PhD and has led to an ongoing network of international experts in this area. The Intensive Care Foundation, ANZCA and Alfred Small Projects Grant supported the work in the PHARLAP trial which was appreciated and will lead to a large future trial in ARDS.

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Publications and presentations arising from research reported in this thesis

Published Journal Articles

- Hodgson CL, Bradley S, Davies AR, Holland AE, Keating JL, Smirneos L, Tuxen DV 2009 A systematic review of recruitment manoeuvres for adults receiving mechanical ventilation with acute lung injury. *Cochrane Database of Systematic Reviews* Issue 2.

- Hodgson CL, Tuxen DV, Holland AE, Keating JL. 2009 Comparison of forehead MAX-FAST pulse oximetry sensor with finger sensor at high PEEP in adult patients with ARDS *Anaesth and Int Care* 37 (6).

In press journal articles

- Hodgson CL, Tuxen DV, Bailey M, Varma D, Pilcher D, Thomson TK, Holland AE, Keating JL. 2010 Oxygen desaturation during a recruitment maneuver and PEEP titration does not indicate failure to respond in patients with ALI. (Accepted) *JICM.*

- Tuxen DV and Hodgson CL. 2010. Lung recruitment: who, when and how. (Accepted) *Crit Care Resus.*

Submitted journal articles

- The reliability and validity of digital portable chest X-rays in intensive care. Hodgson CL, Tuxen DV et al. Submitted to *Int Care Med*.

- A protective lung ventilation strategy with staircase recruitment improves seven day outcomes in patients with ARDS compared to standard ventilation: a pilot randomized controlled trial. Hodgson CL, Nichol A, Tuxen DV et al. Submitted to the *American Journal of Respiratory and Critical Care Medicine*.

Published abstracts

1. Oxygen Desaturation Does Not Prevent a Positive Response to a Staircase Recruitment Maneuver in Early ALI. CL Hodgson, DV Tuxen, AE Holland, JL Keating, and M Bailey. *Am J Respir Crit Care Med*, Apr 2009; 179: A4631

2. A randomised controlled pilot trial of permissive hypercapnia, alveolar staircase recruitment maneuvers, PEEP titration and low airway pressure (PHARLAP) in patients with ARDS – preliminary results. Hodgson CL, Nichol A, Tuxen DV et al. e-*AJP* Vol 55: 4, Supplement, 2009

3. A randomised controlled trial of staircase recruitment manoeuvres, high PEEP and low airway pressure (PHARLAP). C.L. Hodgson, PhD Candidate, A. Nichol, Dr, D. Tuxen, A/Prof, J. Cooper, MD, M. Bailey, PhD, J. Keating, Prof, A. Holland, PhD, D. Pilcher, Dr, A. Westbrook, Dr, A. Davies, MD, A. Hilton, Dr Melbourne/AU *Am J Respir Crit Care Med* 181;2010:A1686

Conference Presentations

1. ANZICS ASM, Roturua 2008 - PHARLAP protocol
2. AAMVC, Melbourne 2008 - Recruitment manoeuvres in ARDS

3. APA Sydney 2009 – PHARLAP (first 24 hours data)*
4. ANZICS Clinical Trials Group, Noosa 2010 - PHARLAP

Poster Presentations

1. ANZICS Sydney 2009 – Hodgson CL, Bradley S, Davies AR, Holland AE, Keating JL, Smirneos L, Tuxen DV 2009 A systematic review of recruitment manoeuvres for adults receiving mechanical ventilation with acute lung injury.

2. ATS 2009 – CL Hodgson, DV Tuxen, AE Holland, JL Keating, and M Bailey. Oxygen Desaturation Does Not Prevent a Positive Response to a Staircase Recruitment Maneuver in Early ALI.

3. ATS 2010 - A randomised controlled trial of staircase recruitment manoeuvres, high PEEP and low airway pressure (PHARLAP). C.L. Hodgson, PhD Candidate, A. Nichol, Dr, D. Tuxen, A/Prof, J. Cooper, MD, M. Bailey, PhD, J. Keating, Prof, A. Holland, PhD, D. Pilcher, Dr, A. Westbrook, Dr, A. Davies, MD, A. Hilton, Dr

International Media

Staircase Recruitment Maneuver Is Effective—Even in 'Nonresponders' SAN DIEGO—Patients with early acute lung injury (ALI) respond well to staircase recruitment maneuvers (SRM), suggest data findings presented at the 2009 International Congress of the American Thoracic Society. *Pulmonary Reviews*, July 2009.

This news story is published online at: http://www.pulmonaryreviews.com

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1. NH&MRC Scholarship (Dora Lush) 2007-2009, $25,853 per annum

2. Jeff Richards Scholarship (Monash) 2006, $20,000 per annum

3. The Alfred Physiotherapy Fellowship June 2009 – June 2010 $18,000 per annum

4. PHARLAP. A randomised phase II trial. Hodgson C, Nichol A, Tuxen D, Cooper, J, Davies A
   a. ANZCA $30,069
   b. ANZICS Foundation $15,000
   c. The Alfred Small Project Grant $6,000

5. Oxygen desaturation does not prevent a positive response to a staircase recruitment manoeuvre in patients with early ALI (2009) Hodgson C, Tuxen D, Holland A, Bailey M, Varma D, Thomson K, Keating J. Monash Travel award $2,115, Equipment donations (Edwards Australia) $6,300

6. Clinician Award for Best Oral Presentation, Australian Physiotherapy Association Scientific Conference, Sydney, 2009

Chapter 1 Thesis overview and introduction

Acute lung injury (ALI) is characterised by the acute onset of hypoxemia (arterial oxygen partial pressure to fraction of inspired oxygen ratio - $PaO_2/F_IO_2 \leq 300$mm Hg) with bilateral chest infiltrates on antero-posterior chest x-ray not caused by left atrial hypertension[17]. A subset of ALI, associated with more severe hypoxaemia ($PaO_2/F_IO_2 \leq 200$mm Hg) is termed acute respiratory distress syndrome (ARDS). ALI is an inflammatory condition resulting from direct or indirect lung injury and affects over 11,000 people annually in Australia [18]. Mortality associated with ARDS and ALI is 30 - 41%[1,3,19]. Ninety percent of people who develop ARDS will require mechanical ventilation in intensive care (ICU)[20]. They are likely to spend an average of 12 to 40 days on mechanical ventilation and longer in ICU[21] at an annual cost of over AU$770,000,000. They are often discharged from ICU with cognitive abnormalities, weakness, depression, or post-traumatic stress disorder[22]. Only 34% are discharged to home[21].

In ARDS, mechanical ventilation is a life saving intervention that maintains gas exchange. A complication of this intervention is that high pressure and high volumes of gas delivered by the ventilator under positive pressure can cause additional lung injury, progress the symptoms of ARDS and increase mortality[23]. A lung ventilated during ARDS becomes oedematous and heavy and undergoes collapse in dependent regions[24]. Three functionally distinct lung zones result:

- The least dependent region that remains inflated throughout ventilation and is at risk of overinflation lung injury (volutrauma)
- An intermediate lung region that collapses and re-expands with each breath resulting in shear stress-induced injury (atelectrauma)
- The most dependent lung region that remains collapsed throughout tidal ventilation resulting in chronic collapse injury.

All of these processes result in biotrauma which is the release of inflammatory mediators that contribute to the injury of the lung and of other organs[25-26]. The majority of patients who ultimately die succumb to progressive organ failure.

Lung recruitment manoeuvres (RMs) reinflate collapsed regions by briefly, transiently raising transpulmonary pressure to levels higher than tidal volume[27]. Gattinoni et al (2006) defined RMs as a sustained inflation of the lungs to higher airway pressures and volumes than are obtained during tidal ventilation[28]. The rationale for the use of recruitment manoeuvres is to recruit collapsed lung regions, increase end expiratory lung volume and attenuate progression of ventilator associated lung injury by reducing chronic collapse injury and possibly also reducing repetitive opening and closing of unstable lung units, particularly in the intermediate lung region[29]. However, techniques that have been described to achieve this vary in terms of time at maximum pressure, maximum pressure and end expiratory pressure[9,30-31]. The variable method of delivering recruitment manoeuvres, the small number of clinical trials evaluating safety and effectiveness and the short-term physiological outcomes have made clinicians hesitate to extrapolate experimental findings to clinical practice. Researchers have suggested that the efficacy of recruitment manoeuvres may depend on the cause of lung injury (eg. pulmonary versus extrapulmonary[32]) or the amount of time the lung has been injured (early versus late)[10,33-35].

The first RM to be proposed was a static pressure elevation; this has been used in two major trials of patients with ALI[27,36]. Both trials used static RMs for 30-40 seconds to a peak pressure of 35-40 cm H_2O with elevated PEEP for the intervention group and compared this to control conditions of standard ventilation. Reduced oxygen saturation and hypotension during the static RM triggered concerns regarding safety of the procedure. The trials showed no benefit of a ventilation strategy that included a static RM as there were no differences between groups for mortality, duration of mechanical ventilation or length of stay in ICU or hospital.

While there are a small number of papers that review the efficacy of recruitment manoeuvres in mechanically ventilated patients[29,37-38], the effect had not been reviewed systematically until late in 2008 when two systematic reviews were published within months of each other[9,30]. In the review by Hodgson and colleagues, we identified that the most common

type of RM used was a sustained inflation (static RM)[30] (Table 1, Figure 1). The systematic review concluded that sustained inflation RM significantly improved oxygenation without any significant difference in the rate of adverse events. However it did not find evidence of an effect on long term outcomes, including duration of mechanical ventilation or survival. The second systematic review reached similar conclusions about oxygenation but did not investigate longer term outcomes [30]. Since the publication of the systematic reviews of RMs, there have been two systematic reviews of ventilation using high positive end expiratory pressure (PEEP) in patients with ARDS[19,39]. High PEEP has been found to independently improve mortality in patients with ARDS, although static RMs were used in several of the included studies. This suggests that the presence of PEEP in studies of RMs is a confounder that needs to be controlled.

Apart from static RM's, other types of RMs have been described that are delivered in conjunction with high pressure-control ventilation (dynamic RM, Table 1, Figure 1), incremental positive end expiratory pressure (PEEP) (staircase or stepwise RM, Table 1, Figure 2) and high tidal volume or sighs[28].

Table 1 Types of recruitment manoeuvres described in the literature

Type of RM	**Definition**
Static (or sustained inflation)	Sustained positive pressure at one pressure level (Figure 1)
Dynamic	Sustained PEEP in PCV mode (Figure 1)
Sigh (or extended sigh)	Large tidal volume breath sustained for longer than normal (Figure 2)
Incremental PEEP (Stepwise or staircase)	PEEP increments of while maintaining pressure control ventilation (Figure 3)

PEEP = positive end expiratory pressure, PCV = pressure control ventilation

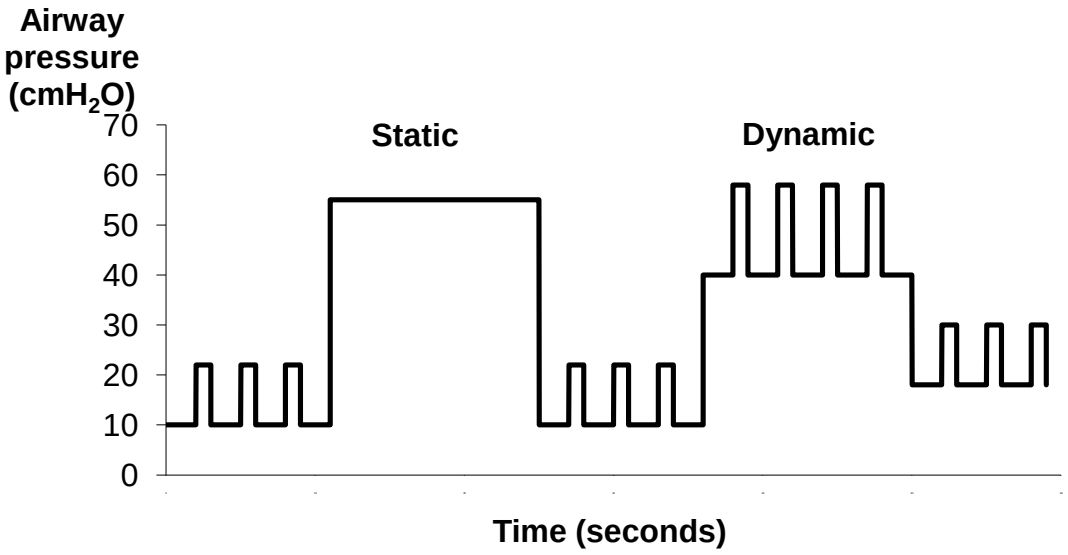


Figure 1 Static and dynamic recruitment manoeuvres as a pressure – time waveform.

A static (or sustained inflation) RM increases the plateau pulmonary pressure to a level higher than baseline and this pressure is maintained constantly for a set period of time (Figure 1)[33,40]. This is different to a dynamic recruitment manoeuvre that systematically increases the positive end expiratory pressure in pressure control mode. This allows an increase and decrease in pressure with inspiration and expiration which may have the potential benefits of increased comfort for the patient and less effect on blood pressure due to the transient nature of the pressure increments[41-42].

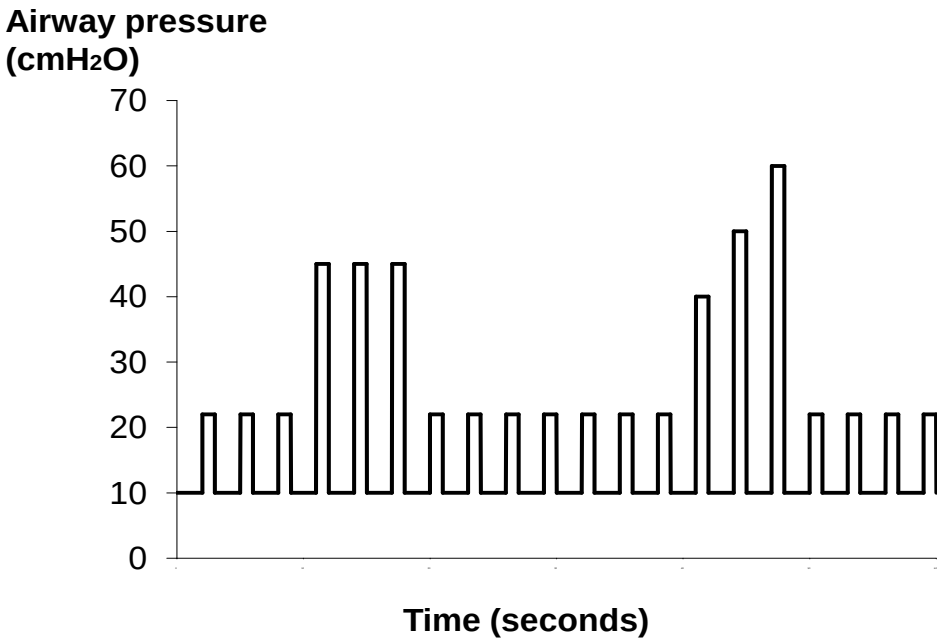
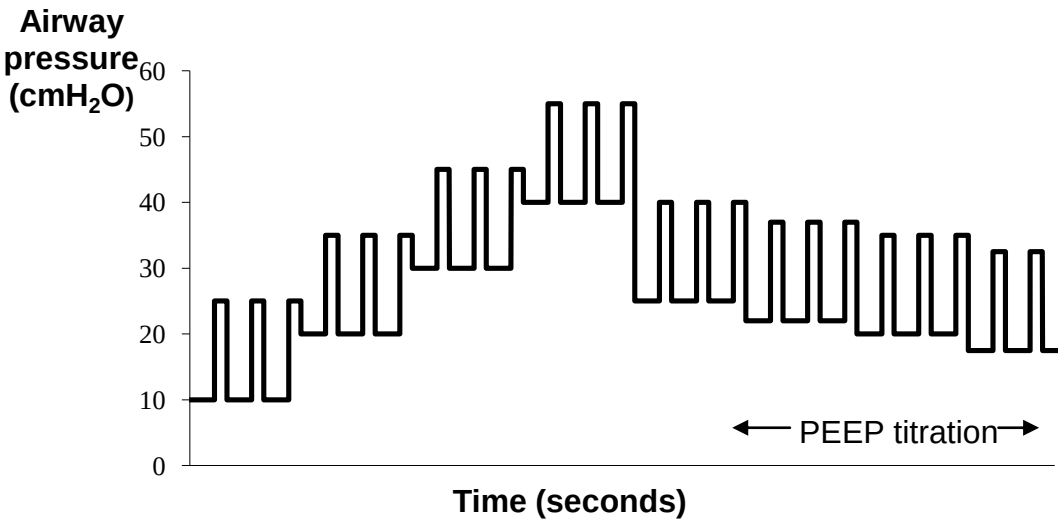


Figure 2 Sigh recruitment manoeuvres as a pressure-time waveform

Sigh (or extended sigh with increasing pressure levels) is a larger than usual tidal volume breath that transiently increases the pulmonary pressure and may be held for a longer period of time than a tidal breath but returns to the original end expiratory pressure at the completion of the breath (Figure 2)[29,31].



PEEP = positive end expiratory pressure

Figure 3 Staircase recruitment manoeuvres as a pressure–time waveform

Lung recruitment methods have been compared in animal models[26,43] and investigated in ventilated patients[5,27-28,44]. Lim and colleagues described the effect of different types of RMs (static, pressure control with incremental PEEP and extended sigh) in experiments on porcine lungs with ARDS[31,43,45]. They concluded that the most effective RM to improve oxygenation was pressure control with incremental PEEP. The incremental increase in pressure during this RM led to the name stepwise or staircase RM (staircase RM, Figure 3)[31]. Following this study, Borges et al (2006) used a stepwise recruitment manoeuvre (SRM) in 26 patients with ARDS. The SRM was thought to maximize the safety of haemodynamic variables on the step up in pressure and to maximize optimal positive end expiratory pressure on the step down in pressure (Figure 3)[46]. Assessment of recruitment efficacy was performed in 9 patients with computed tomography or by online continuous monitoring of oxygenation in 15 patients for up to 6 hours. It was possible to open the lungs and keep them open in 24 of the 26 patients with a mean PEEP of 22 ± 4 cm H_2O after PEEP titration. While the initial investigations into this method of lung recruitment were positive, the effects required further investigation in a randomised controlled trial. The SRM had not been investigated as part of a protective ventilatory strategy for patients with ARDS.

The most common practice in intensive care was to recruit lungs using a static RM which improved oxygenation in the short term, but did not have an effect on lung compliance, duration of mechanical ventilation or length of stay in intensive care[27,36].

It was postulated that the use of a SRM, with gentle increments in airway pressure to a higher mean airway pressure for a longer period of time, may improve lung recruitment, lung compliance and oxygenation without causing ventilator associated lung injury. It was also hypothesised that improved lung compliance may reduce the duration of mechanical ventilation and length of stay in intensive care. The SRM was designed to deliver slow and gentle increments in alveolar pressure from baseline to a maximum of 55 cm H_2O in 10 cm H_2O steps. The maximum alveolar

pressure had previously been shown to be effective and safe in a small observational trial[46]. The SRM was applied intermittently in pressure control mode with incremental PEEP. The intermittent nature of the SRM had previously been studied in animals and found to be more effective than a static RM to the same maximal pressure[31]. The slow steps down in pressure while oxygenation was assessed would determine the optimal PEEP for maintaining an open lung and would prevent repetitive opening and closing of unstable lung units[47-48].

The SRM was a new area of expertise for clinicians who work in intensive care. Careful description of the technique, the indications and the contraindications was required. Despite several large trials which have included RMs for the intervention group, little attention has been paid to the optimal method of delivering a RM[27,36]. The examination of the literature and publication of a systematic review which examined the specifics of a RM, including maximum pressure, time at maximum pressure and optimal end expiratory pressure was conducted to clarify what is known about the best treatment option in ARDS. The hypothesis of this thesis was that a staircase RM (SRM) would be safe and effective when used in a protective ventilation strategy compared to standard care (protective ventilation with no RM) for a number of reasons: it allows the assessment of haemodynamic tolerance during the incremental increase in pressure; it preserves ventilation using the pressure control mode of ventilation; and the pressure cycling may cause less circulatory depression than a static RM to the same maximal pressure

The factors potentially resulting in better lung recruitment with the SRM compared with the static RM include a higher maximum pressure that may be tolerated for a longer period of time because it is applied intermittently in pressure control mode and the decremental PEEP steps that allow assessment of optimal PEEP as part of the RM.

The aims of this thesis were to investigate the safety and short-term effectiveness of a SRM in patients mechanically ventilated with ARDS and

to establish the longer term effects of a SRM on patients with ARDS compared to current best practice.

In order to achieve our primary aim the current research was undertaken in four main parts:

1. Undertake a Cochrane review of the design and efficacy of recruitment manoeuvres
2. Develop and investigate the efficacy of a new staircase recruitment manoeuvre
3. Establish the best bedside methods of assessing response to the recruitment manoeuvre
4. Develop and undertake a randomised trial comparing the staircase recruitment manoeuvre in a protective ventilation strategy compared to determine efficacy over seven days.

A systematic review of recruitment manoeuvres is presented in Chapter Two. The review concluded that static RMs used in protective lung strategies did not improve long term outcomes of patients with ARDS.

The SRM was not used in Australia prior to the pilot study reported in this thesis. Chapter Three describes the design of a SRM and assessment of the safety and short-term outcomes for people with early ALI who receive SRM. This work contributed to the body of knowledge about patients who desaturate during a RM. Despite fears that desaturation during a SRM indicated no response and the need for caution, patients in this trial who desaturated during the SRM nevertheless improved their shunt fraction after the SRM. These findings were disseminated by the Australia New Zealand Intensive Care Society during the H1N1 epidemic in Australia, and the SRM was applied to patients who developed ARDS as a result of the H1N1 virus in other centres to recruit collapsed lung units and improve life threatening hypoxaemia.

An issue requiring research attention identified when this research began was the lack of consistent, meaningful outcome measures to assess the effect of recruitment manoeuvres that are practical and applicable at the

bedside. Chapter Four investigated the bias and precision of two commonly used oxyhaemoglobin sensors, the forehead and finger sensors, during a recruitment manoeuvre. Oxyhaemoglobin sensors need to be affordable, reliable, and responsive to immediate changes in physiological status. Oxyhaemoglobin measured with pulse oximetry was used to investigate the short term physiological effect[13,44,49-50] during RMs and was used to determine the safety of the technique in individual patients[27]. In patients with ARDS it was not clear whether decreased arterial oxygenation and poor peripheral perfusion would reduce the reliability of finger sensors to detect clinically important changes in oxyhaemoglobin. Chapter Four provides evidence for the use of the finger sensor to measure oxyhaemoglobin in patients with ARDS.

Chest X-rays are used daily in patients mechanically ventilated in intensive care and routinely after RMs to assess the lungs for gross barotrauma. Chapter Five investigated the use of digital chest X-rays to objectively quantify chest X-ray changes in lung area and radiolucency, and the reliability of these measures. This chapter provides evidence for the use of digital chest X-ray to measure lung area and radiolucency scores to quantify within-patient change after a RM.

The use of the SRM was important in patients with ALI but it was only part of the ventilation strategy in this complex patient group. In Chapter Six, we conducted a randomised controlled pilot trial to examine the effectiveness of an “optimal” ventilator strategy consisting of a novel open lung low airway pressure approach (Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures – PHARLAP) compared to the current ARDSnet low tidal volume strategy. This approach applied recent evidence and included multiple features (recruitment[46], PEEP[19,39,51], low airway pressure[12,52]) as a strategy to maximise outcomes in patients with ARDS.

There were three factors included in PHARLAP ventilation strategy. The SRM was used to open the lung units with an optimal recruitment manoeuvre that used a higher plateau airway pressure for a longer time.

Optimal PEEP, as determined by the decremental PEEP trial at the end of the SRM. Minimal airway pressure was used throughout tidal ventilation with plateau airway pressure less than 30 cmH_2O by delivering low tidal volumes and therefore allowing permissive hypercapnia.

The final chapter includes a discussion of the clinical implications of the research findings and proposes directions for future studies. The SRM, in a protective ventilatory strategy, needs to be studied in a larger trial to verify the findings reported in this thesis. The trial should be adequately powered to detect differences in duration of mechanical ventilation and length of intensive care and hospital stay that may significantly improve outcomes and reduce the cost of patients with ARDS in the future.

Chapter 2 (Manuscript) Systematic literature review of recruitment manoeuvres (RMs) in adult ventilated patients with acute lung injury

2.1 Declaration for Thesis Chapter 2

Declaration by candidate

In the case of Chapter 2 the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study concept, design, analysis and writing of the manuscript	70

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Anne Holland	Revision of manuscript	
Jenny Keating	Study concept and design, revision of manuscript	
David Tuxen	Revision of manuscript	
Andrew Davies	Revision of manuscript	
Scott Bradley	Second score for quality of papers, data input	

Candidate's Signature	[redacted]	**Date**

Declaration by co-authors

The undersigned hereby certify that:

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

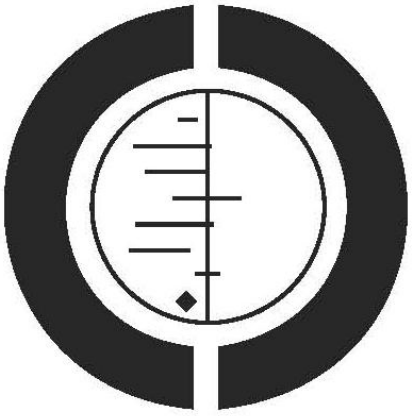
Location(s)	The Alfred Hospital, Melbourne

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

Name	**Signature**	**Date**
Anne Holland	[redacted]	20/07/10
Jenny Keating	[redacted]	20/07/10
David Tuxen	[redacted]	20/07/10
Andrew Davies	[redacted]	26/07/10
Scott Bradley		26/07/10

Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation (Review)

Hodgson C, Keating JL, Holland AE, Davies AR, Smirneos L, Bradley SJ, Tuxen D



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[Intervention Review]

Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation

Carol Hodgson[1], Jennifer L Keating[2], Anne E Holland[3], Andrew R Davies[4], Lorena Smirneos[5], Scott J Bradley[1], David Tuxen[4]

[1]Department of Physiotherapy, The Alfred Hospital, Melbourne, Australia. [2]Department of Physiotherapy, Monash University, Melbourne, Australia. [3]Physiotherapy, Alfred Health / La Trobe University, Melbourne, Australia. [4]Department of Intensive Care, The Alfred Hospital, Melbourne, Australia. [5]The Ian Potter Library, The Alfred Hospital, Melbourne, Australia

Contact address: Carol Hodgson, Department of Physiotherapy, The Alfred Hospital, Commercial Road, Melbourne, 3181, Australia. carol.hodgson1@bigpond.com. (Editorial group: Cochrane Anaesthesia Group.)

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ABSTRACT

Background

Recruitment manoeuvres are often used to treat patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) but the effect of this treatment on clinical outcomes has not been well established.

Objectives

The objective of this review was to examine recruitment manoeuvres compared to standard care as therapy for adults with acute lung injury in order to quantify the effects on patient outcomes (mortality, length of ventilation, and other relevant outcomes).

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 2); MEDLINE (January 1966 to May 2008); EMBASE (January 1980 to May 2008); LILACS (1982 to May 2008); CINAHL (1982 to May 2008); and Current Controlled Trials (www.controlled-trials.com).

Selection criteria

We included randomized controlled trials of adults who were mechanically ventilated comparing recruitment manoeuvres to standard care for those patients diagnosed with ALI or ARDS.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted study authors for additional information.

Main results

Seven trials met the inclusion criteria for this review (the total number of included participants was 1170). All trials included a recruitment manoeuvre as part of the treatment strategy for patients on mechanical ventilation for ARDS or ALI. However, two of the trials included a package of ventilation that was different from the control ventilation in aspects other than the recruitment manoeuvre. The intervention group showed no significant difference on 28-day mortality (RR 0.73, 95% CI 0.46 to 1.17, P = 0.2). Similarly there

was no statistical difference for risk of barotrauma (RR 0.50, 95% CI 0.07 to 3.52, P = 0.5) or blood pressure (MD 0.9 mm Hg, 95% CI -4.28 to 6.08, P = 0.73). Recruitment manoeuvres significantly increased oxygenation above baseline levels for a short period of time in four of the five studies that measured oxygenation. There were insufficient data on length of ventilation or hospital stay to pool results.

Authors' conclusions

There is not evidence to make conclusions on whether recruitment manoeuvres reduce mortality or length of ventilation in patients with ALI or ARDS.

PLAIN LANGUAGE SUMMARY

Recruitment manoeuvres compared to standard care for treatment of acute lung injury or acute respiratory distress syndrome.

A ventilated patient with acute lung injury or acute respiratory distress syndrome may be given a recruitment manoeuvre to open lung units that are collapsed. This is done by using a pressure that is higher than a normal breath for a longer period of time than is required for a normal breath. The effects of recruitment manoeuvres have not, however, been well established. We included seven trials in this review, totalling 1170 participants with acute lung injury or acute respiratory distress syndrome. We found that there was no significant difference in survival between groups given an 'open-lung' ventilatory strategy that included recruitment manoeuvres and groups given standard ventilatory care. Recruitment manoeuvres briefly increased arterial oxygen partial pressure compared to standard care. Recruitment manoeuvres did not affect blood pressure, heart rate, or risk of air leak from the lungs. The main limitation of the review was the design of included trials that either did not isolate recruitment manoeuvres from other variables or assessed only short-term outcomes.

BACKGROUND

Patients in intensive care (ICU) with acute lung injury may require mechanical ventilation to survive (Amato 1998; Sevransky 2004). However, mechanical ventilation can injure lungs by alveolar distension, cyclic collapse and reopening of alveolar units, and failure to expand collapsed alveolar units (Gattinoni 2006). To minimize damage to injured lungs, small ventilatory volumes and low plateau pressures have been used. These reduce mortality and the duration of mechanical ventilation (Amato 1998; ARDSnet 2000).

Lung recruitment manoeuvres (RM) have been used in the ventilatory management of acute lung injury and acute respiratory distress syndrome. Recruitment manoeuvres re-inflate collapsed regions of the lungs by briefly raising transpulmonary pressure to levels higher than achieved during tidal ventilation (Brower 2003). The use of a ventilation strategy that included recruitment manoeuvres and higher positive end-expiratory pressure (PEEP) based on the pressure-volume curve, which was higher than in the control group, improved survival in patients with acute respiratory distress syndrome (Amato 1998). Recruitment manoeuvres have been investigated in animal models (Funk 2004; Lim 2004) and in ventilated patients (Amato 1998; Brower 2003; Levy 2005) with variable outcomes. The reasons for the variability in responses are not well understood. Recruitment manoeuvres remain controversial because they may be harmful. Recruitment manoeuvres increase intrathoracic pressure and can reduce venous return and cardiac output (Odenstedt 2005). The increase in intrapulmonary pressure may also cause barotrauma (Brower 2003; Levy 2005).

The techniques used to apply a recruitment manoeuvre can vary in duration, maximum pressure, and end-expiratory pressure (Brower 2003; Lim 2004). This variation has made it difficult to extrapolate research findings to clinical practice (Hedenstierna 2002). The effects of a recruitment manoeuvre may also vary with the method of delivery and with the cause of lung injury (Borges 2006; Brower 2003; Kacmarek 2007). A small number of papers review the safety and efficacy of recruitment manoeuvres in ventilated patients (Fan 2008; Lapinsky 2005; Piacentini 2004; Richard 2004), however none have reported on long-term effect.

OBJECTIVES

Our primary objective was to determine the effects of recruitment manoeuvres on mortality, duration of mechanical ventilation, and duration of hospitalisation in adults with acute lung injury.

Our secondary objective was to determine, in the same population, the effects of recruitment manoeuvres on oxygenation, car-

diovascular stability (heart rate, blood pressure, and arrhythmia) and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We included prospective, randomized controlled trials (RCTs).

Types of participants

We included adults (at least 18 years of age) with acute lung injury (Bernard 1994) who were intubated and mechanically ventilated in intensive care for at least 24 hours.
We excluded studies including children aged less than 18 years of age, or animals.

Types of interventions

We included RCTs that compared recruitment manoeuvres to standard care. We defined a recruitment manoeuvre as any technique that transiently increased the alveolar pressure above normal tidal ventilation (which may have included an increase in any pressure, such as plateau, peak, or end-expiratory pressure) and sustained that pressure beyond the normal time.

Types of outcome measures

Primary outcomes

We included studies that reported the following primary outcomes:

1. mortality;
2. duration of mechanical ventilation;
3. duration of hospital stay.

Secondary outcomes

We included studies that reported with the following secondary outcomes:

1. oxygenation;
2. cardiovascular stability (heart rate, blood pressure, and arrhythmia);
3. adverse events (such as barotrauma).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2008, Issue 2); MEDLINE (January 1966 to May 2008); EMBASE (January 1980 to May 2008); LILACS (1982 to May 2008); CINAHL (1982 to May 2008); and Current Controlled Trials (www.controlled-trials.com, last search May 2008) using the Ovid platform.
We adapted our MEDLINE search strategy for use with other electronic databases. You can find our search strategies in the appendices (MEDLINE, Appendix 1; CINAHL, Appendix 2; CENTRAL, Appendix 3; EMBASE, Appendix 4; LILACS, Appendix 5).

Searching other resources

We handsearched the bibliographies of all retrieved articles in order to identify potentially relevant trials.
We did not apply language restrictions.
We attempted to identify unpublished trials by contacting experts in the field of recruitment manoeuvre research.
We tracked the citations of authors of included studies.

Data collection and analysis

Study selection

We (CH, SB) independently and sequentially excluded studies by reading the titles, abstracts, then full papers. We resolved any disagreement by discussion.

Quality assessment

We (CH, SB) independently rated included studies on a scale (adapted from PEDro 1999). This scale contains 10 items, which we analysed independently to provide an estimate of methodological rigour of identified randomized controlled trials (Maher 2003). These items are: random allocation, concealed allocation, similarity at baseline, participant blinding, therapist blinding, assessor blinding, greater than 85% follow up for at least one primary outcome, intention-to-treat analysis, between-group statistical analysis for at least one primary outcome, and point estimates of variability for at least one primary outcome (see Table 1). We marked items as either present (YES), absent (NO), or not stated (NS). The scale has been reported as adequately reliable (Maher 2003). We resolved, where necessary, differing opinions between authors by discussion with a third author (JK). One of us (CH) contacted study authors for additional information, as required.

Table 1. Quality assessment of included studies

study	Amato 1998	Brower 2003	Dyhr 2003	Fori 2000	Lasocki 2005	Meade 2008	Oczenski 2004
random allocation	NS	NS	NS	NS	NS	Y	Y
concealed allocation	Y	NS	Y	NS	NS	Y	NS
similarity at baseline	Y	Y	N	NS	Y	Y	Y
subject blinding	Y	Y	Y	Y	Y	Y	Y
therapist blinding	N	N	N	N	N	N	N
assessor blinding	N	NS	NS	NS	NS	NS	NS
greater than 85% follow up for one key outcome	Y	NS	Y	Y	Y	Y	Y
intention-to-treat analysis	Y	NS	Y	Y	Y	Y	Y
between group statistical analysis for at least one key outcome	Y	Y	Y	Y	Y	Y	Y
point estimates of variability for at least one key outcome	Y	Y	Y	Y	Y	Y	Y

Y = yes, N = no, NS = not stated

Data extraction

We (CH, SB) independently extracted relevant data from included trials. We extracted the study location, population description, intervention description, intervention dosage (frequency, intensity, repetition, duration), hospital environment, and participant and hospital outcome data. We resolved disagreements by discussion.

Data analysis

Dichotomous data

We calculated the relative risk (RR) and absolute risk reduction (ARR), and associated 95% confidence intervals (CI). Where possible, we calculated and reported the number needed to treat to benefit (NNTB).

Continuous data

We calculated the mean difference (MD) and associated 95% CI. We used the standardized mean difference (SMD) for data that we could not convert to a uniform scale.
We pooled data using either the random-effects model or the fixed-effect model, depending on the presence or absence of statistical heterogeneity.

Clinical heterogeneity

We used 'clinical heterogeneity' to describe differences in participants, interventions, and outcomes that might reasonably impact on the effect of recruitment manoeuvres. We measured statistical heterogeneity using the I^2 statistic (Higgins 2002). This describes the percentage of variability in effect estimates that is due to heterogeneity rather than sampling error or chance. We considered a value greater than 50% to indicate that an outcome was significantly heterogeneous. We pooled studies in the absence of clinical heterogeneity on a case by case basis. We assessed the interaction of study variables with the effect of recruitment manoeuvres in predefined sensitivity and subgroup analyses.

Subgroup analyses

We planned to assess the interaction between cause of lung injury (intrapulmonary compared with extrapulmonary) (Richard 2004) and the effects of recruitment manoeuvres.

We planned to assess the interaction between the type of recruitment manoeuvre with effect, dichotomising studies by the two following definitions.

- A manoeuvre that included a plateau pressure of 40 cm H_2O or higher that was sustained for 40 seconds or longer and had a PEEP after the manoeuvre of at least 15 cm H_2O, with a plan to or actual repetition of the recruitment manoeuvre.
- All other recruitment manoeuvres.

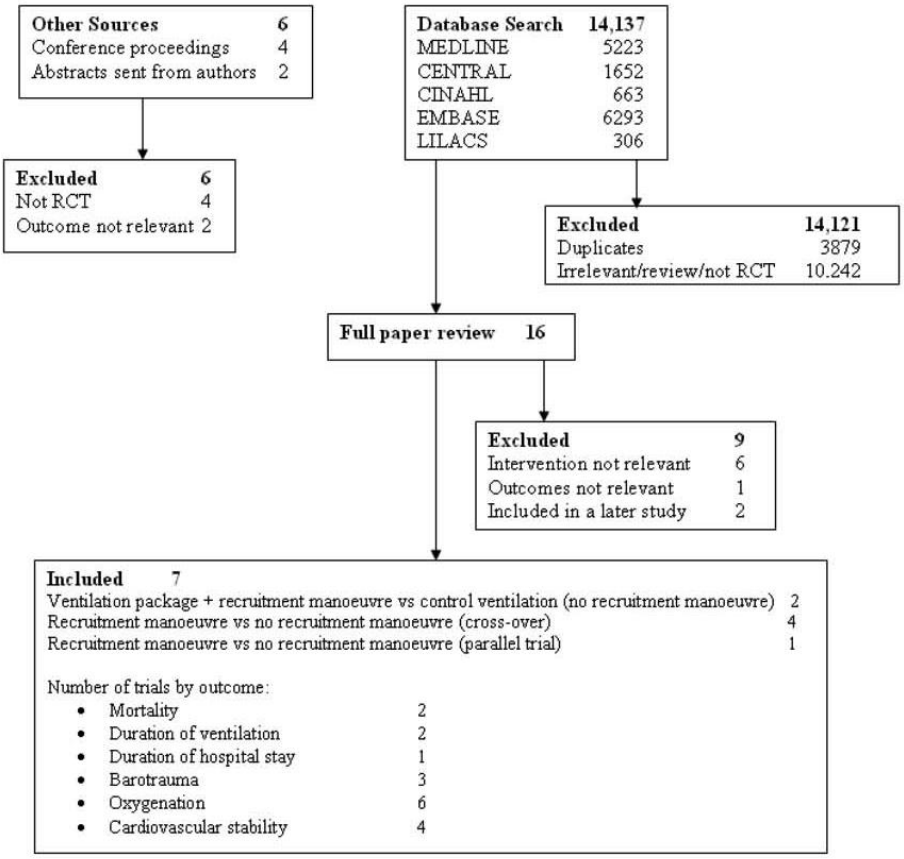
We planned to include funnel plots for any analyses that contained at least five studies. Funnel plot asymmetry may be caused by: selection bias (publication or location bias); poor methodological quality of smaller studies (design, analysis, fraud); true heterogeneity (variation with effect size); artefact or chance (Egger 1997). We performed a meta-analysis using the Cochrane Collaboration Review Manager software (RevMan 5).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
We initially identified 14,137 citations from the database searches, manual searches, citation review, and contact with experts (Figure 1). After screening by title and then abstract, we obtained full-paper copies of 16 citations that were potentially eligible for inclusion in the review. We excluded nine of these for the reasons described in the Characteristics of excluded studies table.

Figure 1. Seaching results



Seven studies met our inclusion criteria. The studies enrolled 1170 participants. The number of participants in each study varied from eight in a cross-over trial (Dyhr 2003) to 983 in a multicentre RCT (Meade 2008). All studies included participants with either acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Some studies defined ALI and ARDS with the lung injury severity score (LISS) (Amato 1998; Foti 2000) while others used the definition from the North American-European consensus conference (NAECC) (Brower 2003; Lasocki 2005; Oczenski 2004). One study used the NAECC definition: ratio of arterial oxygen partial pressure to inspiratory oxygen fraction (PaO_2/FiO_2) less than 250 (Meade 2008). One study included participants with ALI and ARDS without further definition (Dyhr 2003). For full details of the seven included studies see the Characteristics of included studies table. One study (Amato 1998) had 54 participants of which four were between the ages of 15 and 18 years old. We contacted the author directly, who did not have separate analyses of participants younger than 18 years old. We included this study in the review, even though the inclusion of children contravened our protocol, because this was one of only two RCTs that examined longer-term outcomes.

The studies fell broadly into two groups.

1. Long-term effects of a package of ventilation

Participants were allocated to either a package of ventilation that could include a recruitment manoeuvre; or a control group that did not receive the ventilatory package. Outcome measures included mortality, duration of ICU and hospital stay, and barotrauma (Amato 1998; Meade 2008). In addition, Meade 2008 reported the change in PaO_2/FiO_2 at 24, 48, and 72 hours after allocation.

2. Short-term effects of recruitment manoeuvres

Participants were allocated to either receive a recruitment manoeuvre or not. Studies measured oxygenation, blood pressure, and heart rate over a short time. One study had a parallel group design (Oczenski 2004) and four were cross-over studies (Brower 2003; Dyhr 2003; Foti 2000; Lasocki 2005).

Recruitment manoeuvres varied. Studies that assessed recruitment manoeuvres after ventilator disconnection increased airway pressure to 40 cm H_20 for 40 seconds during pressure control ventilation with the volume limited to less than 6 ml/kg (Amato 1998; Meade 2008). The study with a parallel group design sustained an airway pressure of 50 cm H_20 for 30 seconds (Oczenski 2004). The remaining studies varied the mode of ventilation, duration of recruitment manoeuvre, and maximum airway pressure (see the Characteristics of included studies table).

Outcome measures varied (Table 2). Mortality was measured at 28 days, in intensive care, and at hospital discharge in two studies (Amato 1998; Meade 2008) (Table 2). Mortality was also reported during mechanical ventilation (Meade 2008) and after weaning (Amato 1998). Only Meade 2008 reported the duration of mechanical ventilation, while Amato 1998 reported weaning at 28 days. Three studies reported the rate of radiological pneumothorax (Amato 1998; Brower 2003; Meade 2008).

Table 2. Outcomes considered for this review

Study	mortality	duration of ventilation	duration of hospital stay	oxygenation	cardiovascular stability	adverse events
Amato 1998	1. 28 day 2. in hospital 3. in ICU	weaning at 28 days	N/A	N/A	N/A	barotrauma
Brower 2003	N/A	N/A	N/A	1. SpO_2 2. FiO2/PEEP step	1. HR 2. SBP	barotrauma
Dyhr 2003	N/A	N/A	N/A	PaO_2	1. HR 2. MAP	N/A
Foti 2000	N/A	N/A	N/A	PaO_2	1. MAP 2. CO	N/A
Lasocki 2005	N/A	N/A	N/A	PaO_2	N/A	N/A

Table 2. Outcomes considered for this review *(Continued)*

Meade 2008	1. 28 day 2. in hospital 3. in ICU 4. during mechanical ventilation	days on mechanical ventilation	days of hospitalization	PaO_2/F_IO_2	N/A	barotrauma
Oczenski 2004	N/A	N/A	N/A	PaO_2/F_IO_2	1. HR 2. MAP	N/A

ICU = intensive care unit, N/A = not available, SpO_2 = oxygen saturation from pulse oximetry, FiO_2/PEEP step = changes in level of inspired oxygen at set levels of positive end expiratory pressure, HR = heart rate, SBP = systolic blood pressure, MAP = mean arterial pressure, CO = cardiac output, PaO_2/FiO_2 = fraction of arterial oxygen to inspired oxygen

Five studies reported changes in oxygenation at 24 hours or less (Brower 2003; Foti 2000; Lasocki 2005; Meade 2008; Oczenski 2004). Four studies reported changes in blood pressure after the recruitment manoeuvre (Brower 2003; Dyhr 2003; Foti 2000; Oczenski 2004) and three studies reported changes in heart rate (Brower 2003; Dyhr 2003; Oczenski 2004).

Risk of bias in included studies

The three parallel group studies (Amato 1998; Meade 2008; Oczenski 2004) clearly used adequate randomization and allocation schemes (see table Characteristics of included studies). One reported a programming error in the allocation procedure that occurred late in the study and disrupted the specific randomization blocks; this may have accounted for modest baseline imbalances in age and presence of sepsis (Meade 2008). This was addressed through secondary analysis adjusting for age, sepsis, acute physiology, and duration of hospitalization.

The four cross-over studies did not provide information about the randomization method or allocation concealment. We attempted to contact all authors and had two responses (Brower 2003; Dyhr 2003). Results from these discussions are included in the Characteristics of included studies table.

The intervention did not allow the investigators or bedside staff to be blinded to group allocation. We assumed that participants were unaware of group allocation because they were critically ill and consent for participation in the study was gained from the next of kin. Blinding of the outcome assessor was not described in any of the studies. One study described the data analysis as blinded (Meade 2008).

The follow up was short in the cross-over trials (Brower 2003; Dyhr 2003; Foti 2000; Lasocki 2005) and one parallel group trial (Oczenski 2004). Losses to follow up were rare (Brower 2003).

The study by Amato 1998 was stopped early due to apparent benefit.

The recruitment manoeuvres varied between the studies in terms of maximum pressure achieved, duration of maximum pressure, mode of delivery, and PEEP after the recruitment manoeuvre (Table 3).

Table 3. Description of recruitment manoeuvre procedure

Study	mode	peak pressure (cmH_2O)	time (sec)	mean PEEP after RM (cmH_20)	repetitions
Amato 1998	CPAP	40	40	16.4	frequently after disconnections
Brower 2003	CPAP	35	30	13.8	once

Table 3. Description of recruitment manoeuvre procedure (*Continued*)

Dyhr 2003	CPAP	45	20	12	twice with 1 minute between
Fori 2000	CPAP	44.5 6.2	NS	16.2	once
Lasocki 2005	VCV	≤70 (but delivered as twice the baseline tidal volume)	NS	10	once
Meade 2008	CPAP	40	40	14.6	frequently after disconnections
Oczenski 2004	PCV	50	30	15.1	once

Fori 2000 - RM held for 2 consecutive breaths
Lasocki 2005 - RM held for 20 consecutive breaths at twice the baseline tidal volume
CPAP = continuous positive airway pressure, VCV = volume cycled ventilation, PCV = pressure cycled ventilation, sec = seconds, NS = not stated

Effects of interventions

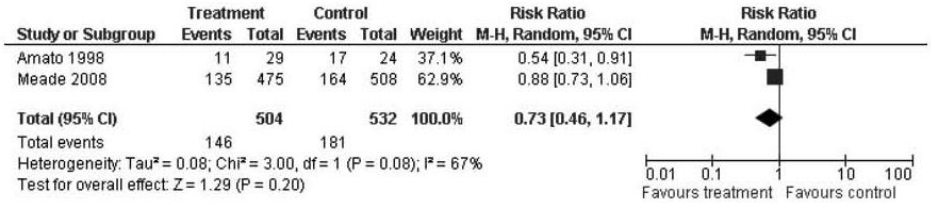
Primary outcomes

Unfortunately there were no studies in this review that assessed the effects of recruitment manoeuvres alone on the primary outcomes of mortality, length of ventilation, or length of stay. However, there were two studies involving 1036 participants that assessed the effects of a package of ventilatory care that included recruitment manoeuvres (with other confounding variables such as differences in PEEP and plateau pressure) and reported the primary outcomes (Amato 1998; Meade 2008) (see Table 2). As these studies were randomized controlled trials that included recruitment manoeuvres in a package of ventilation, we have included the results below but we acknowledge that the effects of recruitment manoeuvres can not be isolated from the other parts of the package of care, as outlined in the discussion.

01.01. 28-day mortality

Analysis 1.1: Amato 1998 and Meade 2008 both examined 28-day mortality. We used the random-effects model to pool the data from both trials (I^2 = 67%). 'Open-lung' ventilatory strategies that could include recruitment manoeuvres did not significantly reduce 28-day mortality (RR 0.73, 95% CI 0.46 to 1.17, P = 0.2) (Figure 2).

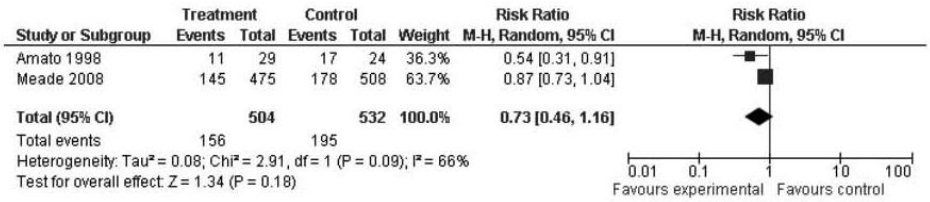
Figure 2. Forest plot of comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres, outcome: 1.1 28 day mortality.



01.02. ICU mortality

Analysis 1.2: Amato 1998 and Meade 2008 both examined ICU mortality. We used the random-effects model to pool data from both trials (I^2 = 66%). 'Open-lung' ventilatory strategies that included recruitment manoeuvres did not significantly affect mortality in intensive care (RR 0.73, 95% CI 0.46 to 1.16, P = 0.18) (Figure 3).

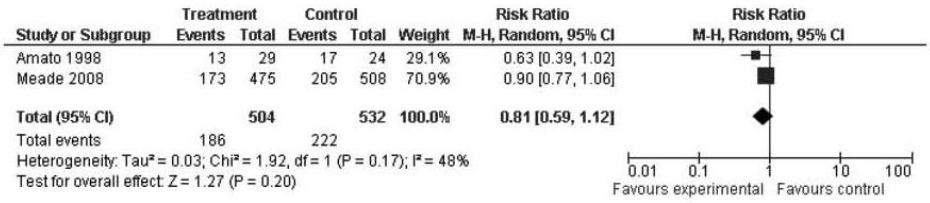
Figure 3. Forest plot of comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres, outcome: 1.7 ICU mortality.



01.03. In-hospital mortality

Analysis 1.3: Amato 1998 and Meade 2008 both examined in-hospital mortality. We used the random-effects model to pool data from both trials (I^2 = 48%). 'Open-lung' ventilatory strategies that could include recruitment manoeuvres did not significantly affect mortality in hospital (RR 0.81, 95% CI 0.59 to 1.12, P = 0.2) (Figure 4).

Figure 4. Forest plot of comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres, outcome: 1.6 In hospital mortality.



Length of time on mechanical ventilation

We did not pool the data for this outcome. Amato 1998 reported that all survivors were weaned by day 28 (18 of 29 intervention participants (62%) and 7 of 24 control participants (29%), P = 0.13). Meade 2008 reported days of mechanical ventilation and found no difference between the groups (treatment group 10, control group 10, P = 0.92).

Length of time in hospital

Meade 2008 found no difference in length of hospitalization: mean 28 days following 'open-lung' ventilatory strategies; 29 days following control ventilation (P = 0.96).

Secondary outcomes

Many of the secondary outcomes described in this section were measured at different time points. Where possible, we pooled the results based on short-term outcomes if the time points of measurement were similar. Some of the studies were cross-over trials and individual patient data were not available at the time of this

review. We compared effects for interventions tested in cross-over trials using data analysis that assumed the data came from independent groups. Obtained effect estimates are therefore conservative but this unit of analysis error was considered less serious than other methods of analysing cross-over trials.

01.04. Barotrauma

Analysis 1.4: three trials reported rates of barotrauma (Amato 1998; Brower 2003; Meade 2008). We used the random-effects model to pool data from Amato 1998 and Meade 2002 (I^2 = 86%). 'Open-lung' ventilatory strategies that could include recruitment manoeuvres did not significantly affect the risk of barotrauma (RR 0.50, 95% CI 0.07 to 3.52, P = 0.5) (see Figure 5). Brower 2003 reported one new barotrauma in the treatment group and one new barotrauma in the control group in their cross-over trial that randomized participants to one day with a recruitment manoeuvre and one day with a sham recruitment manoeuvre. We did not include this trial in the meta-analysis as it was a cross-over trial.

Figure 5. Forest plot of comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres, outcome: 1.2 Rate of Barotrauma.

01.05. Oxygenation

Six trials reported changes in oxygenation with a recruitment manoeuvre (Brower 2003; Dyhr 2003; Foti 2000; Lasocki 2005; Meade 2008; Oczenski 2004). All trials reported changes in oxygenation within 24 hours (range: one minute to 24 hours). Four of the trials were cross-over trials (Brower 2003; Dyhr 2003; Foti 2000; Lasocki 2005).

Some papers reported per cent change from baseline (Brower 2003, Dyhr 2003). For the other trials we calculated the per cent change from baseline with and without a recruitment manoeuvre. The per cent change was calculated using the formula: post-intervention score for the treatment group minus the post-intervention score for the control group divided by the baseline score (which was the pooled mean for the treatment and control groups at baseline, in order to provide the best estimation of the baseline score of the population). The results of changes in oxygenation with a recruitment manoeuvre, including per cent changes from baseline, are presented in Table 4. Several studies had more than one time point where oxygenation was measured. For these studies we chose the time point closest to one hour after the recruitment manoeuvre for inclusion in the table of per cent changes from baseline. This was because one trial had a positive response to a recruitment manoeuvre that was maintained for only a few minutes (Oczenski 2004).

Table 4. Changes in oxygenation from baseline

Study	Measure of oxygen	Time of measurement from baseline	Mean SD after a recruitment manoeuvre versus without a recruitment manoeuvre (test for significance between groups)	Mean % change from baseline with a recruitment manoeuvre	Mean % change without a recruitment manoeuvre
Brower 2003	SpO_2 reported as % change only	<10 minutes	1.7 0.2* v 0.6 0.3* (P<0.01)	1.7	0.6
Dyhr 2003	PaO_2 reported as % change only	7 minutes	21.8 7.8 v -8.5 5.1 (P<0.05)	21.8	-8.5
Foti 2000	PaO_2	30 minutes	117.9 40.6 v 79.4. 13.6 (P<0.01)	48.5	baseline**

Table 4. Changes in oxygenation from baseline *(Continued)*

Meade 2008	PaO_2/F_IO_2	24 hours	187.4 68.8 v 149.1 60.6 (P=0.001)	29.5	3.0
Oczenski 2004	PaO_2/F_IO_2	30 minutes	138 39 v 155 52 (P=0.32***)	-2.8	9.2

* SE
** cross-over trial where the only comparison to the recruitment manoeuvre was the baseline value (0%)
*** 2 tailed t-test calculated on means and standard deviation provided

Foti 2000 measured arterial oxygen partial pressure (PaO_2) 30 minutes after a period of volume cycled ventilation at low PEEP (mean: 9.4 3 cm H_2O) or volume cycled ventilation at low PEEP with a recruitment manoeuvre, in 15 patients. Dyhr 2003 measured PaO_2 at 3, 7, 15, and 25 minutes after endotracheal suction with and without recruitment manoeuvres, in eight patients. They found that the PaO_2 decreased significantly after endotracheal suction and returned to baseline at three minutes after a recruitment manoeuvre and at seven minutes without. The PaO_2 was significantly higher from three to seven minutes after suctioning if followed by a recruitment manoeuvre ($P < 0.05$). Lasocki 2005 measured the PaO_2 10 minutes after open endotracheal suction and compared it to closed endotracheal suction with a recruitment manoeuvre, in nine patients. The results were not included in the table because open versus closed suction was itself a variable that may have affected the outcome.

Brower 2003 reported the change in oxygen saturation and FiO_2/PEEP 10 minutes and two hours after a recruitment or sham manoeuvre delivered in random sequence. Brower 2003 reported the oxygen saturation as the per cent change from baseline (measured by pulse oximetry) at 10 minutes. Recruitment manoeuvres improved oxygen saturation when compared to sham manoeuvres (1.7 0.2% versus 0.6 0.3%, $P < 0.01$). There was no difference between the recruitment and sham manoeuvres in FiO_2/PEEP two hours after treatment; the odds ratio comparing the proportion of participants in each group whose FiO_2/PEEP had improved or not changed was 1.54 (95% CI 0.78 to 3.02, P = 0.21).

Meade 2008 investigated the effects on PaO_2/FiO_2 at days one, three, and seven of the study by comparing the package of ventilation that could include a recruitment manoeuvre and the control group. They found a statistically significant improvement in PaO_2/FiO_2 on all three days with the package of ventilation (P = 0.001).

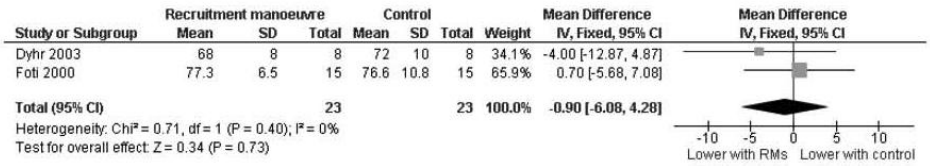
Oczenski 2004 randomly assigned 30 patients from a PEEP trial who had low tidal volumes and high PEEP to either receive a recruitment manoeuvre or not. Compared to control, a recruitment manoeuvre significantly increased the PaO_2/FiO_2 (139 46 versus 246 111, $P < 0.001$) and shunt fraction (30.8 5.8 versus 29.2 7.4) three minutes later. In both groups values returned to baseline by 30 minutes, with no significant difference.

01.06. Blood pressure

Analysis 1.5: one study reported that mean arterial blood pressure fell by less than 14 mm Hg, and was always greater than 50 mm Hg, during the recruitment manoeuvre (Dyhr 2003).

Four studies reported the effects on mean arterial blood pressure: at two minutes after a recruitment manoeuvre (Dyhr 2003); three minutes after a recruitment manoeuvre (Oczenski 2004); and 30 minutes after a recruitment manoeuvre (Foti 2000; Oczenski 2004). We used the fixed-effect model to pool the data from Dyhr 2003 and Foti 2000 ($I^2 = 0\%$). Recruitment manoeuvres did not significantly affect mean arterial blood pressure (MD 0.90, 95% CI -4.28 to 6.08 mm Hg, P = 0.73, Figure 6).

Figure 6. Forest plot of comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres, outcome: 1.4 Blood pressure.



Systolic blood pressure fell (Brower 2003) (recorded as least square means SEM, P < 0.01). Brower 2003 terminated recruitment manoeuvres early in three instances because of transient hypotension or low oxygen saturation without apparent sequelae.

01.07. Heart rate

Three studies reported the effects of a recruitment manoeuvre on heart rate (Brower 2003; Dyhr 2003; Oczenski 2004). Brower 2003 recorded the highest and lowest heart rate during the 10 minutes after starting the recruitment manoeuvre. Heart rate was compared to baseline after a recruitment manoeuvre at two minutes (Dyhr 2003) and after three minutes and 30 minutes (Oczenski 2004).

Brower 2003 and Oczenski 2004 both reported no significant change in heart rate after a recruitment manoeuvre when compared to a treatment without a recruitment manoeuvre. Dyhr 2003 reported a higher heart rate after endotracheal suction and a lung recruitment manoeuvre compared to endotracheal suction alone (mean SD: 96 9 versus 91 7, P < 0.05). The authors did not consider this an adverse event.

Subgroup analyses

We found insufficient data in the trials to perform the planned subgroup analyses.

DISCUSSION

Summary of main results (benefits and harms)

We pooled data from five of seven randomized controlled trials and showed no statistically significant difference in mortality, rate of barotrauma, or blood pressure. There was a transient increase in arterial oxygen partial pressure after recruitment manoeuvres.

Two studies reported on rates for our primary outcomes (mortality, duration of ventilation, hospital stay). The experimental interventions in both Amato 1998 and Meade 2008 included PEEP, permissive hypercapnia, and plateau pressure. Recruitment manoeuvres were not allowed in control participants. In Meade 2008 the intervention group (n = 423) received a recruitment manoeuvre at the start of the study and 366 received at least one more following ventilator disconnections (whilst 57 did not). It is not clear how many intervention participants in Amato 1998 did or did not receive a recruitment manoeuvre; or whether these were only given after ventilator disconnections, always given after disconnections, or in other circumstances. The composite designs of these studies means that any difference in outcomes between control and intervention groups could be due to any one of the four or more systematic treatment differences; or, as likely, the combined synergistic or antagonistic effects of two or more of these treatments. We did not find a single study that isolated the effects of recruitment manoeuvres on our primary outcomes. In addition both studies linked recruitment manoeuvres with ventilatory disconnections. Even if control and intervention groups had the same end-expiratory pressure, plateau pressure and arterial carbon dioxide partial pressure, any differences in outcomes could be attributed to differences in rate and also causes of ventilatory disconnections.

It is also important to note that the package of ventilation used by Amato 1998 was different compared to Meade 2008 and therefore the pooling of the data may be misleading. For example, Amato 1998 included a package of ventilation that compared low tidal volume at less than 6 ml/kg and high PEEP (possibly with recruitment manoeuvres) compared to the control group that had high tidal volumes at 12 ml/kg and the lowest PEEP to attain acceptable oxygenation. On the other hand, Meade 2008 compared a package of ventilation that included tidal volumes at 6 ml/kg with plateau pressures not exceeding 40 cm H_2O, high PEEP, and recruitment manoeuvres compared to the control of tidal volumes at 6 ml/kg, plateau pressures not exceeding 30 cm H_2O and conventional levels of PEEP. The difference in survival between Amato 1998 and Meade 2008 may be due to chance. It may also be explained by the difference in tidal volumes delivered to the treatment and control groups (Petrucci 2007), the different PEEP levels used between the treatment and control groups (Mercat 2008), or other differences in the package of ventilation, such as the higher plateau pressure in the treatment group in Meade 2008. It is also possible that the difference in survival may be a result of the severity of illness as Meade 2008 included patients with acute lung injury and ARDS whereas Amato 1998 only included patients with ARDS. However, this was further investigated by Meade 2008 who reported that they did not detect an interaction between baseline severity of lung injury and treatment effect. Interestingly Amato 1998 included the youngest population but reported the highest mortality in the control group (71%), which may be as a result of severe prognostic factors at baseline.

The effect of ventilatory strategies on length of ventilation is unclear as the results could not be pooled. Amato 1998 weaned all survivors from ventilation by day 28. Meade 2008 also found no difference in the duration of ventilation for survivors.

Recruitment manoeuvres did not affect the rate of barotrauma, nor blood pressure. This may indicate that recruitment manoeuvres were safe. However, it is possible that some patients might not respond well and their blood pressure could fall during a recruitment manoeuvre. There is recent evidence from computerized tomography (Gattinoni 2006) that the response to PEEP is heterogeneous in ARDS and may lead to overdistension as opposed to lung recruitment. Therefore, some patients with ARDS may benefit from a recruitment manoeuvre and high PEEP while for others it may be harmful.

Recruitment manoeuvres increased short-term arterial oxygenation compared to control. This was indirectly supported by the ventilatory package in Meade 2008, which increased the PaO_2/FiO_2 at 24 hours, 48 hours, and 72 hours. However, the isolated effect of recruitment manoeuvres in Oczenski 2004 only increased the PaO_2/FiO_2 for three minutes (returning to baseline

levels within 30 minutes).

Overall completeness and applicability of the evidence

In the two trials comparing different packages of ventilation (Amato 1998; Meade 2008) sample size was calculated prior to commencement of the study. The target sample was reached in Meade 2008 and there was no loss to follow up. The Amato 1998 trial was stopped early, after the fifth interim analysis, because of a significant survival difference between the groups. It is unclear which part of the package of ventilation was effective in improving survival.

The loss to follow up is unclear in one large cross-over trial (Brower 2003). The authors stated that treatment order, day, and baseline values were controlled. However they state that data were lost due to weaning (37%), hypotension or hypertension (9%), tachycardia or bradycardia (2%), participants being withdrawn from the study (2%), or for reasons that were not specified (5%).

All of the cross-over trials had short-term outcomes (oxygenation, blood pressure, and heart rate changes) from 10 minutes to eight hours but no long-term outcomes. The selection of patients allocated to treatment or control groups for the first intervention period may have affected the baseline measures. There may also have been carry-over effects; the interval between treatment or control was described by three of the cross-over trials (Brower 2003; Dyhr 2003; Lasocki 2005) but not by Foti 2000. Ideally the cross-over trials would report data at the point of cross-over in order for the study to be appraised and pooled with other parallel trials. We attempted to contact all of the authors to ask for individual patient data.

Quality of the evidence

There were several limitations to this review. The first is that there were only three parallel trials and four cross-over trials identified. The effects of additional ventilatory interventions were not controlled for in Amato 1998 and Meade 2008, recruitment manoeuvres were applied inconsistently, and were linked to ventilatory disconnections. There was minimal blinding of the therapist or assessor. There may have been carry-over effects in the cross-over trials (particularly Dyhr 2003; Foti 2000).

The cross-over trials reported only aggregate data. No individual patient data were available for inclusion at the time of this review.

Potential biases of the review process

Agreement and disagreement with other studies and reviews

Some issues remain open for debate.

- Recruitment manoeuvres may improve oxygenation in the short term but do they have an impact on outcomes such as survival and length of ventilation in the longer term? We cannot answer this question because the effects of recruitment manoeuvres have not been isolated from the effects of other ventilatory variables. It is plausible that recruitment manoeuvres alone are not sufficient to improve longer-term outcomes but that they add value when used with a package of low tidal volumes, high PEEP, and limited plateau pressures (Kacmarek 2007; Meade 2008). It is also plausible that recruitment manoeuvres are harmful (Kacmarek 2007).
- If recruitment manoeuvres have more than a transient effect on oxygenation what would be the optimal transpulmonary pressure, length of time, and level of PEEP to maintain such effects? All of the studies used different transpulmonary pressures, for different lengths of time, and with varying levels of PEEP (Table 3). The mode of ventilation used to achieve a recruitment manoeuvre also varied widely. Any given transpulmonary pressure might be effective in some patients, ineffective in some, and harmful in other patients (for instance by overdistending lung units). It may be important to determine the minimum PEEP that sustains the benefits of a recruitment manoeuvre (Kacmarek 2007; Lapinsky 2005; Piacentini 2004; Richard 2004).
- There is not enough evidence to support the optimal frequency of delivering a recruitment manoeuvre in patients with acute lung injury or acute respiratory distress syndrome.
- Cross-over studies on the effects of recruitment manoeuvres in ARDS and ALI are not ideal as there may be carry-over effects.

AUTHORS' CONCLUSIONS

Implications for practice

There is no available evidence to determine whether recruitment manoeuvres alter mortality, duration of mechanical ventilation, or hospital stay. Arterial oxygen partial pressure is increased for a short period of time after a recruitment manoeuvre has been completed. Further research is required to determine if recruitment manoeuvres in isolation increase oxygen partial pressure for a longer period of time and whether this has any impact on longer-term outcome.

Implications for research

If clinicians wish to persist in the use of recruitment manoeuvres they should participate in sufficiently well-designed randomized controlled trials to isolate the effects of recruitment manoeuvres from effects due to other ventilatory variables or events.

A systematic review that uses individual patient data may help determine whether the effects of recruitment manoeuvres vary with the severity and cause of ARDS.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Amato 1998

Methods	Prospective, multicentre RCT.
Participants	n = 53. Inclusion criteria: age: > 13 years and < 71 years, PaO_2/FiO_2 < 200, LISS ≥ 2.5, PCWP < 16mmHg. Excluded if previous lung or neuromuscular disease, MV > 1 week, uncontrolled terminal disease, previous barotrauma, previous lung surgery, age > 70 years, raised ICP, progressive acidosis, terminal disease, coronary insufficiency.
Interventions	Treatment: RM = CPAP 35 to 40 cmH_2O for 40 seconds (frequently after circuit disconnection) with PCV (including inverse ratio ventilation), high PEEP (2 cmH_2O above LIP or 16 cmH_2O) and V_T < 6 ml/kg, plateau pressure < 20 mmHg, permissive hypercapnia. Control: VCV, V_T 12 ml/kg, unlimited plateau pressure, PEEP titrated to best PaO_2/FiO_2, $PaCO_2$ 35 to 38 mmHg. Amato described the recruitment manoeuvre "The control group never received a recruiting manoeuvre. The recruitment manoeuvre was a CPAP of 40, for 40 seconds. It was used in 3 occasions: after accidental disconnection, at the beginning of the protocol, or during the time course of treatment, whenever the physician suspected that there was some worsening of oxygenation related to derecruitment (maximum of once per day)."
Outcomes	Primary: 28-day mortality. Secondary: time to unassisted breathing, rate of clinical barotrauma, ICU LOS, hospital LOS, nosocomial pneumonia, neuropathy, dialysis. Also reported mortality to hospital discharge.
Notes	There were 4 patients with ages varying from 15 to 18 years, which contravened the review protocol, however the author was contacted and there was no separate analysis done to exclude the children < 18 years. This study included recruitment manoeuvres as part of a package of ventilation. Other differences between the intervention group and the control group were PEEP, tidal volume, arterial carbon dioxide target, and therefore plateau pressure and peak pressure.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated.

Amato 1998 *(Continued)*

Allocation concealment?	Yes	Author contacted directly and stated "Sealed envelopes with random, but balanced number of patients in each arm".
Blinding? All outcomes	No	Blinding of treatment: no. Blinding of outcome assessment: not stated. Blinding of data analysis: not stated.
Incomplete outcome data addressed? All outcomes	Yes	Trial stopped early due to apparent benefit.
Free of selective reporting?	Yes	
Intention to treat?	Yes	

Brower 2003

Methods	Prospective, randomized, multicentre cross-over trial with 24 hours washout.
Participants	n = 72. ALI/ARDS (ancillary study conducted to patients randomized to the high PEEP arm of the study (Brower 2004). Excluded if weaning, SBP > 200mmHg or < 100mmHg, HR < 70/min or > 140/min.
Interventions	Treatment: RM = CPAP 35 cmH_2O for 30 sec, VCV. Control: sham RM. Alternate days, once only.
Outcomes	HR, SBP, barotrauma, SpO_2, FiO_2/PEEP steps.
Notes	Daily RM versus sham. Loss of paired data - there were data for 66 recruitment manoeuvres and 70 sham recruitment manoeuvres. Short-term outcomes. Outcomes expressed as a % change from baseline. Individual patient data available through the ARDSnet with ethics approval.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not clearly stated - the author was contacted directly and stated central randomization.
Allocation concealment?	Unclear	Not clearly stated.

Brower 2003 *(Continued)*

Blinding? All outcomes	Unclear	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	

Dyhr 2003

Methods	Prospective, randomized, single-centre, cross-over trial. Intention to treat: yes.	
Participants	n = 8. ARDS and ALI. Excluded if COPD, pneumothorax, haemodynamic instability.	
Interventions	RM = CPAP 20 seconds at 45 cmH_2O twice with a minute between.	
Outcomes	MAP, HR, CVP, PaO_2, EELV.	
Notes	Outcomes expressed as a % change from baseline.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Cross-over trial: treatment sequence generation not stated but author contacted directly and stated "eight patients fulfilling the inclusion criteria were randomized (envelope blinded: four in the order alfa - beta and another four in the order beta - alfa) to one of two sequences of two standardized open endotracheal suction (ETS) procedures".
Allocation concealment?	Yes	Contact with author - sealed envelopes.
Blinding? All outcomes	No	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Incomplete outcome data addressed? All outcomes	Yes	

Dyhr 2003 *(Continued)*

Free of selective reporting?	Yes	
Intention to treat?	Yes	

Foti 2000

Methods	Prospective, randomized, single-centre, cross-over trial. Patients received 3 treatments in random order without description of the randomization or allocation procedures.
Participants	n = 15. ARDS - PEEP responders, LISS $\geq$ 2.5. Excluded if: COPD, air leak, bronchospasm.
Interventions	Patients received either continuous positive pressure at low PEEP, continuous positive pressure at high PEEP, or continuous positive pressure at low PEEP with periodic RM (which was PEEP High as determined in the PEEP trial for 2 breaths).
Outcomes	Arterial and mixed venous blood (PaO_2, $PaCO_2$, Qva/Qt, Vd/Vt), HR, CO, PAP, CVP, PIP, Crs, FRC, EELV.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Cross-over trial: treatment sequence generation not stated.
Allocation concealment?	Unclear	Method of allocation to treatment group not clearly stated.
Blinding? All outcomes	No	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Intention to treat?	Yes	

Lasocki 2005

Methods	Prospective, randomized, single-centre, cross-over trial. Closed endotracheal suction and a recruitment manoeuvre versus open endotracheal suction.
Participants	n = 9. ALI (NAECC PaO_2/FiO_2 < 300, PEEP ≥ 5 cmH_2O, PCWP 18mmHg and/or LVEF < 50%). Excluded if head trauma.
Interventions	RM = 20 tidal volumes set at twice the baseline value without changing the respiratory rate, VCV.
Outcomes	PaO_2, $PaCO_2$, VT, RR, Ppeak, Pplat, compliance.
Notes	This trial compared open versus closed suction - where closed suction included a RM.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Cross-over trial: treatment sequence generation not stated.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	No	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Intention to treat?	Yes	

Meade 2008

Methods	Prospective, multicentre, controlled RCT.
Participants	n = 983. ALI and ARDS. Excluded if: left atrial hypertension, anticipated MV < 48 hours, inability to wean from experimental strategies, severe chronic respiratory disease, neuromuscular disease, intracranial hypertension, morbid obesity, pregnancy, conditions with expected 6-month mortality risk > 50%.

Meade 2008 *(Continued)*

Interventions	Treatment: RM = after allocation to treatment group CPAP 40 cmH_2O for 40 seconds with FiO_2 1.0. Subsequent RMs after circuit disconnection (up to four each day) were not defined. PCV, V_T 6 ml/kg, Pplat < 40, high PEEP (mean 14.6 cmH_2O). Control: V_T 6 ml/kg, Pplat < 30, standard PEEP (mean 9.8 cmH_2O).
Outcomes	Primary: hospital mortality. Secondary: ICU mortality, 28-day mortality, time to independent breathing, refractory hypoxaemia, barotrauma, use of rescue therapies.
Notes	Recruitment manoeuvres were part of a package of ventilation. The other differences between the intervention group and the control group ventilation packages were tidal volume, plateau pressure, fraction of inspired oxygen, inspiratory:expiratory ratio and PEEP.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-stratified enrolment by site using variable permuted blocks.
Allocation concealment?	Yes	Central computerized telephone system used for allocation.
Blinding? All outcomes	No	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: yes.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Intention to treat?	Yes	

Oczenski 2004

Methods	Prospective, single-centre RCT.
Participants	n = 30. Extrapulmonary ARDS for < 72 hours (NAECC PaO_2/FiO_2 < 200, PEEP $\geq$ 5 cmH_2O, PCWP 18mmHg and/or LVEF < 50%). Excluded if: direct lung injury (pulmonary ARDS), SBP < 100, arrhythmias, APO, barotrauma.

Oczenski 2004 *(Continued)*

Interventions	Treatment: RM = CPAP 50 cmH_2O for 30 sec once only, V_T 6 ml/kg, Pplat < 30, PEEP determined by incremental PEEP trial. Control: V_T 6 ml/kg, Pplat < 30, PEEP determined by incremental PEEP trial, no RMs.	
Outcomes	P/F, HR, MAP 3 min and 30 min postRM.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated.
Allocation concealment?	Unclear	Not stated.
Blinding? All outcomes	Unclear	Blinding of treatment: no. Blinding of assessor: not stated. Blinding of data analysis: not stated.
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Intention to treat?	Yes	

ALI = acute lung injury, APO = acute pulmonary oedema, ARDS = acute respiratory distress syndrome, CPAP = continuous positive airway pressure, CO = cardiac output, COPD = chronic obstructive airways disease, Crs = respiratory system compliance, CVP = central venous pressure, EELV = end expiratory lung volume, FiO_2 = fraction of inspired oxygen, FRC = functional residual capacity, HR = heart rate, ICP = intracranial pressure, ICU = intensive care unit, LIP = lower inflection point, LISS = lung injury severity score, LOS = length of stay, LVEF = left ventricular ejection fraction, MAP = mean arterial pressure, Min = minutes, MV = mechanical ventilation, NAECC = North American-European Consensus Conference, PaO_2 = arterial oxygen partial pressure, $PaCO_2$ = arterial carbon dioxide partial pressure, PAP = pulmonary artery pressure, PCV = pressure control ventilation, PCWP = pulmonary capillary wedge pressure, PEEP = positive end expiratory pressure, P/F = PaO_2/FiO_2, PIP = peak inspiratory pressure, Ppeak = peak pressure, Pplat = plateau pressure, Qva/Qt = venous admixture, RCT = randomized controlled trial, RM = recruitment manoeuvre, RR = respiratory rate, SBP = systolic blood pressure, sec =seconds, SpO2 = arterial oxygen saturation from pulse oximeter, VCV = volume cycled ventilation, Vd/Vt = dead space, V_T = tidal volume.

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

Amato 1995	Patients in this study were included in the subsequent larger study published in 1998
Barker 2002	Not a recruitment manoeuvre using the ventilator but a manual breath using a rebreathing bag
Bollen 2005	RCT of high frequency oscillatory ventilation which is not covered as part of this review
Derdak 2002	RCT of high frequency oscillatory ventilation (Wunsch 2004)
Gattinoni 2006	Not a RCT of recruitment manoeuvres versus no recruitment manoeuvres
Holzapfel 1987	RCT of high frequency oscillatory ventilation (Wunsch 2004)
Hurst 1990	RCT of high frequency oscillatory ventilation (Wunsch 2004)
Meade 2002	Not a RCT of recruitment manoeuvres versus no recruitment manoeuvres
Stewart 2002	Not a RCT of recruitment manoeuvres versus no recruitment manoeuvres

DATA AND ANALYSES

Comparison 1. Recruitment manoeuvres versus no recruitment manoeuvres

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 28 day mortality	2	1036	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.17]
2 ICU mortality	2	1036	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.46, 1.16]
3 In hospital mortality	2	1036	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.12]
4 Rate of Barotrauma	2	1036	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.07, 3.52]
5 Blood pressure	2	46	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-6.08, 4.28]

Analysis 1.1. Comparison 1 Recruitment manoeuvres versus no recruitment manoeuvres, Outcome 1 28 day mortality.

Review: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation

Comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres

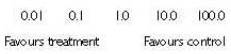
Outcome: 1 28 day mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Amato 1998	11/29	17/24		37.1 %	0.54 [0.31, 0.91]
Meade 2008	135/475	164/508		62.9 %	0.88 [0.73, 1.06]
Total (95% CI)	**504**	**532**		**100.0 %**	**0.73 [0.46, 1.17]**

Total events: 146 (Treatment), 181 (Control)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 3.00$, df = 1 (P = 0.08); $I^2 = 67\%$

Test for overall effect: Z = 1.29 (P = 0.20)

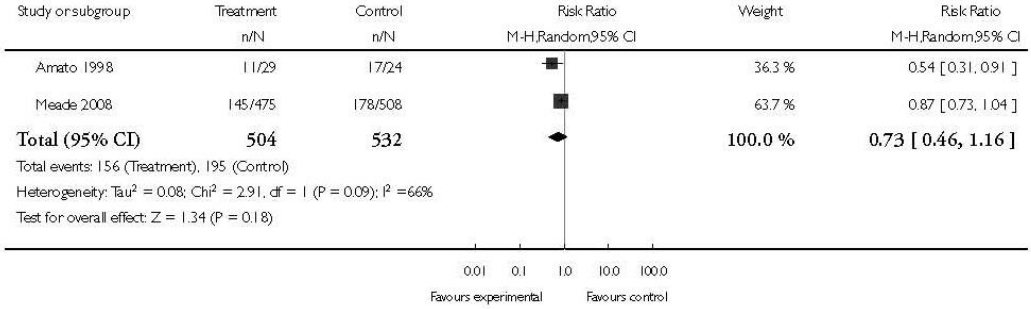


Analysis 1.2. Comparison 1 Recruitment manoeuvres versus no recruitment manoeuvres, Outcome 2 ICU mortality.

Review: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation

Comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres

Outcome: 2 ICU mortality

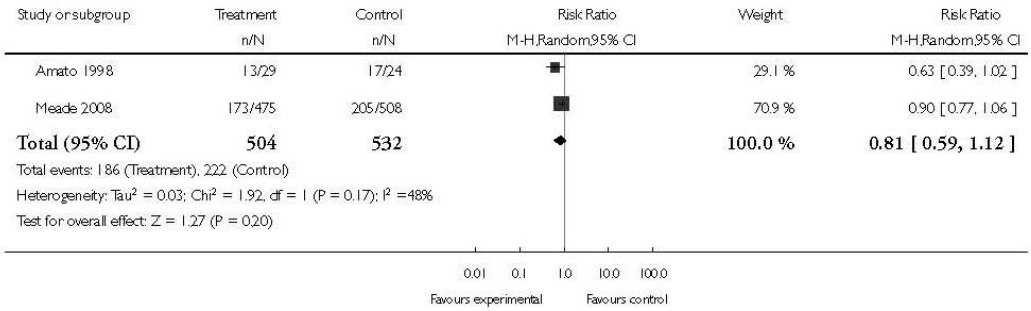


Analysis 1.3. Comparison 1 Recruitment manoeuvres versus no recruitment manoeuvres, Outcome 3 In hospital mortality.

Review: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation

Comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres

Outcome: 3 In hospital mortality

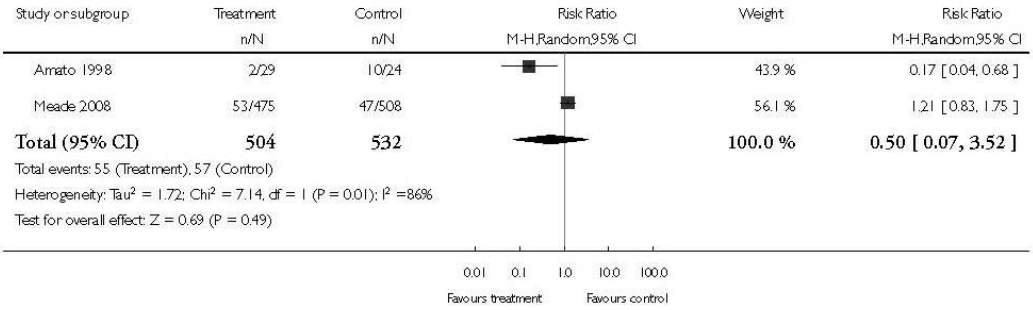


Analysis 1.4. Comparison 1 Recruitment manoeuvres versus no recruitment manoeuvres, Outcome 4 Rate of Barotrauma.

Review: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation

Comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres

Outcome: 4 Rate of Barotrauma

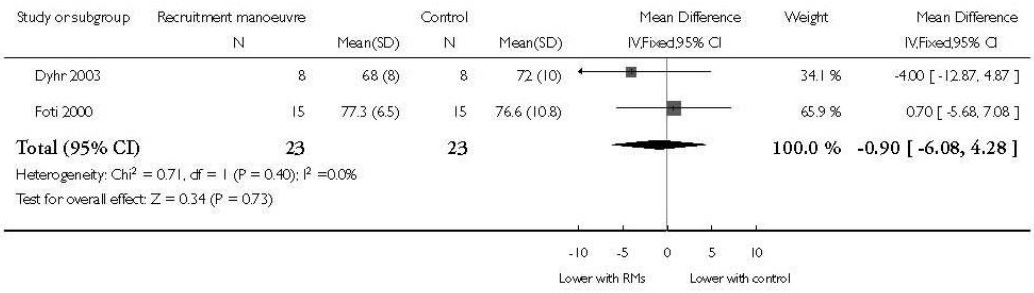


Analysis 1.5. Comparison 1 Recruitment manoeuvres versus no recruitment manoeuvres, Outcome 5 Blood pressure.

Review: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation

Comparison: 1 Recruitment manoeuvres versus no recruitment manoeuvres

Outcome: 5 Blood pressure



APPENDICES

Appendix 1. MEDLINE OVID (January 1966 to May 2008)

#1 (recruit$ and (manoeuv$ or manouev$ or maneuv$ or manuev$)).af.
#2 (recruitment or derecruitment).ti,ab.
#3 exp respiration, artificial/ or exp positive pressure respiration/ or ventilat$.ti,ab.
#4 (recruit$ and (respirat$ or lung or pulmon$ or airway$)).af.
#5 #2 or #3 or #4
#6. exp Lung/ or exp Respiratory Distress Syndrome, Adult/ or exp Atelectasis/
#7 ((lung adj injury) or (lung adj collapse$) or (alveoli adj collapse$) or atelecta$ or hypox?emia or hypoxic or oxygenation).ti,ab.
#8 #6 or #7
#9 #5 and #8
#10 #1 or #9
#11 clinical trial$.af.
#12 randomi?ed.ti,ab.
#13 placebo.ti,ab.
#14 dt.fs.
#15 (random or randomly).ti,ab.
#16 (trial or trials).ti,ab.
#17. groups.ti,ab.
#18 #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 Animals/
#20 Humans/
#21 #19 and #20
#22 #19 not #21
#23 #18 not #22
#24 #10 and #23

Appendix 2. CINAHL OVID (January 1982 to May 2008)

#1 (recruit$ and (manoeuv$ or manouev$ or maneuv$ or manuev$)).af.
#2 (recruitment or derecruitment).ti,ab.
#3 exp Ventilation, Mechanical/ or exp Positive Pressure Ventilation/ or ventilat$.ti,ab.
#4 (recruit$ and (respirat$ or lung or pulmon$ or airway$)).af.
#5 #2 or #3 or #4
#6 exp Lung/ or exp Respiratory Distress Syndrome, Acute/ or exp Atelectasis/
#7 ((lung adj injury) or (lung adj collapse$) or (alveoli adj collapse$) or atelecta$ or hypox?emia or hypoxic or oxygenation).ti,ab.
#8 #6 or #7
#9 #5 and #8
#10 #1 or #9
#11 clinical trial$.af
#12 randomi?ed.ti,ab
#13 placebo.ti,ab.
#14 dt.fs.
#15 (random or randomly).ti,ab.
#16 (trial or trials).ti,ab
#17 groups.ti,ab.
#18 #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #10 and #18

Appendix 3. CENTRAL, *The Cochrane Library* (Issue 2, 2008)

#1 (recruit* and (manoeuv* or manouev* or maneuv* or manuev*))
#2 (recruitment or derecruitment):ti,ab
#3 MeSH descriptor Respiration, Artificial explode all trees
#4 MeSH descriptor Positive-Pressure Respiration explode all trees
#5 (ventilat*):ti,ab
#6 (recruit* and (respirat* or lung or pulmon* or airway*))
#7 (#2 or #3 or #4 or #5 or #6)
#8 MeSH descriptor Lung explode all trees
#9 MeSH descriptor Respiratory Distress Syndrome, Adult explode all trees
#10 MeSH descriptor Atelectasis explode all trees
#11 (lung NEXT injury):ti,ab or (lung NEXT collaps*):ti,ab or (alveoli NEXT collaps*):ti,ab or (atelecta* OR hypox?emia OR hypoxic OR oxygenation):ti,ab
#12 (#8 or #9 or #10 or #11)
#13 (#7 and #12)
#14 (#1 or #13)

Appendix 4. EMBASE OVID (January 1980 to May 2008)

#1 (recruit$ and (manoeuv$ or manouev$ or maneuv$ or manuev$)).af.
#2 (recruitment or derecruitment).ti,ab.
#3 exp Artificial Ventilation/ or exp Positive End Expiratory Pressure/ or ventilat$.ti,ab.
#4 (recruit$ and (respirat$ or lung or pulmon$ or airway$)).af.
#5 #2 or #3 or #4
#6 exp atelectasis/ or exp acute lung injury/ or exp adult respiratory distress syndrome/ or exp Lung Injury/
#7 ((lung adj injury) or (lung adj collapse$) or (alveoli adj collapse$) or atelecta$ or hypox?emia or hypoxic or oxygenation).ti,ab.
#8 #6 or #7
#9 #5 and #8
#10 #1 or #9
#11 clinical trial$.af.
#12 random?ed.ti,ab.
#13 placebo.ti,ab.
#14 dt.fs.
#15 (random or randomly).ti,ab.
#16 (trial or trials).ti,ab.
#17 groups.ti,ab.
#18 #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 exp Animal/
#20 Human/
#21 #19 and #20
#22 #19 not #21
#23 #18 not #22
#24 #10 and #23

Appendix 5. LILACS OVID (January 1982 to May 2008)

(("recruit$" or "derecruit$" or "respiration, artificial" or "artificial respiration" or "respiration, artificial/" or "recruitment" or "positive-pressure respiration" or "ventilat$")) and (("oxygenation" or "hypoxic" or "hypoxaemia" or "hypoxemia" or "atelecta$" or "alveoli collapse$" or "lung collapse$" or "lung injury" or "lung" or "respiratory distress syndrome, acute/" or "respiratory distress syndrome, adult/" or "atelectasis"))

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2009

2 September 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Carol Hodgson (CH) and Jennifer L Keating (JK)

Co-ordinating the review: CH and JK

Undertaking manual searches: CH and Lorena Smirneos (LS)

Screening search results: CH and Scott J Bradley (SB)

Organizing retrieval of papers: CH and LS

Screening retrieved papers against inclusion criteria: CH and SB

Appraising quality of papers: CH and SB

Abstracting data from papers: CH and SB

Writing to authors of papers for additional information: CH

Providing additional data about papers: CH

Obtaining and screening data on unpublished studies: CH

Data management for the review: CH and JK

Entering data into Review Manager (RevMan 5): CH and JK

RevMan statistical data: CH, JK and Anne Holland (AH)

Other statistical analysis not using RevMan: CH, JK and AH

Double entry of data: data entered by person one, CH; data entered by person two, JK

Interpretation of data: CH, JK and AH

Statistical inferences: CH and JK

Writing the review: CH, AH, David Tuxen (DT); JK, SB, LS, Andrew N Davies (AD)

Securing funding for the review: CH, DT, AH and JK

Performing previous work that was the foundation of the present study: DT

Guarantor for the review (one author): CH

Person responsible for reading and checking review before submission: DT

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support, Australia.

External sources

- No sources of support, Australia.

Chapter 3 A positive response to a recruitment manoeuvre with PEEP titration in patients with ARDS, regardless of transient oxygen desaturation during the manoeuvre (In press, Journal of Intensive Care Medicine, 2011)

3.1 Declaration for Thesis Chapter 3

Declaration by candidate

In the case of Chapter 3 the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study concept and design, data collection and analysis, writing of manuscript	65

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Anne Holland	Revision of manuscript	
Jenny Keating	Assistance with data analysis, revision of manuscript	
David Tuxen	Study concept and design, revision of manuscript	
Michael Bailey	Statistical advice	
David Pilcher	Revision of manuscript	
Dinesh Varma	Revision of manuscript	
Ken Thomson	Revision of manuscript	

Candidate's Signature	[redacted]	**Date 20/07/2010**

Declaration by co-authors

The undersigned hereby certify that:

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

Location(s)	The Alfred Hospital, Melbourne

Name	**Signature**	**Date**
Anne Holland	[redacted]	20/07/10
Jenny Keating	[redacted]	20/07/10
David Tuxen	[redacted]	20/07/10
Michael Bailey	[redacted]	20/07/10
David Pilcher	[redacted]	22/07/10
Dinesh Varma		26/07/10
Ken Thomson		27/07/10

A positive response to a recruitment maneuver with PEEP titration in patients with ARDS, regardless of transient oxygen desaturation during the maneuver.

Mrs Carol L Hodgson BAppSc (Physiotherapy); PostGrad Dip (Cardio); M(Research); PhD Candidate Monash University; Senior ICU Physiotherapist, Alfred Hospital

A/Prof David V Tuxen MB BS, FRACP, Dip DHM, MD, FJFICM. Senior Intensivist, Department of Intensive Care, The Alfred Hospital, Melbourne

A/Prof Anne E Holland BAppSc (Physiotherapy); PhD. Associate Professor of Physiotherapy, La Trobe University / Alfred Health.

A/Prof Michael Bailey PhD, MSc(statistics), BSc(hons) Statistical Consultant/Senior Research Fellow ANZIC-RC Department of Epidemiology & Preventive Medicine School Public Health & Preventive Medicine, Monash University Alfred Hospital

Prof Jenny L Keating PhD; BAppSc(Physiotherapy); PostGrad Dip Manip Physiotherapy; Head of Department of Physiotherapy, Monash University

Dr David Pilcher MBBS. MRCP (UK). FRACP. FJFICM. Senior Intensivist, Department of Intensive Care, The Alfred Hospital, Melbourne

Prof Thomas Ken Thomson MD, FRANZCR, Director Radiology Alfred Campus, Monash University

Dr Dinesh Varma, MB BS, FRANZCR, Deputy Director Radiology and Head of Emergency Radiology, The Alfred, Hospital, Hon Senior Lecturer, Dept of Surgery, Monash University, Melbourne.

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Reprints will be ordered as a copy for each author.

Correspondence to:
Carol Hodgson
[redacted]
4 Sussex St, Brighton, VIC, Australia, 3186
fax 613 9076 2702
phone 613 9076 3450

Statistical support from the ANZICS-RC, Monash University, Melbourne
Short running head: Staircase recruitment maneuver
Key Words: respiratory distress syndrome, adult respiration, artificial, intensive care

0

Abstract
Recruitment maneuvers (RMs) can expand collapsed alveoli in ventilated patients. The optimal method for delivering recruitment maneuvers is unknown.
Purpose: to evaluate the safety and the respiratory and haemodynamic effects of a staircase recruitment maneuver (SRM) with decremental PEEP titration and the consequences of desaturation during the SRM in patients with early acute lung injury.
Methods: 20 consecutive patients with early acute lung injury (ALI) were enrolled and received a SRM. Patients were given 15 ± 3 cmH_2O pressure controlled ventilation. PEEP was increased from baseline (range 10-18) to 20, 30, 40 cmH_2O every 2 minutes to achieve maximum alveolar pressure of 55 ± 3cmH_2O then decreased at 3 minute intervals to 25, 22.5, 20, 17.5 and 15 cmH_2O until a decrease of 1-2% oxygen saturation from maximum was detected. PEEP was left at the level where the fall in oxygen saturation occurred. Standard respiratory and circulatory variables, arterial and central venous gases were measured before, during and after the SRM.
Results: There were significant improvements in shunt fraction (36.3 ± 10%, to 26.4 ± 14%, $P<0.001$), oxygen saturation (93.4 ± 2% to 96.8 ± 3%, $P=0.007$), PaO_2/FiO_2 (150 ± 42 to 227 ± 100, $P=0.004$), lung compliance (33.9 ± 9.1 to 40.1 ± 11.4 ml/cmH_2O, $P<0.01$) and chest x-ray (CXR) after the staircase recruitment maneuver. 80% of patients responded and response was maintained at 1 hour. Eight patients desaturated 6.1 ± 2.8% in SaO_2 during the SRM but 5 of those improved SaO_2 relative to baseline by the end of the SRM.
Conclusions: Eighty percent of patients with early ALI responded to the SRM with decremental PEEP titration. Desaturation during the SRM did not indicate a failed response one hour later.

Introduction

Recruitment maneuvers (RMs) elevate alveolar pressures above usual tidal ventilation pressure for a short time to enable inflation of collapsed lung regions [1]. This inflation is maintained by optimal PEEP after the RM [2]. RMs inflate collapsed lung regions and are believed to reduce progression of lung injury [3] but have not proven a survival benefit [4].

It has not been determined whether RMs are more beneficial than simply increased levels of PEEP. Two studies have compared PEEP alone to PEEP and a RM [5, 6]. Lim et al (2003) compared PEEP alone to a level of 15cmH_20 PEEP with a SRM to 30cmH_20 and PEEP or a SRM without PEEP in 47 patients with early ALI. PEEP and a SRM was significantly more effective in improving arterial oxygenation than PEEP alone or a SRM alone [6]. Badet et al (2009) reported a cross-over study that compared optimal PEEP and a single RM (sustained inflation of 40cmH_2O for 30 seconds) to optimal PEEP and sigh breaths (twice the tidal volume every 25 breaths) or optimal PEEP alone in 12 patients [5]. There were no significant differences between the PEEP and RM and PEEP alone groups in static lung compliance or oxygenation after an hour. In the optimal PEEP plus sighs group the changes in oxygenation and static compliance were significantly greater than in the 2 other groups.

Key variables that influence the success of RMs are the maximum alveolar pressure achieved, time at maximum pressure, PEEP levels maintained after the RM and re-recruitment strategies [2, 3, 7, 8]. A recent Cochrane systematic review concluded that reasons for observed effects were difficult to decipher due to different modes of ventilation used in different studies and varying maximum alveolar pressure, time at maximum pressure and post-recruitment PEEP levels [8]. However, RMs appear to significantly increase oxygenation above baseline levels for a short period of time [8, 9].

The most common method of a RM is sustained application of CPAP [10-13], however this provides no ventilatory support during the RM, can be uncomfortable and may induce circulatory depression. Possibly to minimise these effects, pressures of 35-40cmH_2O for short periods of time (30-40 seconds) have been applied in two large randomized studies [11, 13] without a significant difference in outcome. It has been hypothesized that low airway pressures applied for less time may reduce effectiveness. Borges et al [2] studied a staircase recruitment maneuver (SRM) to 60cmH_2O and found that it appeared effective, was well tolerated with no barotrauma, despite transient hypotension and cardiac depression at maximum PEEP. Animal studies [12] have compared RMs using PCV and CPAP to the same maximum alveolar pressure and time. PCV was better tolerated with less circulatory depression than a static RM with sustained CPAP, and resulted in better oxygenation. The latter study suggests intermittent application of high pressure may also be a factor determining efficacy in addition to the factors defined above.

It remains difficult to determine who will respond to a RM [1-3, 14] or to define a non-responder. A decrease in SaO_2 during RMs has been viewed as a failed RM with termination of the procedure [11]. However this may result from a decrease in venous oxygen saturation due to cardiovascular depression despite successful recruitment. It is not clear whether RMs should be terminated if arterial oxygen saturation falls.

The aim of this pilot study was to prospectively evaluate the safety and efficacy of a SRM with decremental PEEP titration in patients with early ALI on mechanical ventilation. The SRM was applied using PCV and incremental PEEP to a maximum intermittent alveolar pressure of 55 ± 3 cmH_2O then decremental PEEP reduction to determine the point of first

desaturation [2, 5, 15]. The use of decremental PEEP titration meant that final PEEP may be different from initial PEEP and hence this study was not intended to determine the effects of the SRM alone. This has been demonstrated in 2 previous studies [5,6]. Outcome measures included gas exchange (shunt fraction, SaO_2 and PaO_2/FiO_2) and haemodynamic function in patients with early ALI on mechanical ventilation. Our second aim was to determine whether a positive response occurred after the SRM regardless of transient oxygen desaturation during the SRM.

4

Materials and Methods

Twenty consecutive mechanically ventilated patients with early ARDS [16] were included. Inclusion criteria were age >15 years, an arterial line for blood gas sampling and invasive blood pressure monitoring and central venous catheter in situ. Patients were excluded if they had an intercostal catheter with an air leak, pneumothorax on chest x-ray, bronchospasm on auscultation, raised intracranial pressure, acute cardiogenic pulmonary oedema, mean arterial pressure less than 60mmHg, unstable arrhythmias or cardiac compromise. The study was approved by the hospital and university Ethics Committees. Written informed consent was gained from the person responsible (next of kin).

Patients were entered into the study within 3 days of commencing mechanical ventilation when ventilation, sedation and circulatory resuscitation were complete and stabilized. Patients who were not in pressure control ventilation (PCV) were converted to PCV (mean 15, range 7-18 cmH_2O) on the same level of PEEP as the time of enrolment and positioned in supine, 30 degrees head up. Fraction of inspired oxygen was reduced to achieve oxygen saturation of 90-92% so that an increase in SpO_2 could be clearly observed.

For the SRM, the PEEP was increased from baseline to 20, 30 and 40 cmH_2O every two minutes, then reduced to 25, 22.5, 20, 17.5 or 15 cmH_2O every three minutes until a decrease in SaO_2 of 1-2% from maximum SaO_2 was detected (Figure 1). The SRM increases in PEEP did not continue if there was a heart rate less than 60 or greater than 140 beats per minute, a new arrhythmia, systolic blood pressure less than 80mmHg or pulse oximeter saturation (SpO_2) less than 85%. Pressure control level was not changed during the SRM. Circulatory

supports (fluids, inotropes) were not changed during the study. Plateau pressure was kept ≤ 30cmH_2O after the SRM.

Pressure control level, PEEP, tidal volume, respiratory rate, peak and mean inspiratory pressure, heart rate and rhythm, central venous pressure, blood pressure, inotropes levels, and transcutaneous SpO_2 and were measured at baseline, each PEEP level and at 30 and 60 minutes after the SRM. Arterial and central venous blood gases were taken invasively at baseline, maximum PEEP, end of the SRM and 30 and 60 minutes after the SRM. Blood gas samples were taken with the patient in supine and analyzed (Blood Gas Analyser, CIBA-Corning, Medfield MA, USA). Derived variables were PaO_2/F_IO_2, ratio, shunt fraction, Sa-cvO_2 difference, alveolar dead space (Vd/Vt%) and dynamic compliance.

The primary outcome measure was shunt fraction calculated using standard formulae [17]. We reviewed the published definitions of a responder[1-3, 11, 14]. We were unable to source definitive data in the estimates of error in shunt fraction using $ScvO_2$ from central venous blood samples. In order to define responders we sought data on the minimal detectable change that would enable us to be 84% confident that real change had occurred. We estimated this to be a change of greater than 6.3% shunt fraction based on repeated measures data obtained in this study after the SRM with all other variables constant. Changes in SaO_2 (measured not calculated from the arterial blood gas) and PaO_2/FiO_2 ratio were also study outcomes and were similar to other studies [2, 14]. CXRs were taken at baseline and 30 minutes after the SRM and assessed as improved, the same or worse by a senior radiologist blinded to the timing.

We also grouped the results for patients who desaturated **during** the SRM and compared their results with remaining patients who improved their saturation during the SRM, to determine whether they had a different outcome.

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). A priori, changes over time from baseline at four time points (maximum PEEP, end of the SRM and 30 and 60 minutes after the SRM) were determined using repeat measures ANOVA with posthoc pair wise comparisons, with results reported as means and standard deviation. To adjust for multiple comparisons, a two-sided p-value of alpha was set at 0.01 for two sided tests to indicate statistical significance. Before and after comparisons of lung compliance at PEEP 20cmH_2O were compared using a paired t-test and p-value alpha of 0.05. Data was normally distributed.

Results

Twenty patients (12 males) with a mean age of 49 (range 22 to 79) years were enrolled in the study over a period of one year. One patient was studied twice during separate admissions to the ICU for periods of mechanical ventilation and the data treated as independent. The first admission was for burns and the second admission 6 weeks later was for pneumonia. Median duration of ventilation was 9 days (interquartile range 5.2 – 12.3). Mean APACHE II score was 18 ± 7. Overall survival for this group was 74%. Demographic data is given in Table 1. The twenty patients studied were consecutive patients with ALI or ARDS and only one other patient who met the inclusion criteria was not enrolled because consent was refused.

At baseline these patients had a mean SaO_2 of 93.4% (range 87-97%) and mean PaO_2 of 74 mmHg (range 52-99 mmHg) on FiO_2 of 50% (range 40-90%) with a mean PaO_2/FiO_2 ratio of 150 (range 67-228, 18 patients <200). Thirteen patients had extra-pulmonary ALI. Eleven patients were on vasopressor support at study entry and the level of support was not changed during the study.

The mean PEEP before the SRM was 12.8 cmH_2O (range 10-18) and at the end of the SRM was 16.6 cmH_2O (range 15-22) (Figure 1). Overall, the SRM was well tolerated. Four patients reached a maximum PEEP of less than 40 cmH_2O due to transient oxygen desaturation or transient hypotension during the SRM that resolved after the first PEEP reduction. There were no lasting adverse events associated with the transient decrease in mean arterial pressure (MAP) or SaO_2. There was no barotrauma.

By the end of the SRM, 16 patients (80%) had responded (Figure 2). There was an absolute *reduction* in shunt fraction of 11% *at maximum* PEEP (from 36.3 ± 10%, to 24.7 ± 14%,

P<0.001). The reduction in shunt fraction at this time was associated with no increase in SaO_2 but a large reduction in ScvO2. There was an absolute reduction in shunt fraction of 9% by the end of the study (from baseline 36.3 ± 10%, to 26.4 ± 14%, P<0.001). Two of the four patients who did not tolerate 40 cmH_2O PEEP were responders.

There was no change in mean SaO_2 from baseline to maximum PEEP (SaO_2 at baseline 93.4 ± 2%, and at maximum PEEP 93.2 ± 5%, P = 0.76) but there was a large decrease in mean ScvO2 from 72.7 ± 9 ml% at baseline to 61.8 ± 16 ml% at maximum PEEP (P =0.001, Figure 3). Eight patients had reduced SaO_2 at maximum PEEP. Regardless of SaO_2 changes at maximum PEEP, SaO_2 was significantly improved immediately after the SRM (93.4 ± 2% to 95.8 ± 3, P = 0.007) and remained improved an hour later (96.8 ± 3, P < 0.001). ScvO2 returned to baseline levels after the SRM (Figure 2).

PaO_2/FiO_2 was improved significantly after the SRM (150 ± 42 to 227 ± 100, P = 0.004) and this was maintained an hour later (217 ± 100, P = 0.01, Figure 2).

At maximum PEEP, there was a decrease in mean arterial pressure (78 ± 9 to 67 ± 13 mmHg, P < 0.001) and a 48% increase in $Sa\text{-}cvO_2$ (21 ± 8 to 31 ± 16, P=0.001) suggesting a reduction in cardiac output (Figure 4). At maximum PEEP, there was an increase in CVP from baseline (15 ± 4 to 22 ± 5 cmH_2O, P < 0.001, Figure 5) and a reduction in mean heart rate (95 to 90 BPM, P =0.09). All these haemodynamic variables returned to baseline values by the end of the SRM and were not significantly different from baseline at any other time point.

The lung compliance graph (Figure 6) shows the lung deflating along a different curve with better lung compliance at comparable PEEP levels after maximum PEEP. Patients commenced and completed the SRM on different PEEP levels. Compliance was compared at the first and last PEEP level common to all patients (20 cmH_2O), and a significant improvement in compliance was found after recruitment from 33.9 ± 9.1 to 40.1 ± 11.4 ($P<0.01$, Fig. 6). There was no significant change in alveolar dead space (Vd/Vt %) calculated from end-tidal PCO_2 during or after the SRM. CXRs were improved after the SRM in 90% of patients.

Despite the overall positive effects, not all subjects had an improvement in SaO_2 at maximum PEEP (Figure 7). Twelve patients improved their SaO_2 at maximum PEEP and this was maintained for an hour (Figure 7). Eight patients had a fall in SaO_2 at maximum PEEP with an *increase* in mean shunt fraction at maximum PEEP (Figure 7). Despite this, shunt fraction *decreased* immediately after the SRM and was significantly reduced at completion of the study ($P=0.01$) suggesting that recruitment had occurred. Of clinical significance, five of the patients who desaturated responded to the SRM with > 6.3% absolute reduction in shunt fraction after the SRM.

$ScvO_2$ was decreased at maximum PEEP in patients who desaturated (74 ± 14% to 60 ± 26%, $P=0.006$) and in patients who increased their saturation (73 ± 11% to 64 ± 22%, $P=0.04$, Figure 7). There was an increase in $Sa\text{-}cvO_2$ between baseline and maximum PEEP in the group of patients who improved their oxygen saturation (21 ± 10% to 34 ± 21%, $P = 0.003$). Patients who desaturated had a slightly smaller increase in $Sa\text{-}cvO_2$ which was not significant ($P = 0.177$, Figure 7).

Six patients did not increase their PEEP from baseline after the SRM and had an increase in SaO_2 of 5 ± 1% and an improvement in shunt fraction of 8 ± 2.4%. The remaining patients who had an increase in their PEEP from baseline after the SRM had an increase in SaO_2 of 3 ± 1% and an improvement in shunt fraction of 13 ± 2.3%. There was no significant difference between the groups for SaO_2 (P=0.18) or shunt fraction (P=0.22).

Discussion

This study found that a SRM with descending PEEP titration was associated with significantly improved shunt fraction, oxygenation, CXR and lung compliance in early ALI. We defined a responder as a change in shunt fraction of more that 6.3% and 16 patients (80%) responded to the SRM. Significant but transient circulatory depression occurred with reduced ScvO2 during the SRM that may have prevented lung recruitment from showing improved SaO_2 in eight patients until after the SRM was complete. Patients improved their shunt fraction, oxygenation and compliance regardless of changes in arterial haemoglobin during the SRM. The technique was associated with hypotension in 2 patients and desaturation in another 2 patients at high PEEP that was transient and resolved with a reduction in PEEP to 25cmH_20 as part of the decremental PEEP maneuver. There were no other adverse events.

The 80% success rates in this paper was high when compared with the large randomised studies that have used a RM of 35-40 cmH_2O CPAP for 40 seconds [5, 10, 11, 13], suggesting that either pressure, time or both were may have been suboptimal in these studies [8, 9]. Also, PEEP titration at the end of the SRM in this trial attempted to detect final, optimal PEEP levels individually (mean 16.6, range 15-22 cmH_2O). This is similar to the PEEP used in Amato's original study [10] but is higher than reported in most recent studies [10, 11, 13].

In this study, despite eight patients (40%) transiently dropping their arterial haemoglobin saturation or developing hypotension during the SRM, they still improved shunt fraction, oxygenation and compliance after the SRM. During the SRM, sixteen patients (80%) had improvements in shunt fraction and oxygenation after the SRM. Five patients (25%) whose

SaO_2 increased during the SRM did not have a significant SaO_2 increase until the alveolar pressure exceeded 50 cmH_2O (PEEP 40 cmH_2O). If our patients had a maximum Palv of 45±3 cmH_2O and their SRM terminated for arterial haemoglobin desaturation during the SRM and had a maximum alveolar pressure $\leq$ 45 cmH_2O, as was protocol for studies using 40/40 RMs, six patients would have been withdrawn from the RM and another five would not have responded. This suggests that only nine (45%) would have had a positive response to a 40/40 RM.

One possible explanation for arterial haemoglobin desaturation seen during the SRM may have been due to a fall in ScvO2 (and an increase in Sa-cvO_2) resulting in a reduction in cardiac output. However, there was an additional factor identified that contributed to desaturation. In the patients who increased saturation at maximum PEEP, the increase in Sa-cvO_2 and the reduction in $ScvO_2$ were outweighed by a large reduction in shunt fraction with the net effect of a significant increase in SaO_2.

The patients who decreased saturation at maximum PEEP, despite a smaller increase in Sa-cvO_2, had no reduction or a small increase in shunt fraction at maximum PEEP with the net effect of a significant reduction in SaO_2. This may have been due to failure of recruitment or even worsening of lung collapse due to over distension of adjacent inflated lung regions, but the eventual improvement in shunt fraction and SaO_2 when PEEP was reduced make the occurrence of successful recruitment at maximum PEEP much more likely [18]. A more plausible explanation for the transient increase in shunt fraction in the patients who decreased saturation at maximum PEEP was that while recruitment was occurring, transient alveolar over-distension in inflated regions was redistributing blood flow to less distended regions

thereby increasing intrapulmonary shunt and that this resolved when PEEP was reduced [3, 19].

The limitations of this study include the small sample size and the short period of time for follow up. This study was designed as a pilot trial for a larger randomized controlled trial in this area. Another limitation was the calculation of shunt fraction from $ScvO_2$. Central venous gases were used instead of the mixed venous gas from a pulmonary artery sample as only one patient had a right heart catheter in situ at the time of study enrolment and we did not believe it justifiable to insert PA catheters for this study. The central venous catheter tips were located in or close to the right atrium in all patients and the difference between the CVC and PA samples have been shown to be small [20-23]. Central venous $ScvO_2$ has been accepted as a surrogate for pulmonary artery $ScvO_2$ in other publications [21, 24]. Furthermore, changes in the $ScvO_2$ and its derived variables were more important in the study than the absolute values and were likely to be of the same magnitude. To this end the measurement error was calculated for shunt fraction in this pilot trial and responders defined accordingly. Further limitations were the use of dynamic lung compliance rather than static lung compliance and the calculation of dead space from end tidal CO_2 rather than from timed collection of exhaled gases or measurement from calorimeter. Optimal PEEP was determined using oxygen desaturation as an end point but this method has not yet been validated.

This study was designed as a SRM with decremental PEEP titration to determine the final PEEP level. This was potentially different to the initial PEEP level and as such, we could not prospectively design the study to determine whether the effects were due to the SRM or elevated PEEP. This was a limitation of the study. However, retrospectively, there were six

patients whose optimal PEEP after the SRM was the same as baseline. These patients had a similar increase in oxygen saturation and shunt fraction one hour after the SRM as the group who increased their PEEP suggesting that the SRM itself was a more important factor determining the improvements in oxygenation than the PEEP increase by the end of the study.

Conclusion

SRM to 55 ± 3cmH_2O with optimal PEEP titration was safe and significantly improved SaO_2, shunt fraction, compliance and chest X-ray appearance in 80% patients with early ALI. This may be a more effective RM than the 40/40 RMs used in many other studies. Arterial oxygen desaturation during the SRM occurred in 40% of patients but this did not preclude a positive response to the SRM.

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Table 1. Demographic data

	Sex	Age years	Diagnosis	Apache II	Initial PaO_2/FiO_2	Initial PEEP cmH_2O
1	m	58	pancreatitis	28	76	15
2	m	36	burns	20	158	10
3	f	22	aspiration	37	127	15
4	f	50	burns	17	120	10
5	f	50	burns/pneumonia	17	179	18
6	m	79	trauma	24	167	18
7	m	85	AAA	23	151	15
8	f	49	AML	24	119	15
9	m	54	trauma	13	177	10
10	f	40	pneumonia	19	67	15
11	m	45	aspiration	25	205	12.5
12	m	46	AAA	20	151	10
13	f	36	burns	16	175	10
14	m	58	pneumonia	29	153	15
15	m	69	burns	24	137	12.5
16	m	74	aspiration	13	228	12.5
17	f	49	aspiration	12	87	15
18	m	43	trauma	4	107	10
19	m	57	trauma	14	180	10
20	f	35	pneumonia	23	164	10

m= male, f = female, AML=acute myeloid leukaemia, AAA=ruptured abdominal aortic aneurysm repair, PEEP= positive end expiratory pressure

Figure Legends

Figure 1
Staircase recruitment maneuver represented as airway pressure versus time with summary data (N= the number of patients who tolerated airway pressure at each time point). Lower heavy line is PEEP level. Upper fine line is pressure control level. Error bars represent the range of initial PEEP levels and of pressure control levels at each level of PEEP

Figure 2
Shunt fraction and PaO_2/FiO_2 during and for an hour after the staircase recruitment maneuver (*P<0.01 compared with baseline)

Figure 3
Arterial and venous oxygen saturation during and for an hour after the staircase recruitment maneuver (*P<0.01 compared with baseline)

Figure 4
Mean arterial pressure (MAP) and central arterial -venous oxygenation difference ($Ca\text{-}cvO_2$) during and for an hour after the staircase recruitment maneuver (*P<0.01 compared with baseline)

Figure 5
Heart rate and central venous pressure during and for an hour after the staircase recruitment maneuver (*P<0.01 compared with baseline)

Figure 6
Dynamic lung compliance at baseline, during and for an hour after the staircase recruitment maneuver. Dotted line is comparison of compliance at $20cmH_20$ PEEP before and after the SRM (*P<0.05)

Figure 7
A comparison of changes between saturators and desaturators in arterial and venous oxygen saturation, shunt fraction and central arterial -venous oxygenation difference (*P<0.01 compared with baseline). pH and temperature constant.

Figure 1

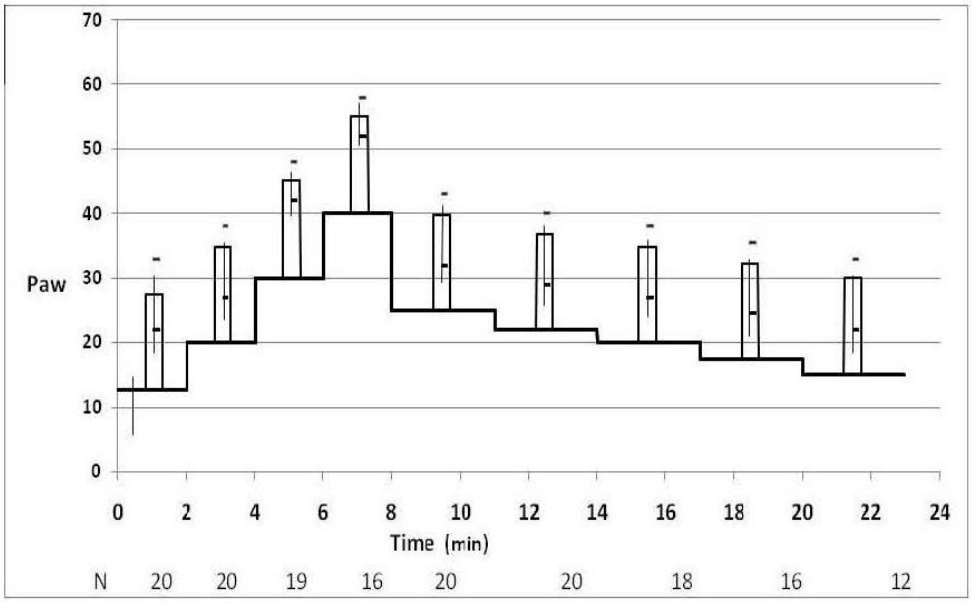


Figure 2

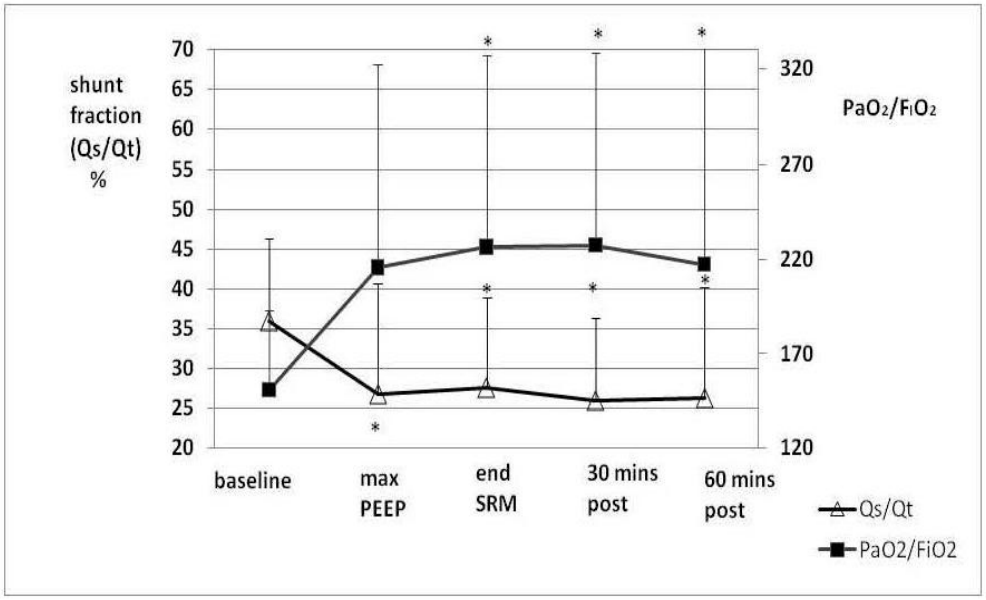


Figure 3

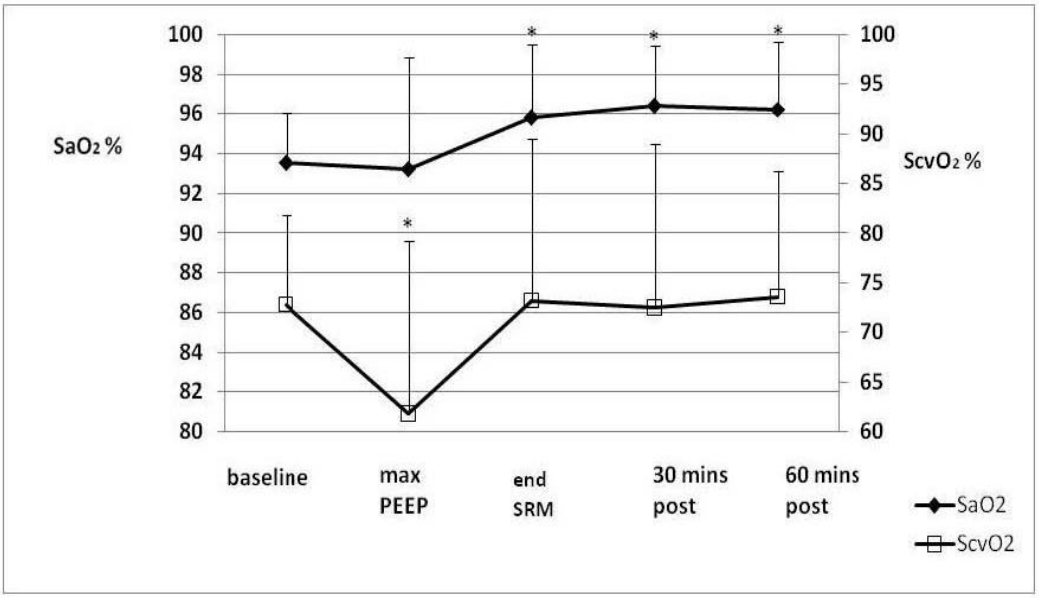


Figure 4

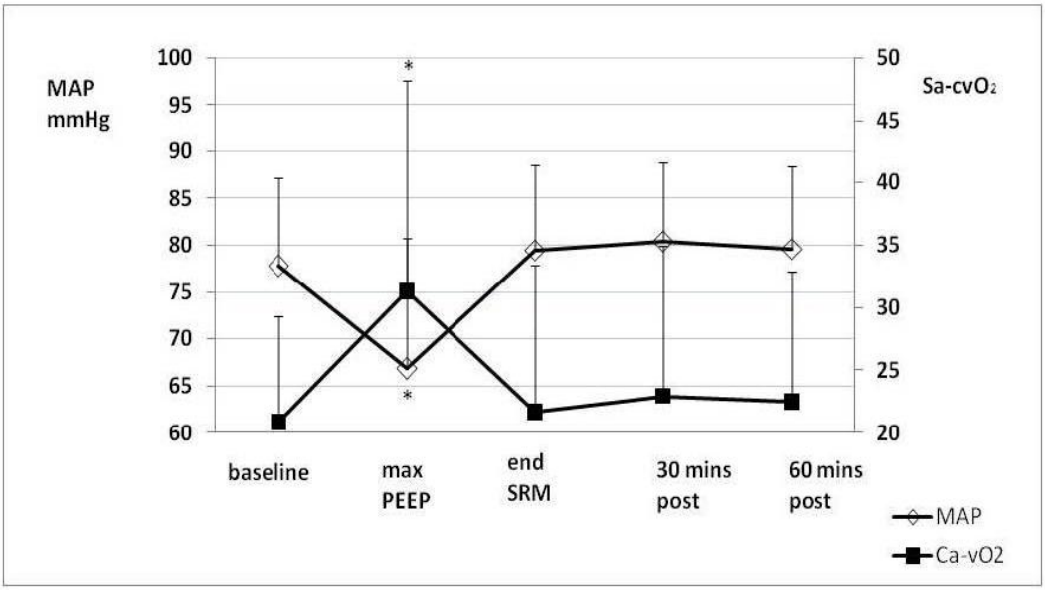


Figure 5

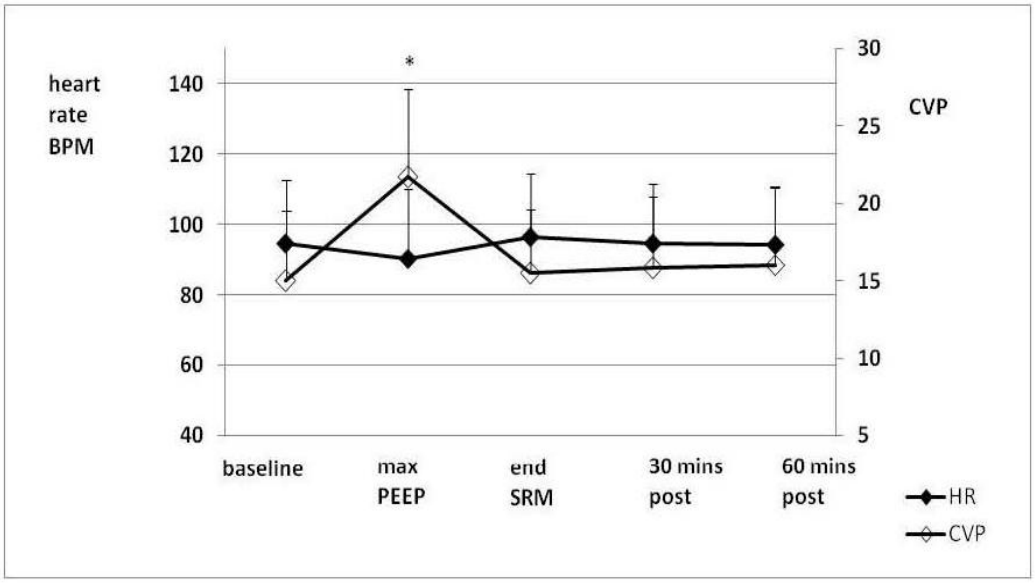


Figure 6

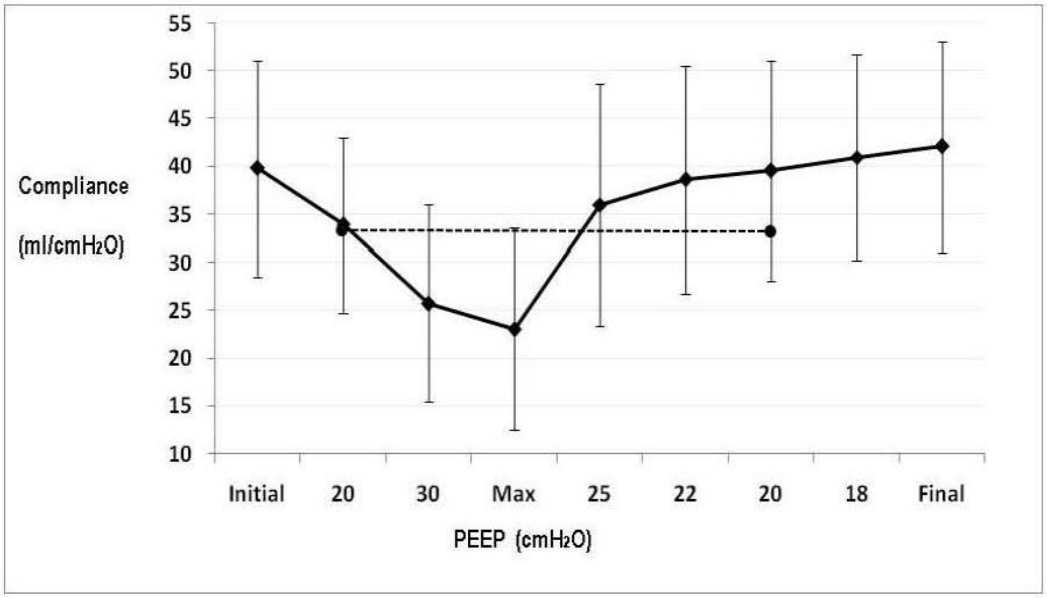
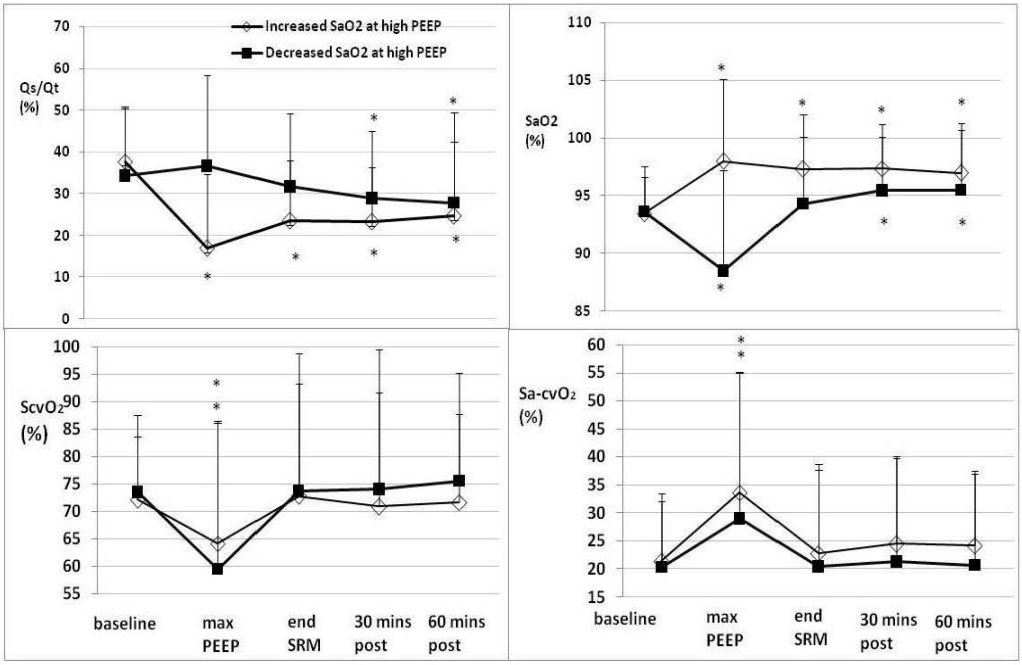


Figure 7


Increased SaO2 at high PEEP
Decreased SaO2 at high PEEP
Qs/Qt (%)
SaO2 (%)
ScvO2 (%)
Sa-cvO2 (%)
baseline
max PEEP
end SRM
30 mins post
60 mins post

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Chapter 4 (Manuscript) Comparison of forehead Max-Fast pulse oximetry sensor with finger sensor at high positive end-expiratory pressure in adult patients with acute respiratory distress syndrome

4.1 Declaration for Thesis Chapter 4

Declaration by candidate

In the case of Chapter 4 the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study concept and design, data collection and analysis, writing of manuscript	70

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Anne Holland	Revision of manuscript	
Jenny Keating	Assistance with data analysis, revision of manuscript	
David Tuxen	Study concept and design, revision of manuscript	

Candidate's Signature	[redacted]	**Date 20/07/10**

Declaration by co-authors

The undersigned hereby certify that:

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

Location(s)	The Alfred Hospital, Melbourne

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

Name	**Signature**	**Date**
Anne Holland	[redacted]	20/07/10
Jenny Keating	[redacted]	20/07/10
David Tuxen	[redacted]	20/07/10

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Comparison of forehead Max-Fast pulse oximetry sensor with finger sensor at high positive end-expiratory pressure in adult patients with acute respiratory distress syndrome

C. L. HODGSON*, D. V. TUXEN†, A. E. HOLLAND‡, J. L. KEATING§

Intensive Care Unit, Alfred Hospital, Melbourne, Victoria, Australia

SUMMARY

In the critical care setting it may be difficult to determine an accurate reading of oxygen saturation from digital sensors as a result of poor peripheral perfusion. Limited evidence suggests that forehead sensors may be more accurate in these patients. We prospectively compared the accuracy of a forehead reflectance sensor (Max-Fast) with a conventional digital sensor in patients with acute respiratory distress syndrome during a high positive end-expiratory pressure (PEEP) recruitment manoeuvre (stepwise recruitment manoeuvre).

Sixteen patients with early acute respiratory distress syndrome were enrolled to evaluate the blood oxygen saturation during a stepwise recruitment manoeuvre. PEEP was increased from baseline (range 10 to 18) to 40 cmH_2O, then decreased to an optimal level determined by individual titration. Forehead and digital oxygen saturation and arterial blood gases were measured simultaneously before, during and after the stepwise recruitment manoeuvre at five time points.

Seventy-three samples were included for analysis from 16 patients. The S_aO_2 values ranged from 73 to 99.6%. The forehead sensor provided measurements that deviated more from arterial measures than the finger sensor (mean absolute deviations 3.4%, 1.1% respectively, P=0.02). The greater variability in forehead measures taken at maximum PEEP was reflected in the unusually large precision estimates of 4.24% associated with these measures. No absolute differences from arterial measures taken at any other time points were significantly different.

The finger sensor is as accurate as the forehead sensor in detecting changes in arterial oxygen saturation in adults with acute respiratory distress syndrome and it may be better at levels of high PEEP, such as during recruitment manoeuvres.

Key Words: pulse oximetry, sensors, digital, forehead, positive end-expiratory pressure, acute respiratory distress syndrome

Monitoring oxygen saturation by pulse oximetry (SpO_2) is a common method of assessing respiratory status in critically ill patients[1,2]. However, hypoperfusion may reduce pulse waveform and it is widely believed that any condition that causes hypoperfusion in the body part attached to the sensor may reduce the ability of the pulse oximeter to accurately read the oxygen saturation[3]. If reduced pulsatile flow impairs light absorption this may result in inaccurate oxygen saturation values and false alarms. There has also been questionable accuracy of pulse oximetry while patients are receiving high levels of positive end-expiratory pressure (PEEP), for example during a recruitment manoeuvre[4]. It is possible that the high intrathoracic pressure caused by high PEEP results in reduced cardiac output and dampened arterial waves which make it difficult to accurately absorb light. If this occurs it may reduce the accuracy of the oxygen saturation value.

The Max-Fast sensor is designed for use on the patient's forehead over the occipital artery[5]. It may have an advantage over the finger sensors because the forehead site is less vulnerable to peripheral vasoconstriction and is reported to maintain signals longer than the digit sensor during conditions of poor peripheral perfusion. The forehead is also described as a lower motion site in the product information and the opaque forehead sensors tolerate

*B.App.Sc (Physio), M. (Research), Ph.D. Candidate, Senior Intensive Care Unit Physiotherapist, Alfred Hospital, Monash University.
†M.B., B.S., F.R.A.C.P., Dip.D.H.M., M.D., F.J.F.I.C.M., Senior Intensivist, Department of Intensive Care.
‡B.App.Sc. (Physiotherapy), Ph.D., Associate Professor of Physiotherapy, La Trobe University, Alfred Hospital.
§Ph.D., B.App.Sc. (Physiotherapy), Post. Grad. Dip. Manip. Physiotherapy, Head of Department of Physiotherapy, Monash University.

Address for correspondence: Mrs C. Hodgson, Intensive Care Unit, Alfred Hospital, Prahran, Vic. 3181.

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high ambient light settings. It is reported to have SpO_2 accuracy comparable to the adult finger sensor of ± 2 saturation points.

Studies have compared finger and forehead sensor sensitivity and accuracy in infants[6], during anaesthesia, mechanical ventilation[7] and in patients with low cardiac index[3]. The forehead sensor was found to be at least as accurate as the finger sensor in all trials. No research was identified that compared the forehead sensor to the finger sensor in patients with acute respiratory distress syndrome (ARDS). Patients with ARDS have reduced oxygenation and can have peripheral hypoperfusion which may reduce the accuracy of a finger sensor.

This study was a head-to-head comparison of forehead (Max P, Nellcor, Tyco Healthcare, Pleasanton, CA, USA) versus finger (Fast-SpO_2, Philips Medical Systems, Andover, MA, USA) pulse oximetry in patients with ARDS at varying PEEP levels. The aim was to determine which of the two non-invasive methods produces measurements of oxygen saturation that most closely approximate the arterial blood gas co-oximetry (S_aO_2) as the gold standard.

MATERIALS AND METHODS

This was a prospective observational study comparing measurements of blood oxygen saturation obtained under three different methods in patients with ARDS. Sixteen forehead sensors were donated to the study. Data were obtained from 16 consecutive patients with early ARDS[8] who were mechanically ventilated in intensive care. Inclusion criteria were: older than 15 years, mechanically ventilated with an arterial line in the radial artery for blood gas sampling, invasive blood pressure monitoring and a central venous catheter in situ. Patients were excluded if they had an intercostal catheter with an air leak, pneumothorax on chest X-ray, bronchospasm on auscultation, raised intracranial pressure, acute pulmonary oedema, mean arterial pressure less than 60 mmHg, unstable arrhythmias or cardiac compromise. The study was approved by the hospital and university ethics committees. Written informed consent was gained from the person responsible (next of kin).

Patients were entered into the study when ventilation, sedation and circulatory resuscitation were complete and stabilised. Patients not in pressure-controlled ventilation were converted to pressure-controlled ventilation (mean 15, range 7 to 18 cmH_2O) on the same level of PEEP. The fraction of inspired oxygen was reduced to achieve oxygen saturation of 90 to 92% so that an increase in SpO_2 could be clearly observed.

For the stepwise recruitment manoeuvre (SRM), the PEEP was increased from baseline to 20, 30 and 40 cmH_2O every two minutes, then reduced to 25, 22.5, 20, 17.5 or 15 cmH_2O every three minutes until a decrease in S_aO_2 of 1 to 2% from maximum S_aO_2 was detected (Figure 1). The SRM increases in PEEP did not continue if the heart rate was less than 60 or greater than 140 beats per minute, a new arrhythmia appeared, systolic blood pressure was less than 80 mmHg or if pulse oximeter saturation (SpO_2) was less than 85%. Measurements of SpO_2 from both the forehead and finger sensors were taken at baseline, each PEEP level and at 30 and 60 minutes after the SRM. Arterial blood gases were taken at baseline, maximum PEEP, end of the SRM and 30 and 60 minutes after the SRM.

Blood oxygen saturation was simultaneously measured with forehead and finger sensors and arterial oxygen saturation measures taken with an arterial blood sample through the existing arterial line. Arterial blood gas samples were taken in the supine position and then immediately run through the blood gas analyser (Rapid Lab 1265 Blood Gas Analyser, Siemens Medical Solutions Diagnostic, Tarrytown, NY, USA). All data were collected at the Alfred Hospital intensive care unit. Measurement of oxygen saturation were obtained with the finger sensor connected to the Philips module (Fast-SpO_2, Philips Medical Systems, Andover, MA, USA) on the opposite hand to the arterial line and from the disposable forehead sensor (Max P, Nellcor, Tyco Healthcare, Pleasanton, CA, USA) connected to the recommended Oximax N-600 pulse oximeter. The sensors were connected to the oximeter recommended by the manufacturer in order to obtain the most accurate reading possible in the clinical setting. Both the Philips finger sensor and module and the forehead sensor and Oximax N-600 pulse oximeter have a selectable fast-averaging mode (two to three seconds) to track changes in saturation and its accuracy is quoted as 70 to 100% ± 2 digits.

DATA ANALYSES

The first analysis examined differences between measurements. Three sets of paired data were considered:

1. finger sensor and arterial oxygen,
2. forehead sensor and arterial oxygen,
3. finger sensor and forehead sensor.

Bias indicates the average deviation from the reference standard (either positive or negative). If

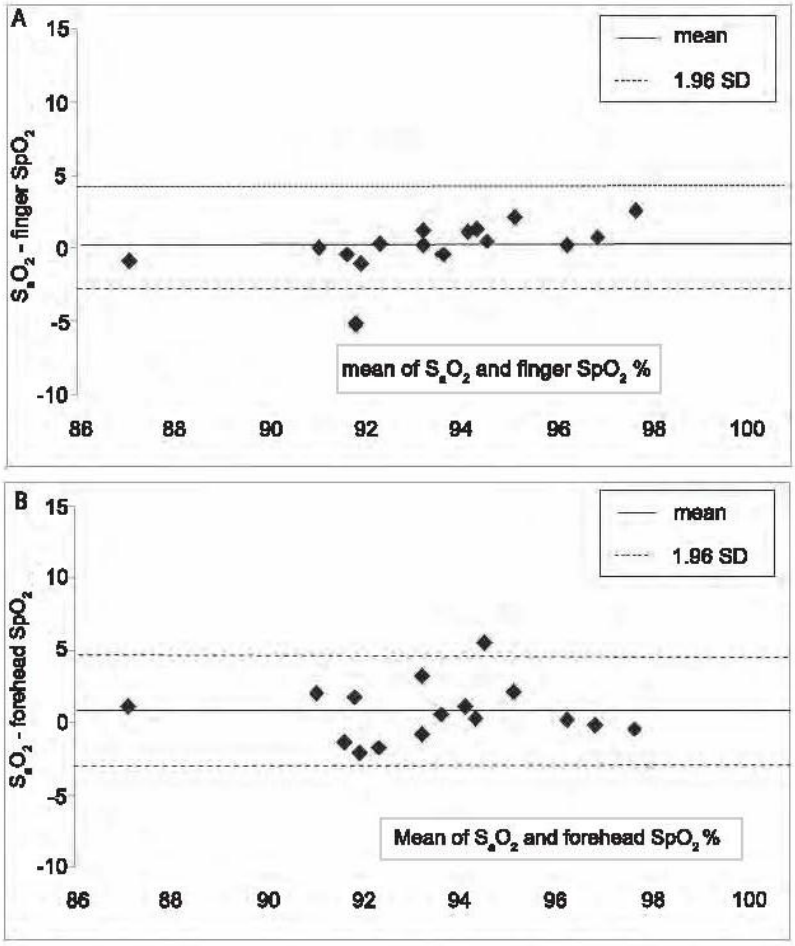

FIGURE 1: A) Mean difference of the finger SpO_2 and S_aO_2 at baseline.
B) Mean difference of forehead SpO_2 and S_aO_2 at baseline.

one subject shows lower scores with pulse oximetry compared to arterial measures, while another shows higher scores for pulse oximetry compared to arterial measures, the overall bias estimates may approach zero. Absolute bias measurements on the other hand indicate the magnitude of deviation from the reference standard regardless of direction.

For each paired set of measurements the following analyses were conducted.

1. Repeated measures t-tests for systematic differences on each of the five test occasions.
2. The differences between the readings from the forehead or finger sensor and the arterial saturation were calculated and, using those values, Bland-Altman analysis was performed. Bias (the mean difference between the values of the gold standard and either the finger or forehead sensor) and precision (1.96 standard deviation of the bias) were calculated for the finger SpO_2 versus S_aO_2 differences and the forehead SpO_2 versus S_aO_2 differences on each of the five test occasions.
3. Random differences between arterial blood gas and the two alternative measurement methods were assessed using a repeated measures t-test comparing the absolute difference scores of the gold standard to the finger and forehead sensor on each of the five test occasions.

For each analysis alpha was set at 0.05. We performed a post-hoc sample size calculation based on the mean and standard deviation that found the probability was 85% that the study would detect a treatment difference at a two-sided 5% significance level, if the true difference between the means was 2%.

RESULTS

A total of 16 patients were studied for a total of 80 sampling periods. Both the forehead and the finger sensor were well tolerated and did not interfere with usual care. A reliable signal could not be obtained from the finger sensor during one sampling period when severe desaturation at maximum PEEP occurred during the recruitment manoeuvre (S_aO_2 73%, forehead SpO_2 71%). Data collection did not occur from both of the pulse oximeters during another two sampling periods due to interruption because of concurrent unrelated procedures. Therefore 73 samples were included for analysis.

Diagnoses varied (Table 1). Participants were aged 22 to 84 years (mean 52.6 years). The mean PEEP at baseline was 13 cmH_2O and the mean maximum PEEP during the recruitment manoeuvre was 36.9 cmH_2O.

S_aO_2 values for the 73 samples ranged from 73 to 100%. Mean oxygen saturation values at baseline for the clinical reference standard (S_aO_2) and non-invasive sensors (finger and forehead) are shown in Table 2.

Differences and limits of agreement between the sensors (finger, forehead) and the reference standard (arterial) were presented as bias ± precision at baseline, maximum PEEP and immediately after the recruitment manoeuvre. These are shown in Table 2.

TABLE 1
Population characteristics

Patient	Gender	Age	Diagnosis	Initial P_aO_2/FiO_2	Initial PEEP	Maximum PEEP
1	F	22	aspiration	127	15	20
2	F	50	burns	120	10	40
3	F	55	burns	179	18	40
4	M	79	trauma	167	18	40
5	M	84	AAA	151	10	30
6	F	48	AML	119	15	40
7	M	54	trauma	177	10	40
8	F	39	pneumonia	67	15	40
9	M	45	aspiration	205	12.5	40
10	M	46	AAA	151	10	30
11	F	35	burns	175	10	40
12	M	60	pneumonia	153	15	40
13	M	59	burns	137	12.5	40
14	M	73	aspiration	228	12.5	40
15	F	49	aspiration	87	15	30
16	M	43	trauma	107	10	40

PEEP=positive end-expiratory pressure, M=male, F=female, AAA=abdominal aortic aneurysm, AML=acute myeloid leukaemia.

TABLE 2
Bias and precision during the PEEP recruitment manoeuvre

Oxygen saturation (%)	Range	Mean	SD	Bias	Precision	*P* value for t-test of differences between S_aO_2 and finger/pulse oximetry	Random difference from S_aO_2 (%)
Baseline							
Arterial blood gas	87.1-97.6	93.4	2.5	NA	NA		
Finger SpO_2	88-97	93.3	2.2	0.14	1.74	0.75	1.14
Forehead SpO_2	86-98	92.7	3.2	0.71	1.95	0.17	1.53
Maximum PEEP (during recruitment manoeuvre)							
Arterial blood gas sample	73-99.6	93.4	7.6	NA	NA		
Finger SpO_2	80-100	94.9	5.8	-0.09	1.74	0.85	1.11
Forehead SpO_2	71-100	91.6	7.5	1.78	4.38	0.11	3.35
End RM							
S_aO_2	86-99.5	96.3	3.9	NA	NA		
Finger SpO_2	89-100	97.1	3.8	*-0.74	1.24	0.03	1.09
Forehead SpO_2	86-100	95.9	4.5	0.45	2.08	0.4	1.18

SD=standard deviation, S_aO_2=oxygen saturation from arterial blood gas co-oximetry, NA=not applicable, SpO_2=oxygen saturation from pulse oximetry, PEEP=positive end expiratory pressure, RM=recruitment manoeuvre.
* Negative values indicate that mean scores are higher than the reference standard.

Bias is defined as systematic differences between measurements obtained with finger or forehead and the reference standard[9,10]. No statistically significant bias was observed when either finger or forehead was compared to arterial measures of oxygen saturation, with the exception of a very small systematic difference between finger measures and arterial measures taken immediately after recruitment manoeuvre. In this instance, finger measures were systematically greater by less than 1% (a difference of 0.74%) which is not considered clinically significant.

When absolute differences between each of the two alternative approaches to measuring blood oxygen saturation and the reference standard were compared, a significant difference was observed at maximum PEEP. The forehead sensor provided measurements that deviated more from arterial measures than did the finger sensor (mean absolute deviations 3.4%, 1.1% respectively, $P=0.02$). The greater variability in forehead measures taken at maximum PEEP is also reflected in the unusually large precision estimates associated these measures (4.38%, see Table 2 and Figure 2). No absolute

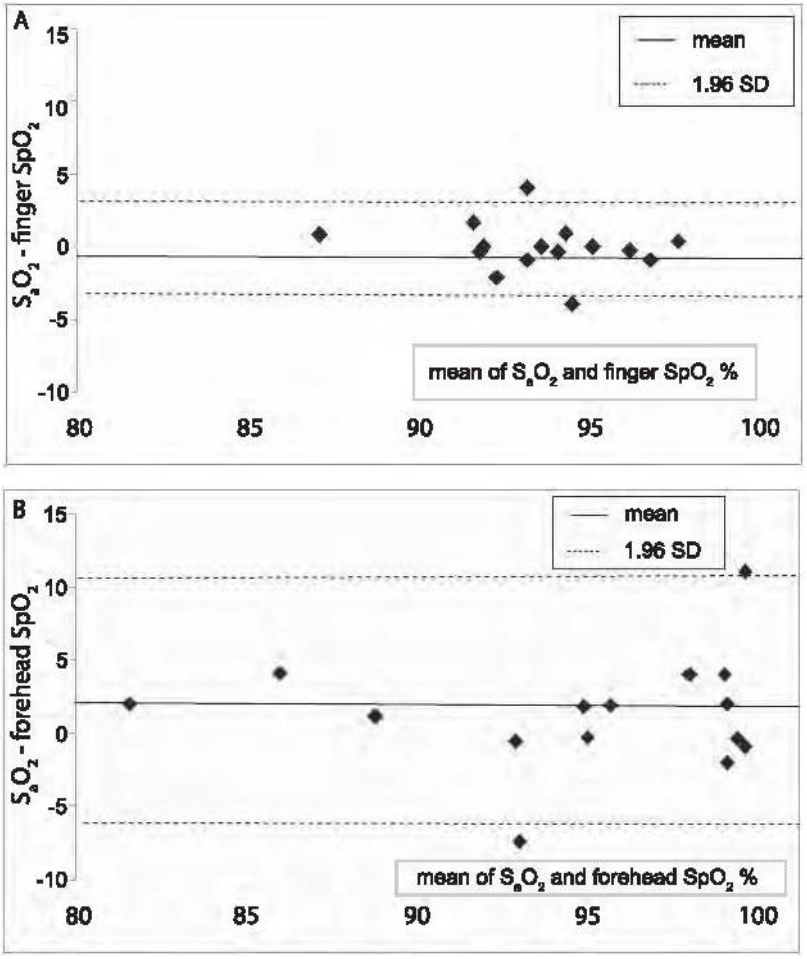

FIGURE 2: A) Mean difference of finger SpO_2 and S_aO_2 at PEEP 40 cmH_2O.
B) Mean difference of the forehead SpO_2 and S_aO_2 at PEEP 40 cmH_2O.

differences from arterial measures taken at any other time points were significantly different (Figures 1 and 3).

DISCUSSION

This study compared the accuracy of a forehead pulse oximetry sensor with a digital sensor at varying PEEP levels in patients with ARDS. The hypothesis was that the forehead sensor would more accurately measure arterial oxygen saturation due to placement of the sensor over a central artery which was not prone to hypoperfusion as were the fingers. However, our findings did not support this hypothesis.

At baseline, where the mean PEEP was 12.8 cmH_2O (range 10 to 18 cmH_2O), there were no differences in measures of oxygen saturation obtained using any method. The differences in oxygen saturation between the arterial blood gas and the forehead sensor appeared to increase as the oxygen saturation decreased. It is important to note that there was drop-out of a reliable signal from one patient with severe desaturation using the finger

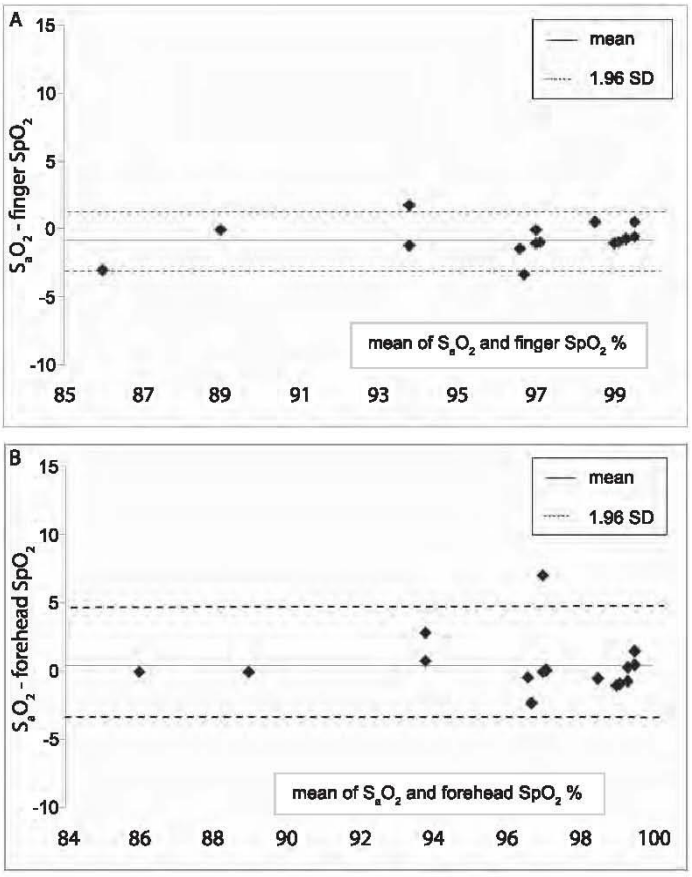

FIGURE 3: A) Mean difference of finger SpO_2 and S_aO_2 after stepwise recruitment manoeuvre. B) Mean difference of forehead SpO_2 and S_aO_2 after stepwise recruitment manoeuvre.

sensor at maximum PEEP. A drop-out is in itself an important indication that the equipment may not be reliable under the circumstances and may need to be considered as a potential problem with the finger sensor. However it occurred in one patient only and the effect of high PEEP on drop-out needs to be confirmed in a larger trial. Overall, 15 patients were included in the analysis at maximum PEEP.

Although sampling error might account for the significantly greater deviation of forehead measures from arterial measures at maximum PEEP (mean PEEP at maximum = 38 cmH_2O), every subject had the same or greater absolute error in the reading of oxygen saturation at maximum PEEP when the forehead sensor was compared to the finger sensor. This potential for error at high PEEP should also be re-examined in a larger trial.

The random variability in forehead measures taken at maximum PEEP were of a considerably greater magnitude (mean absolute difference = 3.35%, range -7 to +11) than those for finger measures (mean absolute difference = 1.11%, range -4 to +4). In addition, a test comparing absolute variation from the reference standard found significantly greater variations for forehead measures compared to finger measures. Although the bias is within the error limits of the device (2%), meaning that it does not consistently over- or under-read at high PEEP, the limits of agreement are very wide and outside the error limits of the device. So for any forehead reading, there is 95% probability that the true saturation lies within 4% either side of the reading.

At maximum PEEP, every subject showed greater error in the reading of oxygen saturation from the forehead sensor compared to the finger sensor. It has been hypothesised that the increase in PEEP and the subsequent increase in intrathoracic pressure and reduced cardiac output may cause a dampening of the arterial pulse wave, such that the sensor has difficulty determining an arterial wave from a venous wave. It is unclear why this would occur with the forehead sensor and not the finger sensor, although perhaps it is more apparent with the arteries that are closer to the thorax. Clinically, the measurement of oxygen saturation from a non-invasive device may be used to start and stop a procedure such as a recruitment manoeuvre[2,4] and may be used to measure clinical effectiveness[11] after such a treatment. The use of pulse oximetry with a forehead probe must be re-assessed based on the findings of this study, as the precision at high PEEP is not adequate to accurately evaluate the effects of the procedure.

At levels of PEEP that are usual practice (10 to 25 cmH_2O), the measurement of arterial oxygen saturation was within an acceptable range of ±2% from both the forehead and the finger sensor. Both methods are quick and easy to apply and the decision may be determined primarily by cost. At the time of this publication, in our intensive care unit the cost of the forehead sensors was higher than that of the finger sensors.

One of the obvious limitations of this study was that the probes and oximeters were different. This makes it difficult to extrapolate the results due simply to the difference in the sensors. However, the pulse oximeters were recommended by the manufacturer as the most accurate model to be used with the particular sensor under investigation and it was decided that the test should reflect clinical practice in the intensive care unit. The other limitation of this study was the small sample size. Although the numbers were small, the random error was higher in every patient at maximum PEEP with the forehead sensor and this observation certainly warrants closer evaluation in a larger trial.

CONCLUSION

The Philips finger sensor was as accurate as the Max-Fast forehead sensor in detecting changes in arterial oxygen saturation in adults with ARDS at varying PEEP levels. This preliminary work indicates that finger sensors may be more accurate than forehead sensors at high levels of PEEP, such as during recruitment manoeuvres.

ACKNOWLEDGEMENT

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Chapter 5 Digital Chest x-ray as an outcome in ICU: reliability and validity (submitted, Intensive Care Medicine, 2010)

5.1 Declaration for Thesis Chapter 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study concept and design, data collection and analysis, writing of manuscript	70

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

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
Anne Holland	Revision of manuscript	
Jenny Keating	Assistance with data analysis, revision of manuscript	
David Tuxen	Study concept and design, data collection, revision of manuscript	
Michael Bailey	Revision of manuscript	
Dinesh Varma	Revision of manuscript	
Ken Thomson	Revision of manuscript	

Candidate's Signature	[redacted]	**Date 20/07/10**

Declaration by co-authors

The undersigned hereby certify that:

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

Location(s)	The Alfred Hospital, Melbourne

Name	**Signature**	**Date**
Anne Holland	[redacted]	20/07/10
Jenny Keating	[redacted]	20/07/10
David Tuxen	[redacted]	20/07/10
Michael Bailey	[redacted]	20/07/10
Dinesh Varma		
Ken Thomson		

Reliability and validity of change in portable digital chest x-rays in intensive care

Mrs Carol L Hodgson BAppSc (Physiotherapy); PostGrad Dip (Cardio); M(Research); PhD Candidate Monash University; Senior ICU Physiotherapist, Alfred Hospital. c.hodgson@alfred.org.au

A/Prof David V Tuxen MB BS, FRACP, Dip DHM, MD, FJFICM, FCICM. Senior Intensivist, Department of Intensive Care, The Alfred Hospital, Melbourne. dtuxen2@bigpond.com

A/Prof Anne E Holland BAppSc (Physiotherapy); PhD. Associate Professor of Physiotherapy, La Trobe University / Alfred Health. a.holland@alfred.org.au

A/Prof Michael Bailey PhD, MSc(statistics), BSc(hons) Statistical Consultant/Senior Research Fellow ANZIC-RC Department of Epidemiology & Preventive Medicine School Public Health & Preventive Medicine, Monash University Alfred Hospital. michael.bailey@med.monash.edu.au

Prof Thomas Ken Thomson MD, FRANZCR, Director Radiology Alfred Campus, Monash University k.thomson@alfred.org.au

Dr Dinesh Varma MB BS, FRANZCR, Deputy Director Radiology and Head of Emergency Radiology, The Alfred, Hospital, Hon Senior Lecturer, Dept of Surgery, Monash University, Melbourne. d.varma@alfred.org.au

Prof Jenny L Keating PhD; BAppSc(Physiotherapy); PostGrad Dip Manip Physiotherapy; Head of Department of Physiotherapy, Monash University. jenny.keating@med.monash.edu.au

All work was performed at the Alfred Hospital, Melbourne, Australia.

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Reprints will be ordered as a copy for each author.

Correspondence to:

Carol Hodgson

c.hodgson@alfred.org.au

Department of Intensive Care, The Alfred, Commercial Rd, Prahran, VIC, Australia, 3181

fax 613 9076 2702

phone 613 9076 3450

Statistical support from the ANZICS-RC, Monash University, Melbourne

Short running head: Digital chest x-ray

Key Words: chest x-ray, adult respiration, artificial, intensive care

Abstract

The aim of this study was to evaluate the capacity of digital chest x-rays to detect changes in lung area and lung radiolucency in mechanically ventilated patients with acute respiratory distress syndrome (ARDS).

28 patients who had digital chest X-rays before and after a recruitment manoeuvre (RM) with subjective improvement and 40 patients who had digital chest X-rays before and after a central venous catheter insertion (no change subjectively) were evaluated. Chest X-rays were viewed using GE digital radiology technology (GE AMX-4 General Electric Company Medical Systems, Milwaukee, Wisconsin, USA). The outline of each lung was traced electronically and computer generated area and radiolucency scores of the outlined region were recorded. Test-retest reliability was assessed using chest X-rays before and after central venous catheter insertion. Inter-rater reliability was assessed using the same 40 chest X-rays, examined in random order, by two clinicians.

The RM, which was associated with significant improvements in gas exchange, compliance and subjective lungfield radiolucency, was also associated with significant increases in lung area (right $P<0.001$, left $P=0.002$) and significant increases in radiolucency (right $P=0.03$, left $P=0.02$). Re-test reliability for lung area was good (Intra-class correlation co-efficient (ICC)= 0.96) but lower for lung radiolucency (ICC = 0.41). Inter-rater reliability values were good for both lung area (ICC =0.91) and radiolucency (ICC =0.99).

Lungfield area and radiolucency measurements from portable digital chest X-rays can be used to objectively quantify radiological change. Lung area was more reliable than radiolucency measurements. Clinicians were very accurate in interpreting individual images.

Introduction

Portable antero-posterior chest X-rays are performed daily in most patients in intensive care. It is safer and more convenient than transporting a critically ill patient to a radiology department. In an inpatient setting, portable chest X-rays are more common than the standard postero-anterior and lateral chest X-rays performed in the radiology department. Traditionally, the portable chest X-ray is subject to technical errors: errors of exposure, inconsistency and variability of radiographic technique, grid cut-off, apices cut off, rotation and respiratory motion [1]. It has been considered difficult to use the chest X-ray as an objective measure of improvement or deterioration due to technical errors and subjective reporting.

The gold standard in the assessment of lung volume, lung density and the physiological effects of treatment modalities in ICU is computer assisted tomography [2, 3]. Significant changes in lung volume of patients with acute respiratory distress syndrome (ARDS) have been assessed by high resolution computerised tomography (HRCT) in several studies before and after a recruitment manoeuver (RM) [4, 5], however the technique is expensive, time consuming, labour intensive and has the increased risk associated with patient transport. It is valuable to have a bedside technique to quantify the effect of treatment modalities if it is reliable and adequately sensitive to important change [6]. Even given the limitations of portable chest X-rays, it would be of significant clinical value if digital radiology could reliably quantify changes in lung area and radiolucency. There could be a high degree of confidence that an increase in lung area on chest X-ray would be associated with an increase in lung volume.

A digital radiograph consists of individual picture elements (pixels)[7]. Each pixel can have a grey scale value assigned that increases in proportion with the intensity of radiation detected. Thus it is a radiolucency value. A region of interest (ROI), such as the lungfield, can be outlined on the image and digital measures of area and average radiolucency can be computed automatically. Comparison of pixel measures at different time points can only be made under similar exposure conditions, for example amperage (mA), and time product, X-ray energy, kilovoltage (kVp) and focal film distance and with the patient in the same position and end-inspiratory time.

In a recent study [8] of a recruitment manoeuvre in patients with ARDS, we found that significant improvements in lung gas exchange and compliance were associated with significant improvements in blinded qualitative assessment of lung field density on plain portable digital chest X-rays performed before and after the manoeuvre.

The aim of this study was to evaluate the capacity of digital chest x-rays to detect changes in lung area and radiolucency in mechanically ventilated patients with acute respiratory distress syndrome (ARDS). To do this, we measured lung field area and radiolucency on chest X-rays before and after a recruitment manoeuvre in patients with ARDS, where a change was expected, and in the same patient group before and after a central venous catheter insertion, where no change was expected.

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Methods

Participants

Forty consecutive mechanically ventilated patients with early ARDS as defined in the 1998 consensus conference [9] were included in the study. Twenty-eight of these patients took part in studies examining the clinical effects of a recruitment maneuver (RM) [8]. Inclusion criteria were age greater than 15 years, an arterial line for blood gas sampling and invasive blood pressure monitoring and central venous catheter (CVC) in situ. Patients were excluded if they had an intercostal catheter with an air leak, pneumothorax on chest x-ray, bronchospasm on auscultation, raised intracranial pressure, acute cardiogenic pulmonary oedema, mean arterial pressure less than 60mmHg, unstable arrhythmias or cardiac compromise. These studies were approved by the hospital and university Ethics Committees. Written informed consent was gained from the person responsible (next of kin).

Forty CVC lines were replaced during the study period and a chest X-ray was performed before and immediately after the CVC line change which is part of routine safety practice. There were no clinical reasons for any systematic changes in chest X-rays over this short time frame. These chest X-rays were assessed for test-retest error in the estimates of chest X-ray area and radiolucency scores. If any barotrauma was reported, then the chest X-ray was excluded from the re-test reliability assessment study.

The 28 patients who had a RM also had a chest X-ray immediately before and after the RM. For the RM, patients were placed in pressure control ventilation (PCV 15 ± 3 cmH2O), PEEP was increased in increments to a maximum of 40 cmH2O and then reduced in increments to a minimum of 15 cmH2O [8]. In the first 20 patients this resulted in a final increase in mean PEEP from 12.8 cmH2O (range 10-18) to 16.6 cmH2O (range 15-22), improvements in mean SaO_2 (93.4 ± 2% to 95.8 ± 3%, P= 0.007), PaO_2/FiO_2 (150 ± 42 to 227 ± 100, P=0.004), shunt fraction (36.3 ± 10%, to 24.7 ± 14%, P<0.001), and in blinded qualitative assessment of lungfield opacity [8].

The chest X-ray procedures were standardised for all patients. Radiographers were blinded to the study and were instructed to take digital chest X-ray for all participants in upright sitting with the bed head at 60 degrees to the horizontal at full inspiration. For each patient the distance between the patient and the machine was measured and standardised for repeated measurements. The exposure of the film was consistent for each participant.

Chest x-rays were viewed using GE digital radiology technology (GE AMX-4 General Electric Company Medical Systems, Milwaukee, Wisconsin, USA) and the outline of each lung was traced and the area and radiolucency score for that x-ray region was computed (Figure 2). Each pixel in the ROI had a grey scale value assigned that increases in proportion with the intensity of radiation detected. The radiolucency score was based the average pixel value calculated by the General Electric Picture Archive and Communication System (GE PACS, GE Healthcare, Waukesha, WI 53188,U.S.A.). Using this method, a normal lung field may score approximately 3000 ± 170 and a very opaque lung field may score 1500 ± 50. The lung area in the selected ROI is measured 2 dimensionally in sq/mm. The assessors were instructed to electronically outline the right lung from the inner rib edges of the lateral rib cage, the diaphragm and the mediastinal border. For the study comparing chest X-ray before-after a recruitment manoeuver the left lung was also measured both including and excluding the cardiac silhouette. The assessor was given one practice trial before commencing the study. (Figure 1)

Inter-rater reliability

Chest X-rays from the first 20 consecutive study participants entered into the study were placed an electronic file and viewed by the chief radiologist and an intensive care clinician in separate rooms on the same day. The outline of each right lung was traced electronically as described above. The computer generated scores of lung radiolucency and area were entered into a spreadsheet by the person outlining the lung. The two assessors were blind to all patient details and to each other's measurements. Only the unique radiological identifying number of the chest X-ray enabled between assessor comparison of lung radiolucency and area scores. The lung outline was then deleted before proceeding to the next chest X-ray. Once both assessors had completed this process the data from both spreadsheets were compiled by an independent investigator.

Test-retest reliability of repeated chest X-rays of unchanged participants

Forty pairs of chest X-rays were available before and after a central venous catheter (CVC) was reinserted and these provided the data for studying the stability of measurements derived from repeated chest X-rays. Chest X-ray before and after CVC reinsertion on the same day were included if there was no barotrauma or known changes in lung pathology during the day of the catheter change. If variation was noted in standardised chest X-ray procedures, the chest X-ray was not included. Chest X-ray before and after the CVC reinsertion were viewed by a senior intensive care physician who was blinded to timing of the chest X-ray and the pairing. The physician

was shown 80 de-identified chest X-rays in random order on the GE PACS computer screen and asked to outline the right lung as described above. The lung radiolucency and area were recorded electronically by the investigator in a spreadsheet beside a unique identifying number for the chest X-ray. These could not be matched as pairs by the assessor but could be matched by the investigator with a code that was kept in a locked computer file until all data had been collected. Chest X-ray scores of area and radiolucency before and after CVC reinsertion were then compared for each patient.

Validity in chest X-ray before-after a recruitment manoeuver (RM)

An investigator chose in random order chest X-rays from 28 patients who received a chest X-ray before and immediately after a RM. These chest X-rays were viewed by a radiologist who was blinded to the timing (before or after RM) of the chest X-ray , the identity of the patient and the purpose of the study. The area and radiolucency scores for each x-ray region were computed and recorded electronically by the investigator. Scores were compared before and after recruitment in the same patient. A RM was chosen to assess validity of the digital chest X-ray score as a measure of area change as it was an intervention that is known to improve lung volume on HRCT [4]. In addition, in this group of patients a blinded radiologists had viewed the chest X-ray before and after the RM and subjectively described it as improved [8].

Statistical Analysis

Statistical analysis was performed using STATA version 10 (StataCorp, College Station, Texas, USA). Inter-rater and test-retest reliability were summarised using Intraclass Correlation Co-efficient (ICC) and Pearson's r [10, 11]. For test-retest reliability random error magnitude was quantified using the metricated change index MDC90 [12]. The overall SEM and standard deviation of the difference score (SD_{Diff}) were calculated .The confidence interval calculator developed by Hopkins [13] was used to determine 95% confidence intervals. Systematic differences between group mean scores were assessed using a paired, two tailed t-test and alpha was set at 0.05. A sample of 20 provided power of .80 to detect r^2 of 0.57 at an alpha of 0.05. In the 28 patients with ARDS who received a RM validity was assessed by computing the effect size for change over time in area using a paired t-test, with results reported as means and standard deviation and alpha was set at 0.05.

Results

Forty consecutive patients (22 males) with ARDS [9] with a mean age of 54 (range 22 to 81) years were enrolled in the study over a period of three years. Median duration of ventilation was 9 days (interquartile range 5.2 – 12.3). Mean (±SD) APACHE II score was 20 ± 7.

Results are presented in Table 1 for lung area and Table 2 for lung radiolucency.

Inter-rater reliability

There was good correlation between raters with no statistically significant difference in the measurements of computer generated chest X-ray scores of area (ICC =0.91, mean difference -2.5 sqcm ± 9.9 and 95% CI [-7.2 – 2.1]) (Table 1, Figure 2) or radiolucency (ICC= 0.99, mean difference 1 ± 10 pixel and 95% CI [-4.0 – 5.7]) (Table 2, Figure 3).

Test-retest reliability of repeated chest X-rays of unchanged participants

There was good correlation in mean area scores before and after CVC insertions with no statistically significant differences between mean scores (ICC = 0.96, mean difference (±SD) -1.8 ± 12.3sqcm and 95% CI [-5.8 – 2.2]) (Table 1). The MDC_{90} indicated that the change in an individual's result that is required for clinical confidence (90%) that real change has occurred was 20.8sqcm. (Table 1). Overall test-retest reliability for lung area was excellent (Figure 4).

There were no differences in mean radiolucency scores for test-retest reliability but only moderate reliability (ICC= 0.41, mean difference 12 ± 200 pixels and 95% CI [-53.1 – 76.5]) (Table 2, Figure 5). The MDC_{90} indicated that the change in an individual's result that is required for clinical confidence (90%) that real change has occurred was 337pixels.

Validity in chest X-ray before-after a RM

After a RM there were significant increases in the lung area of both the right (from 185±36 to 212±39 sqcm, P <0.001) and left lungfield (from 198±45 to 217±46 sqcm, P =0.002) with and without inclusion of the cardiac silhouette area (Table 3). There were significant increases in the lung radiolucency of both the right (from 2827±238 to 2939±189 pixels, P = 0.03) and left lungfield (from 2725±315 to 2868±272 pixels, P = 0.02) (Table 3)

Discussion

This study investigated the reliability and the validity of the lungfield area and radiolucency scores of digital chest X-rays at quantifying radiological change in intensive care patients who received a RM. Our results show that the chest X-ray area measures had excellent intra-rater, test-retest reliability and validity. While the chest X-ray radiolucency scores had lower reliability they were still able to quantify a significant change that correlated with qualitative observation.

Digital area scores using chest X-ray were very reliable. This holds whether you consider two different assessors assessing the same chest X-ray or test-retest correlation for a single assessor of matched unchanged chest X-ray . The correlations were high because the absolute error in area estimates (MDC90) was small in proportion to the overall variability in scores. In addition to small random errors there were no significant systematic differences in measures taken by different raters or on different occasions. Differences in mean scores were very small in absolute terms and were more than adequate to determine the change before and after a RM.

In contrast to area, test-retest radiolucency estimates lower reliability. Absolute errors were high, there was poor ranking accuracy (Pearson's r = 0.4) and poorly identified changes in chest X-ray that were expected to occur before and after RM. Only 5 of the 28 participants had changes in the radiolucency score after a RM that exceeded the MDC_{90} associated with unchanged patient's x-rays (Table 2). Accuracy in inter-rater measurement was very high (Pearson's r = 0.99). Therefore the errors in radiolucency estimates are likely to be procedural and associated with real differences in the obtained image.

Advances in improving estimates of radiolucency scores may therefore be made by improving the procedures around image capture. We attempted to standardise several variables, including distance from the machine, timing of inspiration, exposure and angle of projection. Other pathways to controlling errors may be using a breath hold at maximum inspiration to correctly identify the respiratory cycle or linking chest X-ray technology with ventilation software to automatically capture an image at maximum inspiration, added accuracy in distance measures between the chest X-ray and the patient, and timing sedation to minimise spontaneous breaths at varying lung volume when chest X-ray images are being captured.

We examined the effects of RMs on chest x-ray lung area and radiolucency scores readily available with digital radiology. It was calculated before and after RM within the same patient in the same position using the same

exposure and showed that chest x-ray area calculated in this manner has low inter-observer variability, unlike previously described subjective scores such as the Murray's core [14]. To our knowledge this has not been previously described as a method of assessing response to respiratory interventions.

It was expected that after RM, both area and radiolucency measures would improve supporting the validity of digital chest X-ray to identify lung recruitment. This was supported by improvement in lung function and in blinded qualitative evaluation of radiolucency change [8]. Further support for the data was high reproducibility when left and right lung data was compared (Table 3). This study clearly supported the use of GE digital chest X-ray for measuring changes in two-dimensional lung area as reliable and valid. Area increased by approximately 10% after a RM which may indicate lung recruitment had occurred. However the error associated with the radiolucency score was higher, and hence this measure must be used with care when evaluating change in an individual patient.

There are several limitations to this study. The GE digital chest X-ray score of area and radiolucency were not compared to the current "gold standard", HRCT, which would be ideal in this patient population with ARDS to determine collapsed and overdistended lung. This preliminary work provides some evidence that it may be beneficial to compare HRCT volume changes with the more simplistic measure of chest X-ray area. HRCT it is not accessible to all patients in intensive care and not practical to apply in every clinical situation or study. An alternative that is readily available to ICU patients is digital chest X-ray. However, in the clinical setting, the measure of lung area and radiolucency may have value, for example quantification of changes in studies where radiological change is a potential outcome. This study did not analyse digital chest X-ray scores in different positions (supine or erect) or different exposure factors or between different patients. Further research is required to determine whether this can be used as an outcome measure in other patient groups or with other applications of mechanical ventilation.

In conclusion, this pilot study suggests that both lung field area and radiolucency scores derived from digital chest X-rays can be used to quantify significant within-patient changes.

Acknowledgements

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There are no competing interests.

CH completed study design, data collection, data analysis and writing of this manuscript.
DT completed study design and data collection and input into the writing of this manuscript.
JK assisted with study design and analysis and input into the writing.
AH assisted with study design and analysis and writing.
DV assisted with background information, data collection, access to equipment and input into writing.
KT assisted with background information, access to equipment and input into writing.
MB assisted with data analysis and input into writing.

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Table 1 Change in the mean right lungfield area scores (sqcm) between test 1 and test 2 and paired t test results for three studies: test-retest, inter-rater and before versus after RM score (*P<0.05)

Lungfield Area	Test-retest (CVC) One rater two chest X-rays n=40	Inter-rater Two raters one chest X-ray n=20	Before v after RM One rater two chest X-rays n=28
Test 1 mean (SD)	162 (45) sqcm	202 (26) sqcm	181 (25) sqcm
Test 2 mean (SD)	160 (45) sqcm	200 (21) sqcm	207 (27) sqcm
Differences between means (SD) and [95%CI]	-1.8 (12.3) sqcm [-5.8 – 2.2]	-2.5 (9.9) sqcm [-7.2 – 2.1]	26 (33) sqcm [10.5 – 41.5]
p value for test of differences between means	0.36	0.27	0.002*
SEM (sqcm)	8.7 (7.1 – 11.2)	7.3 (5.6 - 10.7)	23.4 (17.8 – 34.2)
SD_{Diff} (sqcm)	12.3	10.4	33.1
MDC_{90} (sqcm)	20.8		
Pearson's r	0.96	0.93	
ICC	0.96	0.91	

Table 2 Change in the mean right lung radiolucency scores (pixel value) between test 1 and test 2 and paired t test results for test-retest, inter-rater and before versus after RM score

Radiolucency	Test-retest (CVC) One rater, two chest X-ray n=40	Inter-rater Two raters, one chest X-ray n=20	Before v after RM One rater, two chest X-ray n=20
Test 1 mean (SD)	2874 (198)	2023 (256)	2795 (251)
Test 2 mean (SD)	2886 (168)	1998 (212)	2899 (27)
Differences between means (SD) and [95% CI]	12 (200) [-53.1 – 76.5]	1 (10) [-4.0 – 5.7]	104 (226) [-22.9 – 230.5]
p value for test of differences between means	0.72	0.71	0.03
SEM and (95% CI)	141.3 (115.5 – 182.1)	7.32 (5.6 – 10.7)	191.4 (-145.6 – 279.6)
D_{Diff} (sqcm)	199.8	10.4	270.7
MDC_{90} (sqcm)	336.5		
Pearson's r	0.41	0.99	
ICC	0.41	0.99	

Table 3. Chest x-ray before and after recruitment manoeuvre (RM) scores, n=28

		Pre RM		Post RM		
		mean	SD	mean	SD	P
Area	R Lung	185	36	212	39	<0.001
(sqcm)	L Lung	198	45	217	46	0.002
	LL ex H*	145	43	162	42	0.01
Radiolucency	R Lung	2827	238	2939	189	0.03
	L Lung	2725	315	2868	272	0.02
	LL ex H*	2827	292	2954	244	0.04

*Left lung excluding cardiac silhouette area

Figure Legend:

Fig. 1 Practice example of the electronic outline of the lung from the chest X-ray using GE digital radiology technology

Fig. 2 Plot of inter-rater reliability for chest X-ray area (sqcm)

Fig. 3 Plot of inter-rater reliability for chest x-ray radiolucency (pixels)

Fig. 4 Plot of test-retest reliability for chest X-ray area (sqcm)

Fig. 5 Plot of test-retest reliability for chest X-ray radiolucency (pixels)

Figure 1.

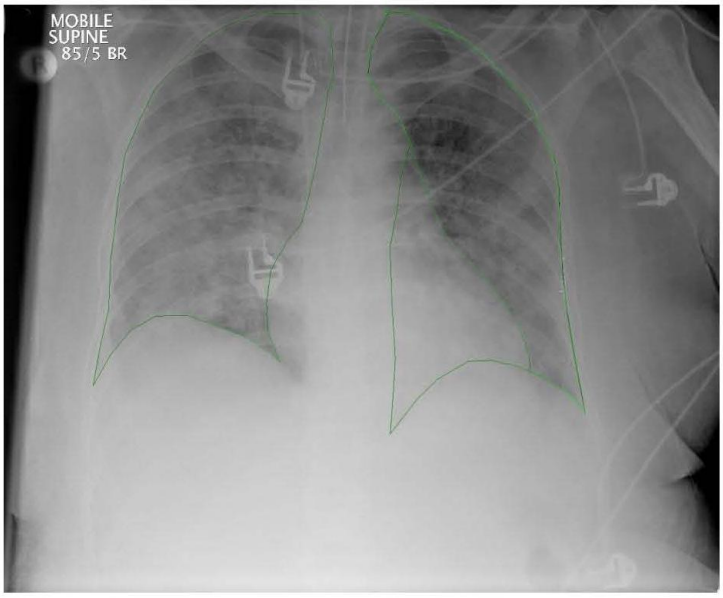
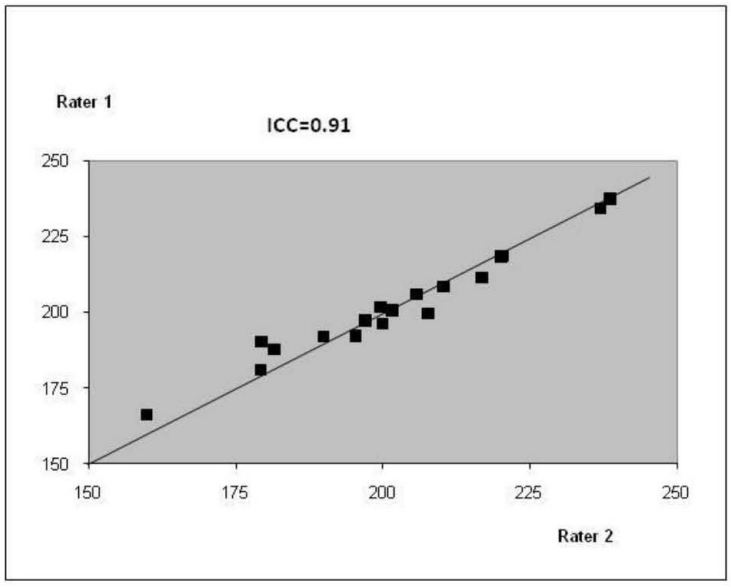


Figure 2



16

Figure 3

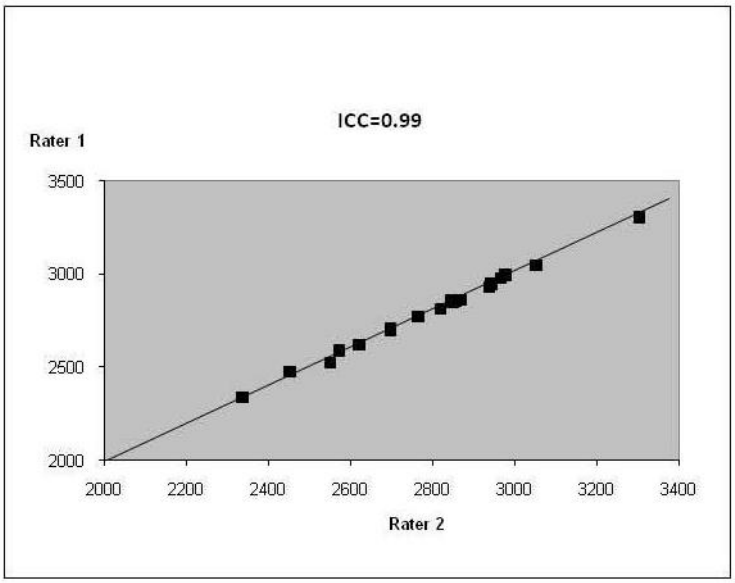


Figure 4

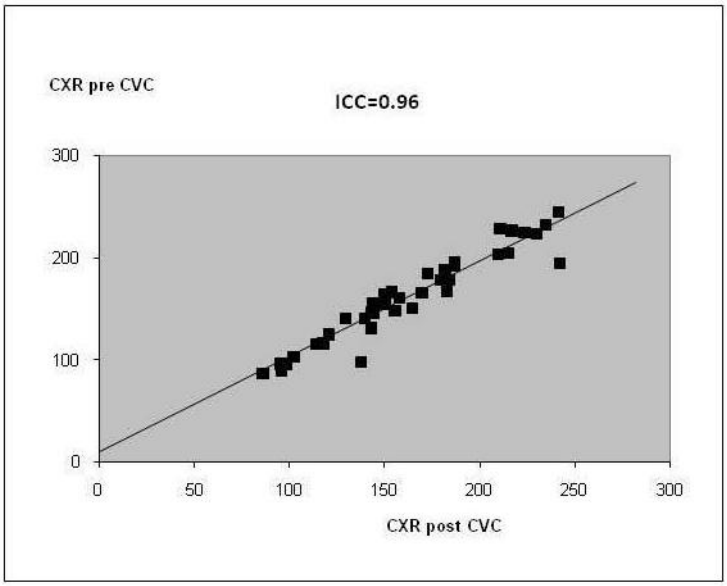


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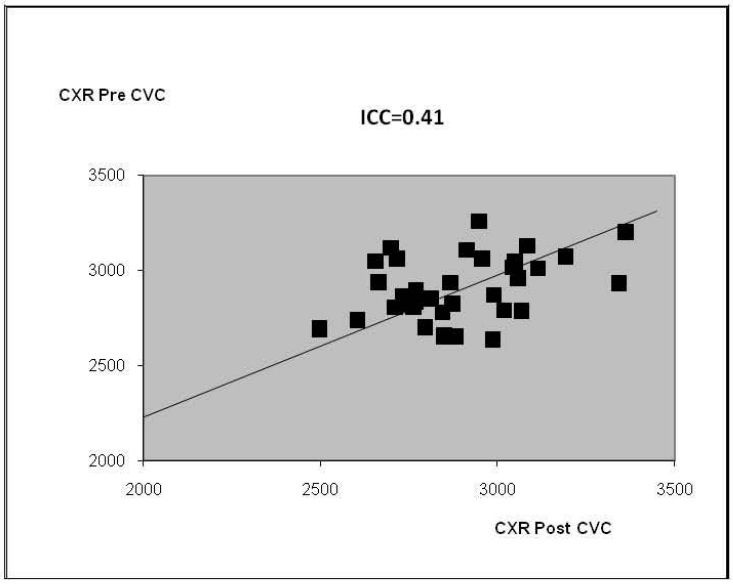
Figure 5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3000
2500
2000
2000
2500
3000
3500
CXR Post CVC

18

Chapter 6 Permissive Hypercapnia, Alveolar Recruitment and Low Airway Pressure (PHARLAP) A Randomised Controlled Trial

6.1 Declaration for Thesis Chapter 6

Declaration by candidate

In the case of Chapter 6 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study concept and design, data collection and analysis, writing of manuscript	60

The following co-authors contributed to the work.

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Alistair Nichol	Study concept and design, data collection and analysis, review of manuscript	
David Tuxen	Study concept and design, review of manuscript	
Jamie Cooper	Study concept and design, review of manuscript	
Jenny Keating	Study concept and design, review of manuscript	
Anne Holland	Review of manuscript	
David Pilcher	Review of manuscript	
Lisa Higgins	Study concept and design, review of manuscript	
Michael Bailey	Data analysis	
Andrew Davies	Study concept and design, review of manuscript	
Andrew Westbrook	Data collection, review of manuscript	

Candidate's Signature	[redacted]	Date 20/07/10

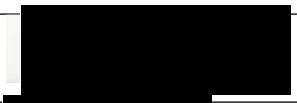
Declaration by co-authors

The undersigned hereby certify that:

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

Location(s)	**ANZICS Research Centre, Monash University, Dept Epidemiology**

Name	Signature	Date
Alistair Nichol	[redacted]	22/07/10
David Tuxen	[redacted]	22/07/10
Jamie Cooper	[redacted]	22/07/10
Jenny Keating	[redacted]	20/07/10
Anne Holland	[redacted]	22/07/10

Name	Signature	Date
David Pilcher		22/07/10
Lisa Higgins		26/07/10
Michael Bailey		20/07/10
Andrew Davies		
Andrew Westbrook		

A PROTECTIVE VENTILATION STRATEGY WITH STAIRCASE RECRUITMENT IMPROVES SEVEN DAY OUTCOMES IN PATIENTS WITH ARDS

Hodgson CL[1,2*]

Nichol A[1,2,4*]

Tuxen DV[1,2]

Bailey MJ[1,2,4]

Davies AR[1,2,4]

Higgins AM[2,4]

Keating JL[2]

Holland AE[1,3]

Pilcher D[1]

Westbrook AJ[2]

Cooper DJ[1,2,4]

*** Joint first authors.** [1]The Alfred Hospital, Melbourne, Australia [2]Monash University, Melbourne, Australia [3]La Trobe University, Melbourne, [4]ANZIC-Research Centre, Australia

Corresponding author: Carol Hodgson, Intensive Care Unit, The Alfred, Commercial Rd, Prahran, VIC, Australia, 3181. c.hodgson@alfred.org.au

Phone: 61 3 9076 2000 (pager 8016) Fax: 61 3 9076 2702

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Short title: A ventilation strategy improves 7 day outcomes in ARDS

Descriptor: Clinical research in intensive care

Word Count for manuscript:

At a glance (scientific knowledge and what it adds to field:

This randomized controlled trial of a multi-faceted protective ventilation strategy with staircase recruitment maneuvers and PEEP titration showed improved oxygenation, static lung compliance and reduced plasma cytokines levels for 7 days compared with standard ventilation.

Abstract

Rationale: The optimal mechanical ventilation strategy for patients with ARDS is unknown.

Objectives: To examine the effectiveness of a novel protective ventilation strategy comprising staircase recruitment maneuvers, low airway pressure with PEEP titration.

Patients: Twenty patients with ARDS were randomised to treatment or ARDSnet control ventilation strategies.

Intervention: The treatment group received staircase recruitment maneuvers with decremental PEEP titration and had plateau pressure<30 cm H_2O.

Measurements: Gas exchange and lung compliance were measured daily for 7 days and plasma cytokines as inflammatory indices of lung injury in the first 24 hours and at days 1, 3, 5 and 7 post enrolment (mean ± SE). In addition we collected data on hospital mortality and length of ventilation and stay (median and interquartile range).

Main Results: PaO_2/F_IO_2 and static lung compliance were significantly improved in the treatment group compared to the control group over 7 days (204.1 ± 8.8 versus 164.7 ± 8.8 mmHg, P = 0.005 and 49.1 ± 2.9 versus 33.7 ± 2.7 cm H_2O, P<0.001 respectively). There was a significant overall reduction in serum tumour necrosis factor-alpha and interleukin-8 in the treatment group compared with the control group (-0.45 ± 0.37 versus 0.98 ± 0.38pg/ml, P = 0.01, and -0.20 ± 0.07 versus 0.02 ± 0.07pg/ml, P = 0.04 respectively). The treatment strategy was associated with a non-significant reduction in duration of ventilation compared to the control group (180 (87-298) versus 341 (131-351) hrs, P = 0.13) and ICU stay (9.9 (5.6-14.8) versus 16.0 (8.1-19.3) days, P = 0.19).

Conclusion: The treatment strategy improved oxygenation and compliance and reduced cytokine response over a 7 day period compared with the control group. These findings warrant further study in a larger trial.

Registration: ACTRN12607000465459

Words: 245

Key Words: acute respiratory distress syndrome, mechanical ventilation, recruitment, respiration, critical illness, intensive care, acute lung injury

Introduction

Acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lungs that is associated with high mortality[1]. Mechanical ventilation is a life supporting intervention that aims to maintain gas exchange in these patients, but it can also augment or initiate lung injury[2]. Lung-protective mechanical ventilation strategies that aim to minimise tidal volume and plateau pressure have been the only intervention associated with improved patient survival[3-4].

Clinicians frequently use high positive end-expiratory pressure (PEEP) to improve alveolar recruitment in patients with ARDS. PEEP aims to counter the pulmonary shunt due to increased lung collapse resulting from inflammation. High PEEP maintains functional residual capacity and improves oxygenation[5-6] and may even have an effect on reducing mortality associated with ARDS[7-8]. The best strategy to set optimal PEEP for an individual patient has not yet been established[9-10].

It is unclear whether lung recruitment maneuvers (LRM) add benefit to low tidal volume protective ventilation strategies in ARDS[11-12]. The most commonly used LRM requires the application of sustained continuous positive airway pressure (CPAP) at 35-40 cm H_2O for 40 seconds[2, 13-14]. However this LRM method can be uncomfortable, may induce circulatory depression and has not been associated with improved outcomes in patients with ARDS[13-14].

We previously demonstrated that a staircase recruitment maneuver (SRM) was safe and effective for improving oxygenation and lung compliance for one hour in patients with ARDS[15]. The SRM involves a progressive increase in PEEP (up to 40 cm H_2O) over several minutes with mandatory pressure control ventilation, resulting in intermittent higher pressures (55 cm H_2O) for longer duration and increased alveolar recruitment compared with static recruitment methods[15]. Borges and co-workers found that oxygenation benefits of the SRM can be maintained for up to six hours with the application of “optimal” PEEP using a PEEP titration maneuver (described below)[16]. To our knowledge the effect of SRM and PEEP

titration on inflammatory markers or physiological indices has not been investigated beyond 6 hours.

The potentially deleterious higher airway pressures observed in previous strategies that incorporated high PEEP and LRM's may be avoided by reducing tidal volume, a practice that may require permissive hypercapnia. It has been demonstrated in animals and humans that the acidosis induced by this hypercapnia, independent of any changes in ventilator strategy, may also confer benefit in ARDS[17-19].

The aim of this pilot trial was to compare a pressure control ventilation strategy that utilised SRM, high PEEP and permissive hypercapnia to limit airway pressures (PHARLAP; Permissive Hypercapnia, Alveolar Recruitment, Low Airway Pressures) with a control strategy (conventional ARDSnet 'protective' volume controlled ventilation[20]) in patients with ARDS to determine the effect on inflammatory cytokines, physiological lung injury (arterial oxygenation and lung compliance) and rates of barotrauma over a seven day period.

Methods

This pilot randomized, controlled, parallel-group study was conducted between January 2008 and October 2009 at the Alfred Hospital. The Ethics Committees of The Alfred Hospital and Monash University approved the study. Informed consent was obtained from the next of kin.

Twenty mechanically ventilated patients with ARDS[21] were randomized to treatment (PHARLAP) or control groups using sequentially numbered sealed envelopes and stratified for severe sepsis[22-24].

Inclusion criteria were the diagnosis of ARDS[25-26], age > 15 years, and the presence of both an intra-arterial and central venous catheter. Exclusions were chest trauma, intercostal catheter with air leak, pneumothorax on chest x-ray, bronchospasm on auscultation, raised intracranial pressure, mean arterial pressure ≤ 60mmHg, arrhythmias or ventilation > 72 hours.

Interventions

PHARLAP ventilation strategy included pressure control ventilation (PCV, 15 cm H_2O above PEEP) with patient's 30 degrees head up. For the SRM the fraction of inspired oxygen (F_IO_2) was reduced until SaO_2 stabilised at 90-92%, then PEEP was increased in a stepwise manner to 20, 30 and then 40 cm H_2O every two minutes, then stepwise reduced from 25 cm H_2O by 2.5cmH20 every three minutes until a decrease in SaO_2 ≥ 1% from maximum SaO_2 was observed (the de-recruitment point). PEEP was then increased to 40 cm H_2O for one minute and returned to a PEEP level 2.5 cm H_2O above the de-recruitment point. PEEP was not increased to the next step if there was bradycardia or tachycardia (< 60 or > 140 bpm), new arrhythmia, hypotension (systolic blood pressure < 80mmHg) or hypoxaemia (SaO_2 < 85%). Following the SRM, the tidal volume was decreased to achieve a plateau pressure ≤ 30 cm H_2O. Hypercapnia was tolerated if pH was ≥ 7.15, but if not, respiratory rate was increased to a maximum of 38 bpm, and/or sodium bicarbonate was considered. PEEP was transiently elevated to 40 cm H_2O for one minute for SaO_2≤ 90% or after ventilator disconnection. The SRMs were repeated daily (with decremental PEEP titration) until the patient was ready for weaning (for weaning protocol see the online supplement).

Control ventilation strategy was the ARDSnet protocol, with assist control ventilation and FiO_2/PEEP titration[20]. Tidal volumes were limited to 6 mls/kg and plateau pressures < 30 cm H_2O. Acidosis (pH < 7.3) was managed by increasing minute ventilation and, if resistant, bicarbonate was recommended. LRMs and PCV were not used.

Outcome measures

The primary outcome was plasma interleukin-6 (IL-6) concentration. Plasma IL-6, IL-8, -IL-1β, IL-10, soluble-tumour necrosis factor receptor 1 (s-TNF R1) and tumour necrosis factor-alpha (TNF-alpha) were measured from arterial blood samples at baseline, 3 hours, day 1, 3, 5 and 7. Cytokines were detected from centrifuged and aspirated plasma using

enzyme-linked immune-absorbent assays (ELISA, R&D Systems, Inc., Minneapolis, MN, USA).

Respiratory and cardiovascular variables were measured at baseline, 1, 3, 6 and 24 hours and then daily for up to 7 days. Derived variables were PaO_2/F_IO_2 ratio and static lung compliance. Length of stay (LOS), length of mechanical ventilation (LOV) and hospital survival were recorded.

Sample size

Fifteen patients per group had 90% power to detect differences in the primary outcome in IL-6 based on a two-sided test for differences between groups of one standard deviation, (P 0.01 intraclass correlation of 0.2).

Statistical analysis

Normally distributed data was reported as means ± standard errors and non-normal data reported as medians (interquartile range). Group comparisons over time were performed using repeated measures analysis of variance. All models were fitted using the PROC Mixed procedure in SAS (SAS Version 9.1 SAS Institute Inc., Cary, NC, USA). A two-sided P-value ≤ 0.05 was considered significant.

Results

Twenty patients with ARDS were enrolled (Figure 1). Baseline demographic data of the control and treatment groups are displayed in Table 1. The groups were similar at baseline. Nineteen of the twenty patients had severe sepsis. The patient without severe sepsis was randomised to the PHARLAP group and was ventilated for 873 hours, stayed in ICU for 51 days and did not survive. Slow recruitment resulted in revision to 10 subjects per group with 83% power to detect a difference.

In the PHARLAP group, all 10 patients received a SRM with maximum PEEP of 40 cm H_2O and a maximum plateau airway pressure of 55 cm H_2O. Three patients transiently desaturated to <90% at maximum PEEP of 40 cm H_2O with no lasting adverse effects. There was no radiographic evidence of barotrauma during the seven day study period.

Two patients from the control group developed severe hypoxaemia (SaO_2 ≤ 90% whilst receiving FiO_2 0.9 and PEEP 18) and received rescue therapies (rescue recruitment maneuvers and inhaled nitric oxide). One patient in the control group died. Five patients in the PHARLAP group were extubated within the seven days compared to three in the control group. At day seven there were 5 PHARLAP group patients and 6 control group patients who remained on mechanical ventilation.

There was no significant difference between the treatment and control groups in serum IL-6 or IL-1ß. There was a significant overall reduction in the baseline to day 7 plasma IL-8 reduction which was greater in the PHARLAP group (0.53 ± 0.12 to 0.21 ± 0.13 pg/ml) when compared to the control group (0.25 ± 0.12 to 0.24 ± 0.14 pg/ml, P = 0.04, Figure 2). There was a greater reduction in the baseline to day 7 plasma TNF-alpha in the PHARLAP group (4.1 ± 0.7 pg/ml to 3.3±0.8 pg/ml) when compared to the control group (2.3 ± 0.7 pg/ml to 3.3 ± 0.9 pg/ml ,P = 0.01, Figure 2). There were differences in baseline values of IL-8 and serum TNF-alpha between groups but the groups remained significantly different under an analysis of covariance with baseline IL-8 and TNF-alpha as the covariate (P=0.006 and 0.02 respectively).There were insufficient samples to complete measurement of IL-10 or s-TNF R1 because re-assay was required for several cytokines to meet the manufacturer's guidelines.

Static lung compliance was significantly higher in the PHARLAP group compared to the control group over 7 days (49.1 ± 2.9 versus 33.7 ± 2.7, P < 0.001, Figure 3). PaO_2/F_IO_2 was significantly higher in the PHARLAP group compared to the control group over the first 24 hours (Figure 4) and over 7 days (204 ± 9 versus 165 ± 9, P = 0.005) despite no significant difference in F_IO_2 between the groups (Figure 5). To account for possible bias arising from differing extubation or dropout rates between groups, additional sensitivity analyses were conducted for compliance and PaO_2/F_IO_2 with patients carrying their last observation forward (P = 0.01 and 0.03 respectively).

PEEP was significantly higher in the PHARLAP group over the first 24 hours (Table 2) and throughout the 7 days compared to the control group (PHARLAP 12 ± 0.5, control 9.5 ± 0.5, P = 0.004, Table 3).

There were no other significant differences between the groups (Table 3) in respiratory and haemodynamic variables, peak or plateau pressures, pH, $PaCO_2$ or SOFA scores during the 7 day period. Of note, the plateau pressures were kept less than 30 cm H_2O throughout the study in both groups and the plateau pressures were not significantly higher in the PHARLAP group compared to the control group. This occurred without a significant reduction in pH or elevation in $PaCO_2$ in the PHARLAP group.

The reductions in length of ventilation, length of stay in ICU and in hospital for the PHARLAP group were not statistically significant (Table 4). There was no significant difference in hospital mortality (Table 4).

Discussion

This pilot, randomised controlled study examined the efficacy of a multi-faceted mechanical ventilation strategy that included permissive hypercapnia, staircase recruitment maneuvers, decremental PEEP titration, low airway pressure and pressure control ventilation in patients with ARDS[27]. This strategy appeared safe and led to significant improvements in oxygenation and lung compliance while reducing serum IL-8 and TNF-alpha over a seven day period. While the reductions in duration of mechanical ventilation, ICU and hospital length of stay in the PHARLAP group compared with the control group were not significant, our results suggest the PHARLAP ventilation strategy is promising and warrants further investigation.

Static lung compliance decreased by nearly 30% in the control group over the first 24 hours and remained low for the duration of the study compared with the PHARLAP group, which had a significant increase in compliance. This suggests a greater degree of lung recruitment was sustained throughout the study in the PHARLAP group. This effect of the PHARLAP

strategy may be an important factor in ARDS to minimise the potential negative effects of ventilator induced lung injury.

Arterial oxygenation, as measured by the PaO_2/F_IO_2, in the PHARLAP strategy group was significantly improved at 24 hours compared to the control group, with significant improvements maintained for seven days. The beneficial effects of PEEP on oxygenation have been shown in a systematic review to be associated with improved survival in patients with ARDS[8]. It is unclear from our results whether the improved oxygenation was as a result of the increased PEEP, the SRM, both or another aspect of our multi-pronged strategy. However, the results of this trial expand to 7 days the previous work by our group which demonstrated that the SRM with decremental optimal PEEP titration improved lung compliance and oxygenation for one hour[15].

The shorter duration of mechanical ventilation in the PHARLAP group resulted in smaller group size contributing to the mean values of PaO_2/F_IO_2 and compliance as days progressed. This may have given the incorrect appearance of decreasing differences between the 2 groups especially considering that patients with better PaO_2/F_IO_2 and compliance values are more likely to be extubated. We have attempted to correct for this by including a sensitivity analysis with last observation carried forward (Figures 3 and 5). In both analyses the differences between the PHARLAP and the control ventilation strategies were statistically significant with PHARLAP strategy improving PaO_2/F_IO_2 and static lung compliance over 7 days.

It is unclear if these physiological improvements would translate into clinically meaningful outcomes such as improved survival. However, in our study the use of ‘hypoxic’ rescue therapies was only required in the control group. Two of the patients in the control group required nitric oxide and PEEP levels higher than specified by the control group strategy to maintain adequate oxygenation.

Although the study protocol recommended permissive hypercapnia and low airway pressures as two of the three components of the PHARLAP

strategy, mean $PaCO_2$, pH and plateau pressure values were similar in both the PHARLAP and control groups. This suggests that these factors were not responsible for the different outcomes between the groups. The primary differences in strategies were the application of the recruitment maneuver and the higher PEEP level with a lower driving pressure (a consequence of higher PEEP and unchanged plateau pressure) in the PHARLAP group. This is in contrast to several randomised trials[13-14, 28] all of which delivered a higher plateau pressure in the treatment group in association with a higher PEEP level. A recent meta-analysis has suggested that a low driving pressure may be an important independent variable in patient outcome in ARDS[8]. Interestingly our strategy achieved similar peak and plateau airway pressures in both groups despite increased levels of PEEP in the PHARLAP group.

The potential for transient desaturation at maximum PEEP during SRMs with recovery to an improved saturation above baseline when PEEP was reduced has previously been described by our group[15] and by others[16]. In this study maximum PEEP was associated with transient desaturation for three of the 10 patients who received SRM. There were no other adverse events reported. Previously, it has been reported that transient desaturation does not indicate a failure of the lungs to respond to a recruitment maneuver[15]. PHARLAP strategy ventilation improved lung compliance and oxygenation throughout the 24 hours despite transient desaturation in these three patients.

Lung recruitment maneuvers that involve high airway pressures to achieve and maintain lung recruitment have the potential to cause overdistension[29]. Plasma levels of TNF-alpha, sTNF, IL1-beta, IL-8 and IL-6 were analysed to determine if the SRM caused an increase in inflammatory markers which might reflect the systemic effects of over-distension lung injury. Our results showed that the PHARLAP strategy resulted in an overall reduction of plasma IL-8 and TNF-alpha over 7 days that may have indicated a protective benefit associated with the treatment strategy. These results were not confirmed by the results of IL-6 and IL1-beta, which may reflect the large heterogeneity of the patient population

and the small sample size. However further analysis of covariance, with baseline as a covariate, did not support this.

Although this study was not adequately powered to determine longer term outcomes, it is interesting to note that the PHARLAP ventilation strategy was associated with about a one-third reduction in time on mechanical ventilation. Whilst these results were not statistically significant, we feel they should be investigated in a larger randomized trial. This pilot trial was designed to generate feasibility data for a larger randomized controlled trial in this area, however the PHARLAP strategy was found to be efficacious in improving physiological derangements.

This study has a number of limitations. The unblinded nature of the study, coupled with the use of adjunctive interventions at the discretion of the intensive care physician in the case of severe hypoxaemia, could confound our results. Other limitations include the small sample size, the slow recruitment, which resulted in a reduction in the anticipated number of patients enrolled, and the single-centre design, which allowed rigorous education of the SRM but may confound the generalisability of the results to other populations. The small sample size meant the study was underpowered to detect significant differences in length of mechanical ventilation, ICU and hospital stay. Also, despite random allocation the static lung compliance at baseline was slightly higher and the PEEP was slightly lower in the treatment group (Table 1). These differences were not statistically significant at baseline, but may have influenced our results. Despite these limitations the PHARLAP intervention resulted in a significant increase in lung compliance and PaO_2/F_IO_2 and a decrease in plasma IL-8 and TNF-alpha which was not observed in the control group.

Conclusion

This randomized controlled trial showed that the PHARLAP ventilation strategy was more effective than conventional protective ventilation in improving static lung compliance, oxygenation and plasma cytokines (IL-8 and TNF-alpha) over 7 days. While reductions in duration of mechanical ventilation, ICU and hospital stay were not statistically significant, the

magnitude of these reductions warrant further investigation in a larger randomized trial.

Acknowledgments

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Table 1. Baseline demographic data (mean ± SE)

	PHARLAP	**Control**	**P**
Number in group	10	10	
Male, number	7	6	
Age, years	60 ± 5	58 ± 4	0.65
APACHE 2 score	20.1 ± 3	20.1 ± 2	0.99
APACHE 3 score	66.3 ± 8	64.8 ± 7	0.89
SOFA score	8.6 ± 0.9	8.4 ± 0.5	0.86
PaO_2/F_IO_2, mmHg	155 ± 8	149 ± 12	0.65
Diagnostic group	5 pneumonia 2 AAA 1 necrotising fasciitis 2 trauma	6 pneumonia 2 AAA 1 burn 1 sepsis	
Static lung compliance, ml/cm H_2O	45.8 ± 5.4	37.3 ± 5.4	0.48
PEEP, cm H_2O	11.8 ± 0.7	14.2 ± 1.2	0.09

AAA: abdominal aortic aneurysm repair, APACHE: acute physiology and chronic health evaluation, PEEP: positive end expiratory pressure, SE: standard error, SOFA: sequential organ failure assessment score

Table 2. Respiratory variables during the first 24 hrs of treatment (mean ± SE) *P < 0.05 for differences between PHARLAP and control groups.

	1 hour		3 hours		6 hours		24 hours	
	PHARLAP	Control	PHARLAP	Control	PHARLAP	Control	PHARLAP	Control
V_T, mls	519 ± 56	501 ± 30	517 ± 51	529 ± 58	529 ± 56	542 ± 49	463 ± 42	563 ± 65
RR, bpm	21 ± 2	21 ± 1	20 ± 2	21 ± 2	21 ± 2	21 ± 2	22 ± 2	20 ± 2
F_IO_2	0.47 ± 0.03	0.59 ± 0.04	0.5 ± 0.04	0.5 ± 0.03	0.4 ± 0.05	0.57 ± 0.05	0.4 ± 0.04	0.5 ± 0.04
PEEP, cm H_2O	17.4 ± 1	11.6 ± 1	17.4 ± 1*	11 ± 0.5	16.7 ± 1*	10 ± 0.6	15 ± 1*	10 ± 0.5
Pplateau, cm H_2O	28.9 ± 1.2	27.1 ± 1.2	28.3 ± 1.1	26.6 ± 1.1	29 ± 0.8	26 ±0.8	27.6 ± 1.5	26.9 ± 1.4
Arterial pH	7.34 ± 0.02	7.36 ± 0.02	7.34 ± 0.02	7.34 ± 0.03	7.34 ± 0.02	7.36 ± 0.01	7.36 ± 0.01	7.35 ± 0.01
$PaCO_2$, mm Hg	49 ± 5	46 ± 5	47 ± 4	48 ± 6	48 ± 3	45 ± 3	45 ± 3	46 ± 3

V_T: tidal volume, RR: respiratory rate, F_IO_2: fraction of inspired oxygen, PEEP: positive end expiratory pressure, Pplateau: plateau pressure, PaO_2/F_IO_2: partial pressure of oxygen to inspired fraction of oxygen ratio, $PaCO_2$: partial pressure of carbon dioxide

Table 3. Respiratory variables during 7 days of treatment (mean ± SE) * P < 0.05 for differences between PHARLAP and control groups.

	Baseline		**Day 1**	
	PHARLAP	Control	PHARLAP	Control
V_T, mls	519 ± 56	501 ± 30	463 ± 42	563 ± 65
RR, bpm	21 ± 2	21 ± 1	22 ± 2	20 ± 2
FiO_2	0.48 ± 0.06	0.57 ± 0.06	0.4 ± 0.04	0.5 ± 0.04
PEEP, cm H_2O	11.8 ± 0.7	14.2 ± 1.2	15 ± 1*****	10 ± 0.5
Pplateau, cm H_2O	28.4 ± 1.5	29 ± 1.5	27.6 ± 1.5	26.9 ± 1.4
Arterial pH	7.34 ± 0.02	7.36 ± 0.02	7.36 ± 0.01	7.35 ± 0.01
$PaCO_2$, mm Hg	49 ± 5	46 ± 5	45 ± 3	46 ± 3

	Day 3		**Day 7**	
	PHARLAP	Control	PHARLAP	Control
V_T, mls	586 ± 58	511 ± 55	528 ± 76	579 ± 78
RR, bpm	19 ± 2	24 ± 2	22 ± 2	22 ± 2
FiO_2	0.5 ± 0.07	0.55 ± 0.06	0.5 ± 0.07	0.5 ± 0.09
PEEP, cm H_2O	12.1 ± 1.5	9.3 ± 1.4	8.5 ± 1.8	7.8 ± 2.0
Pplateau, cm H_2O	24.2 ± 2.4	24 ± 2.1	21 ± 2.9	20.± 3.4
Arterial pH	7.38 ± 0.03	7.44 ± 0.03	7.42 ± 0.03	7.42 ± 0.04
$PaCO_2$, mm Hg	47.6 ± 3.7	44 ± 3.5	43.3 ± 4	56.5 ± 5

Vt: tidal volume, RR: respiratory rate, F_IO_2: fraction of inspired oxygen, PEEP: positive end expiratory pressure, Pplateau: plateau pressure, $PaCO_2$: partial pressure of carbon dioxide

Table 4. Outcomes

	PHARLAP	Control	P
Hospital mortality, number	3	2	0.61
LOV, hours	180 (87-298)	341 (131-351)	0.13
ICU LOS, days	9.9 (5.6-14.8)	16.0 (8.1-19.3)	0.19
Hospital LOS, days	17.9 (13.7-34.5)	24.7 (20.5-39.8)	0.16
Barotrauma, number	0	0	
Rescue therapies, number of patients	0	2	0.46
SOFA score (day 7)	8.6 ± 0.3	8.4 ± 0.6	0.27

LOV: length of ventilation, ICU LOS: intensive care length of stay, LOS: length of stay, SOFA: sequential organ failure assessment

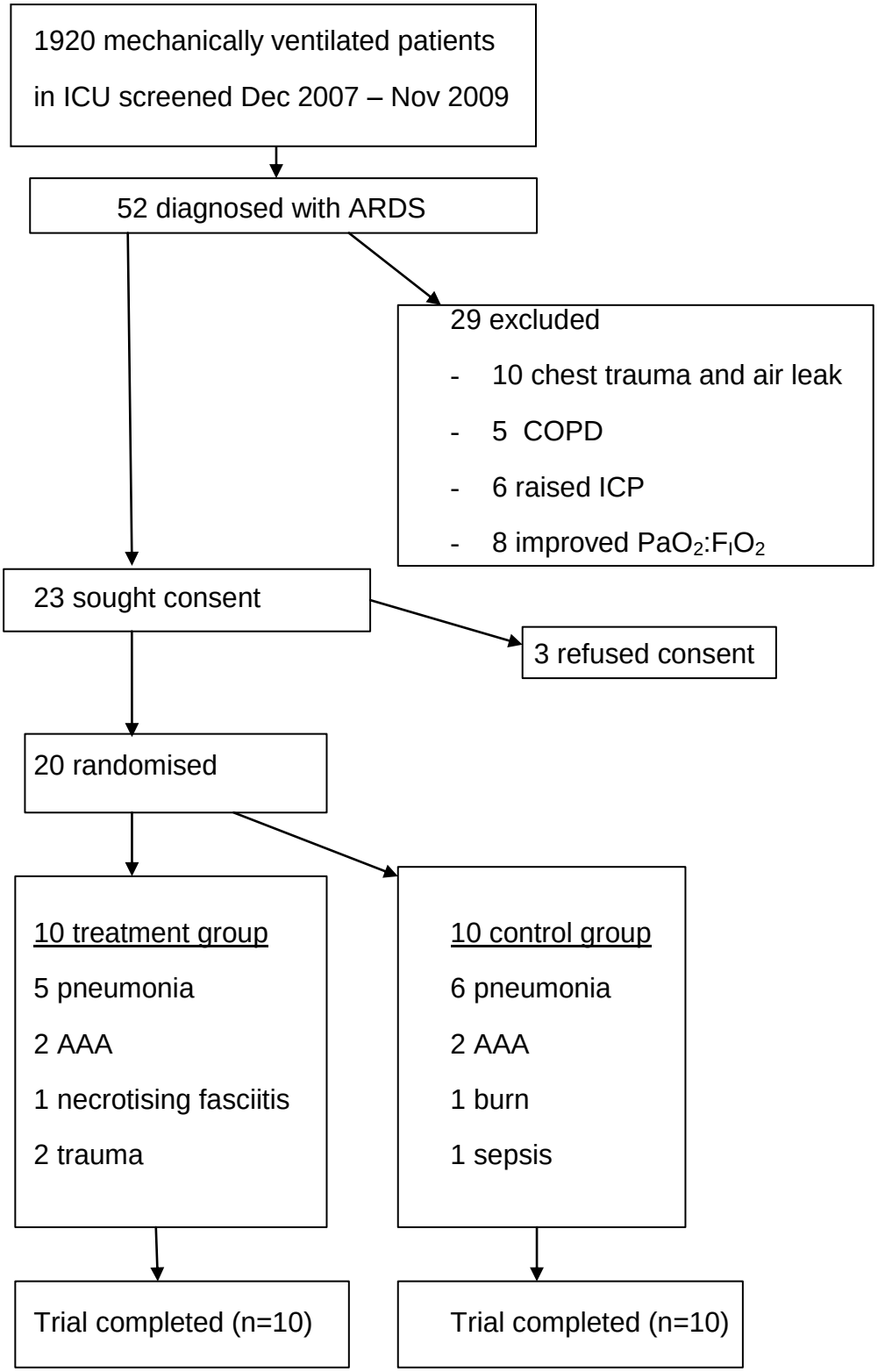
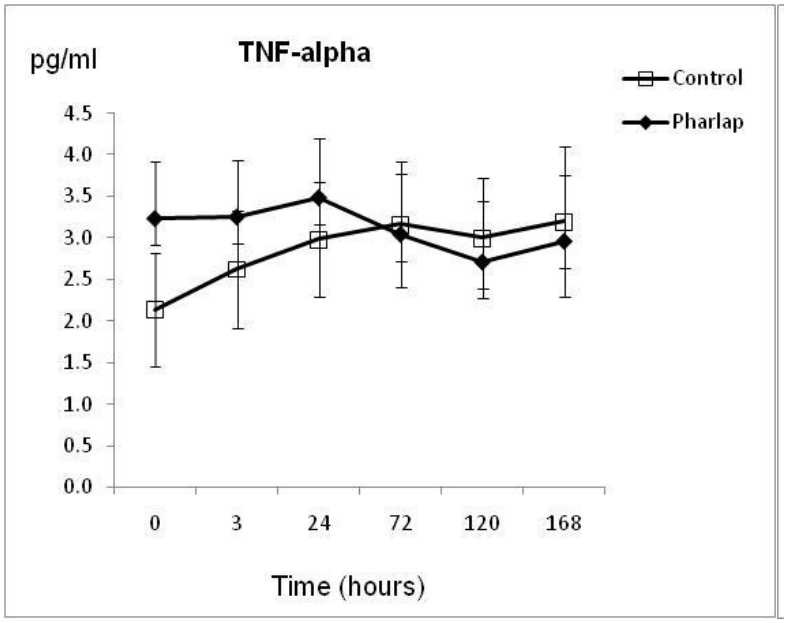


Figure 1. CONSORT flowchart of the study. CONSORT=Consolidated Standards of Reporting Trials; AAA=abdominal aortic aneurysm; COPD=chronic obstructive lung disease; ICP=intracranial pressure; PaO_2/F_IO_2= partial pressure of oxygen to inspired fraction of oxygen ratio.



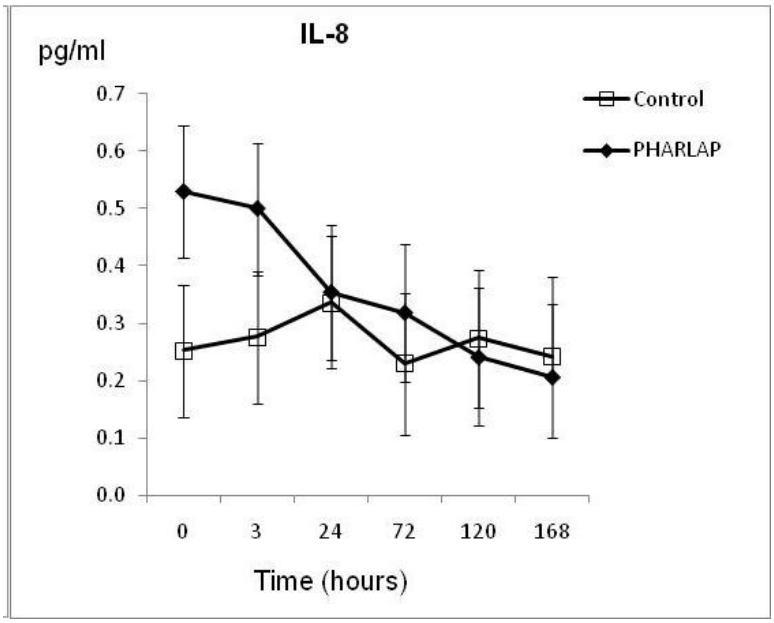


Figure 2. IL-8 and TNF-aplha measured over 168 hours or 7 days (mean ± SE). There was a significant overall reduction in serum tumour necrosis factor-alpha and interleukin-8 in the treatment group compared with the control group (-0.45±0.37 versus 0.98±0.38pg/ml P=0.01 and -0.20±0.07 versus 0.02±0.07pg/ml P=0.04 respectively).

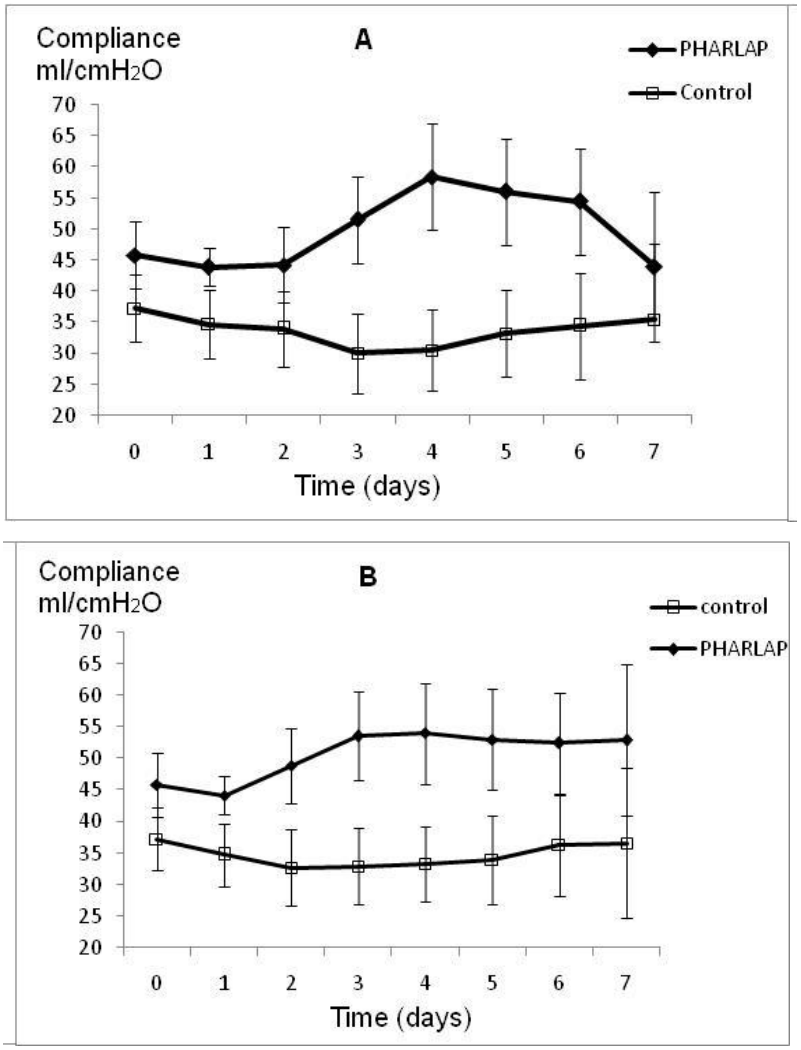


Figure 3. Static lung compliance measured in ventilated patients for 7 days (mean ± SE). There was a significant overall improvement in static lung compliance in the PHARLAP group compared to control group patients. A= missing data analysed as random P=0.001, B = last observation carried forward P=0.01

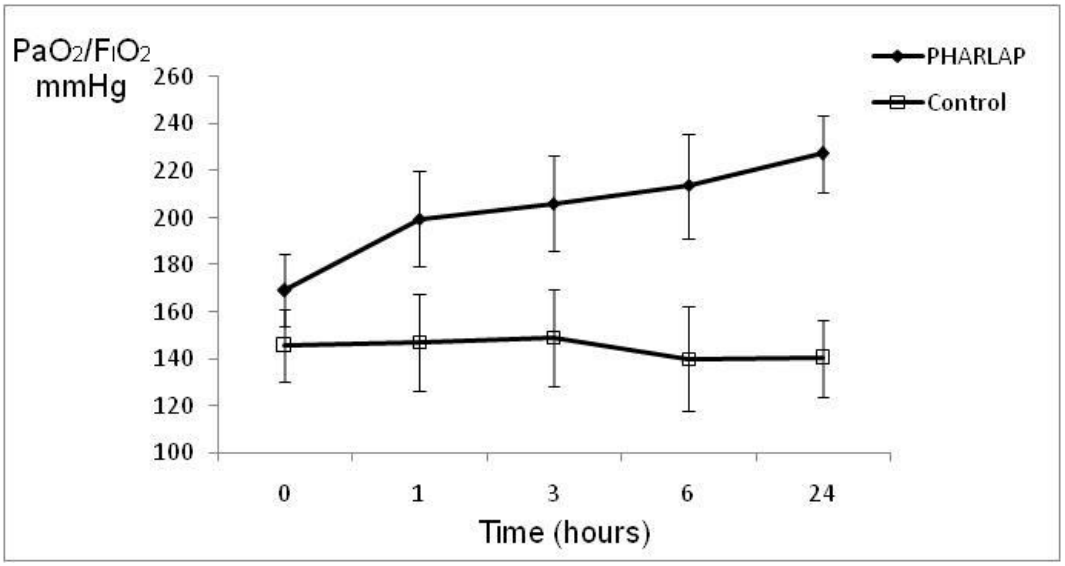


Figure 4. PaO_2/F_IO_2 measured over the first 24 hours in ventilated patients (mean ± SE). PHARLAP group had a significant overall increase in PaO_2/F_IO_2 compared to control group patients (*P<0.01).

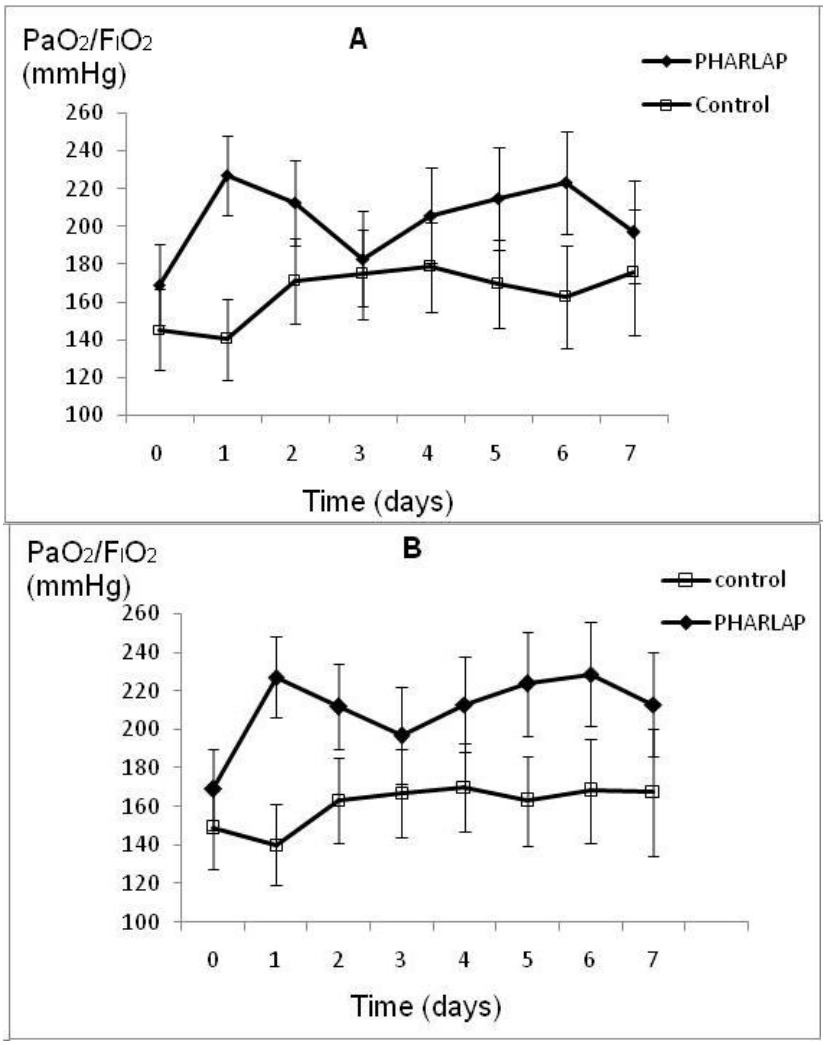


Figure 5. PaO_2/F_IO_2 measured over 7 days in ventilated patients (mean ± SE). There was a significant overall improvement in PaO_2/F_IO_2 ratio in PHARLAP compared to control group patients. A= missing data analysed as random, P = 0.005. B=last observation carried forward, P=0.03.

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Chapter 7 Conclusions and future directions

Main findings and advances to knowledge in this thesis

The primary aim of the research reported in this thesis was to examine the efficacy of a new staircase recruitment manoeuvre in ventilated adult patients with ARDS. This study was motivated by a desire to improve the care and outcome of patients with severe ARDS with life threatening illness. At the outset of this research there was little guidance in the literature regarding suitable recruitment manoeuvres for such patients or how they should be applied[11].

The absence of consistent recommendations regarding the use of RMs in patients with ARDS, coupled with the knowledge of the importance of low tidal volume ventilation strategies (protective ventilation strategies)[5] required that the safety and efficacy of RMs be clarified from the current literature. The Cochrane review applied meta-analysis and concluded that RMs were not associated with adverse events such as reduced blood pressure or rate of barotrauma compared to standard care in patients with ARDS. In addition, the review concluded that ventilation strategies that included static RMs had no apparent effect on ICU mortality, 28 day mortality or in hospital mortality. The only type of RM that had been included in a trial of ventilation for patients with ARDS at the time of the review was a static RM (40cmH_2O for 40 seconds). The effect of the RM could not be clearly isolated from other components of the ventilatory strategies.

The systematic review highlighted the limited number of trials assessing the effects of RMs in patients with ARDS. Only three randomized controlled parallel trials and four cross-over trials were available at the time the review was completed. Recruitment manoeuvres varied in design across studies with regards to maximum alveolar pressure, duration of the RM and mode of ventilation used. There was a risk of bias as there was no blinding of assessors. Cross-over trials rely on a washout period to reduce carry-over effects and as full effect removal after the point of cross over cannot be guaranteed in the trials of RMs, the best data for analysis in such a design would be obtained at the point of cross. Despite attempts

to contact authors for additional information, these data were not available for any of the included studies. Oxygenation was improved with a RM for a transient period of time (10 minutes) but there were no data available about longer time periods. There was insufficient evidence to make confident recommendations about optimal transpulmonary pressure, length of time at that pressure, optimal frequency of delivering a RM or level of PEEP to maintain after a RM in patients with ARDS. The findings of the systematic review confirmed that static RMs were safe and improved oxygenation for a short period of time but did not improve longer term outcomes. The limitations of the sustained inflation are further discussed in the editorial for Critical Care and Resuscitation[53] (Appendix 11).

This thesis reports the outcomes of a new staircase recruitment manoeuver with increased transpulmonary pressures (55 cm H_2O versus 40 cm H_2O used with a static RM) held for a longer period of time (8 minutes versus 40 seconds used with the static RM). The SRM was found to be safe in an observational trial of 20 patients with ARDS, despite transient desaturation or hypotension during the SRM[13]. The SRM used decremental PEEP titration to determine optimal PEEP for each person. It appeared to be effective in improving shunt fraction, lung compliance and oxygenation for a period of an hour even in patients who had transient desaturation during the SRM. Patients who desaturate during RMs have previously been classified as non-responders and unsuitable for a strategy including RMs. Our results indicated that while some patients reduce their oxygen saturation during the SRM these effects are transient and 30 minutes after the SRM these patients had increased their shunt fraction and PaO_2/F_IO_2 significantly from baseline and it was maintained for at least an hour.

This thesis identified two important bedside outcome measures used to assess the effect of RMs and discussed the limitations of some of the other methods used. Lung recruitment can be measured using imaging techniques such as computerised tomography and electrical impedance tomography, however these are expensive and not readily available at the

bedside[10,54-57]. Lung recruitment can also be assessed using indices of oxygenation or ventilator waveforms[27,58-59]. A study was performed to compare two methods of assessing the immediate arterial oxygenation saturation response of a patient with ARDS to a RM. In chapter three a comparison of forehead sensors versus finger sensors with pulse oximetry found that the finger sensor was more reliable and sensitive at high levels of PEEP compared to the forehead sensor. This has led to world-wide distribution of important product information that limits the reliability of the Maxfast forehead sensors under conditions of high PEEP despite theoretical advantages.

The work in this thesis included the testing of a digital scoring procedure for chest X-rays in intensive care which measures changes in lung area after a SRM. The digital technology allowed the development of a protocol to quantify changes in lung area which was both reliable and valid, but the measurement of lung radiolucency was less useful in clinical practice as there was significant test-retest variations.

Finally, the SRM with decremental PEEP titration was included in a randomised controlled trial comparing protective ventilation (permissive hypercapnia, alveolar recruitment and low airway pressure; PHARLAP) to a standard protective ventilation strategy[15]. A pilot trial was required to determine physiological changes with the PHARLAP ventilation strategy and surrogate outcome measures were used, including plasma cytokine response. It was found that PHARLAP ventilation strategy was more effective than conventional ARDSnet ventilation, with improved lung compliance and oxygenation for at least seven days. There were no changes in plasma cytokines that may be expected with a ventilation strategy that included RMs to a maximum pressure of 55 cm H_2O. There were trends towards reduced length of ventilation and reduced intensive care and hospital length of stay. The primary differences between PHARLAP and control ventilation were the SRM, higher PEEP and a smaller difference between inspiratory and expiratory pulmonary pressures[60]. This was the first randomized trial describing a SRM as part of a ventilation strategy. Results will be used as feasibility data to apply for

funding to support a larger trial powered to detect clinically relevant long term outcomes, including duration of mechanical ventilation and length of stay in intensive care and hospital.

Future Directions

Over the past 12 years there have been at least eight large randomized trials investigating the management of ALI and ARDS[4-5,36,51,61-64]. Only two of these trials had positive outcomes, with significant reductions in mortality. In the two positive trials there was a large clinical difference in tidal volume delivered between the treatment group and the control group (6ml/kg versus 12 ml/kg) which resulted in a reduction in mortality (10%[4] and 30%[5] absolute reduction in mortality). In the negative trials it is possible that the difference in treatment strategies between the groups was inadequate to demonstrate a statistically significant reduction in mortality, despite consistent but small reductions in this outcome[36,61-65]. Even when the overall power of the trials was increased, with dramatically larger samples, there was no difference in mortality[36,51,62,64]. In the most recent trials, the numbers of patients included totaled 767 and 980 respectively, but the ventilation strategies between the control and treatment groups were similar, particularly with regard to the plateau pressures (less than 30 cm H_2O)[36,51]. It is possible that each of the trials investigated a small aspect of the management of patients with ARDS, such as high PEEP or recruitment manoeuvres, and showed a small mortality benefit that was not significant. It is hypothesized that the synergy of treatment is important in managing patients with ARDS. It is possible that future trials may require a treatment strategy that combines the effects of several different factors in order to show a significant difference in longer term outcomes. These factors may include combining low tidal volumes, low plateau pressure, high PEEP and recruitment manoeuvres[19,39,66].

We have demonstrated that SRMs as part of a protective ventilation strategy are effective in improving lung compliance and oxygenation for seven days in patients with ARDS. Future research needs to be

undertaken to determine the effect of the same ventilation strategy included in a randomized controlled trial powered adequately to detect changes in length of time on mechanical ventilation and length of stay in intensive care and in hospital. Power calculations performed using the data presented in this thesis indicated that to detect a difference in duration of mechanical ventilation with 90% power, this will require a large multi-centre trial with 70 patients in each group.

The prevalence of patients with ARDS in the intensive care units in Australia is 42/678 (6.2%) of total ICU admissions (Australia New Zealand Intensive Care Society Clinical Trials Group Point Prevalence Data, 2009). It is possible that only half of the patients with ARDS may be included in a trial due to issues related to consent, requirements for surgery and other interventions or criteria that exclude them from a trial. Therefore any future trial of 140 patients with ARDS will require two years of data collection from a minimum of eight different sites.

This proposed study should examine a number of aspects of the efficacy of treatment. These may include:

- Adherence to the SRM protocol and to the control protocol
- Adverse events, including whether the entire SRM was tolerated
- Time to spontaneous ventilation
- Cost effectiveness, particularly if significant outcomes include reduced duration of ventilation or length of stay
- The relationship between lung compliance and duration of mechanical ventilation
- Long term comparison of the quality of life of survivors
- Long term comparison of respiratory function tests of survivors

In the PHARLAP strategy, optimal PEEP was approximated by titrating PEEP according to the response to arterial oxygen saturation. The method used in this work was simple but may have a number of limitations. The detection of oxygen saturation may be delayed if the lungs do not deflate immediately, or if the gas exchange is inadequate due to compressed

blood vessels under pressure or if oxygen saturation is offset by improved circulation and reduced venous oxygen saturation[13]. While the method used in the PHARLAP study was simple to perform at the bedside it may not be the most accurate method of setting PEEP in patients with ARDS[48,67-69]. Further work is required to determine the most accurate and effective method of establishing optimal PEEP after SRMs.

Other researchers have attempted to evaluate chest X-rays using a variety of methods[70-72] but the gold standard for the assessment of lung recruitment remains computerised tomography[72-73]. We have identified a simple and effective way of assessing change in lung area that may be used with digital radiology using chest X-rays in intensive care. This method of assessing lung area should be compared head to head with computerised tomography to assess whether the more clinically accessible measure of lung area on chest X-ray is sufficient to direct clinical decision making in people with ARDS undergoing RMs.

Currently no randomized controlled trial has compared long term outcomes of a ventilation strategy including recruitment manoeuvres to mechanical ventilation without recruitment manoeuvres where all other parts of the strategy are constant. This may be difficult in the clinical setting as RMs should be used as part of a strategy that includes individual PEEP titration and protective ventilation.

Further investigation is required to directly compare the effect of the static RM (40 cmH_2O for 40 seconds) compared to the SRM in ventilated patients with ARDS. This is particularly important as the international trend is to include the static RM in clinical trials despite the fact that it has not improved outcomes in two large randomized trials[27,36]. This would determine whether

- the static RM was tolerated compared to the SRM in terms of desaturation and hypotension
- patients who desaturate during the RM respond by improving their oxygenation after the RM with both the static and staircase RM

- the effects of both types of RMs are maintained for similar periods of time

Analysis of the literature indicated that it would be advantageous to conduct an individual patient data meta-analysis to determine the effect of RMs on patients with ARDS. This was attempted during the work presented in this thesis by contacting all authors included in the Cochrane review; however we were unable to attain the individual patient data required to perform the analysis. Individual patient data may provide insight into differences in outcome between patients with ARDS versus ALI, pulmonary versus extrapulmonary ARDS and early versus late inclusion of patients with ARDS into trials. International research groups investigating patients with ARDS might consider sharing deidentified individual patient data via an ARDS website, similar to the current use of data by the US ARDS network.

Although these results indicate that it may be possible to use SRMs safely and effectively in patients with ARDS, it is unclear whether SRMs would be safe and effective in other patient groups. Patients with acute lung collapse might be treated with manual or ventilator hyperinflation to increase tidal volumes and open collapsed alveoli. It may be possible to use SRMs to recruit collapsed lung in this patient group. Potentially, this may result in overdistension of normal lung units rather than recruitment of collapsed lung units. It may also result in increased transpulmonary pressure which may affect venous return, reduce cardiac output and dramatically reduce blood pressure.

Patients with ARDS may require rescue therapies to treat severe hypoxemia such as high frequency oscillatory ventilation or extra-corporeal membrane oxygenation. It may be possible to reduce the requirement for such rescue therapies by introducing a protocol to trial the use of a SRM rather than commencing these other therapies. During the H1N1 epidemic the SRM protocol was used with severely hypoxic patients with ARDS and two of these patients did not require the planned rescue therapies after the SRM (personal communication between the intensive

care consultants, The Alfred Hospital, Melbourne). It is important to determine whether delaying the use of rescue therapies is indeed beneficial or detrimental to long term outcomes in a larger sample of patients with ARDS.

Further investigation is required to assess the use of high frequency oscillatory ventilation in patients with severe hypoxemia as a rescue therapy. It is possible to perform a RM using the oscillator to slowly increase mean alveolar pressure to recruit collapsed alveoli[74-77]. The alveoli may then be maintained by the increased mean alveolar pressure delivered by the oscillatory ventilator. The optimal RM to use with the oscillator has not been determined.

The primary treatment for ARDS is low tidal volume ventilation; however our clinical experience, mirrored by other reports in the literature[28,78-79], is that low tidal volume ventilation alone is not enough to improve gas exchange, lung compliance and ultimately reduce lung injury associated with collapse and re-expansion of alveolar units. Clinicians seeking to provide evidence-based treatment for patients with ARDS are confronted with an array of literature about recruitment manoeuvres that is often conflicting. This thesis provides evidence that staircase recruitment manoeuvres in patients with ARDS appears to have positive physiological outcomes and could also result in improved longer term outcomes. The work reported here contributes to the refinement of recruitment manoeuvres, and enables more effective ventilatory strategies for those who are critically ill with ARDS.

Appendix 1 Ethics Committee approval

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 138/06

Project Title The cardiac and respiratory response to a stepwise recruitment maneuver in ventilated patients with acute lung injury

Principal Researcher: Mrs Carol Hodgson

Protocol No: 138/06

Participant Information and Consent Form version 2 **dated:** 31-Jul-2006
Next-of-Kin/Authorized Representative Plain Language Statement & Consent Form version 2 **dated** 31-Jul-2006

was considered by the Ethics Committee on 27-Jul-2006 and is ***APPROVED.***

Approval date: 31-Jul-2006 **Expiry date:** 31-Jul-2008

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report every 12 months for the duration of the project *(forms to be provided)*;
- A Request for Extension of the project prior to the expiry date, if applicable; and,
- A detailed Final Report at the conclusion of the project.

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Research Involving Humans (1999).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Research Involving Humans (1999).

SPECIAL CONDITIONS

None

SIGNED: [redacted]

Chair, Ethics Committee (or delegate)

Please quote Project No and Title in all correspondence

R. FREW
SECRETARY
ETHICS COMMITTEE

Appendix 2 Person responsible consent form

Person Responsible Consent Form

THE ALFRED

Person Responsible

Plain language statement

Principal Researcher:

Carol Hodgson

Associate Researchers:

A/Prof D Tuxen

Prof Jenny Keating

Dr A Holland

Dr A Davies

Title: The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.

Project number: 138/06 Version number:5 Date: 20.06.07

This plain language statement is 6 pages long. Please make sure you have all the pages

Introduction

We would like to include your relative in this research project “The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.” and we understand that he/she cannot consent for him/herself, at this stage. As the ‘person responsible’ for your relative, you are invited to consider your relative’s participation in this research project. Victorian law allows the person responsible for a patient to consent to the patient taking part in medical research where the patient is unable to provide consent for themselves. Before you decide whether or not you would like your relative to participate we would like to give you more information about the study to help you make the decision that will be best for your relative. One of the researchers will explain the background and purpose of the study to you and why your relative may be suitable to participate. You will also be given this plain language statement to keep.

This plain language statement contains detailed information about the research study. Its purpose is to explain to you as openly and clearly as possible all procedures involved with this study before you decide whether or not you would like your relative to take part in it. Please read the information carefully and ask any questions as they come to you. You may wish to discuss this study with other family members, friends or your local health worker. Please feel free to do this.

Once you understand what the project is about and if you do not have any objections to your relative taking part in it you will be asked to sign the acknowledgment form. By signing the acknowledgment form, you indicate that you understand the information and that you acknowledge your relative’s participation in the research project.

What is the study about?

This study involves collecting information about the heart and lungs when a patient is undergoing a procedure called a “recruitment manoeuvre”. A recruitment manoeuvre is used as standard care with a patient on a

ventilator to try and increase the amount of oxygen they receive by opening areas of the lung that have collapsed with illness and mechanical ventilation. A recruitment manoeuvre will be performed on your relative as part of standard care and separately to this study as decided by the intensive care doctors.

For the purpose of the research project we would like to measure their heart and lungs during the recruitment manoeuvre using the lines and monitors already in place.

Why is my relative suitable for this study on recruitment manoeuvres?

Your relative is suitable for the study because they have an acute lung injury and the intensive care doctor has decided to perform a recruitment manoeuvre as part of their care. Only patients with acute lung injury requiring help with their breathing on a ventilator are able to take part in this study. We propose to collect data about the heart and lungs if the intensive care doctor performs a recruitment manoeuvre.

What will happen during the study?

For the study we will measure the heart and lungs (oxygen levels, heart rate, blood pressure, lung compliance) using the equipment they are already attached to in intensive care throughout this time. No extra lines or tubes will need to be attached for this study. We will measure their heart and lung function for the period of the recruitment manoeuvre (18 minutes altogether) and for an hour after the manoeuvre. We will collect approximately one teaspoon of extra blood to look at their oxygen levels. We will also collect information about your relatives stay in hospital including their illness, how long they stay in intensive care and on a respirator and the outcome of their illness. We will collect information about the effects of the recruitment manoeuvre was and whether there were complications associated with performing the manoeuvre.

What are the benefits of the study?

This study is about collecting data during a recruitment manoeuvre. There is no additional benefit to your relative as a result of the data collected however the results will help us to provide the best possible care to our patients.

What are the risks/side effects associated with the study?

This procedure is performed in our intensive care unit is already used in patients with acute lung injury as standard care. The patient will be monitored at all times for side effects, which is also our usual practice.

There are no extra risks associated with data collection for this study.

How many participants will be involved?

Twenty patients entering the Alfred Intensive Care Unit will be enrolled over one year.

Does my relative have to take part in the study?

Participation in any research project is voluntary. If you do not want your relative to take part, you are not obliged to include them. If you agree at this stage for them to take part and then later change your mind, you can withdraw them from the study at any time. If you have any questions about your relative's involvement in the study at any time please contact **Carol Hodgson,** the **main investigator on 9206 3450.**

Any decision you make will not affect your relationship with the Alfred or your relative's treatment and his/her relationship with the Alfred. If you decide that you do not want your relative to participate in the study they will continue to receive the best possible current treatment and care.

If you decide that you would like your relative to participate in the study, then the researchers will make sure they discuss the study with your relative when he/she is well enough to understand. Your relative can then make a decision about whether he/she want to continue with the study.

Once again, any decision they make will not affect their treatment or their relationship with the Alfred.

Is anyone else involved with decision making?

The decision about involving your relative in the study is entirely up to you and any other family members that you want involved in the decision making process.

Will taking part in the study cost my relative anything?

There will be no cost to your relative if they take part in the study.

How will results be kept confidential and how will they be reported?

No identifying information will be used in any reports or publication of this study. Your relative cannot be identified. Records for the study will be kept in a secure filing cabinet in a secure office. A database with study information will be generated and this will be kept in a computer that is password protected. Records pertaining to the study will be kept indefinitely.

The findings of the study will be published in a medical journal. A report for participants and their families will be prepared and will be available from the researchers listed below. The findings will not be available until such time that all participants have completed follow up and the data collected and analysed (June 2008).

Where can I get further information about the study?

You can get further information about the study by contacting the project manager or study researchers.

Carol Hodgson	Project Manager	9076 3450 or 9206 2000
A/Prof David Tuxen	Principal Investigator	9076 3050
Andrew Davies	Principal Investigator	9076 3036

Ethical guidelines

This project will be carried out according to the National Statement on Ethical Conduct involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. The Human Research Ethics Committee of this hospital has approved the ethical aspects of this study.

In the event that you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you.

If I have any issues about my relative's involvement who do I contact?

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about the rights of research participants, then you may contact

Ms Rowan Frew

Ethics Manager

Research & Ethics Unit

Ph: 9076 3848

Person Responsible Consent Form

Principal Investigators:

Carol Hodgson, A/Prof D Tuxen, Prof Jenny Keating, Dr A Holland, Dr A Davies

Title: The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.

Project number: 138/06 Version number:5 Date: 20/06/2007

I have read, or have had read to me and I understand the Participant Information version ***5*** dated ***20/06/2007***.

I am the Person Responsible for _____ I consent to the participation of

_____in the research project named above, according to the conditions in the Participant Information.

I believe the carrying out of the procedure is not contrary to the best interests of

_____.

I will be given a copy of the Person Responsible Information and Consent Form to keep.

The researcher has agreed not to reveal _____'s identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) ……

Name of Person Responsible (printed) ……

Relationship to participant: ……

Signature Date

Witness to Signature (printed) ……

Signature Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the person named above as the Third Party has understood that explanation.

Researcher's Name (printed) ……

Signature Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.

Person Responsible Revocation of Consent

Principal Investigators: Carol Hodgson

Title: The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.

Project number: 138/06 Version number: 5 Date: 20/06/2007

I hereby wish to WITHDRAW my consent to the participation of _____ in the research proposal named above and understand that such withdrawal WILL NOT jeopardise any treatment or my relationship with The Alfred Hospital.

Participant's Name (printed) …….

Signature Date

Appendix 3 Delayed patient consent and information

Participant information sheet and continuing consent form

Principal Investigator: Carol Hodgson

Title: The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.

Project number: 138/06 **Version number: 4** **Date: 16.03.2007**

This participant information sheet is 5 pages long. Please make sure you have all the pages.

Introduction

The Alfred Ethics Committee has approved your enrolment in this research study at a time when you were unable to give your consent. We now wish to know whether you would like to continue to participate in this study. Before you decide whether or not to continue to be involved, we would like to give you more information about the study to help you make the decision. One of the researchers will explain the background and purpose of the study to you and why you were suitable to participate in it. You will also be given this information sheet to keep.

This participant information sheet contains detailed information about the research study. Its purpose is to explain to you as openly and clearly as possible all procedures involved with this study before you decide whether or not you would like to continue to take part in it. Please read the information carefully and ask any questions as they come to you. You may wish to discuss this study with other family members, friends, or your local health worker. Please feel free to do this.

Once you understand what the project is about and if you decide to continue to be involved you will be asked to sign the consent form. By signing the consent form, you indicate that you understand the information and that you agree to continue to participate in the research study.

What is the study about?

This study is about collecting data during a standard procedure in intensive care. Over the past few years, a sustained deep breath called a “recruitment manoeuvre” has been used as standard care to try to reverse the effects of lung injury and pneumonia in patients on respirators. What we are aiming to do in this study is to find out whether patients who have developed lung injury or pneumonia are better off to receive a recruitment manoeuvre from time to time to improve the level of oxygen in their blood.

How did I become involved in the study?

You were suitable for the study because you became very unwell and you were admitted to the ICU to receive treatment using a ventilator (breathing) machine for acute lung injury.

Was anyone else involved with decision making?

Your family were asked to give consent for your participation in the study at a time when you were unable to give your own consent.

What happened/happens to me during the study?

As part of the standard care given to you while you were unwell you were positioned on your back with the ventilator set to deliver the recruitment manoeuvre very slowly.

As part of the study we measured your heart and lungs (oxygen levels, heart rate, blood pressure, lung compliance) using the equipment attached to you in intensive care throughout this time. No extra lines or tubes were needed to be attached for this study however we did take approximately one teaspoon extra of blood to measure your oxygen levels during the manoeuvre. We measured your heart and lung function for the period of the recruitment manoeuvre (18 minutes altogether) and for an hour after the manoeuvre. We also collected information about your stay in hospital including your illness, how long you stayed in intensive care and on a respirator and the outcome of your illness. We collected information about the effects of the recruitment manoeuvre and whether there were complications associated with performing the manoeuvre.

What are the benefits to me of being involved in the study?

We cannot guarantee or promise that you will have individually benefited from the study. The results of this study are aimed at improving clinical care of our patients.

What are the risks/side effects associated with the study?

This procedure (recruitment manoeuvre) is performed in our intensive care unit and is used in some patients with acute lung injury as standard care. You were monitored at all times for side effects, which is also our usual practice.

There were no extra risks associated with the data collection for this study.

How many participants will be involved?

20 patients from intensive care will be enrolled over a 1 year period at the Alfred.

Do I have to take part in the study?

Participation in any research project is voluntary. If you do not wish to continue to participate in this study you are not obliged to. If you decide to continue to take part and then later change your mind, you can withdraw from the study at any time. If you have any questions about your involvement in the study at any time please contact Carol Hodgson the Principal Investigator on 9076 3450.

Whatever decision you make your relationship with Alfred staff will not be affected. If you decide to continue your participation and later change your mind, again your relationship with Alfred staff will not be affected.

Will taking part in the study cost me anything?

There will be no cost to you if you take part in the study.

How will results be kept confidential and how will they be reported?

No identifying material will be used in any reports or publications of this study. Records for the study will be kept in a secure filing cabinet in a secure office. A database with study information will be generated and this will be kept in a computer that is password protected. Records relating to the study will be kept indefinitely.

The findings from the study will be published in a medical journal. If you wish to know the results of the study, please contact one of the researchers listed below. The findings will not be available until all the participants have completed follow up and the data has been collected and analysed.

Where can I get further information about the study?

You can get further information about the study by contacting one of the investigators

.

Carol Hodgson	Principal Investigator	9076 3450 or 9076 2000
Dr Andrew Davies	Co-investigator	9076 3036 or 9076 2000

Dr Anne Holland	Co-investigator	9076 3450 or 9076 2000
A/Prof David Tuxen	Co-investigator	9076 2000

Ethical guidelines

This project will be carried out according to the National Statement on Ethical Conduct involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. The Human Research Ethics Committee of this hospital has approved the ethical aspects of this study.

If I have any other issues with the study, whom do I contact?

If you have any concerns about your involvement in the study, any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

Ms Rowan Frew

Ethics Manager

Research and Ethics Unit

Ph: 9076 3848

Consent Form

Principal Investigators: Carol Hodgson

Title: The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.

Project number: 138/06 Version number: 4 Date: 16/03/2007

I have read, or have had read to me and I understand the Participant Information version ***4*** dated ***16/03/2007***.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to continue participation in this project according to the conditions in the Participant Information.

I will be given a copy of the Participant Information and Consent Form to keep.

I understand that the researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) ……

Signature Date

Name of Witness to Participant's Signature (printed) ……

Signature Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher's Name (printed) ……

Signature Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.

Revocation Of Consent Form

Principal Investigators: Carol Hodgson

Title: The cardiac and respiratory response to a stepwise recruitment manoeuvre in ventilated patients with acute lung injury.

Project number: 138/06 Version number: 4 Date: 16/03/ 2007

I hereby wish to WITHDRAW my consent to participate in the research project described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with ***The Alfred Hospital***.

Participant's Name (printed) _____

Signature _____ Date _____

Appendix 4 Data collection form

Staircase Lung Recruitment Study

Patient ID Sticker

Patient No

Date M / F

APACHE II Score APACHE III

Reason for ICU Admission:

Relevant PHx:

ALI Cause:

Criteria:

Score:

Initial P/F (Should be <250):

Intubation Status – oral/nasal/trache

Ventilation: Mode

Rate

PEEP

FiO2

PIP

CXR Findings:

	R UL	R ML	R LL	L UL	L Mid	L LL
Collapse						
Consolidation						

Lung Recruitment Study Screening

Inclusion:

- Mechanical ventilation on PB 840
- PaO_2/FiO_2 < 250
- ARDS / ALI (CXR – bilateral lung infiltrates)
- Arterial line
- CVC
- 16 years old or more

Exclusion:

- Cardiac suspected as primary cause
- Transplant (heart or lung or bone marrow)
- Mechanical ventilation > 5 days
- ICC with current air leak
- Pneumothorax on CXR
- Acute bronchospasm
- Raised ICP
- Acute pulmonary oedema
- Recent AMI or ischaemic changes
- Pregnancy
- Haemodynamic instability – MAP<60 mmHg, unstable arrythmias

Early termination of stepwise recruitment manoeuvre:

- **SBP < 80mmHg**
- **SpO2 < 85%**
- **New arrhythmia**
- **New air leak (ICC)**
- **Heart rate < 60 or > 140**

Nursing Information Sheet for the Lung Recruitment Study

The lung recruitment study is being conducted in the Alfred ICU which involves patients with ARDS or ALI. The primary investigator is Carol Hodgson (PhD student – ext 3450) with A/Prof David Tuxen and Dr Andrew Davies as co-researchers.

We would like to include your patient in the lung recruitment study. The study will involve a stepwise recruitment manoeuvre performed by one of the intensive care doctors. The PEEP will be slowly increased every 2 minutes for 8 minutes then slowly reduced to an optimal level (between 25 and 15 cmH_2O). The entire procedure will take about 20 minutes and then we will collect data for the next hour.

If you have any questions or concerns before or during the procedure please speak to Carol or the intensive care doctor performing the recruitment manoeuvre.

Information on cardiac and respiratory parameters (including venous and arterial gases) will be collected and recorded on the patients throughout the manoeuvre at 2 minute intervals and for 1 hour after the treatment has ceased. Patients will be subject to all of the usual safety procedures in intensive care during this treatment. PEEP will be reduced if systolic BP falls below 80 mmHg.

During the procedure the patient will be supine and cannot be rolled or suctioned unless it is an emergency. The patient will be placed into pressure control mode at $15cmH_20$ and their PEEP will be gradually increased to a peak of $40cmH_2O$ and then decreased to optimal levels (determined by SpO_2). They will need to stay in this mode of ventilation for the entire duration of data collection (assume 2 hours from the start).

We thank-you for your assistance.

Data Collection Forms

Time (mins)	Pre 10	Pre 5	0	2	4	6	8	10	12	14	16	18	30	60
PEEP	10	10	10	10	20	30	40	25	22.5	20	17.5	15		
ABG **PH** **PaCO2** **PaO2** **HCO3** **SaO2**			*				*					*	*	*
SaO_2	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Vt	*	*	*	*	*	*	*	*	*	*	*	*	*	*
HR	*	*	*	*	*	*	*	*	*	*	*	*	*	*
SBP	*	*	*	*	*	*	*	*	*	*	*	*	*	*
DBP														
MBP														
CVP	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PCP	*	*	*	*	*	*	*	*	*	*	*	*	*	*
CO			*				*					*	*	*
SvO_2			*				*					*	*	*
CT (static)	*	*	*	*	*	*	*	*	*	*	*	*	*	*

* the point at which measurement is taken

PEEP = positive end expiratory pressure, Palv = internal lung pressure, ABG = arterial blood gases, SaO2 = arterial oxygen saturation, Vt = tidal volume, HR = heart rate, BP = blood pressure – mean, systolic, diastolic (MAP,SBP,DBP) CVP= central venous pressure, PCP = pulmonary capillary wedge pressure, CO = cardiac output, SvO2 = venous oxygen saturation, CT = static lung compliance

Appendix 5 Certificate of approval of amendments

Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project **98/07 Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures (PHARLAP): a phase II randomised trial in ARDS patients**

Principal Researcher: **Professor Jamie Cooper**

Amendment: **Addition of associate researcher**
Revised Module One **version 1.6** dated: **7-Aug-2007**
Patient Information Sheet **Version 1.6** dated: **13-Sep-2007**
Person Responsible Information Sheet & Consent Form
Version 1.6 dated: **13-Sep-2007**

have been approved in accordance with your amendment application on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

[redacted]

Chair, Ethics Committee (or delegate)
R. FREW
SECRETARY
ETHICS COMMITTEE

Date: 26-Nov-2007

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).

Person responsible and consent form PHARLAP

Person Responsible information sheet and consent form

Principal Researcher: Jamie Cooper

Associate Researchers: *Alistair Nichol, David Tuxen, Andrew Westbrook, Andrew Davies, Carol Hodgson.*

Title: Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures: a phase II randomised trial in ARDS patients

Project number: 98/07 Version number: 1.8 Date: 18.09.08

This information sheet is 7 pages long. Please make sure you have all the pages.

As the 'person responsible' for your relative, you are invited to consider your relative's participation in this research project. Victorian law allows the person responsible for a patient to consent to the patient taking part in medical research where the patient is unable to provide consent for themselves. Before you decide whether or not to involve your relative in this study, we would like to give you more information about the study to help you make the decision. One of the researchers will explain the background and purpose of the study to you and why your relative is suitable to participate in it. You will also be given this information sheet to keep.

This participant information sheet contains detailed information about the research study. Its purpose is to explain to you as openly and clearly as possible all procedures involved with this study before you decide whether or not you would like your relative to take part in it. Please read the information carefully and ask any questions as they come to you. You may wish to discuss this study with other family members, friends, or your local health worker. Please feel free to do this.

Once you understand what the project is about and if you decide to enrol your relative in the study you will be asked to sign the consent form. By signing the consent form, you indicate that you understand the information and that you agree for your relative to participate in the research study.

Purpose and Background?

When a patient is admitted to the intensive care unit (ICU) and needs help with their breathing they are connected to a ventilator (breathing machine). However, because the patient needs help from the breathing machine their lungs do not work as they normally would. This can lead to lung injury, areas of lung collapse and the amount of oxygen in their blood may be reduced. The injury which occurs in the lungs can lead to injury in other organs of the body.

Over the past few years, both reducing the size of each breath delivered by the ventilator and an occasional sustained deep breath called a “recruitment manoeuvre” have been used to try to prevent the damaging effects of lung injury in patients. These protective strategies frequently result in higher than normal levels of carbon dioxide, a gas produced by normal tissue and organs, which we exhale. However it has been argued that these higher levels of carbon dioxide may actually be protective and measures to reduce the carbon dioxide levels to normal may actually be damaging.

What we are aiming to do in this study is to find out whether patients who have developed lung injury are better off when we further reduce the size of each ventilator breath and receive a sustained deep breath (recruitment

manoeuvre) from time to time and permit elevated levels of carbon dioxide.

This trial has been initiated by the investigator, Professor Jamie Cooper. The results of this research may be used to help researcher Ms Carol Hodgson to obtain a degree.

Why is my relative suitable for the study?

Your relative is suitable for the study because he/she became very unwell and has been admitted to the ICU to receive treatment using a ventilator (breathing) machine for acute lung injury. At the start of this study an assessment of the degree of damage to the lungs will be made to confirm that your relative is suitable to proceed in this study.

What will happen to my relative during the study?

At the start of the study patients will be randomly placed into either the current standard ICU treatment for patients with lung damage group or the PHARLAP study treatment group. The patient will be placed into a particular group based on chance and the treating doctors will not decide. In the current intensive care practice group patients will receive the best standard of care and will not be denied any treatments or medications that have be shown to improve survival. In the PHARLAP study treatment group the size of each breath the respirator will deliver will be reduced to keep the pressure on the patient's lungs low. Up to four times a day the pressure of the ventilator will be set to increase slightly and then reduced slowly to a level that provides the best oxygen levels to the blood. In the PHARLAP group patients will not be denied any treatments or medications that have been shown to improve survival. We will measure the patients heart and lungs (oxygen levels, heart rate, blood pressure, lung pressures, cardiac output) using the equipment attached to them in intensive care throughout this time. A special probe will be placed into an existing line in the vein for additional readings of the heart and lungs.. The only tests performed in addition to routine care will be 8 blood samples (under 10mls or 2 teaspoonfuls each) will be taken over the whole duration of this study, 2 urine tests (10mls or 2 teaspoonfuls each) and a daily cardiac echo

(picture of the blood flow via ultrasound) if your relative is in the treatment group. These will allow measurement of the degree of inflammation and the levels of oxygen and the blood flow in the patient's body. The patient will remain in the study while they are in the intensive care unit. We also collect information about the patient's stay in hospital including illness, how long they stay in intensive care and on a respirator and the outcome of their illness.

Continual review and monitoring of this project will take place, regarding the benefit and safety to enable early detection of any problems that patients may suffer.

What are the possible risks to my relative if they take part?

Patients with Acute Lung Injury are very ill and frequently develop complications of this disease and a high proportion of patients die (4 in 10). It has not been shown that the study interventions in the PHARLAP treatment group will increase the level of complications in patients. However we will closely monitor patients in both treatment groups for the common complications of this disease (i) air leak from the lung (1 in 10), (ii) very low blood pressure (1 in 2), (iii) injury to other organs in the body (1 in 2) and the development of infections(1 in 2).

What are the benefits to my relative of being involved in the study?

Some possible benefits of the study are that the patient may have reduced inflammation in the lungs and body and in addition may have received greater amounts of oxygen in the blood which assists all of the body's functions, however we cannot guarantee or promise that the patients will individually benefit from the study.

Will any blood or urine samples be taken?

Yes, 8 separate blood samples of up to10mls (2 teaspoonfuls) each will be taken over the whole time spent in the intensive care unit. These blood samples will be taken from the drips that are already in place for treatment and monitoring of the patient.

Yes, two urine samples of 10 mls each (2 teaspoonfuls) will be taken. These urine samples will be taken from a tube that has already been placed in the bladder to monitor the kidney function of the patient.

All these samples will be stored in a secure fridge until the study has been completed. We expect that this study will take about 18 months to complete and measure the inflammatory markers in the blood and urine. These samples will be stored in a locked laboratory with no accompanying identifying information to preserve confidentiality. These samples will be analysed to determine the degree of inflammation markers in the blood and urine and then destroyed. While this information may allow us to determine whether this new respirator treatment is beneficial to patients in the future, this information is not useful in selecting treatment for the patient at the moment.

How many participants will be involved?

30 patients from intensive care will be enrolled over a 18 month period at the Alfred.

Does my relative have to take part in the study?

Participation in any research project is voluntary. If you do not wish to enrol your relative in this study you are not obliged to. If you later change your mind, you can withdraw your relative from the study at any time. If you have any questions about their involvement in the study at any time please contact Dr Alistair Nichol the Co-Investigator on 99005113.

Whatever decision you make you and your relative's relationship with the Alfred and with those treating them will not be affected.

Will taking part in the study cost anything?

There will be no cost to you or the patient for taking part in the study.

How will results be kept confidential and how will they be reported?

No identifying material will be used in any reports of this study. Records for the study will be kept in a locked filing cabinet in a locked office. A database with study information will be generated and this will be kept in a

computer that is password protected and only accessible by the researchers involved in the study. Records relating to the study will be kept indefinitely.

The findings from the study will be published in a medical journal. If you or the patient wish to receive a one page summary of the overall results of the study, please contact one of the researchers listed below. The findings will not be available until all the participants have completed follow up and the data has been collected and analysed. We hope that the study will be completed by December 2008.

New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that your relative can no longer participate in this research. If this occurs, the person(s) supervising the research will stop their participation. In all cases, they will be offered all available care to suit their needs and medical condition.

Where can I get further information about the study?

You can get further information about the study by contacting one of the investigators

Alistair Nichol	Associate Researcher	9903 0513
Jamie Cooper	Principal Researcher	9076 8806
Dr Andrew Davies	Associate Researcher	9076 3036
A/Prof David Tuxen	Associate Researcher	9076 2000

Ethical guidelines

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. The Alfred Hospital Ethics Committee has approved the ethical aspects of this study.

Injury

In the event that your relative suffers an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you or them.

If I have any other issues with the study, whom do I contact?

If you have any concerns about your relative's involvement in the study, any aspect of the project, the way it is being conducted or any questions about your relative's rights as a research participant, then you may contact:

Ms Rowan Frew

Ethics Manager

Research and Ethics Unit

Ph: 9076 3848

‘Person Responsible’ Consent Form

Principal Researcher: Jamie Cooper

Associate Researchers: ***Alistair Nichol, David Tuxen, Andrew Davies, Andrew Westbrook, Carol Hodgson.***

Title: Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures: a phase II randomised trial in ARDS patients

Project number: 98/07 Version number: 1.6 Date: 13th September 2007

I have read, or have had read to me in my first language, and I understand the Participant Information version ***1.6*** dated ***13.09.2007***.

I am the Person Responsible for ……..

I consent to the participation of ……in the research project named above, according to the conditions in the Participant Information.

I believe the carrying out of the procedure is not contrary to the best interests of

…….

I will be given a copy of the Person Responsible Information and Consent Form to keep.

The researcher has agreed not to reveal …….s identity and personal details if information about this project is published or presented in any public form.

Participant’s Name (printed) ……

Name of Person Responsible (printed) ……

Relationship to participant: ……

Signature Date

Witness to Signature (printed) ……

Signature Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the person named above as the Third Party has understood that explanation.

Researcher’s Name (printed) ……

Signature Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the Consent Form must date their own signature.

Person Responsible Consent Form For Blood And Urine Sample Storage And Use

Principal Researcher: Jamie Cooper

Associate Researchers: ***Alistair Nichol, David Tuxen, Andrew Westbrook, Andrew Davies, Carol Hodgson.***

Title: Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures : a phase II randomised trial in ARDS patients

Project number: 98/07 Version number: 1.6 Date: 13th September 2007

I have read and I understand the Participant Information version ***1.6*** dated *13**.09.**2007.*I am the Person Responsible for .....

I consent to the storage and use of blood taken from..... for use in further research as described in this Person Responsible Information Form by .....

By signing this Consent Form, I agree to the storage and use of blood for the purposes of testing for inflammatory mediators. Seven of these blood samples (Thirteen in total) and urine samples (TWO) will be stored until blood analysis is complete and then destroyed.

Person Responsible's name (printed).....

Signature Date

Name of Witness to Participant's signature (printed).....

Signature Date

Appendix 5 : Certificate of approval of amendments

Researcher's name……..

Signature Date

Note: All parties signing the Consent Form must date their own signature.

Revocation Of Consent Form

Principal Researcher: Jamie Cooper

Associate Researchers: ***Alistair Nichol, David Tuxen, Andrew Westbrook, Andrew Davies, Carol Hodgson.***

Title: Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures: a phase II randomised trial in ALI patients

Project number: 98/07 Version number: 1.6 Date:13 September 2007.

As the person responsible for ……..

I hereby wish to WITHDRAW my consent for [participant's name] to participate in the research project described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or their relationship with ***The Alfred Hospital***.

Person Responsible's Name (printed) _____

Signature _____ Date _____

Appendix 6 Patient information sheet

Patient information sheet

Principal Researcher: Jamie Cooper

Associate Researchers: ***Alistair Nichol, Carol Hodgson, David Tuxen, Andrew Davies, Andrew Westbrook.***

Title: Permissive Hypercapnia and Alveolar Recruitment with Limited Airway Pressures: a phase II randomised trial in ARDS patients

Project number: 98/07 Version number: 1.8 Date: 18.09.2008

This information sheet is 1 page long.

During your critical illness you developed a severe lung injury called acute respiratory distress syndrome. The 'person responsible' for your care, entered you in a research project which was looking at better ways to treat this condition. This participant information sheet contains detailed information about the research study.

The aim of this study is to find out whether patients who have developed lung injury are better off when we further reduce the size of each ventilator breath and receive a sustained deep breath (recruitment manoeuvre) from time to time and permit elevated levels of carbon dioxide.

At the start following a brief assessment of the degree of lung damage, patients were randomly placed into either the current standard ICU treatment for patients with lung damage group or the PHARLAP study treatment group. In the PHARLAP study treatment group the size of each breath that the respirator delivered was reduced to keep the pressure on your lungs low. Up to four times a day the pressure of the ventilator was increased slightly (each breath was at this higher pressure) and then

reduced slowly to a level that provides the best oxygen levels to the blood. In the standard treatment or PHARLAP group patients were not denied any treatments or medications that have been shown to improve survival. No extra lines or tubes were needed to be attached for this study. The only tests performed in addition to routine care were continuous readings of your heart and oxygen levels with a small probe into the existing lines in your veins, up to 8 blood samples (under 10mls or 2 teaspoonfuls each) taken over the whole duration of this study, 2 urine tests (10mls or 2 teaspoonfuls each) and a non-invasive measure of the blood flow in your heart (echocardiography). These tests allowed measurement of the degree of inflammation and levels of oxygen in your body. You remained in the study while you were in the intensive care unit.

What were the benefits to me of being involved in the study?

Some possible benefits of the study are that you may have had reduced inflammation in the lungs and body and in addition may have received greater amounts of oxygen in the blood which assists all of the body's functions, however we cannot guarantee or promise that the patients will individually benefit from the study.

Where can I get further information about the study?

You can get further information about the study by contacting the researcher, Dr Alistair Nichol on 9903 0513. If you have a concern or complaint about how the project is being run, please contact the Manager of the Alfred Hospital Ethics Unit, Ms Rowan Frew, on 9076 3848.

Appendix 7 PHARLAP Study Form 1 Screening check list

PHARLAP Study	anzic research centre	**Screening Check list** **FORM 1**	**Hospital ID:** ☐☐☐ **Patient Initials:** ☐☐☐ **Patient Study Number:** ☐☐☐ ☐☐☐

This form should be completed for all patients who meet the 5 clinical inclusion criteria below:

1.01 Inclusion Criteria, (mark with an `x`, see over page for definitions)

(a) ☐ Endotracheal intubation or tracheostomy

(b) ☐ Acute onset respiratory distress (<28 days).

(c) ☐ Severe hypoxemia (PaO_2/FiO_2 ratio <200mmHg).

(d) ☐ Bilateral infiltrates on frontal Chest X-ray.

(e) ☐ No evidence of left atrial hypertension (PAOP `wedge pressure` < 18mmHg if measured). Primary cause of the respiratory failure is not cardiac.

1.02 Stratification Criteria for severe sepsis (see over page for definitions)

NB. Not inclusion or exclusion criteria.

(a) ☐ Strongly suspected or confirmed site of sepsis

(b) ☐ Presence of ≥ 3 SIRS criteria in the 48 hours prior to randomisation

(c) ☐ Presence of Organ Dysfunction in at least one of the following systems in the 24 hours prior to randomisation

- Cardiovascular system dysfunction :
- Renal dysfunction
- Respiratory system dysfunction
- Haematologic system dysfunction.
- Unexplained metabolic acidosis

1.03 Exclusion Criteria (tick all that apply)

(a) ☐ Age < 18 years or >90 years

(b) ☐ Death is imminent (<24 hrs)

(c) ☐ Pregnancy or breast feeding

(d) ☐ Anticipated to require mechanical ventilation less than 48 hours (determined by attending physician)

(e) ☐ More than 48 hours of mechanical ventilation prior to randomisation.

(f) ☐ Pre-existing severe chronic obstructive pulmonary disease/ lung transplant

(g) ☐ Conditions where hypercapnia-induced intracranial hypertension should be avoided.

(h) ☐ Significant history of ventricular fibrillation or tachyarrhythmia (excluding atrial fibrillation).

(i) ☐ Enrolment in another interventional study or previous enrolment in this study.

(k) ☐ Patient not for aggressive treatment

(l) ☐ Malignancy or irreversible condition with a 6 month mortality > 50%

(m)☐ Human Immunodeficiency Virus (HIV) infection with a CD4 count ≤ 50/mm^3

(n)☐ Anticipated to require under 48hours mechanical ventilation.

1.04 Eligible non-randomized patients.

(a) ☐ Greater than 48 hours since mechanical ventilation prior to randomisation.

(b) ☐ Current participation in a competing trial.

(c) ☐ Lack of physician consent.

(d) ☐ Lack of patient or proxy consent.

If the patient meets ALL inclusion criteria and NONE of the exclusion criteria then obtain consent and proceed to assessment of PaO_2 / FiO_2 ratio on standard settings and subsequent randomisation if <200.

.

(Print this on the back of page 1)

Presence of ≥ 3 SIRS criteria in the 48 hours prior to randomisation

- Core Temperature ≤ 36.0^{o}C or ≥ 38.0^{o}C
- HR > 90 beats/min
- Respiratory Rate > 20 breaths/minute OR PaCO2 < 32 mm Hg OR mechanically ventilated (positive pressure only)
- WCC >12.0 x 10^{9}/L or < 4.0 x 10^{9}/L OR > 10% bands

Organ Dysfunction in the 24 hours prior to randomisation

- **Cardiovascular system dysfunction :**
  - Systolic blood pressure < 90 mmHg for one hour despite adequate fluid resuscitation
  - Mean Arterial blood pressure < 70 mmHg for one hour despite adequate fluid resuscitation
  - Need for vaso-active agents to maintain Mean Arterial blood pressure > 70 mmHg
- **Renal dysfunction**
  - Urine output < 0.5 ml/kg/hr for one hour or more
- **Respiratory system dysfunction**
  - PaO_2:FiO_2 ratio ≤ 250 in the presence of other organ dysfunction
  - PaO_2:FiO_2 ratio < 200 if the lung is the only organ dysfunction
- **Haematologic system dysfunction**
  - Platelet count < 80 x 10^{9}/L
  - Platelet count decrease by ≥ 50% in 3 days before randomisation
- **Unexplained metabolic acidosis**
  - pH ≤ 7.3 AND lactate > 1.5 ULN
  - Base deficit ≥ 5.0 mmol/L AND lactate > 1.5 ULN

Appendix 8 PHARLAP Study Form 2 Baseline check list

PHARLAP Study	anzic research centre	**Baseline Check list** FORM 2	Hospital ID: |__|__|__| Patient Initials: |__|__|__| Patient Study Number |__|__|__|__|__|__|__|

Patients Demographics

2.01	**I__I__I/I__I__I/I__I__I__I__I *(dd/mm/yyyy)***	**Date of Birth**
2.02	Male ☐ Female ☐	**Patient Gender**
2.03	**I__I__ I__I**	**Patient Height (cm)**
2.04	**I__I__ I__I**	**(a) Patient Weight (kg)** ☐ **estimated or documented** ☐ **Measured**
2.05	**I__I__ I__I**	**(a) Predicted body weight.** **Male PBW= 50.0 + 0.91x (height in cm -152.4)** **Female PBW= 45.5 +0.91x(height in cm -152.4)**

Hospital and ICU admission Details

2.06	**I__I__I/I__I__I/I2I0I0I__I *(dd/mm/yyyy)***	**Hospital admission date**
2.07	**I__I__ I:I__I__ I**	**Hospital admission time (24 hour clock)**
2.08	**I__I__I/I__I__I/I2I0I0I__I *(dd/mm/yyyy)***	**ICU admission date**
2.09	**I__I__ I:I__I__ I**	**ICU admission time (24 hour clock)**

2.10	**I__I__ I__I**	**Hospital Admission Diagnosis Code (APACHE III):**
2.11	**I__I__ I__I**	**Please enter the patient's APACHE II score for the 24 hour period preceding ICU admission**

Inclusion Criteria, (mark with an `x`, see over page for definitions)		
2.06	Endotracheal intubation Tracheostomy	☐ Yes ☐ No (excluded if no to both) ☐ Yes ☐ No (excluded if no to both)
2.09	Acute onset respiratory distress (<28 days).	within I__I__ I days (excluded if >28 days)
2.09	Severe hypoxemia (PaO2/FiO2 ratio <200mmHg).	PaO_2/FiO_2 ratio I__I__I__ I (excluded if >200 days)
2.09	Chest X ray	☐ Bilateral infiltrates ☐ No infiltrates (excluded)
2.09	Evidence of left atrial hypertension PAOP `wedge pressure` < 18mmHg .	☐ No ☐ Yes (excluded) PAOP I__I__ I mmHg ☐ Not measured

Stratification criteria severe sepsis

If the patient meets all criteria then stratify to the severe sepsis group

Site of Sepsis

2.2 Strongly suspected or confirmed site of sepsis? ☐ Yes ☐ No

≥ 3 Systemic Inflammatory Response Syndrome Criteria

2.3 Presence of ≥ 3 SIRS criteria in the 48 hours prior to randomisation: ☐ Yes **- Continue below.** ☐ No **- Patient is excluded.**

2.3.1 Core Temperature ≤ 36°C or ≥ 38.0°C: ☐ Yes → **If YES, 2.3.1(i)** Value: ☐☐·☐ °C ☐ No **2.3.1(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

2.3.2 Heart Rate > 90 beats/min: ☐ Yes → **If YES, 2.3.2(i)** Value: ☐☐☐ beats/min ☐ No **2.3.2(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

2.3.3 Respiratory: ☐ Yes **- continue below** ☐ No **- skip to Q 2.3.4**

a) Respiratory rate > 20 breaths/minute: ☐ Yes → **If YES, 2.3.3a(i)** Value: ☐☐ breaths/minute ☐ No **2.3.3a(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

b) $PaCO_2$ <32 mmHg: ☐ Yes → **If YES, 2.3.3b(i)** Value: ☐☐ mmHg ☐ No **2.3.3b(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

c) The patient is mechanically ventilated: ☐ Yes → **If YES, 2.3.3c(i)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes) ☐ No

2.3.4 White Cell Count: ☐ Yes **- continue below** ☐ No **- skip to Q 2..4**

a) WCC > 12.0 x 10^9/L or 4.0 x 10^9/L: ☐ Yes → **If YES, 2.3.4b(i)** Value: ☐☐·☐ x10^9/L ☐ No **2.3.4b(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

b) White Cells > 10% bands: ☐ Yes → **If YES, 2.3.4b(i)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes) ☐ No

Stratification- Organ Dysfunction

Organ Dysfunction

2.4 Presence of Organ Dysfunction in at least one of the following systems in the 24 hours prior to randomisation:
☐ Yes **- Continue below.**
☐ No **- Patient is excluded**

2.4.1 Cardiovascular System Dysfunction: ☐ Yes **- continue below**
☐ No **- skip to Q 2.4.2**

a) SBP < 90mmHg: ☐ Yes → **If YES, 2.4.1a(i)** SBP: ☐☐ mmHg
☐ No
2.4.1a(ii) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

b) MAP < 70mmHg: ☐ Yes → **If YES, 2.4.1b(i)** MAP: ☐☐ mmHg
☐ No
2.4.1b(ii) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

c) Vaso-active agents: ☐ Yes → **If YES, 2.4.1c(i)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)
☐ No

2.4.2 Renal Dysfunction: ☐ Yes **- continue below**
☐ No **- skip to Q 2.4.3**

a) Urine output < 0.5 ml/kg/hour: ☐ Yes → **If YES, 2.4.2a(i)** Value: ☐☐ mL/kg/hr
☐ No
2.4.2a(ii) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

2.4.3 Respiratory System Dysfunction: ☐ Yes **- continue below**
☐ No **- skip to Q 2.4.4**

a) PaO_2:FiO_2 ratio ≤ 250 (or 200 if the lung is the only organ dysfunction: ☐ Yes → **If YES, 2.4.3a(i)** PaO_2:FiO_2: ☐☐☐
☐ No
2.4.3a(ii) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

2.4.4 Haematologic System Dysfunction: ☐ Yes **- continue below**
☐ No **- skip to Q 2.4.5**

a) Platelet count < 80 x 10^9/L: ☐ Yes → **If YES, 2.4.4a(i)** Platelet count: ☐☐ x10^9/L
☐ No
2.4.4a(ii) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

b) Platelet count decrease by ≥ 50% in 3 days before randomisation: ☐ Yes → **If YES, 2.4.4b(i)** Initial platelet count: ☐☐☐ x10^9/L
☐ No
2.4.4b(ii) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)
2.4.4b(iii) Last platelet count: ☐☐☐ x10^9/L
2.4.4b(iv) Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

Organ Dysfunction *continued*

2.4.5 Unexplained Metabolic Acidosis: ☐ Yes - **continue below**
☐ No - **skip to Q 2..5**

a) Lactate > 1.5 ULN: ☐ Yes → **If YES, 2.4.5a(i)** Lactate: ☐☐ . ☐ mmol/L
☐ No **2.4.5a(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

AND

b) pH ≤ 7.3: ☐ Yes → **If YES, 2.4.5b(i)** pH: ☐ . ☐☐
☐ No **2.4.5b(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

OR

c) Base deficit ≥ 5.0 mmol/L: ☐ Yes → **If YES, 2.4.5c(i)** Base deficit: ☐ . ☐☐ mmol/L
☐ No **2.4.5c(ii)** Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) **(iii)** Time: ☐☐:☐☐ (hours:minutes)

Sepsis site and causative organism

5.1 Please record the suspected or proven site of sepsis.

5.1.1a	Lung:	☐ Yes → **If YES, 5.1.1b** ☐ No	☐ Suspected ☐ Proven
5.1.2a	Urinary Tract:	☐ Yes → **If YES, 5.1.2b** ☐ No	☐ Suspected ☐ Proven
5.1.3a	Soft Tissue:	☐ Yes → **If YES, 5.1.3b** ☐ No	☐ Suspected ☐ Proven
5.1.4a	Blood stream:	☐ Yes → **If YES, 5.1.4b** ☐ No	☐ Suspected ☐ Proven
5.1.5a	Central Nervous System:	☐ Yes → **If YES, 5.1.5b** ☐ No	☐ Suspected ☐ Proven
5.1.6a	Intra-abdominal:	☐ Yes → **If YES, 5.1.6b** ☐ No	☐ Suspected ☐ Proven
5.1.7a	Wound:	☐ Yes → **If YES, 5.1.7b** ☐ No	☐ Suspected ☐ Proven
5.1.8a	Other (specify): _____	☐ Yes → **If YES, 5.1.8b** ☐ No	☐ Suspected ☐ Proven

If the patient has ALL of

1. Site of suspected or proven sepsis.

2. ≥3 SIRS criteria

3. Organ dysfunction within the last 24 hours

Then stratify to the severe sepsis group.

Risk factors for Acute Respiratory Distress Syndrome

2.12		**Risk factor(s) for Acute Respiratory Distress Syndrome? (tick all that apply box only)**		
	Y	**Pneumonia**	Y	**Acute pancreatitis**
	Y	**PCP pneumonia**	Y	**Burn Injury**
	Y	**Gastric aspiration**	Y	**Inhalation injury**
	Y	**Pulmonary contusion**	Y	**Drug over dose**
	Y	**Multiple transfusion**	Y	**Other (Specify)**
	Y	**Multiple major fractures**		
	Y	**Prolonged shock**		**----------**
	Y	**Sepsis**		**-------**

Baseline co morbidities

2.14	Y **(*tick all boxes that apply*)**		**Did the patient have any of the following co-morbid conditions on admission to ICU?**
Y	**Heart failure**	Y	**Cerebro Vascular Disease**
Y	**Diabetes**	Y	**Congenital Valve Heart Disease**
Y	**Hypertension**	Y	**Pancreatitis**
Y	**Ischaemic Heart Disease**	Y	**Epilepsy**
Y	**Morbid Obesity**	Y	**Connective Tissue Disease**
Y	**Hypothyroidism**	Y	**Intravenous Drug Use**
Y	**Peripheral Vascular Disease**	Y	**Alcoholism**
Y	**Chronic Obstructive Airways Disease**	Y	**Immunosuppression**
Y	**Neutropenia**	Y	**Renal Failure**

Other Therapy At Randomisation				
2.13				
	Y	**Paralytic agents- bolus or continious infusion**	Y	**Antibiotic therapy**
	Y	**Sedative- continious infusion**	Y	**Intravenous colloids within prior 12 hours**
	Y	**Narcotic- continious infusion**	Y	**Diuretics within prior 12 hours**
	Y	**Inotropes or vasopressors**	Y	**Prone ventilation within prior 12 hours.**
	Y	**Pulmonary artery catheter**	Y	**Corticosteriods for ARDS**
	Y	**Intermittent or continious dialysis**	Y	**Corticosteriods for adrenal replacement**
	Y	**Enteral nutrition**	Y	**Activated protien C**
	Y	**TPN**		

Appendix 9 PHARLAP Study Form 3 Ventilator set up

PHARLAP Study	anzic research centre	Ventilator set up DATA FORM 3	**Hospital ID:** ☐☐☐ **Patient Initials:** ☐☐☐ Patient Study Number: ☐☐☐ ☐☐☐

Initial ventilation parameters.

☐☐ ☐☐ 2 0 0 ☐ **Date of Birth*(dd/mm/yyyy)***

Male☐ Female☐ **Patient Gender**

☐☐☐ ***cm*** **Patient Height (cm)**

☐☐☐ ***Kg*** **(a) Patient Weight (kg)**

☐ Estimated or documented

☐ Measured

☐☐☐ ***Kg*** **(a) Predicted Body Weight.**

Male PBW= 50.0 + 0.91x (height in cm -152.4)

Female PBW= 45.5 +0.91x(height in cm -152.4)

Blood Results-*(last prior to randomisation)*

Sodium (mEq/L) ..... highest ☐☐☐ lowest ☐☐☐

Potassium (mEq/L) ..... highest ☐☐.☐ lowest ☐☐.☐

Creatinine (umol/L)..... highest ☐☐☐☐ lowest ☐☐☐☐ Acute rise in creatinine? Y ☐ N ☐

Total bilirubin (umol/L) ..... highest ☐☐☐

Albumin (g/L) ..... lowest ☐☐

Hematocrit (%) ..... highest ☐☐.☐ lowest ☐☐.☐

WBC ($x10^9$/L) ..... highest ☐☐.☐ lowest ☐☐.☐

Platelets ($x10^9$/L) ..... lowest ☐☐☐☐

PaO_2/FiO_2 ratio ..... lowest ratio ☐☐☐ / ☐.☐☐

Venous HCO_3 (mEq/L) ..... highest ☐☐.☐ lowest ☐☐.☐ ☐ not available

When $FiO_2 < 0.5$ ..... lowest PaO_2 ..... ☐☐☐ ☐ not applicable

When $FiO_2 \geq 0.5$ ..... highest A-a $PO_2 = \left[(713 \times FiO_2) - \frac{PaCO_2}{0.8}\right] - PaO_2$ ☐☐☐ ☐ not applicable

Vital signs*(24 hours in ICU preceding randomisation)*

☐☐.☐ **Highest** ☐☐.☐ **Lowest**	**Temperature (^oC)**
☐☐.☐ **Highest** ☐☐.☐ **Lowest**	**MAP (Systolic+(Dialstolic*2))/3**
☐☐.☐ **Highest** ☐☐.☐ **Lowest**	**Heart rate**
☐☐.☐ **Highest** ☐☐.☐ **Lowest**	**Systolic Blood pressure.**

Vital signs*(24 hours in ICU preceding randomisation)*

Glascow Coma Scale, lowest GCS in 24 hour period preceding randomization

Eye opening ☐
1 = never
2 = to pain
3 = to sound
4 = spontaneous

Best verbal response ☐
1 = generally unresponsive
3 = confused communication
5 = communicates clearly with ETT tube present

Best motor response ☐
1 = none
2 = extension
3 = flexion (abnormal)
4 = flexion (withdraws)
5 = localizes pain
6 = obeys commands

Invasive haemodynamics *(last prior to randomisation)*	
☐	**Not available**
☐☐.☐	**Cardiac Index (preferable)** ☐ **Cardiac output** ☐
☐☐.☐	**Mean Pulmonary artery pressure**
☐☐.☐	**Pulmonary artery occlusion pressure (Wedge)**

Chest X-ray *(last prior to randomisation), mark all that apply*				
Barotrauma	☐	**None**	☐	**Pneumoperitonem**
	☐	**Pneumothorax**	☐	**Pnemoretroperitoneum**
	☐	**Pnemomediastinum**	☐	**Subcutaneous**
	☐	**Pneumopericardium**		**emphjysema**

☐ Yes ☐ No	**Is there a chest tube with an active air leak?**
☐☐	**Number of chest drains**
☐☐	**Number of quadrants with consolidation**

Initial Mode of Ventilation *(prior to randomisation)*				
Mode of Mechancial ventilation	☐	**SIMV PC**	☐	**APRV**
	☐	**SIMV VC**	☐	**HFO**
	☐	**PSV**	☐	**Other (specify)**
	☐	**VS**	☐	**.....**
	☐	**PRVC**		**.....**
	☐	**AC**		
☐☐.☐ **litres/minute**	**Minute ventilation**			
☐☐☐☐ **ml** ☐☐.☐ **ml/Kg**	**Tidal volume**			
☐☐☐ **bpm**	**Resp Rate**			
☐☐.☐ **cmH20**	**PEEP External**			
☐☐.☐ **cmH20**	**PEEP intrinsic (if measured)**			
☐☐.☐ **cmH20**	**Pplat ☐ / P peak ☐**			
☐.☐☐	**FiO_2**			

ABG*(last performed)*	
☐.☐☐	**pH**
☐☐.☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐.☐	**HCO_3^-**
☐☐.☐	**BE ☐ Negative ☐Positive**
☐☐.☐	**Lactate**
☐☐☐	**SpO_2**
☐☐☐	**PaO_2/ FiO_2 Ratio**

If PaO2 / FiO_2 ratio <200 assess again on standard ventilator settings.

However if standard setting goals are already fulfilled proceed to randomisation.

Standard ventilation Goals

Y	**Mode** **SIMV** **PC/PS**		**Goal** **(acceptable range)** **Rate 18** **(≥10 and ≤35)** **Tv 6mls/Kg** **(≥4 and ≤8)** **PC / PS** **(≥10 and ≤20cmH_20)** **PEEP 10** **(≥10 and ≤25cmH_20**

Standard Mode of Ventilation ***(post randomisation)***				
Mode of Mechancial ventilation	☒	**Mode** **SIMV PC**		**Goal (acceptable)** **Rate 18 (≥10 and ≤35)** **Tv 6mls/Kg ((≥4 and ≤8)** **PC / Ps (≥10 and ≤20cmH_20)** **PEEP 10 (≥10 and ≤25cmH20)**

☐☐.☐ **litres/minute**	**Minute ventilation**
☐☐☐☐ **ml** ☐☐.☐ **ml/Kg**	**Tidal volume**
☐☐☐ **bpm**	**Resp Rate**
☐☐.☐ **cmH20**	**PEEP External**
☐☐.☐ **cmH20**	**PEEP intrinsic (if measured)**
☐☐.☐ **cmH20**	**Pplat☐ / P peak☐**
☐.☐☐	**FiO_2**

ABG ***(standard settings 10 min)***	
☐.☐☐	**pH**
☐☐.☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐.☐	**HCO_3^-**
☐☐.☐	**BE ☐ Negative ☐Positive**
☐☐.☐	**Lactate**
☐☐☐	**SpO_2**
☐☐☐	**PaO_2/ FiO_2 Ratio (MUST BE ≤ 200 to continue and randomise)**

If the FiO_2/SpO_2 on standard settings is UNDER 200 take the baseline bloods / urine and randomise.

If the FiO_2/SpO_2 on standard settings is OVER 200 take the patient is excluded.

Randomisation

Stratified to severe sepsis group

☐ Yes ☐ No

Ventilation strategy assigned at randomization ☐ Control ☐

PHARLAP

Predicted body weight (provided at randomization) ☐☐☐ kg

Tidal volume at 6 ml/kg (provided at randomization) ☐☐☐☐ ml

Tidal volume at 8 ml/kg (provided at randomization) ☐☐☐☐ ml

Date of randomization (mm/dd/yyyy) ☐☐ ☐☐ 2 0 0☐

Time (24 hour clock) ☐☐:☐☐

Venous Blood Gas (standard settings 10 min)

☐.☐☐	**pH**
☐☐.☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐.☐	**HCO_3^-**
☐☐.☐	**BE** ☐ **Negative** ☐**Positive**
☐☐.☐	**Lactate**
☐☐☐	**SpO_2**

Initial venous serum sample for future analysis.		
☐ Yes	☐ No	**Was the baseline blood sample taken?**
☐ Yes	☐ No	**Was the blood sample allowed to coagulated, centrifuged and frozen within 30 minutes? If not go to protocol violation form.**
Initial urine sample for future analysis.		
☐ Yes	☐ No	**Was the baseline mid stream urine sample taken?**
☐ Yes	☐ No	**Was the urine sample centrifuged and frozen within 30 minutes? If not go to protocol violation form.**

If PHARLAP group go to page 7 / If control group go to page 9.

PHARLAP

PHARLAP Stepwise recruitment manoeuvre *(only PHARLAP group)*	
☐ Yes ☐ No	**Was the whole stepwise manoeuvre performed?** **If yes go to**
☐ **20cmH20** ☐ **30cmH20** ☐ **40cmH20**	**What was the max PEEP reached?**
☐ Yes ☐ No	**Was the manoeuvre abandoned secondary to desat or red MAP. If yes go to A/E form.**
☐ Yes ☐ No	**Following stabilisation was the recruitment manoeuvre repeated up to the previously tolerated max PEEP**
☐ **20cmH20** ☐ **30cmH20** ☐ **40cmH20**	**Was this tolerated?** **If yes go to, If no go to A/E form**

PHARLAP Decremental PEEP Manoeuvre. *(only PHARLAP group)*	
☐ **25→22.5 cmH_20** ☐ **22.5→20cmH_20** ☐ **20→17.5 cmH_2O** ☐ **17.5→15 cmH_20**	**What was the step which resulted in a ≥ 1% decrease in SpO_2.**

PHARLAP `40cm$H_20$ for 60s` Recruitment Manoeuvre. *(only PHARLAP group)*	
☐ Yes ☐ No	**Was the whole 40 for 60 manoeuvre performed?**
☐☐.☐ **cmH_20**	**What was the PEEP setting.**
☐ Yes ☐ No	**Was there an adverse event? If yes go to adverse event form**
PHARLAP Setting Minimal Tidal Volume.	
☐☐ **bpm**	**Resp Rate (inc spont resp)**
☐☐.☐ **cmH20**	**PEEP External**
☐☐.☐ **cmH20**	**PEEP intrinsic (If measured)**
☐☐.☐ **cmH20**	**Pplat □ Ppeak □**
☐☐☐ **ml**	**Tidal volume**
☐☐.☐ **ml/Kg**	**Tidal volume**
☐.☐☐	**FiO_2**
☐☐☐ **%**	**SpO_2**

Control

Control Mode of Ventilation	
Mode of Mechancial ventilation	**AC VC +/- PS**
□□ . □ **litres/minute**	**Minute ventilation**
□□□ □□□ **ml** □□ . □ **ml/Kg**	**Tidal volume (total)** **Tidal volume (mls/Kg)**
□□□ **bpm**	**Resp Rate (ic spont resp)**
□□ . □ **cmH20**	**PEEP External**
□□ . □ **cmH20**	**PEEP intrinsic (If measured)**
□□ . □ **cmH20**	**Pplat □ PPeak □**
□ . □□	**FiO2**

Data Collection (hour 1)

ABG (1 hour following establishment of control / PHARLAP ventilation)	
☐ . ☐☐	**pH**
☐☐ . ☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐ . ☐	**HCO_3^-**
☐☐ . ☐	**BE**
☐☐ . ☐	**Lactate**
☐☐☐	**SpO_2**

Venous blood gas (1 hour following establishment of control / PHARLAP ventilation)	
☐ . ☐☐	**pH**
☐☐ . ☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐ . ☐	**HCO_3^-**
☐☐ . ☐	**BE**
☐☐ . ☐	**Lactate**
☐☐☐	**SpO_2**

Mode of Ventilation	
☐☐ . ☐ **litres/minute**	**Minute ventilation**
☐☐☐ ☐☐☐ **ml** ☐☐ . ☐ **ml/Kg**	**Tidal volume (total)** **Tidal volume (mls/Kg)**
☐☐☐ **bpm**	**Resp Rate (ic spont resp)**
☐☐ . ☐ **cmH20**	**PEEP External**
☐☐ . ☐ **cmH20**	**PEEP intrinsic (If measured)**
☐☐ . ☐ **cmH20**	**Pplat ☐ PPeak ☐**
☐ . ☐☐	**FiO_2**

Data Collection (hour 3)

ABG (3 hours following establishment of control / PHARLAP ventilation)	
☐☐ . ☐☐	**pH**
☐☐☐ . ☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐☐ . ☐	**HCO_3^-**
☐☐☐ . ☐	**BE**
☐☐☐ . ☐	**Lactate**
☐☐☐	**SpO_2**
Venous blood gas (3 hours following establishment of control / PHARLAP ventilation)	
☐☐ . ☐☐	**pH**
☐☐☐ . ☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐☐ . ☐	**HCO_3^-**
☐☐☐ . ☐	**BE**
☐☐☐ . ☐	**Lactate**
☐☐☐	**SpO_2**
Hour 3 venous serum sample.	
☐ Yes ☐ No	**Was the 3 hour blood sample taken?**
☐ Yes ☐ No	**Was the blood sample allowed to coagulated, centrifuged and frozen within 30 minutes. If not go to protocol violation form**

Ventilation Parameters	
☐☐ . ☐ **litres/minute**	**Minute ventilation**
☐☐☐ ☐☐☐ **ml** ☐☐ . ☐ **ml/Kg**	**Tidal volume (total)** **Tidal volume (mls/Kg)**
☐☐☐ **bpm**	**Resp Rate (inc spont resp)**
☐☐ . ☐ **cmH20**	**PEEP External**
☐☐ . ☐ **cmH20**	**PEEP intrinsic (If measured)**
☐☐ . ☐ **cmH20**	**Pplat ☐ PPeak ☐**
☐ . ☐☐	**FiO_2**

Data Collection (hour 6)

ABG (6 hours following establishment of control / PHARLAP ventilation)	
□□ . □□	**pH**
□□ . □	**$PaCO_2$**
□□□	**PaO_2**
□□ . □	**HCO_3^-**
□□ . □	**BE**
□□ . □	**Lactate**
□□□	**SpO_2**
Venous blood gas (6 hour following establishment of control / PHARLAP ventilation)	
□□ . □□	**pH**
□□ . □	**$PaCO_2$**
□□□	**PaO_2**
□□ . □	**HCO_3^-**
□□ . □	**BE**
□□ . □	**Lactate**
□□□	**SpO_2**

Ventilation Parameters	
□□ . □ **litres/minute**	**Minute ventilation**
□□□ □□□ **ml** □□ . □ **ml/Kg**	**Tidal volume (total)** **Tidal volume (mls/Kg)**
□□□ **bpm**	**Resp Rate (ic spont resp)**
□□ . □ **cmH20**	**PEEP External**
□□ . □ **cmH20**	**PEEP intrinsic (If measured)**
□□ . □ **cmH20**	**Pplat □ PPeak □**
□□ . □□	**FiO_2**

Appendix 10 PHARLAP Study Form 4 Daily data collection

PHARLAP Study	anzic research centre	Daily Data Collection DATA FORM 4	**Hospital ID:** ☐☐☐ **Patient Initials:** ☐☐☐ Patient Study Number: ☐☐☐ ☐☐☐

Pre Randomisation ventilation parameters.

Study day ☐☐

Ventilation strategy assigned at randomization ☐ Control ☐

PHARLAP

Predicted body weight (provided at randomization) ☐☐☐ kg

Tidal volume at 6 ml/kg (provided at randomization) ☐☐☐☐ ml

Tidal volume at 8 ml/kg (provided at randomization) ☐☐☐☐ ml

Ventilation Parameters *(at 8 hours ± 2hours)*

	1st	2nd	3rd
Assessment time (24 hour clock)	□□:□□	□□:□□	□□:□□
Set respiratory rate	□□□	□□□	□□□
Total respiratory rate	□□□	□□□	□□□
$Vt_{(insp)}$ on set AC or PC, or $Vt_{(exp)}$ on PS (ml)	□□□□	□□□□	□□□□
Minute ventilation (L/min)	□□.□□	□□.□□	□□.□□
Set PEEP (cm H_2O)	□□.□	□□.□	□□.□
Automated total PEEP (cm H_2O)	□□.□	□□.□	□□.□
Plateau pressure (AC = 0.5 s pause; PS = not applicable PC = set PEEP + driving pressure)	□□	□□	□□
Pressure support level (if not on PC or AC)	□□	□□	□□
PIP on AC	□□	□□	□□
Mean airway pressure	□□	□□	□□
I:E ratio (on set parameters)	1:□.□□	1:□.□□	1:□.□□
FiO_2	□.□□	□.□□	□.□□
Arterial pH	□.□□	□.□□	□.□□
$PaCO_2$ (mmHg)	□□□	□□□	□□□
PaO_2 (mmHg)	□□□	□□□	□□□
HCO_3 (mEq/L)	□□.□	□□.□	□□.□
SaO_2 (%) (from ABG)	□□□	□□□	□□□
SpO_2 (%) (pulse oximetry)	□□□	□□□	□□□

Vital signs *(Calender day)*

Lowest hemoglobin (g/L) ..... ☐☐☐ Lowest platelets (x10^9/L) ..... ☐☐☐☐

Highest creatinine (umol/L) ..... ☐☐☐☐

Highest total bilirubin (umol/L) ..... ☐☐☐ Lowest albumin (umol/L) ..... ☐☐

Systolic blood pressure (mmHg) ..... lowest ☐☐☐ highest ☐☐☐

Lowest mean arterial pressure (MAP) (mmHg) ..... ☐☐☐

Heart rate at lowest MAP (bpm) ..... ☐☐☐ CVP at lowest MAP (mmHg) ..... ☐☐

Mean pulmonary pressure (mmHg) ..... lowest ☐☐ highest ☐☐ ☐ N/A

Pulmonary artery occlusion pressure (mmHg) ..... lowest ☐☐ highest ☐☐ ☐ N/A

Cardiac index (CI) (L/min x m^2) ..... lowest ☐.☐ highest ☐.☐ ☐ N/A

PaO_2/FiO_2 ..... lowest ratio ☐☐☐/☐.☐☐ ☐☐☐/☐.☐☐ highest ratio

Net 24-hour fluid balance (ml) ..... (+) ☐ (-) ☐ ☐☐☐☐☐

Glascow Coma Scale, (lowest GCS for this calendar day)

Eye opening ☐
1 = never
2 = to pain
3 = to sound
4 = spontaneous

Best verbal response ☐
1 = generally unresponsive
3 = confused communication
5 = communicates clearly with ETT tube present

Best motor response ☐
1 = none
2 = extension
3 = flexion (abnormal)
4 = flexion (withdraws)
5 = localizes pain
6 = obeys commands

SOFA Scores *(last prior to randomisation)*

Cardiovascular: ☐

Respiratory: ☐

Liver: ☐

Renal: ☐

Coagulation: ☐

Chest X-ray *(last prior to randomisation), mark all that apply*

a. CXR today? ..... Y ☐ N ☐

b. Barotrauma (please check all that apply with an 'X') ☐ 1. **None**

☐ 2. pneumothorax ☐ 4. pneumopericardium ☐ 6. pneumoretroperitoneum

☐ 3. pneumomediastinum ☐ 5. pneumoperitoneum ☐ 7. subcutaneous emphysema

c. Number of chest tubes ..... ☐

d. Are there bilateral infiltrates present? (Infiltrates may be interstitial and/or alveolar, and may be patchy, diffuse or asymmetric. Infiltrates may not be clearly related to a lobar or segmental process) Y ☐ N ☐

e. Number of quadrants (0-4) with alveolar consolidation ☐

PHARLAP 40cmH$_2$0 for 60s` recruitment manoeuvre *(only PHARLAP group)*

☐☐	**What was the max PEEP reached?**
☐ Yes ☐ No	**Was an adverse event detected? Go to adverse event form.**

PHARLAP Decrimental PEEP Manoeuvre. *(only PHARLAP group)*

☐ **25→22.5 cmH20** ☐ **22.5→20cmH20** ☐ **20→17.5 cmH20** ☐ **17.5→15 cmH20**	**What was the step which resulted in a >1% decrease in SpO2.**

Co-interventions.

☐ 1. paralytic agents - bolus or continuous infusion
☐ 2. sedative - continuous infusion
☐ 3. narcotic - continuous infusion
☐ 4. inotropes or vasopressors (excluding dopamine ≤ 3 mcg/kg/min)
please specify number of agents... ☐
☐ 5. renal dopamine (0-3 mcg/kg/min)
☐ 6. pulmonary artery catheter
☐ 7. intermittent or continuous dialysis
☐ 8. enteral nutrition
☐ 9. TPN
☐ 10. rotational bed therapy
☐ 11. antibiotics
☐ 12. intravenous colloids
☐ 13. diuretics
☐ 14. prone ventilation
☐ 15. corticosteroids for fibroproliferative ARDS
☐ 16. corticosteroids for adrenal replacement

☐ 17. $NaHCO_3$ If selected, please estimate the number of ampules..... ☐☐
...and the lowest pH for which $NaHCO_3$ was infused..... ☐.☐☐
...and the corresponding values for ...

$PaCO_2$ (mmHg) ☐☐☐ Potassium (mEq/L) ☐.☐ HCO_3 (mEq/L) ☐☐.☐

Protocol violation/ Adverese events and weaning.

Was there a violation in the PEEP/FiO_2 chart today?	N ☐	Y ☐
Was there a violation in the Vt or Pplat threshold today?	N ☐	Y ☐
Was an alternative ventilation strategy (other than the assigned protocol) used today?	N ☐	Y ☐
Did a serious adverse event occur today that the intensivist believes is directly related to the ventilation strategy that the patient is receiving?	N ☐	Y ☐
Did this patient qualify for a trial of unassisted breathing today?	N ☐	Y ☐
Did this patient undergo a trial of unassisted breathing today?	N ☐	Y ☐
Did this patient pass a 1-2 hour trial of unassisted breathing today?	N ☐	Y ☐
Was the patient extubated on this day of study?	N ☐	Y ☐
Has the patient been extubated >24 hours today or discharged from ICU?	N ☐	Y ☐
Did the patient die on this day of study?	N ☐	Y ☐
For patients in the LOVS group only, was this patient disconnected from the ventilator today **while on FiO_2 > 0.40**?	N ☐	Y ☐

Biological Sample collection

Venous Blood Gas (AM on DAY 1 ONLY same time as ABG)	
☐.☐☐	**pH**
☐☐.☐	**$PaCO_2$**
☐☐☐	**PaO_2**
☐☐.☐	**HCO_3^-**
☐☐.☐	**BE** ☐ **Negative** ☐**Positive**
☐☐.☐	**Lactate**
☐☐☐	**SpO_2**
Venous serum sample for future analysis. (Day 1, 3 5, 7 10, 14).	
☐ Yes ☐ No	**Was the baseline blood sample taken today?**
☐ Yes ☐ No	**Was the blood sample allowed to coagulated, centrifuged and frozen within 30 minutes? If not go to protocol violation form.**
Urine sample for future analysis. (DAY 3 ONLY)	
☐ Yes ☐ No	**Was the baseline mid stream urine sample taken?**
☐ Yes ☐ No	**Was the urine sample centrifuged and frozen within 30 minutes? If not go to protocol violation form XX.**

Appendix 11 Lung recruitment: who, when and how

Declaration for Thesis Appendix 11

Declaration by candidate

In the case of Appendix 11 the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Study concept and design, data synthesis, writing of manuscript	50

The following co-authors contributed to the work.

Name	**Nature of contribution**	**Extent of contribution (%) for student co-authors only**
David Tuxen	Study concept and design, writing of manuscript	

Candidate's Signature	[redacted]	**Date 20/07/2010**

Declaration by co-authors

The undersigned hereby certify that:

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

Location(s)	**ANZICS Research Centre, Monash Dept Epidemiology**

Name	**Signature**	**Date**
David Tuxen	[redacted]	20/07/10

Lung recruitment: who, when and how

Editorial, Critical Care and Resuscitation

A/Prof David Tuxen and Carol Hodgson

The role of recruitment in acute lung injury (ALI), usually as part of an "open lung" ventilation strategy, remains controversial. A large randomised controlled trial[1] (LOVS) that included a recruitment manoeuvre (RM) of sustained static lung inflation to pressures of 40 cm H_2O for 40 sec (40/40 RM) failed to improve patient survival. Two systematic reviews of multiple studies using similar RMs have shown improved short-term oxygenation but have failed to show improvement in other clinically relevant variables[1-3]. The study in this issue by Edul et al. using a similar RM (40 cm H_2O for 45 sec) has not only shown no improvement in oxygenation but also transient deleterious haemodynamic effects. Does this mean we should abandon RMs?

The motivation for using RMs is based on the CT findings in ALI[4]. The lung, which can appear to have relatively uniform injury on plain chest X-ray, has 3 functionally distinct zones during tidal ventilation. The most dependent lung region that remains collapsed throughout tidal ventilation, despite high PEEP levels, resulting in chronic collapse injury[5], an intermediate lung region that collapses and re-expands with each breath resulting in shear stress-induced injury (atelectrauma), and the least dependent lung regions, that remain inflated throughout tidal ventilation, receive most of the tidal volume, and can receive overinflation lung injury (volutrauma) by tidal volumes exceeding 6ml/kg and plateau airway pressure exceeding 30-35 cm H_2O. All these processes augment the pulmonary elaboration and systemic concentration of injurious cytokines that contribute to the risk of multiple organ failure and mortality in patients with ALI [6-7].

The "protective" mechanical ventilation strategy, characterized by low tidal volume, limitation of plateau pressure and intermediate PEEP levels, has shown reductions in mortality and is now widely accepted[8-12]. However,

this strategy may fail to expand the most dependent lung regions and inadequately reduce cyclic alveolar collapse. These effects may contribute to the progression of lung injury and multiple organ failure. The “open lung” ventilation strategy is based on re-inflating these collapsed lung regions then preventing collapse during the subsequent mechanical ventilation. The aim of this is not simply to improve oxygenation but to improve lung health, reduce injurious cytokine production, shorten time to recovery and improve patient survival.

Three large randomised studies have been performed to address this hypothesis using higher PEEP levels with and without RMs[1, 13-14]. One used static RMs (35-40 cm H_2O for 30 sec) in a small subset of patients[13], one used the 40/40 RM in all patients[1] and the third did not use RMs[14]. All three studies were potentially disadvantaged by using a similar tidal volume in the treatment and control groups resulting in a higher plateau pressure level in the treatment group and all three studies failed to demonstrate a survival advantage compared with control ventilation. However, a meta-analysis of these studies[15] has suggested benefit from higher PEEP in ARDS patients (PaO_2/FiO_2 ratio <200) but not in ALI patients without ARDS (PaO_2/FiO_2 ratio 200-300).

In contradistinction, a meta-analysis of ventilation trials including 40/40 RMs found no significant improvement in length of ventilation, length of ICU or hospital stay or mortality[3]. Although more data was required to exclude benefit, this did suggest that the 40/40 RM with the associated ventilatory strategies was probably ineffective. Unlike the study by Edul et al. two RM meta-analyses did find a significant improvement in oxygenation without significant side effects[2-3]. The reason for this difference may lie in the severity of ALI.

Table 1. Comparison of Edul et al with RM meta-analyses for PaO_2/FiO_2 [2-3]

	Hodgson (2009)	Fan (2008)	Edul (2010)
Study type	meta-analysis	meta-analysis	RCT
Studies included	RCT (2)	RCT & obs* (20)	1
No Patients	490	1185	11
% ARDS	87%	not available	30%
Initial PEEP	11±3	11±3	13±3
Baseline P/F	144±48	139±31	215±66
Post RM P/F	185±69	251±117	212±78

(obs* = observational)

The meta-analyses that reported improved oxygenation with RMs had much lower initial PaO_2/FiO_2 values with 87% ARDS in one analysis and a probable similar high percentage of ARDS in the other analysis based on the lower PaO_2/FiO_2 values. In contrast, the Edul study had a high initial PaO_2/FiO_2 value and lower percentage of patients with ARDS suggesting a lower severity of lung injury, possibly with less potential to show improvement in oxygenation. This is similar to the high PEEP meta-analysis which showed benefit only in the ARDS group[15]. The higher initial PEEP in the Edul study may reduce the potential for improvement[16].

The haemodynamic effects of RMs are well documented[17-19] and are usually transient. Although transient hypotension is reported in many papers, most report no significant adverse events[2-3]. In this issue Edul et al reported only a modest reduction in systolic and mean arterial pressure during the RM but a large and significant reduction (23%) in cardiac index. Although this blood pressure and cardiac index had recovered 2 minutes after the RM in this study, it highlights the importance of circulatory depression which can cause abandonment of an RM and the importance of not performing RMs in hypovolemic or hypotensive patients where occasionally severe and prolonged circulatory depression may occur.

Apart from short term oxygenation improvement, the major RMs trials and the RM meta-analyses have failed to show any improvements in outcome. This stimulates consideration of whether the 40/40 RMs themselves are

the most effective form of RM and whether any recruitment achieved was adequately maintained after the RM by sufficiently high PEEP levels and by re-recruitment when desaturation, disconnection or suctioning occurred.

When lung recruitment was first proposed[20], it was suggested that a static lung inflation to 60 cm H_2O for 60 seconds was required maximise recruitment but possibly because of poor haemodynamic and ventilatory tolerance, patient discomfort, concerns with of barotrauma and physician discomfort, a more conservative version, the 40/40 RM became much more widely used but with little clear success.

The search for better RMs lead to the use of pressure control ventilation with incremental PEEP during the RM[21] with the goal that higher alveolar pressure applied intermittently would enable better lung recruitment with ongoing ventilation and less circulatory depression. Steps up to the maximum PEEP allow assessment of tolerance and steps down in PEEP after the maximum PEEP allow determination of the point where oxygenation first decreased to determine the PEEP level to use after the RM. The PEEP increments during the RM led to the name stepwise or staircase RM.

Lim and colleagues studied the effect of different types of RMs (static, pressure control with incremental PEEP and extended sigh) in porcine lungs with ARDS[17, 22-23]. They found the most effective RM to improve oxygenation was pressure control with incremental PEEP. Borges[21] used a stepwise manoeuvre in 26 patients with ARDS to maximum Pplat of 60 cm H2O over a total time for PEEP steps up and down of 20 min. This showed a sustained positive response in 24 out of 26 patients (92%) with a mean PEEP of 22 ± 4 cm H_2O after PEEP titration. Hodgson et al[24] studied 20 patients with ARDS with a similar staircase RM to a maximum Pplat of 55±3 cm H_2O with incremental and decremental PEEP titration over a total time of 15-20 min and found significant improvements in PaO_2/FiO_2 ratio and shunt fraction sustained for an hour after the RM in 90% of patients. This study also found that that 40% of patients

desaturated at maximum PEEP during the RM but still improved their oxygenation when PEEP was reduced. Hodgson suggested that only 45% of those patients would have responded to a 40/40 RM and Borges stated that 54% of patients required Pplat >40 cm H_2O for full recruitment (ie only 46% would have fully responed with a 40/40 RM). Both these studies reported transient haemodynamic changes during the RM with no significant consequences[21, 24].

A subsequent randomised controlled study of 20 patients with ARDS by Hodgson & Nichol et al[25] compared the staircase RM with an ARDS-net based control group. In this study the treatment group, after PEEP titration, received a higher PEEP (15 ± 1 vs 10 ± 0.5 cm H2O) and a lower driving pressure (Pplat-PEEP, 13 ± 1 vs 17 ± 1 cm H2O) compared with the control group resulting in the same safe Pplat (28 ± 2 cm H2O) in both groups. This strategy resulted in improved PaO_2/FiO_2, compliance and systemic cytokine levels and a non-significant reduction in length of ventilation, ICU and hospital stay[25]. While the findings in relation to this method of lung recruitment are positive, they require further investigation in larger randomised controlled trials before long term benefit can be confirmed.

Our group also provides ECMO for patients with severe acute lung injury (SaO_2 <90% despite FiO_2 1.0 and PEEP ≥17.5 cm H_2O) and have found that the staircase RM averted the need for ECMO in >30% of patients who would have otherwise proceeded to that support.

These findings suggest that ARDS (initial (PaO_2/FiO_2 ratio <200) responds better to recruitment and high PEEP than ALI without ARDS (PaO_2/FiO_2 ratio 200-300) and that staircase RMs may be effective in a higher percentage of patients with ARDS than 40/40 RMs. Also, many RM studies describe responders and non-responders[26-27] and there may be benefit in the former subset that is not seen when all patients are included in large study analysis.

In conclusion, studies to date, including the work by Edul et al, indicate that sustained lung inflation to a pressure of 40 cm H_2O (40/40 RM) may

not be effective in patients with mild ALI and have no established long-term benefit in patients with ARDS. Further trials are needed to establish the role of RMs, particularly with regard to disease severity (ARDS versus ALI) and their effect on clinically relevant outcomes. But in the meantime, this does not mean that RMs should not be used. There is emerging evidence that RMs with incremental PEEP and pressure controlled ventilation to pressures in excess of 50 cm H_2O (such as the staircase RMs) are safe and well tolerated in patients with ARDS, more effective than 40/40 RMs, and can be successfully used in patients with significant hypoxaemia.

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