Titrating Open Lung PEEP in Acute Lung Injury

A clinical method based on changes in dynamic compliance

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Abstract

The recognition that supportive mechanical ventilation can also damage the lung, the so called ventilation induced lung injury (VILI), has revived the more than 40 year long debate on the optimal level of PEEP to be used. It is established that the prevention of VILI improves patient outcome and that PEEP exerts protective effects by preventing unstable diseased alveoli from collapsing. Therefore, the term “open lung PEEP” (OL-PEEP) has been introduced as the end-expiratory pressure that keeps the lung open after its collapse has been eliminated by an active lung recruitment manoeuvre. The determination of such an optimal level of PEEP under clinical circumstances is difficult and remains to be investigated.

The aim of this study was to investigate the usefulness of breath by breath monitoring of dynamic compliance (Cdyn) as a clinical means to identify OL-PEEP at the bedside and to demonstrate the improvement in lung function resulting from its application.

In a porcine lung lavage model of acute lung injury PEEP at maximum Cdyn during a decremental PEEP trial after full lung recruitment was related to the onset of lung collapse and OL-PEEP could be found 2 cmH2O above this level. Ventilation at OL-PEEP was associated with improved gas exchange, efficiency of ventilation, lung mechanics and less than 5% collapse on CT scans. In addition, dead space, especially its portion related to alveolar gas changed characteristicly during recruitment, PEEP titration and collapse thereby helping to identify OL-PEEP.

The beneficial effects of OL-PEEP on lung function and mechanics was demonstrated in a porcine model of VILI. OL-PEEP improved lung function and mechanics when compared to lower or higher levels prior to or after lung recruitment. By using electrical impedance tomography it could be shown that PEEPs within the range of 14 to 22 cmH2O resulted in a similar redistribution of both ventilation and perfusion to the dorsal regions of the lung. OL-PEEP resulted in the best regional and global matching of ventilation and perfusion explaining the drastic improvements in gas exchange. Also regional compliance was greatly improved in the lower half of the lung as compared to all other situations.

In ARDS patients OL-PEEP could be identified applying the same protocol. The physiological changes described could now be reproduced and maintained during a four hours study ventilation period in real patients at four study centres.

In conclusion, the usefulness of dynamic compliance for identifying open lung PEEP during a decremental PEEP trial was demonstrated under experimental and clinical conditions. This PEEP should then be used as an essential part of any lung protective ventilation strategy. The impact of ventilating ARDS patients according to the principles described in these studies on outcome are currently being evaluated in an international randomized controlled trial.

Keywords: PEEP, open lung, recruitment, dead space, electrical impedance tomography, ARDS.

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urn:nbn:se:uu:diva-8460 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-8460)
To my parents Isaias and Karin
List of Papers

This dissertation is based on the following studies which will be referred to in the text by their Roman numerals I – IV


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ABBREVIATIONS

ARDS  acute respiratory distress syndrome
ALI   acute lung injury
Cdyn  dynamic compliance
Cstat static compliance
DeltaP inspiratory driving pressure
CI    cardiac index
CT    computed tomography
CT NA CT percentage of normally aerated tissue
CT NonA CT percentage of non-aerated tissue
CVP   central venous pressure
EIT   electrical impedance tomography
ETCO2 end-tidal carbon dioxide
FiO2  inspired oxygen fraction
HU    hounsfield units
I:E   inspiratory to expiratory ratio
LPV   lung protective ventilation
MAP   mean systemic arterial pressure
OL-PEEP open lung PEEP
OL-PEEPcom open lung PEEP according to Cdyn
OL-PEEPox open lung PEEP according to oxygenation
PaCO2 partial pressure of carbon dioxide in arterial blood
Pa-ETCO2 arterial to end-tidal carbon dioxide gradient
PaO2  partial pressure of oxygen in arterial blood
PAPM  mean pulmonary arterial pressure
PCV   pressure controlled ventilation
Pmean mean airway pressure
Pplat end-inspiratory plateau pressure
PEEP  positive end-expiratory pressure
PEEPi intrinsic PEEP
Raw   airway resistance
RM    recruitment manoeuvre
RR    respiratory rate
SBT-CO2 simple breath test of carbon dioxide
SpO2  arterial oxygen saturation
SvO2  mixed venous saturation
VCV   volume controlled ventilation
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>VDalv</td>
<td>alveolar dead space</td>
</tr>
<tr>
<td>VDaw</td>
<td>airway dead space</td>
</tr>
<tr>
<td>VDphys</td>
<td>physiological dead space</td>
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<tr>
<td>VD/VT</td>
<td>physiologic dead space-tidal volume ratio</td>
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<tr>
<td>VILI</td>
<td>ventilation induced lung injury</td>
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<tr>
<td>Vt</td>
<td>tidal volume</td>
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INTRODUCTION

Background
The beneficial effects of positive end-expiratory pressure (PEEP) for treating patients with acute hypoxemic respiratory failure was first described by Ashbaugh and Petty in the late 60’s. In their landmark publication for the then new field of mechanical ventilation they described the improvement in oxygenation induced by PEEP in a series of acutely ill patients suffering from a diffuse severe form of respiratory insufficiency that they later on termed “Adult Respiratory Distress Syndrome” (ARDS) (1, 2). Since then, extensive clinical and experimental research leading to hundreds of publications has examined the effects of PEEP and proposed a rationale for its optimal use in patients on mechanical ventilation. However, to date PEEP still seems to be adjusted trying to find the lowest level that results in an adequate arterial oxygenation at minimal hemodynamic effects (3, 4). This approach is not substantially different from the way it was first described decades ago.

Suter et al. (5) were the first to deviate from the traditional approach to PEEP titration by introducing the concept of “optimum PEEP” according to the best respiratory system compliance. They showed that when applying incremental levels of PEEP the point of maximal compliance coincided with an improved oxygenation, but more importantly, with the best oxygen delivery and a better efficiency of ventilation at reduced dead-spaces. In their treatment concept they tried to unify two essential but opposing aspects of PEEP: its positive effects on gas exchange and its negative effects on hemodynamics (6, 7).

Recognizing that mechanical ventilation in itself can induce or worsen previous lung injury (i.e ventilator-induced lung injury = VILI) has challenged the traditional views on PEEP. Two mechanisms are intimately linked to the damage induced by positive pressure ventilation, namely overdistension that results from applying excessive levels of tidal volume and/or airway pressures and, more importantly, repetitive opening and closing of small airways and alveoli with each respiratory cycle (8-10). Recent clinical trials have shown a significant reduction in morbidity and mortality in ARDS patients when applying a lung protective ventilation strategy aimed at preventing the injurious effects of ventilation by mechanically stabilizing the lung at higher levels of PEEP instead of just
optimizing gas exchange (11-13). However, these strategies have been focusing mainly on the prevention of lung overdistension by limiting high inspiratory tidal volumes and plateau pressures. The role of PEEP in lung protection has therefore not been clearly established, yet according to our current understanding the essential protective role of PEEP should be the prevention of repetitive opening and closing of unstable lung units (14, 15). This so called tidal recruitment results in shear stress that has been associated with a worsening of lung injury (14,16-18), surfactant inactivation (19), bacterial translocation (20-22) and activation of a local inflammatory response that could eventually trigger and maintain systemic multiple organ dysfunction syndrome (23, 24).

However, high levels of PEEP alone, may have limited protective effects (25) or might even be deleterious (26) and are prone to demonstrate the known negative consequences such as cardiovascular depression, lung hyperinflation and impaired gas exchange (27-30). It has therefore been hypothesized that a lung protective PEEP should be used in conjunction with a lung recruitment manoeuvre (RM) that re-opens collapsed lung units (31) and thus homogenizes the distribution of ventilation within the lung. Once recruited, the lung is stabilized by the open lung PEEP (OL-PEEP), a pressure level that prevents end-expiratory collapse (32). Ventilation is then maintained within a “safe window” by applying the lowest possible inspiratory pressure amplitude or driving pressure on top of PEEP in order to minimize overdistension while maintaining sufficient alveolar ventilation.

Although physiologically sound the clinical confirmation of this hypothesis still remains elusive and has yet to be proven. Two reasons may account for this lack of evidence: Firstly, recruitment is a highly empirical intervention with ill-defined methods and endpoints, which are particularly difficult to assess at the bedside. Secondly, alveolar collapse and tidal recruitment are difficult if not impossible to detect with the technologies for lung monitoring currently available for clinical use (33).

Oxygenation, due to the ease of its measurement, has been used as one of the key parameter describing the recruitment and collapse phenomena. However, arterial oxygenation has a number of limitations such as the need for frequent invasive assessment and most importantly its lack of sensitivity to detect lung overdistension, and injurious tidal recruitment (33).

Lung mechanics have also been studied extensively and pressure volume (PV) curves were transferred from the lung physiology laboratory to the patient’s bedside in an attempt to characterize the mechanical behaviour of the sick ARDS lung. Important observations about the shape of the pressure-volume curve could be made and a methods for establishing PEEP based on the identification of the lower inflection point of the inflation limb of the PV curve were proposed (34, 35) This method was also used to determine the level of PEEP for the lung protective ventilation strategy. Subsequently conducted randomized controlled clinical trials resulted in improved
outcomes for those ARDS patients managed with such a PEEP strategy (11, 13) but the isolated role of PEEP in lung protection and patient outcome could not be established. Many clinical, experimental and mathematical studies about PV curves have improved our understanding and interpretation skills (36). As opposed to previous believes, it is now accepted that the inflation limb of any PV curve is related to an ongoing recruitment of alveolar units (37) while only the deflation limb of the PV curve provides information about the lung’s closing pressure, i.e the onset of collapse and hence OL-PEEP (38, 39). However, PV curves are not easily obtained at the bedside and their interpretation is still complex as they are profoundly affected by a lung’s volume history. Most importantly, however, PV curves never reflect steady state conditions (40).

A decremental PEEP trial (DPT) after fully recruiting the lung allows PEEP to be titrated along the deflation limb of the PV curve while observing changes in lung morphology (CT scan) and lung function as clinically represented by changes in gas exchange and lung mechanics. During a DPT the point of maximal tidal compliance and curvature has been shown to correspond to OL-PEEP (38, 39).

As of to date there is no bedside method, however, that a clinician can use to accomplish the difficult task of selecting the “right” level of PEEP for an individual ARDS patient. The possibility of being able to clinically detect and apply OL-PEEP could be of great therapeutic importance because even if solid evidence is still lacking there is general consensus that PEEP plays an essential role in lung protection and patient outcome. Furthermore, if the lung protective PEEP level were to be determined at the bedside with reasonable effort researchers and clinicians would finally be able to study systematically the hypothesized protective effect of PEEP for patients with acute lung injury and ARDS.
AIMS OF THE STUDY

The aim of the series of four studies included in this dissertation was to investigate the usefulness of a continuous monitoring of dynamic compliance, on a breath by breath basis, as a means for clinicians to identify open lung PEEP. The knowledge obtained in these studies could facilitate the implementation of a lung protective ventilation strategy in acute lung injury and hopefully contribute to better patient care and survival.

In a first experimental phase a porcine model of acute lung injury was used to establish the physiological basis for the use of dynamic compliance (Cdyn) for OL-PEEP titration and to characterize the lung’s physiological condition during ventilation at OL-PEEP by:

1. establishing the relationship between the point of maximal dynamic compliance and the onset of lung collapse as measured by CT during a decremental PEEP trial after fully recruiting the lung
2. defining OL-PEEP as being 2 cmH₂O above the so obtained maximal Cdyn and characterizing the lung’s morphological and functional condition at this level
3. investigating the use of dead space-derived variables to further characterize the recruitment-collapse phenomenon and identify the most useful among these parameters to detect lung collapse
4. studying the effects of different levels of PEEP with or without a prior lung recruitment on gas exchange, global and regional lung compliances and on the regional distribution of ventilation and perfusion measured by electrical impedance tomography while taking OL-PEEP as a reference.

In a second clinical phase a multicentre clinical trial was performed aimed at validating the use of Cdyn for OL-PEEP titration in patients with the acute respiratory distress syndrome by:

1. comparing the physiological effects of a traditional incremental PEEP titration with those of a decremental PEEP titration after maximum lung recruitment
2. comparing OL-PEEP titration based on arterial oxygenation with that based on Cdyn, the novel method described in this thesis
3. exploring the ability of the two different levels of OL-PEEP as determined by the above methods in maintaining lung stability during a subsequent four hour ventilation period.
METHODS

Subjects

Study I, II and III: In this series of experimental studies, all of which were approved by the Animal Research Ethics Committee of Uppsala University, a total of 17 mixed Hampshire, Yorkshire and Swedish country breed pigs (Weight 28.4± 2.6 kg) were used. Animals fasted over night prior to the experiments having free access to water.

Study IV: The clinical study was approved by the institutional review board of each of the four participating centres. Informed consent was obtained from each patient’s next of kin. After one hour of ventilation with the following settings, volume controlled ventilation (VCV), Vt 6 ml/kg, PEEP 10 cmH2O and FiO2 1 a total of 26 patients maintaining the diagnostic definition of ALI/ARDS (41), who did not meet any of the exclusion criteria, were included in the study.

Exclusion criteria were the following: Age < 18 years, severe COPD, active bronchospasm or previous advanced lung disease, previous evidence of barotrauma, intracranial hypertension, intolerance to hypercapnia (acute renal failure with uncontrolled metabolic acidosis), hemodynamic instability defined as: 1) mean arterial blood pressure ≤ 60 mmHg despite adequate fluid resuscitation and use of vasoactive drugs, 2) increase in vasoactive drug dosage by > 50% within the last 12h, 3) Blood lactate levels > 20 mg/dL, and/or an increase within the last 24h, coronary disease (acute myocardial infarction or unstable angina diagnosed during the previous month).

Animal anaesthesia

Study I, II and III: In all studies the same animal anaesthesia protocol was used. Animals were pre-medicated with a combination of zolazepam-tiletamine (ZOLETIL®, Reading, Carros, France) 6 mg/kg, xylazine (ROMPUN®, Bayer, Leverkusen AG, Germany) 2.2 mg/Kg and atropine 0.04 mg/kg all given intramuscularly. After five minutes, animals were placed on the operating table in the supine position and a cannula was inserted into an auricular vein to start fluid administration.
Anesthesia was then maintained with a combined infusion of ketamine 25 – 50 mg kg\(^{-1}\)h, midazolam 90 – 180 μg kg\(^{-1}\)h, fentanyl 3 – 6 μg kg\(^{-1}\)h and pancuronium bromide 0.25 – 0.50 μg kg\(^{-1}\)h. Additional doses of fentanyl and pancuronium were given when needed to assure animal comfort. A maintenance fluid administration of ringer’s lactate without any other specific hemodynamic management was administered.

**Patient sedation**

Study IV: in the clinical study all patients included were under sedation following the institutions’ sedation protocols for patients on mechanical ventilation. Only during the study period for PEEP titration, all patients received muscular relaxation with a non-depolarizing agent.

**Ventilation**

Study I, II and III: All animals were tracheotomized and ventilated through a 7 mm inner diameter endo-tracheal tube (Mallinckrodt, Athlone, Ireland) with the cuff inflated so as to achieve a tight seal without leaks. Studies were performed with animals in the supine position. In all experiments a Servo-i ventilator (Maquet Critical Care, Solna, Sweden) was used. Ventilation at baseline and during the experimental protocol was volume controlled ventilation (VCV) at Vt 6 mL/kg, RR 30 bpm, inspiratory to expiratory ration (I:E) of 1:1, with an inspiratory pause of 10% of the inspiratory time, FiO\(_2\) 1 and PEEP 6 cmH\(_2\)O in studies I and II and 10 cmH\(_2\)O in III. The Vt chosen reflected the current recommendations for ventilating patients with ARDS. Ventilation modes were then modified and adjusted according to the specific study protocols.

Study IV: All patients included were also ventilated with the Servo-i ventilator. Baseline ventilation before starting the protocol was VCV with Vt 6 mL/kg, PEEP 10 cmH\(_2\)O, FiO\(_2\) 1, RR 15 to 30 bpm adjusted according to the level of PaCO\(_2\).

**Animal instrumentation**

Through bilateral neck incisions both jugular veins were dissected and prepared for cannulation. A fiber-optic pulmonary artery catheter (CCombo 7.5F, Edwards Life –sciences LLC, Irvine, Ca, USA) was inserted through the right jugular vein, its distal port connected to a zeroed (right atrium level) pressure transducer with the balloon inflated with progressing into the pulmonary artery until a stable wedge waveform was obtained.
Through a right lateral and left inguinal incision both femoral arteries were dissected and cannulated. In studies I, II and III an indwelling catheter was progressed through the right femoral artery for invasive blood pressure monitoring and blood sampling. If the femoral artery turned out to be too small, in these animals the left carotid artery was used instead. In studies I and II an intra-arterial blood gas sensor (Trendcare, Diametrics Medical Ltd., High Newcombe, UK) was used. In study III a 4F fiber-optic catheter Pulsiocath FT PV20204 for trans-pulmonary thermodilution measurements (Pulsion Medical Systems, Munich, Germany) was introduced via either a femoral or the left carotid artery calibrating the continuous cardiac output measurements of the PiCCO system. In all animals the urinary bladder was drained using a conventional appropriately sized catheter inserted via a small supra-pubic incision.

Experimental lung injury model

Studies I and II
Lung injury was induced by lung lavage according to the method described by Lachmann et al. (42). The lungs of 8 animals were submitted to repeated intra-tracheal instillations of 35 mL/kg warm (37°C) normal saline solution until a sustained reduction in the PaO$_2$ < 100 mmHg at FiO$_2$ 1 and a PEEP 6 cmH$_2$O during a period of 60 min was obtained.

Study III
In this study a ventilation induced lung injury (VILI) model was used in order to establish a severe lung injury more closely resembling the ARDS seen in ventilated ICU patients. Therefore, nine animals were submitted to repeated lung lavages until a sustained reduction in PaO$_2$ < 200 mmHg at a FiO$_2$ 1 at a PEEP of 7 cmH$_2$O for more than 10 minutes was confirmed, followed by a 3 hour period of injurious mechanical ventilation. The ventilator settings were as follows: Pressure controlled ventilation (PCV), PEEP 1 cmH$_2$O, Pplat 38 cmH$_2$O, RR 20 bpm and FiO2 1. Arterial blood gases were taken every 30 minutes and adjustments were made according to their results. Increments of PEEP/Plateau pressure of 2 cmH$_2$O were made whenever PaO$_2$ was less than 55 mmHg or SpO$_2$ < 80% according to the following table:
Table 1. Adjustments of PEEP/Plateau pressures in cmH\(_2\)O during VILI

<table>
<thead>
<tr>
<th>PEEP</th>
<th>Pplat</th>
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<tbody>
<tr>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
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<td>5</td>
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<td>42</td>
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<td>44</td>
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<td>11</td>
<td>46</td>
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<td>13</td>
<td>48</td>
</tr>
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As soon as PaO\(_2\) increased above 200 mmHg an additional lung lavage was performed. Figure 1 summarizes the changes in PaO\(_2\) and PEEP levels needed during the VILI period.

**Study protocols**

**Studies I and II**

Study I aimed at validating Cdyn as a means for detecting the onset of lung collapse during a decremental PEEP trial (DPT) after fully recruiting the lung. Hence compliance-based open lung PEEP (OL-PEEPcom) along with other lung mechanics and hemodynamic parameters were systematically evaluated at each PEEP step and compared with the changes in PaO\(_2\) and the morphological changes observed on the CT scans. These parameters were used also to assess the correspondence between morphological (CT scan) and functional (lung mechanics and gas exchange) condition of the lung during the dynamic recruitment-collapse phenomena.

Study II investigated the usefulness of dead space and its derived variables for detecting the onset of lung collapse. A detailed analysis of the changes in dead space fractions helped to further characterize the open lung condition and established the correspondence between the morphological condition and the efficiency of ventilation.

After induction of lung injury, pigs were placed on baseline ventilation with a PEEP level of 6 to 10 cmH\(_2\)O. Having established instrumentation and adequate monitoring, animals were transferred to the radiology department (CT scan facilities) where the entire study protocol was carried out.

Once baseline measurements at a PEEP level of 6 cmH\(_2\)O, were completed, PEEP was gradually increased as a means of preconditioning the
respiratory and cardiovascular system and preparing them to better tolerate the high pressures applied during the recruitment manoeuvre. Confirming hemodynamic stability this way, animals were then submitted to a 2-minute recruitment manoeuvre (RM) for which the ventilation mode was changed to PCV with a PEEP of 40 cmH2O, a Pplat of 60 cmH2O and an inspiratory to expiratory ratio of I:E 1:1. Immediately thereafter the mode was switched back to baseline settings but maintaining PEEP at 24 cmH2O. This marked the beginning of the decremental PEEP trial, during which PEEP levels were reduced in steps of 2 cmH2O from 24 to 6 and finally to 0 cmH2O. Each PEEP was maintained for 10 min to allow the hemodynamic and respiratory systems to stabilize while all other ventilation settings were maintained constant (figure 1).

Figure 1. Study protocol for papers I and II PreRM refers to the preconditioning phase prior to lung recruitment. Each box represents a protocol step of 10 minutes.

Data acquisition at the end of each step included hemodynamic, gas exchange, respiratory, lung mechanics and chest CT scans taken during end inspiratory and end expiratory hold manoeuvres. These holds were also used to determine static lung compliance (Cst) and to rule out the presence of intrinsic PEEP (PEEPi).

An important aspect of these studies was to strictly define lung recruitment and lung collapse with criteria derived from our own group’s past experience and previous studies (43-46).

In study I

Full lung recruitment was defined as:

- \( \text{PaO}_2/\text{FiO}_2 > 400 \text{ mmHg} \) at pure oxygen
- Gain in Cdyn of > 30% compared with baseline
- CT showing an amount of non-aerated tissue (areas with an attenuation value of \( \pm 100 \) Hounsfield Units) ≤ 5% of the total
section of the lung and/or areas of normally aerated tissue (< -500 Hounsfield Units) ≥ 85% of the total lung section.

Lung collapse was defined by all of the following criteria:

- Fall in PaO₂/FiO₂ by ≥ 10% for any individual post-recruitment maximum value
- Maximum value of Cdyn obtained during the decremental PEEP trial
- CT-based amount of non-aerated tissue ≥ 5% of the total lung section

OL-PEEPcom was then defined as the PEEP level prior to (i.e 2 cmH₂O above) the one at maximal Cdyn.

In study II

Full lung recruitment was defined as above but without the compliance criterion:

- PaO₂/FiO₂ > 400 mmHg at pure oxygen
- Amount of non-aerated tissue on the CT < 5%
- Amount of normally aerated tissue on the CT > 85%

Lung collapse was defined by the CT scan criterion, only:

- Amount on non-aerated tissue > 5%

Study III

This study aimed at describing the effects pre-selected widely varying levels of PEEP on gas exchange, lung mechanics and the regional distribution of ventilation, perfusion and compliance in six different ventilatory treatments leading to a partially collapsed, a fully recruited and even an overdistended lung condition taking OL-PEEPcom as a reference. Based on the results of studies I and II and after establishing a stable ventilator-induced lung injury model, animals were first submitted to lung recruitment and PEEP titration in a similar way as described in the previous studies, the only difference being that the decremental PEEP trial was performed in a pressure controlled mode of ventilation. After determining the individual OL-PEEPcom in each animal, this PEEP was used as a reference to define the six different study conditions:

a) Three periods without a previous recruitment manoeuvre (PRE)
   - OL-PEEP<sub>PRE</sub>
   - OL-PEEP-4<sub>PRE</sub> = PEEP set 4 cmH₂O below OL-PEEP
   - OL-PEEP+4<sub>PRE</sub> = PEEP set 4 cmH₂O above OL-PEEP
b) Three periods after a recruitment manoeuvr (POS) as described in study I and II.
- OL-PEEP<sub>POST</sub>
- OL-PEEP-4<sub>POST</sub> = PEEP set 4 cmH<sub>2</sub>O below OL-PEEP
- OL-PEEP+4<sub>POST</sub> = PEEP set 4 cmH<sub>2</sub>O above OL-PEEP

All other ventilator settings were maintained constant in VCV, Vt 6 mL/kg, I:E 1:2, FiO<sub>2</sub> 1 and RR 30 bpm. After a baseline ventilation period, these study conditions were applied in random order and each maintained for 20 minutes to allow for stabilization. Measurements (lung mechanics, hemodynamics, gas exchange, dead space analysis and electrical impedance tomography) were obtained towards the end of each period (figure 2).

![Figure 2. Study protocol paper III. Arrows indicate points of measurements](image)

Study IV
Experiences and information from the above experimental studies set the stage for this clinical study, which had two major objectives: 1) compare the traditional way of titrating PEEP using progressive increments with a corresponding decremental PEEP titration after maximum lung recruitment and 2) compare the value of dynamic compliance with that of oxygenation for identifying OL-PEEP in ARDS patients.

Patients with ALI/ARDS enrolled in 4 different centres were included in the study. Before starting the protocol, patients had to have an adequate volaemic status defined by 1) a central venous pressure ≥ 12 mmHg (47) and 2) arterial pulse pressure variation (PPV) < 13% (48). Patients were then submitted to lung pre-conditioning, a pressure challenge in which ventilation was applied in a pressure controlled mode at PEEP 20 cmH<sub>2</sub>O and inspiratory pressure set 15 cmH<sub>2</sub>O above PEEP, I:E 1:2, RR 15 to 35 cmH<sub>2</sub>O, FiO<sub>2</sub> 1. After a 10-minute stabilization period, patients were evaluated whether any of the following occurred: 1) PPV > 13%, 2) fall in
mean arterial pressure >20% of baseline and when available 3) fall in cardiac output > 20% of baseline. Ventilator settings were returned to baseline and patients received intravascular volume expansion by 500 mL of normal saline or 250 mL of hetastarch 6%. Once preconditioning was completed and tolerated, PEEP titration protocol was started during which a maximum additional volume of 500 ml normal saline solution and 500 mL colloidal solution (6% hetastarch) could be given if required.

**PEEP titration protocol**

During the PEEP titration protocol ventilator settings were as follows: VCV using a Vt of 6 ml/kg, FiO2 1 and I:E 1:1. RR between 15 and 35 bpm could be chosen depending on the degree of hypercapnia at onset. These setting were maintained constant during the entire titration protocol.

Incremental PEEP titration: First, PEEP was increased in 2 cmH2O steps from 8 to 26 cmH2O. Each step was maintained for 10 minutes and a full set of measurements was taken during the last minute of each period.

Lung recruitment: after the last incremental PEEP step, a 2 min RM was performed in PCV combining 40 cmH2O of PEEP with 20 cmH2O of inspiratory pressure above PEEP, thereby reaching a Pplat of 60 cmH2O.

Decremental PEEP titration: Ventilator settings were switched back to VCV and the same protocol as during the incremental PEEP trial was applied but now modifying PEEP in an inverse order starting from 26 down until 8 cmH2O (Figure 3). During the decremental PEEP titration the point of collapse (i.e the closing pressure) was determined by both, oxygenation and compliance according to the definitions used in papers I and II. This determined OL-PEEP according to oxygenation (OL-PEEPox) and compliance (OL-PEEPcom) criteria as the levels of PEEP 2 cmH2O above the respective collapse pressure.

**Figure 3. Clinical study, PEEP titration protocol**
In the second part of the study patients were submitted to two consecutive ventilation periods of four hours each comparing the effects of ventilation at OL-PEEPox with that at OL-PEEPcom. Each period was preceded by a RM as described above and the individual OL-PEEPox and OL-PEEPcom obtained during the decremental PEEP trial was selected in random order together with the following ventilatory settings: PCV, inspiratory pressure above PEEP adjusted to obtain a Vt 6 ml/kg and or a Pplat < 30 cmH2O, I:E 1:1, RR of 15 to 35 depending on the level of hypercapnia. FiO2 was reduced to 0.4 or the lowest level that would keep SpO2 above 90%.

During these two periods the ability of respective OL-PEEP levels to maintain lung stability, marked by a stable oxygenation and Cdyn, were compared. All online parameters were registered during these periods and a full set of measurements was obtained 30 min into the each study period and 30 min before its end. A physician not participating in the study took care of the wellbeing of the patients during the protocol.

Measurements

Respiratory parameters

Ventilatory parameters were recorded by the ventilator’s flow and pressures sensors providing ventilation volumes and pressures. Compressible volume of the ventilatory circuit was measured by the ventilator during initial set up and compensated for in all subsequent measurements.

Dynamic respiratory system compliance (lung plus chest wall compliance) was measured on a breath by breath basis and its value displayed on the ventilator’s screen using the Open Lung Tool® of the Servo-i (Maquet, Critical Care, Solna, Sweden). Dynamic compliance was calculated dividing the inspiratory Vt by the end-inspiratory pressure minus the end-expiratory pressure level of the preceding breath. During all VCV conditions an inspiratory pause time of 10% was applied and during PCV, I:E and RR were adjusted such that end-inspiratory flow was 0 on the flow-time waveforms. Under these conditions a breath by breath “quasi-static” compliance measurement could be obtained. At the end of each protocol step end-inspiratory and end-expiratory hold manoeuvres lasting 5 seconds were performed for calculating truly static compliances and to rule out the presence of intrinsic PEEP.

Airway resistance was calculated using independent flow and pressure sensors at the airway opening (CO2SMO plus in studies I and II and NICO in study III, Respironics, Wallingford CO, USA). This simultaneous data recording allowed for a double check for all respiratory measurements.

22
Haemodynamics

All studies included the following haemodynamic measurements: surface electrode ECG recording, heart rate, invasive systemic and pulmonary artery pressures, central venous pressure, pulmonary artery capillary wedge pressure and cardiac output. Continuous cardiac output was measured either by thermodilution using a pulmonary artery catheter (studies I, II and IV) or the PiCCO plus system (Pulsion Medical Systems, Munich, Germany) by analysing the arterial pulse waveform contour (study III). This latter method required calibration by trans-pulmonary thermodilution using cold saline solution. The mean value of three consecutive measurements at each protocol step was used for calibration purposes.

All intravascular pressures were referenced to atmospheric pressure and zeroed at the mid-thoracic level. Venous pressures were obtained at end expiration.

Gas exchange

In studies I, II and IV blood gases were monitored continuously by an intra-arterial sensor (Trendcare, Diametrics Medical Ltd, High Newcombe, UK). In addition, arterial and mixed venous blood samples were obtained for independent blood gas analysis with the ABL 300/OSM 3 Hemoximeter (Radiometer, Copenhagen, Denmark) at each protocol step in studies I, II and III and at the respective institutions’ laboratories in study IV. Arterial oxygen saturation (by pulse-oximetry) and mixed venous oxygen saturation (by infra-red spectroscopy, using a fibreoptic pulmonary artery catheter) were continuously monitored. Shunt and oxygen-derived parameters were calculated using standard formula for oxygen content in blood. End-tidal CO₂ was monitored with an infra-red spectroscopy sensor available as a mechanical ventilator module of the Servo-i (Maquet Critical Care, Solna, Sweden).

Volumetric capnography

In studies I, II, III dead-space and its derived variables were analyzed according to the single breath test of CO₂ (SBT-CO₂), which is based on an integration of the expiratory flow signal and the respective CO₂ concentration. The SBT-CO₂ was monitored on a breath by breath basis with the CO₂MO plus in study I and II and the NICO in study III (Respironics, Wallingford, Conn, USA). Both systems are based on a mainstream CO₂ sensor using non-dispersive infra-red spectroscopy (accuracy ± 2 mmHg and resolution 1 mmHg). Airflow was measured by a fixed orifice differential pressure flow sensor (range 2 – 180 L/min and accuracy > 3%). The
superimposed instrumental dead-space of 10 ml was included in the airway
dead-space calculations.

Dead space fractions were calculated as follows:
- Airway dead space (VDaw) determined by Fowler’s method (49)
- Physiological dead space (VDphys) was calculated using Enghoff’s
  modification of Bohr’s formula (50) as

\[
VD_{phys} = \frac{(PaCO_2 - P_{AE}CO_2)}{PaCO_2} \times Vt
\]

where \( P_{AE}CO_2 \) is the mean expired alveolar partial pressure, \( PaCO_2 \)
the arterial partial pressure of CO2 and \( Vt \) the tidal volume
- Physiologic dead space to tidal volume ratio (VD/VT) was obtained
  by dividing VDphys by Vt
- Alveolar dead space (VDalv) was computed subtracting VDaw from
  VDphys.
- Alveolar tidal volume was obtained by subtracting VDaw from Vt
- Alveolar dead space to alveolar tidal volume ratio = VDalv/VTalv.

Finally, arterial to end-tidal partial pressure difference of CO2 (Pa-ETCO2)
was calculated.

Computed tomography

In studies I and II lung aeration, the appearance of lung collapse and tidal
recruitment were studied by computed tomography (CT scan) (Somatom
Sensation 16™, Siemens, Forchheim, Germany) obtaining at the end of each
protocol step two images, one during an end-inspiratory, the other during an
end-expiratory hold manoeuvre. All acquisitions were made in the supine
position. At each step the imaging level at 2 cm cranially to the right
diaphragmatic dome was determined from a frontal topogram. Exposure
time was 0.75 s at 120mA and 100kV. Images were reconstructed with a
slice thickness of 6 mm within a 512 x 512 matrix and a pixel spacing of 0,6
x 0,6 mm using a standard body reconstruction filter (Siemens notation:
B40s). Attenuations of the pulmonary parenchyma were analyzed using the
CT image analysis software Maluna (Mannheim Lung Analyzing Tool,
Version 2.02, Mannheim, Germany). Standard definitions of lung aeration
according to the attenuation values in Hounsfield Units (HU) were used (51).
Regions of interest were manually delineated taking the inner rib cage and
the mediastinal structures as the lung boundaries.

Differently aerated lung regions were classified as non-aerated (NonA,
+100 to -100 HU), poorly aerated (PA, -100 to -500 HU), normally aerated
(NA, -500 to -900 HU) and hyperinflated (H, -900 and -1000 HU),
respectively. The amount of NonA (atelectasis) was expressed as a
percentage of the total lung area as the region of interest (52). The extent of
tidal recruitment was computed by subtracting the area of NonA at end-expiration from that at end-inspiration (53). To avoid inter-observer variations, CT analysis was performed by the same investigator who was blinded as to the level of PEEP used.

Electrical impedance tomography

Electrical impedance tomography (EIT) is a noninvasive monitoring tool that allows real-time imaging of regional ventilation, perfusion and compliance. It reconstructs a cross-sectional image of the lung based on the potential differences measured from electrical current injection in the thoracic surface through electrodes placed circumferentially around the thorax (54).

EIT data were acquired using the impedance tomography platform ENLIGHT® (Dixtal, São Paulo, Brazil) capable of producing 50 real time images per second using thirty-two electrodes equidistantly placed around the circumference of the thorax just below the level of the axilla.

Currents were injected in a rotating sequence through pairs of electrodes with three electrodes between each pair. During injection through a single pair of electrodes, 30 differential voltages were measured by the remaining 30 non-injecting electrodes. One complete acquisition cycle of 32 current patterns produced 864 voltage measurements not using the 96 measurements of the electrodes between the injecting electrodes. These measurements comprised one primary voltage-frame with its corresponding relative EIT image. These images were generated by a reconstruction algorithm for an approximately 10 cm wide cross section of the thorax, which is based on a 3-D finite element model (figure 4).

Figure 4. Finite element mesh used for image generation in EIT
A primary relative image was created through comparison of the most recent primary voltage-frame with a reference or baseline frame conveniently chosen. Thus, output pixel values represent percent changes in local tissue impedance from baseline. Maximum image resolution (analyzed as area at half maximum height of a perturbation) was approximately $1:10^{th}$ of the diameter at the centre and $1:20^{th}$ at peripheral locations.

**Ventilation images**

As shown in previous studies, relative impedance changes reliably track local changes in the content of air within the lung (55). Therefore, tidal oscillations in pixel values are proportional to tidal oscillations in tissue aeration. By calculating the amplitude of oscillation ($\Delta Z =$ Delta impedance) for a fixed pixel along a sequence of primary relative images, one can estimate the local rate of ventilation and represent it by a colour code. Such a procedure generates an image called "ventilation-map", which is similar to the functional images introduced by Frerichs and Hahn (56).

**Perfusion images**

For perfusion measurements the animal’s ventilation was put on hold for 20 seconds while PEEP was maintained at the given level. The hold was achieved by temporarily switching the ventilation mode to CPAP at the study PEEP level with 0 inspiratory pressure support. During this state of apnea, 1000 EIT frames were acquired while a bolus of 5 ml of a hypertonic solution of NaCl 20% was injected as quickly as possible into a central venous catheter. Due to its high conductivity, the hypertonic saline solution acted as an EIT contrast agent by lowering lung impedance as it passed through the pulmonary circulation. This way an impedance vs time curve was obtained. During a later off-line analysis, a gamma-function, the mathematics typically used for quantifying indicator dilution curves, was fitted to these dilution curves for each single pixel (57).

**Regional compliance**

Local tidal ventilation can be estimated by dividing the global change in impedance during a tidal breath of known volume by the corresponding change in impedance in each pixel since Victorino et al. showed that impedance variations (delta Z) linearly correlate with changes in the volume of local air (55, 58, 59). Regional compliance for any EIT pixel can thus be calculated as the amount of air entering that compartment (local ventilation) divided by the driving pressure (end-inspiratory pressure minus PEEP). Given a stiff ARDS lung, flow should be zero during an end-inspiratory pause and pressure at the airway opening should be equivalent to alveolar pressure. This way, regional compliance can be calculated even for volume controlled ventilation.
Selecting the regions of interest in EIT images

Four regions of interest (ROI) of equal size along the gravitational vertical axis were selected for off-line analysis. The image reconstruction algorithm for EIT uses a 3D finite element mesh where the position of the electrodes is mathematically modeled as being in a known and fixed position (figure 4).

In the model used, the contour of the thorax was extracted from an average contour of 5 pigs of similar size and weight previously analyzed by computerized tomography and the distances between electrodes along the perimeter line was modeled as being constant (figure 5). After projecting this mesh on a 32x32 grid it is possible to define regions of interest of identical volumes at fixed positions in relation to the mesh or electrodes coordinates (figure 6). Perfusion could always be detected in the all of the selected pixels confirming that true lung parenchyma was analyzed in all circumstances.

Figure 5. Scheme representing the modeling of thorax contour and its correspondence with the finite element mesh model.

Figure 6. Image projection on the 32x32 grid for off-line analysis
Data acquisition
In all studies presented in this thesis custom-made data acquisition software programmed in LabView (Labview version 6.0 and 7 National instruments, Austin, Texas, USA) was used. The software integrated the signals of the mechanical ventilator (Servo-i), a multi-parameter monitor Siemens infinity SC 7000 or SC 9000 (Siemens Electro-Medical Systems, Solna, Sweden) for the haemodynamic data and the on-line blood gases monitor (Trendcare). A full set of data was obtained with each respiratory cycle (data acquisition was triggered and controlled by the Servo-i ventilator) and stored in a laptop. Volumetric capnography and airway opening flow and pressure data were recorded separately by either the Aplus® or the datacol® software (Respironics, Wallingford, Conn, USA).

In Study III hemodynamic data coming from the PiCCO system were recorded with the PiCCOWin Software (Pulsion Medical Systems, Munich, Germany). Representative values for continuously measured variables were obtained by averaging the data of the last minute before the inspiratory and expiratory hold manoeuvres of each protocol step. EIT data were recorded and analyzed by the dedicated software ENLIGHT® (Dixtal, São Paulo, Brazil).

Statistics
Significance was assumed at p < 0.05. The Kolmogorov-Smirnov test was used to test for normal distribution. Two point comparisons were performed by using the Student’s paired t-test. Continuous variables were analyzed by ANOVA using Bonferroni's correction for multiple comparison tests for post-hoc analysis. In papers I and II correlations between CT data and oxygenation as well as CT data and dead space variables were performed by linear regression analysis. Agreement between dynamic and static compliance was tested by the Bland-Altman method (60). Also, the sensitivity and specificity of dynamic compliance, oxygenation and dead space variables for detecting a 5% lung collapse on the CT scan (the reference method) were determined by constructing respective receiver-operator curves (ROC) (61). In paper III, EIT differences in regional compliance were analyzed by calculating the area under the curve corresponding to the integral of the pixel compliance curve over the antero-posterior distance for each ROI as a surrogate for the average compliance in that region. Thereafter, a repeated-measures ANOVA test, comparing the following within factors: PEEP (OL-PEEP, -4-, and +4), recruitment (PRE/POS), and ROIs (1 to 4) was performed. Statistical analysis was performed with SPSS 11.0 (SPSS Inc., Chicago, IL, USA) and MatLab, (MatLab the Mathworks, Inc, Natick, Mass, USA).
RESULTS

Experimental lung injury

In studies I and II between 5-10 lung lavages were needed in each animal to establish the experimental model. The CT of an example animal after induction of lung injury is shown in figure 7.

*Figure 7. CT image after induction of lung injury*

In study III an average of 5 lung lavages with subsequent 3 hours of injurious ventilation were applied. Figure 8 summarizes the changes in PaO$_2$ and the progressively increasing PEEP levels needed to keep the animals alive during the ventilation induced lung injury period. Only one animal died during the injurious ventilation period due to a pneumothorax.

*Figure 8. Evolution of PaO$_2$ and PEEP for all animals during injurious ventilation*
Table 2 summarizes gas exchange, lung mechanics, hemodynamic and CT scan data obtained after establishing the injury while animals were ventilated in VCV, a Vt 6 ml/kg, PEEP 6 cmH₂O in studies I and II and 10 cmH₂O in study III and FiO₂ 1.

Table 2. Comparison of physiologic variables of the two different experimental models

<table>
<thead>
<tr>
<th>Variables</th>
<th>Studies I and II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP cmH₂O</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Pplat cmH₂O</td>
<td>25 ± 3</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Pmean cmH₂O</td>
<td>11 ± 1</td>
<td>16 ± 1</td>
</tr>
<tr>
<td>Delta P cmH₂O</td>
<td>19 ± 2</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>Vt mL/cmH₂O</td>
<td>196 ± 15</td>
<td>175 ± 16</td>
</tr>
<tr>
<td>Cdyn mL/cmH₂O</td>
<td>10.2 ± 1.9</td>
<td>8.3 ± 1.5</td>
</tr>
<tr>
<td>Raw cmH₂O·L⁻¹·sec⁻¹</td>
<td>23.2 ± 4.8</td>
<td>18.3 ± 3.7</td>
</tr>
<tr>
<td>PaO₂/FiO₂ mmHg</td>
<td>89 ± 65</td>
<td>62 ± 9</td>
</tr>
<tr>
<td>PaCO₂ mmHg</td>
<td>60 ± 7</td>
<td>75 ± 21</td>
</tr>
<tr>
<td>pHa</td>
<td>7.23 ± 0.06</td>
<td>7.17 ± 0.11</td>
</tr>
<tr>
<td>Shunt</td>
<td>0.44 ± 0.13</td>
<td>0.58 ± 0.07</td>
</tr>
<tr>
<td>VD/VT</td>
<td>0.59 ± 0.1</td>
<td>0.75 ± 0.1</td>
</tr>
<tr>
<td>VDphys mL</td>
<td>119 ± 12</td>
<td>128 ± 12</td>
</tr>
<tr>
<td>Vdaw mL</td>
<td>78 ± 17</td>
<td>74 ± 15</td>
</tr>
<tr>
<td>Vdav mL</td>
<td>40 ± 11</td>
<td>54 ± 9</td>
</tr>
<tr>
<td>Pa-ETCO₂ mmHg</td>
<td>20 ± 6</td>
<td>31 ± 6</td>
</tr>
<tr>
<td>CT Non-A %</td>
<td>38 ± 11</td>
<td>NA</td>
</tr>
<tr>
<td>CT NA %</td>
<td>27 ± 4</td>
<td>NA</td>
</tr>
<tr>
<td>MAP mmHg</td>
<td>90 ± 12</td>
<td>103 ± 17</td>
</tr>
<tr>
<td>PAPM mmHg</td>
<td>42 ± 5</td>
<td>39 ± 6</td>
</tr>
<tr>
<td>CI L/min/m²</td>
<td>6.6 ± 2.2</td>
<td>5.4 ± 2.2</td>
</tr>
</tbody>
</table>

Detection of lung collapse and identification of open lung PEEP

A priori definitions were used to define full lung recruitment and collapse in the experimental studies. In the clinical trial similar definitions as for studies I and II were used to define lung collapse. In addition a recently validated definition of full lung recruitment in ARDS patients was used to evaluate the response to RM (32).

According to these definitions all animals and 24 of the 26 ARDS patients could be fully recruited. Table 3 shows the changes in PaO₂ and Cdyn from baseline to open lung conditions.
Table 3. Changes in main parameters across the studies

<table>
<thead>
<tr>
<th>EXPERIMENTAL STUDIES</th>
<th></th>
<th>CLINICAL STUDY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study III</td>
<td>Study IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>OLP</td>
</tr>
<tr>
<td><strong>P/O/F</strong>&lt;sub&gt;2&lt;/sub&gt; (mmHg)</td>
<td></td>
<td>Baseline</td>
<td>OLP</td>
</tr>
<tr>
<td>89 ± 65</td>
<td></td>
<td>520 ± 47</td>
<td>62 ± 9</td>
</tr>
<tr>
<td><strong>Cdyn</strong> (mL/cmH&lt;sub&gt;2&lt;/sub&gt;O)</td>
<td>10.2 ± 1.9</td>
<td>22.1 ± 4.2</td>
<td>8.3 ± 1.5</td>
</tr>
<tr>
<td><strong>CT Non A (%)</strong></td>
<td>38 ± 11</td>
<td>2.7 ± 2.3</td>
<td>—</td>
</tr>
<tr>
<td><strong>CT NA (%)</strong></td>
<td>27 ± 4</td>
<td>80 ± 7.5</td>
<td>—</td>
</tr>
</tbody>
</table>

Legend: Baseline after injury, in study IV at study entry; OL-PEEP: ventilation at open lung PEEP determined by dynamic compliance. All measurements were made under FiO<sub>2</sub> 1. CT Non A (%) CT percentage of non-aerated tissue. CT NA (%). CT percentage of normally aerated tissue.

The open lung PEEPs according to oxygenation progressively increased from one study to the next and became higher than those determined by dynamic compliance with the mean difference between them widening as severity of lung disease increased.

Table 4. Different levels of Open Lung PEEP in the different studies

<table>
<thead>
<tr>
<th></th>
<th>Studies I and II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OL-PEEPcom</strong></td>
<td>15.3 ± 1.7</td>
<td>18.6 ± 1.9</td>
<td>18.6 ± 4.1</td>
</tr>
<tr>
<td><strong>OL-PEEPox</strong></td>
<td>15.7 ± 2.6</td>
<td>17.4 ± 2.3</td>
<td>20.8 ± 3.8</td>
</tr>
<tr>
<td><strong>Mean difference</strong></td>
<td>0.5 ± 1.7</td>
<td>1.25 ± 1</td>
<td>3.8 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>(p = 0.45)</td>
<td>(p &lt; 0.05)</td>
<td>(p &lt; 0.05)</td>
</tr>
</tbody>
</table>

**OL-PEEPox** in studies I, II and III was determined using the same definition as described in study IV, a PEEP level 2 cmH<sub>2</sub>O above the oxygenation defined collapse.
Study I: Validation of dynamic compliance for OL-PEEP titration

The pressure at maximum Cdyn during a DPT after full lung recruitment marked the onset of lung collapse as measured by CT and by changes in oxygenation, the clinical and morphological reference methods (Table 3). Maximum Cdyn occurred at PEEP 14 cmH2O, the same level at which PaO2 decreased by >10% from its post-RM maximum. At this level the % of non-aerated tissue on the CT was 4.4 ± 3.8%. At PEEP 12 the amount of non-aerated tissue increased above the threshold of 5% to 7.3 ± 5.4%. Consequently, OL-PEEPcom was identified at 16 cmH2O. In all animals any reduction of PEEP below the point of maximum Cdyn was associated with progressive lung collapse and tidal recruitment. On the other hand, at PEEP levels above OL-PEEP both, collapse and tidal recruitment were negligible (< 3% and < 0.25% respectively). Definitions of collapse according to Cdyn and PaO2 both had a sensitivity of 84.4% and a specificity of 87.5 and 95.5% respectively (p < 0.001) for detecting a fraction of non-aerated tissue on the CT images >5%, the criterion defining collapse.

Oxygenation showed a plateau during the first decremental PEEP steps reaching its maximum value at PEEP 22 cmH2O (557 ± 26 mmHg), which together with the CT findings confirmed the maintenance of an open lung at these high PEEPs.

Airway resistance significantly decreased after recruitment and then diminished in parallel with PEEP reaching minimum values at PEEP 12 cmH2O only to increase again as the lungs collapsed further.

Changes in Cdyn during the DPT showed a similar pattern in all animals and the maximum for each individual animal could easily be identified by simple visual inspection of the Cdyn trend curve (figure 9).

Figure 9. Individual changes in dynamic compliance during a decremental PEEP trial
Changes in Cdyn paralleled changes in static compliance and both measurements showed a high correlation (R = 0.92, p < 0.01).

Ventilation at OL-PEEP resulted in a Pplat of 25 cmH₂O, a deltaP of 9 cmH₂O and an airway resistance of 10.4 cmH₂O·L⁻¹·sec⁻¹. Haemodynamic parameters were in the normal range except for an increased mean pulmonary artery pressure that decreased from an initial 42 ± 5 mmHg at baseline to 36 ± 2 mmHg at OL-PEEP.

**Study II: Monitoring changes in dead space during lung recruitment and PEEP**

Dead space variables were closely related to the recruitment-collapse phenomena as observed by CT and oxygenation. Full lung recruitment was associated with a significant reduction in all dead space variables as compared to the collapsed condition (Table 5) even at the highest post recruitment PEEP levels (24 cmH₂O). Despite these high PEEPs a functional alveolar overdistension could not be shown at inspiratory plateau pressures as high as 41 ± 3.5 cmH₂O. CT analysis revealed an area < 0.7% of hyperinflated lung according to standard definitions (51).

Table 5. Changes in dead space variables at different study points

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post RM</th>
<th>OL-PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP (cmH₂O)</td>
<td>6</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>Vdaw (mL)</td>
<td>78 ± 17</td>
<td>101 ± 12*</td>
<td>89 ± 14†</td>
</tr>
<tr>
<td>Vdalv (mL)</td>
<td>40 ± 11</td>
<td>11 ± 8.4*</td>
<td>12 ± 8.6†</td>
</tr>
<tr>
<td>VDphys (mL)</td>
<td>119 ± 12</td>
<td>112 ± 14*</td>
<td>101 ± 14†</td>
</tr>
<tr>
<td>Vd/VT</td>
<td>0.59 ± 0.1</td>
<td>0.58 ± 0.1*</td>
<td>0.54 ± 0.1†</td>
</tr>
<tr>
<td>Pa-ETCO₂</td>
<td>20 ± 6</td>
<td>4.3 ± 3.9*</td>
<td>4 ± 2.5†</td>
</tr>
</tbody>
</table>

* p < 0.05 for compared to baseline; † p < 0.05 compared to Post RM

During the decremental PEEP titration VDalv, VDalv/VTalv and Pa-ETCO₂ showed the best correlation (r² min/max) with the amount of non-aerated tissue on the CT: 0.84/0.89; 0.90/0.98 and 0.97/0.99 respectively (p< 0.05), whereas VD/VT, VDphys and VDaw showed weaker correlations (-0.70/0.77; -0.70/0.95; -0.78/0.75 respectively, p<0.05).

It was VDalv, VDalv/VTalv and Pa-ETCO₂ again that showed the highest sensitivity and specificity for detecting > 5% non-aerated tissue area on the CT. Changes in VDalv paralleled changes in shunt and in Pa-ETCO₂ during the decremental PEEP trial. As expected, VDaw markedly increased after
recruitment at highest PEEP levels and then decreased continuously and in parallel with the decreasing PEEPs.

**Study III: Regional distribution of ventilation and perfusion at different lung conditions**

This experiment used a model of more severe lung injury as is shown in Table 2. Accordingly, higher closing pressures for the lung were found. The average OL-PEEPcom was 18.6 ± 1.9 that is 3.3 cmH₂O higher than the respective pressure found in the pure lavage model. Mean PEEP levels for the study conditions were therefore 12 cmH₂O for OL-PEEP-4, 18 for OL-PEEP and 22 cmH₂O for OL-PEEP+4.

All post recruitment conditions resulted in significantly improved gas exchange, dead space and lung mechanics when compared to their non-recruited peers at OL-PEEP-4, OL-PEEP and OL-PEEP+4.

Figure 10. Relative improvements induced by recruitment

![Relative improvements induced by recruitment](image)

Relative changes in main physiologic variables at same PEEP level as a result of lung recruitment. *p < 0.05; † p < 0.01; ‡ p < 0.001.

When analyzing differences among all the recruited conditions, ventilation at optimum PEEP (OL-PEEP<sub>POST</sub>) compared with the other conditions OL-PEEP<sub>-4POST</sub> and OL-PEEP<sub>+4POST</sub> resulted in improved gas exchange, lung mechanics and reduced dead space. Only VDaw was higher when compared to OL-PEEP<sub>-4POST</sub>.
Haemodynamic variables were similar under all conditions except for a decrease in CI from 6.36 ± 1.7 at OL-PEEP-4 \text{PRE} to 5.19 ± 1.5 l/min/m² at OL-PEEP-4 \text{POST} \,(p< 0.05).

The induction of lung injury resulted in a redistribution of regional ventilation towards the upper non-dependent regions, especially ROI 2, while ventilation in the lower regions decreased markedly. Perfusion did not change significantly. Table 6 shows the regional distribution of ventilation and perfusion at similar ventilator settings before and after inducing the injury.

Table 6. Relative distribution of ventilation and perfusion before and after induction of lung injury

<table>
<thead>
<tr>
<th>Relative Ventilation (%)</th>
<th>Before Injury</th>
<th>After Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROI 1</td>
<td>11.9 ± 1.9</td>
<td>14.8 ± 3.6</td>
</tr>
<tr>
<td>ROI 2</td>
<td>33.0 ± 3.0</td>
<td>54.0 ± 10.7</td>
</tr>
<tr>
<td>ROI 3</td>
<td>40.0 ± 4.2</td>
<td>25.4 ± 10.3</td>
</tr>
<tr>
<td>ROI 4</td>
<td>14.9 ± 2.7</td>
<td>5.7 ± 5.3</td>
</tr>
</tbody>
</table>

The regional distribution of ventilation was characterized by a significant redistribution of ventilation from the upper to the lower regions with increasing PEEPs when compared with healthy and injury conditions at baseline. The most pronounced differences between the recruited and the non-recruited conditions were seen at OL-PEEP-4.

The differences in the relative distribution of perfusion within the regions of interest were less pronounced than those of ventilation. With increasing levels of PEEP perfusion tended to diminish in ROIs 1 and 4 only to increase in ROI 3. However, none of these differences reached statistical significance. Also no major differences could be found between the recruited and non-recruited states.

Matching (calculated by dividing the lower value of either ventilation or perfusion by the respective other and multiplying the result by 100) between relative distributions of regional ventilation and perfusion was highest during healthy condition (78.7 ± 10.6 %) and lowest after injury (57.2 ± 17.9%). The condition resulting in the best matching was OL-PEEP \text{POST} (76.1 ± 14.8 %).
Lung recruitment improved overall lung compliance in conditions OL-PEEP-4 and OL-PEEP. This improvement occurred mainly in regions 3 and 4 with little changes in region 1. There were no clear recruitment benefits for global or regional compliance in OL-PEEP+4 as compared to OL-PEEP-4. Compliance for the entire lung was best at OL-PEEP\textsubscript{POST} when compared to the other post recruitment conditions with regional compliances being best in ROIs 3 and 4 but not in ROIs 1 and 2. OL-PEEP-4\textsubscript{POST} showed a marked decrease in compliance in region 4 and OL-PEEP+4\textsubscript{POST} in regions 1 and 2 (p = 0001 for both when compared to OL-PEEP\textsubscript{POST}).

**Study IV: Lung protective PEEP titration in ARDS**

Decremental PEEP values resulted in an overall improved lung condition as witnessed by better lung mechanics and gas exchange without significant differences in the haemodynamic response when compared with their corresponding incremental pairs. However, these differences were negligible when extreme (lowest and highest) PEEP values were compared as these conditions were associated with lung collapse or overdistension in both titration arms. The traditional end-points used for PEEP titration like maximal PaO\textsubscript{2}, maximal compliance or maximal oxygen delivery during the I\textsubscript{PT} resulted in a lung condition far worse than the open lung status as defined in this thesis. At these PEEP levels the lung was either still collapsed or operating at excessive inspiratory plateau pressures even when tidal volumes as low as 6 ml/kg were used.

In some patients OL-PEEP\textsubscript{com} was more difficult to identify since instead of reaching a clear maximum value at a particular PEEP step C\textsubscript{dyn} behaved in a plateau-like fashion during several decremental PEEP steps.

According to the mechanical behaviour of the lung OL-PEEP\textsubscript{com} resulted in lowest deltaP when compared to any other PEEP level during the titration protocol (figure 11) and 18 of 26 patients maintained full open lung conditions according to gas exchange criteria.
**Figure 11.** Comparison of delta P during incremental and decremental PEEP steps.

\[
\begin{array}{c}
\text{Delta Pressure (cmH}_2\text{O)} \\
\hline
8 & 10 & 12 & 14 & 16 & 18 & 20 & 22 & 24 & 26 & \text{Lung Recruitment} & 26 & 24 & 22 & 20 & 18 & 16 & 14 & 12 & 10 & 8 \\
\hline
\end{array}
\]

\[* p<0.05 \text{ and } † p < 0.01 \text{ compared to the same incremental PEEP level}\]

During the four-hour ventilation period at both, OL-PEEPcom and OL-PEEPox oxygenation increased while compliance slightly decreased but the changes in oxygenation and compliance remained within a ± 5% window suggesting that both PEEP levels maintained stable lung conditions.
DISCUSSION

Use of dynamic compliance for open lung PEEP titration

An experimental model of lung injury was used to demonstrate usefulness of dynamic compliance for determining open lung PEEP during a decremental PEEP titration. It could be shown that in fully recruited lungs any decrease $C_{dyn}$ from its maximal value during a decremental PEEP trial marked the onset of lung collapse. These findings were consistent with the ones predicted by a mathematical model for the ARDS lung (39) or observed in a CT study investigating ARDS patients (38).

To correctly interpret the mechanical behaviour of the lung during a decremental PEEP titration the following aspects deserve special attention:

1. Failing to fully recruit the lung by applying insufficient inspiratory pressures will limit the conclusions that can be drawn from observing the mechanical behaviour of the lung during the decremental PEEP trial (39, 62, 63). In such a case, the maximum $C_{dyn}$ value would very likely be achieved at the first PEEP level and any inference about the point of collapse would be elusive.

2. The decremental PEEP trial must start at high levels of PEEP well above the (empirically) estimated OL-PEEP level. Collapse ensues rapidly if the titration process is started at insufficient PEEP (64) resulting in a loss of its expected physiologic responses (65,66), thereby limiting further the interpretability of lung mechanics.

3. During the DPT a constant low tidal volume and/or delta pressure must be maintained because any change in tidal volume would affect compliance measurements (67). Furthermore, the higher the tidal volume the greater the chance of underestimating OL-PEEP by overestimating compliance as tidal recruitment becomes an interfering factor as soon as lung collapse has re-occurred, whereby parts of the lung would be shifted from the expiratory to the inspiratory part of the pressure volume curve.

4. All ventilatory settings - except for the input variable PEEP - must be maintained constant during the decremental PEEP trial in order to make changes in lung mechanics interpretable.
5. Finally, Cdyn measured at the airway opening is a global parameter resulting from contributions of different lung regions that may be heterogeneously diseased. It follows that the final OL-PEEPcom value will always be the one that is capable of stabilizing the most diseased regions while overdistending the healthier ones. As the heterogeneity of the lung disease increases the chance for underestimating true OL-PEEP by means of Cdyn and for unwanted side effects increases.

Although the lung lavage model intrinsically differs from true ARDS and from other experimental models (68), it is an excellent model for studying the dynamics of lung collapse and re-opening. Being aware of the pitfalls associated with an extrapolation of the findings from this experimental model to real patients with acute lung injury, the described general mechanical behaviour, however, should still be similar so that any PEEP level equal to or below maximal Cdyn will be too low to prevent the lung from collapsing.

**Use of dead space monitoring for open lung PEEP titration**

Alveolar dead space fraction was the dead space variable that reflected the changes in the morphologic lung condition the best. It markedly decreased after full lung recruitment and remained at low levels during the first decremental PEEP steps. As recruitment restored ventilation to the dependent regions the resulting homogeneous distribution of ventilation prevented the occurrence of true alveolar overdistension (high ventilation/perfusion zones) even at these high PEEP levels while CT scans could not detect significant areas of hyperinflation, either (51). However, as PEEP was reduced VDalv progressively increased similar to the shunt fraction. This is explained by the shunt-related dead space effect that comes into play when VDalv is calculated using the Enghoff’s modification of Bohr’s formula (49,50). In fact, this apparent limitation turned into an advantage for monitoring the onset of collapse during the DPT as the first statistically significant increase in VDalv coincided with the first increase of non aerated tissue to more than 5%.

Pa-ETCO₂, a sensitive parameter reflecting gas exchange, behaved like shunt and VDalv and proved to be a good indicator of lung collapse, whereas VDphys and VD/VT, the most commonly used dead space parameters in the clinical setting, were poor predictors of the lung’s status. Being composite in nature and global these ratios were contaminated significantly by the changes in airway dead space thereby masking the changes at the alveolar level especially when high levels of PEEP were used. In this respect they shared the same limitations as the changes in functional residual capacity
Thus, if changes at the alveolar level are to be evaluated VDalv/VTalv should be used. Used in combination with the changes in lung mechanics, dead space monitoring provided useful adjuvant information for identifying lung collapse and thus, help to better titrate open lung PEEP. In addition, it has the potential to further optimize ventilation by looking for settings that result in the most efficient ventilation for a given open lung PEEP.

As open lung PEEP resulted in rather high values it was important to discriminate whether the witnessed improvements in lung function could be due to PEEP alone or whether recruitment was necessary to fully exploit the potential of PEEP regarding both lung function and protection. In paper III, recruitment markedly improved lung function and mechanics at each PEEP level studied, especially at low and open lung PEEP levels. As could be expected the major improvements in lung mechanics and gas exchange were obtained at OL-PEEPPOST as this level was carefully selected to represent the minimum pressure level that prevented end-expiratory collapse (32, 70).

These findings support the concept that increasing PEEP without actively recruiting the lung may result in modest overall improvements only or could even become deleterious (71-73). Increasing PEEP further improved oxygenation only marginally at the expense of overdistending the lung as indicated by significant increases in VDalv, VDaw and VD/VT. An additional important finding was the significant reduction of the inspiratory driving pressure obtained at OL-PEEPPOST as compared with all other experimental conditions. The resulting reduction in tidal stretch (74) together with the absence of tidal recruitment should, if maintained over longer time periods provide protective effects even in these very sick lungs.

Effects of PEEP on the regional distribution of ventilation and perfusion measured by EIT

Electrical impedance tomography is a novel promising non-invasive bedside monitoring technology that can provide images of regional ventilation and perfusion under different levels of PEEP and open lung PEEP. In this study the regional distribution of ventilation and perfusion at baseline before inducing the lung injury was similar to what has been reported for healthy subjects under mechanical ventilation (75). The marked reduction in ventilation in the dependent regions after inducing lung injury was consistent with the changes in aeration seen in CT scan of similar and other models (64). Under the different study conditions ventilation was then progressively shifted from non-dependent to dependent regions as PEEP levels increased.

In the healthy lungs, perfusion increased along the gravitational axis reaching its maximum in region 3. After establishing the injury, relative perfusion to the upper regions increased while decreasing in the lower ones with hypoxic pulmonary vasoconstriction being a likely explanation for this
diminished perfusion to these atelectatic regions. One remarkable finding was the small differences in the distribution of regional perfusion between different study conditions despite the range of PEEP being as wide as 8 cmH₂O. At OL-PEEP<sub>POST</sub> the best regional matching between ventilation and perfusion was obtained explaining the significantly improved gas exchange.

**Effects of PEEP on regional compliance measured by EIT**

Lung recruitment improved overall lung compliance at low and open lung levels of PEEP with little effect at higher levels probably because some recruitment effect was already present before performing the RM. Regional analysis of compliance revealed that compliance increased mainly in regions 3 and 4, but only marginally in region 2 showing no improvement in region 1. This reduced compliance in region 1 and 2 as compared to the pre injury condition points towards some degree of overdistension as the price to pay for lung stability and an almost normal compliance in the lower most dependent regions.

**Open lung PEEP titration in ARDS patients**

The principles described in the previous studies were now tested in a population of ARDS patients. Traditional ways of determining optimal PEEP would primarily evaluate its effect on oxygenation during a stepwise increase in PEEP despite any solid physiological basis (72). This is one of the main reasons why the fundamental role of PEEP for lung protection and positive patient outcome has not been established yet (76). In this study oxygenation and lung mechanics were used, not as treatment endpoints, but as means for defining OL-PEEP based on sound physiological principles. This way it was possible to identify a PEEP level, OL-PEEP<sub>com</sub> that resulted in, firstly a better functional status than the corresponding PEEP on the incremental limb and secondly in a much lower plateau and driving pressure while maintaining alveolar end-expiratory stability. This implies that ventilation at OL-PEEP can protect the lung as it reduces the effects of the main contributing factors of ventilation induced lung injury - overdistension and tidal recruitment (9). The stabilizing effects of OL-PEEP<sub>com</sub> and OL-PEEP<sub>ox</sub> could be demonstrated during two consecutive four-hour ventilation periods.

The observation that in some patients maximal compliance was difficult to determine when it behaved in a plateau like fashion together with the fact that there was a slight decrease in compliance during the ventilation period at OL-PEEP<sub>com</sub> raised the concern that OL-PEEP<sub>com</sub> might have been under-estimated in a subset of patients. In these probably more severely diseased patients the measured C<sub>dyn</sub> very likely reflects the balance between two opposing but simultaneously occurring mechanical phenomena: the collapse of lower dependent and the relief of overdistension of upper non
dependent lung regions maintained during several decremental PEEP steps. As it is impossible to determine when exactly collapse ensues, the first PEEP value resulting in such a plateau should be taken as the point of collapse in order to avoid this underestimation of OL-PEEP.

No morphological assessment of the lung i.e. by means of CT was performed in this study since for the known titration process a good correspondence with other less invasive physiological parameters had already been evaluated and validated in previous studies (32, 38, 70). Thus, the main intention of this study was to evaluate the usefulness of Cdyn as a bedside tool for defining optimal ventilatory settings. Dynamic compliance was comparable to oxygenation in identifying OL-PEEP having the advantages of being available less invasively and on a continuous breath by breath basis.

Although OL-PEEPs were rather high the haemodynamic responses were not different from the ones seen at lower PEEPs. This supports the notion that the well described deleterious effects of PEEP on hemodynamics (6, 27) may be enhanced if PEEP is applied in partially collapsed lungs.

**Future considerations and implications of this study**

The methods developed in and the information obtained from the series of studies presented in this thesis have been used to create the protocol for the study arm of a recently started (September 2007) multi-centre randomized controlled clinical trial; an outcome study comparing the ARDSnet LPV strategy (12) with a lung protective ventilation strategy employing OL-PEEP according to dynamic compliance in patients with established severe ARDS. The study involves more than 30 centres in four continents. The study aims at demonstrating a reduced mortality from an expected 45.5% in the ARDSnet group (77) to ≤ 32% (13) in the study group. According to these numbers approximately 500 patients will have to be randomized.
CONCLUSIONS

1. Changes in dynamic compliance during a decremental PEEP trial after fully recruiting the lungs is a useful bedside tool for detecting the onset of lung collapse in acutely injured lungs.

2. Once the point of lung collapse has been detected, open lung PEEP, the pressure level that avoids an end-expiratory collapse of the most unstable alveoli, can be identified as being at least 2 cmH₂O above the point of collapse.

3. Dead space, especially its portion related to the alveolar gas compartment, changes dynamically and consistently during recruitment, PEEP titration and collapse. Monitoring these changes could become useful adjunct information for identifying early signs of lung collapse and for optimizing tidal ventilation.

4. Ventilation at selected levels of PEEP showed marked differences between the recruited and non-recruited state. The best functional condition was achieved at OL-PEEP were gas exchange, efficiency of ventilation and compliance were best and delta pressure significantly reduced. These physiologic improvements seen at open lung PEEP corresponded to a better matching of regional ventilation and perfusion as well as regional compliance in almost all lung regions as could be demonstrated by electrical impedance tomography.

5. PEEP titration in ARDS patients should be performed as a decremental, not an incremental PEEP trial.

6. The bedside determination of open lung PEEP based on dynamic compliance delivered similar results as the one based on oxygenation. Both resulted in a marked decrease in inspiratory driving pressures. However, dynamic compliance is less invasive, quasi continuous and leads to a better lung mechanical condition with the potential of further lowering driving and plateau pressures.

7. Both PEEP levels could maintain the benefits obtained by recruitment and stable lung protective conditions during a four hour ventilation period.
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REFERENCES


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)