Transpulmonary pressure during mechanical ventilation

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"What we learn from academic studies is knowledge: what we learn from experience is wisdom."

Mohandas Karamchand Gandhi
(1869-1948)
ABSTRACT

**Background:** Mechanical ventilation can aggravate lung injury by repetitive opening and closing of lung units, overdistention and undue pressure on pulmonary structures. Guidelines exist for lung protective ventilation, but individualized ventilator settings, based on partitioning of respiratory mechanics in pulmonary and chest wall complex components, would be beneficial. This thesis examines the current practice of respiratory care in the Nordic countries and evaluates a method to assess lung volume changes during mechanical ventilation. A new concept to measure lung and chest wall elastance and determine transpulmonary pressure during mechanical ventilation is validated.

**Methods:** Clinical practice concerning adjunct therapies to mechanical ventilation were addressed in a web-based survey performed in Nordic intensive care units. Changes in lung volume (ΔEELV) were determined by spirometry, where the first ten breaths after a PEEP change were studied. The sum of the differences of inspiratory and expiratory tidal volumes was calculated, with correction for offset. The method was validated in a lung model and in 12 patients with simultaneous measurement of lung volume changes by electrical impedance tomography (EIT). PEEP induced changes in ΔEELV, airway and esophageal pressures were studied both in an animal model and in 12 ventilated patients.

**Results:** One-third of the patients had more than 12 disconnections from the ventilator circuit during 24 hours, with great variations in the individual lowest and highest oxygenation ratios (PaO$_2$/FiO$_2$). The spirometric method showed good agreement with known volume changes in the lung model and with estimated lung volume changes by EIT. PEEP increase resulted in only modest increase in esophageal pressure. The increase in transpulmonary pressure was closely related to increase in PEEP. Lung elastance determined from change in PEEP divided by ΔEELV was closely correlated with that obtained from esophageal pressure measurements.

**Conclusion:** Routine care of ventilated patients leads to repeated derecruitment episodes due to disconnections of the ventilator circuit by frequent use of aerosol therapy and endotracheal suctioning. Spirometric measurements of inspiratory-expiratory tidal volumes as well as impedance changes by EIT can be used to estimate PEEP-induced changes in lung volume. The minimal increase in esophageal pressure after a PEEP increase indicate that the abdomen and chest wall gradually yields and adapts when the diaphragm is pushed in caudal direction. As a consequence, PEEP increase will cause a corresponding increase in transpulmonary pressure. This may explain why lung elastance can be determined from the change in PEEP divided by the change in lung volume without the need for esophageal pressure measurements.

**Keywords:** Mechanical ventilation, Acute lung injury; Acute respiratory distress syndrome; Lung volume measurements; Electric Impedance/diagnostic use; Lung elastance; Transpulmonary pressure; Esophageal pressure

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POPULÄRVETENSkaplig Sammanfattning

Vård av svårt sjuka patienter inom intensivvården medför ofta behov av någon form av andningsunderstödjande behandling, eftersom sviktande andningsfunktion är ett vanligt symptom vid allvarliga sjukdomstillstånd. Respiratorbehandling kan antingen fungera som ett stöd för patientens egna andetag eller helt ersätta andningsrörelsen. I de fall lungans gasutbytesförmåga (förmåga att ta upp syrgas respektive att vädra ut koldioxid) är försämrad av sjukdomstillståndet kan respiratorbehandling till viss del kompensera för detta. Respiratorbehandling kan försämrar eller till och med orsaka lungskada genom övertänjning av lungvävnad eller ofördelaktig tryckfördelning inom lungen. Om det under ett andetag finns delar av lungen som omväxlande är sammanfallna respektive gasfyllda kan detta leda till en inflammatorisk reaktion som i värsta fall kan ha negativa konsekvenser för fler organ än lungen. För att förhindra detta finns generella rekommendationer om begränsning av tryck och volym för respiratorinställningar (platåtryck 30 cm H₂O, andetag 6 ml/kg ideal kroppsvikt). Det är även väsentligt att det lägsta trycket under utandningen, så kallat PEEP, inte är så lågt att delar av lungen faller ihop. Någon generell rekommendation för val av PEEP har inte kunnat fastställas ännu.


Denna avhandling har haft flera syften. Ett syfte var att beskriva hur tilläggsbehandlingar till respiratorvården genomförs i praktiken. Ett annat syfte har vart att utveckla en lättillgänglig metod för att mäta storleken på lungvolymförändringar orsakade av olika PEEP-nivåer. Ytterligare syften har vart att kartlägga effekten av PEEP på förändring av trycket med via ballongkateter i matstrupen och samtida förändringar av lungvolym. Målsättningen har vart att undersöka huruvida transpulmonellt tryck kan bestämmas utan behov av måttning av matstrupstryck.

Rekommendationerna för skonsam respiratorbehandling vad gäller tryck- och volymbegränsning är välkända. Bruk av olika former av tilläggsbehandlingar till respiratorvården kan inverka på hur skonsam behandlingen blir. För att kartlägga detta genomfördes en web-baserad enkät riktad

Studien i det andra delarbetet, innebar utveckling av en metod för bestämning av lungvolymförändringar baserad på den sammanlagda skillnaden i in- och utandetag för de första 10 andetag efter en PEEP-ändring. Metoden ("kumulerad tidalvolymdifferens") validerades i en lungmodell och användes därefter på respiratorvårdade patienter. För jämförelse användes på patienterna ytterligare en annan metod; elektrisk impedans tomografi (EIT). De båda metoderna visade god överensstämmelse. Till skillnad från EIT så kräver metoden "kumulerad tidalvolymdifferens" ingen extra utrustning på patienten. En intensivvårdsrespirator skulle kunna utrustas med en programvara som beräknar lungvolymförändringen enligt denna metod.


CONTENTS

ABBREVIATIONS x
DEFINITIONS IN SHORT xi
LIST OF PAPERS xii

1 INTRODUCTION 1
   1.1 Historical background 1
   1.2 Contemporary background 2

2 AIM OF THIS THESIS 5

3 METHODS 6
   3.1 Ethical issues 6
   3.2 Patients 6
   3.3 Mechanical lung model 6
   3.4 Ex vivo lung model 7
   3.5 Measurements, monitoring equipment and data collections 7
      3.5.1 Pressure and Volume measurements
      3.5.2 Electrical Impedance Tomograpgy
      3.5.3 FRC measurement
      3.5.4 Data collection
   3.6 Calculations 9
      3.6.1 Lung volume changes determined by cumulated tidal volume
            difference and impedance changes
      3.6.2 Driving pressures
      3.6.3 Elastance and compliance
      3.6.4 Two ways to determine change in transpulmonary pressure;
            a conventional approach and a new concept
      3.6.5 Transpulmonary pressure based on esophageal pressure
            measurements
   3.7 Study design 14
      3.7.1 Paper I – Web-based survey
      3.7.2 Paper II – Estimation of changes in end-expiratory lung volume
      3.7.3 Paper III – Lung elastance and transpulmonary pressure in
            an ex vivo model
      3.7.4 Paper IV – Lung elastance and transpulmonary pressure in
            patients
   3.8 Statistical analyses 18
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 MAIN RESULTS</td>
<td>20</td>
</tr>
<tr>
<td>5 DISCUSSION</td>
<td>28</td>
</tr>
<tr>
<td>5.1 Main findings</td>
<td>28</td>
</tr>
<tr>
<td>5.2 Methodological considerations</td>
<td>29</td>
</tr>
<tr>
<td>5.2.1 The survey on the use of adjunct therapies to mechanical ventilation</td>
<td>29</td>
</tr>
<tr>
<td>5.2.2 How to monitor lung volume changes during mechanical ventilation</td>
<td>30</td>
</tr>
<tr>
<td>5.2.3 How to monitor transpulmonary pressure during mechanical ventilation</td>
<td>35</td>
</tr>
<tr>
<td>5.2.4 How to compare methods</td>
<td>38</td>
</tr>
<tr>
<td>5.2.5 Possible improvements of study design</td>
<td>41</td>
</tr>
<tr>
<td>5.3 General discussion</td>
<td>42</td>
</tr>
<tr>
<td>5.3.1 Chest wall complex and the effect of driving pressures</td>
<td>43</td>
</tr>
<tr>
<td>5.3.2 Esophageal pressure as a reflection of pleural pressure</td>
<td>45</td>
</tr>
<tr>
<td>5.3.3 The influence of PEEP on esophageal pressure</td>
<td>46</td>
</tr>
<tr>
<td>5.3.4 Transpulmonary pressure during mechanical ventilation</td>
<td>47</td>
</tr>
<tr>
<td>5.3.5 Theoretical model of the respiratory system</td>
<td>48</td>
</tr>
<tr>
<td>5.3.6 Current praxis in the daily care of mechanically ventilated patients</td>
<td>50</td>
</tr>
<tr>
<td>6 CONCLUSIONS</td>
<td>52</td>
</tr>
<tr>
<td>FUTURE PERSPECTIVES</td>
<td>55</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>56</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>57</td>
</tr>
<tr>
<td>Papers I – IV</td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>ALI</td>
<td>acute lung injury</td>
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<td>ARF</td>
<td>acute respiratory failure</td>
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<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
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<tr>
<td>CTscan</td>
<td>computer tomography scan</td>
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<tr>
<td>CW</td>
<td>chest wall complex; rib cage, diaphragm and abdomen</td>
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<tr>
<td>EELV</td>
<td>end-expiratory lung volume</td>
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<tr>
<td>(\Delta EELV_{EIT})</td>
<td>change in end-expiratory lung volume with EIT</td>
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<tr>
<td>(\Delta EELV_{LM})</td>
<td>change in end-expiratory lung volume in lung model</td>
</tr>
<tr>
<td>(\Delta EELV_{VT(e)})</td>
<td>change in end-expiratory lung volume with spirometry</td>
</tr>
<tr>
<td>EIT</td>
<td>electrical impedance tomography</td>
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<td>ECW</td>
<td>elastance of the chest wall complex</td>
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<td>EL</td>
<td>lung elastance</td>
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<tr>
<td>ETOT</td>
<td>elastance of the total respiratory system</td>
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<tr>
<td>FiO(_2)</td>
<td>inspiratory fraction of oxygen</td>
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<td>FRC</td>
<td>functional residual capacity</td>
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<tr>
<td>ID</td>
<td>inner diameter</td>
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<tr>
<td>paO(_2)</td>
<td>partial pressure of oxygen</td>
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<tr>
<td>Paw</td>
<td>airway pressure</td>
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<tr>
<td>Paw(<em>{EI}), Paw(</em>{EIP})</td>
<td>end-inspiratory plateau airway pressure</td>
</tr>
<tr>
<td>Paw(_{EE})</td>
<td>end-expiratory airway pressure</td>
</tr>
<tr>
<td>(\Delta Paw)</td>
<td>driving pressure of the total respiratory system</td>
</tr>
<tr>
<td>Pes</td>
<td>esophageal pressure</td>
</tr>
<tr>
<td>Pes(_{EE})</td>
<td>end-expiratory esophageal pressure</td>
</tr>
<tr>
<td>(\Delta Pes)</td>
<td>driving pressure of the chest wall complex</td>
</tr>
<tr>
<td>Ptp</td>
<td>transpulmonary pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end-expiratory pressure</td>
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<tr>
<td>P/V curve</td>
<td>pressure/volume curve</td>
</tr>
<tr>
<td>VILI</td>
<td>ventilator induced lung injury</td>
</tr>
<tr>
<td>VT</td>
<td>tidal volume</td>
</tr>
<tr>
<td>VT(_{offset})</td>
<td>tidal volume offset</td>
</tr>
<tr>
<td>(\Delta Z)</td>
<td>impedance change</td>
</tr>
<tr>
<td>ZEEP</td>
<td>zero PEEP</td>
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</tbody>
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DEFINITIONS IN SHORT

For explanation of abbreviations, see previous page.

- Tidal driving pressure of the total respiratory system = $\Delta P_{aw} = P_{aw}^{EIP} - P_{aw}^{EE}$
- Tidal driving pressure of the chest wall complex = $\Delta P_{es} = P_{es}^{EI} - P_{es}^{EE}$
- Tidal driving pressure of the lung = tidal difference in transpulmonary pressure = $\Delta P_{tp} = \Delta P_{aw} - \Delta P_{es}$
- Elastance $= \frac{1}{\text{Compliance}} = \frac{\text{Pressure} \ (\text{cm H}_2\text{O})}{\text{Volume} \ (\text{L})}$
- $E_{TOT} = E_L + E_{CW}$
- $E_{TOT} = \frac{\Delta P_{aw}}{V_T}$
- $E_{CW} = \frac{\Delta P_{es}}{V_T}$
- $E_L = \frac{\Delta P_{tp}}{V_T}$
- Transpulmonary pressure = alveolar pressure – pleural pressure
- PEEP induced change in transpulmonary pressure = lung elastance * change in end-expiratory lung volume = $E_L \times \Delta EELV$; based on the concept in this thesis this implies that $E_L = \frac{\Delta PEEP}{\Delta EELV}$
- Two different ways to determine end-inspiratory transpulmonary pressure by mechanical ventilation with $PEEP_x \ (x \ cm \ H_2O)$:
  - According to Gattinoni et al.$^{1,2}$: $\frac{E_L}{E_{TOT}} \times P_{aw}^{EIP}$
  - According to this thesis: $PEEP_x + E_L \times V_T$;
    where $E_L$ is estimated through a PEEP step maneuver as $\frac{\Delta PEEP}{\Delta EELV}$ (see Calculations section 3.6.4 for details), since $V_T = \frac{\Delta P_{aw}}{E_{TOT}}$ another way for the expression is: $PEEP_x + E_L \times \frac{\Delta P_{aw}}{E_{TOT}}$ = $PEEP_x + \frac{E_L}{E_{TOT}} \times \Delta P_{aw}$
LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. Grivans C, Lindgren S, Åneman A, Stenqvist O, Lundin S.
   A Scandinavian survey of drug administration through inhalation, suctioning and recruitment maneuvers in mechanically ventilated patients.

II. Grivans C, Lundin S, Stenqvist O, Lindgren S.
    Positive end-expiratory pressure-induced changes in end-expiratory lung volume measured by spirometry and electric impedance tomography.

III. Stenqvist O, Grivans C, Andersson B, Lundin S.
    Lung elastance and transpulmonary pressure can be determined without using oesophageal pressure measurements.

IV. Grivans C, Lundin S, Stenqvist O
    Lung elastance and transpulmonary pressure can be calculated from the change in end-expiratory lung volume following a change in end-expiratory airway pressure.
    *Manuscript submitted*
1. INTRODUCTION

The ability to breathe is a prerequisite for terrestrial life. Metabolism requires a continuous supply of oxygen and elimination of waste products such as CO$_2$. In addition to adequate pulmonary gas exchange, the need for effective air transport in and out of the lungs is vital. Development in the field of breathing mechanics has progressed from being focused principally on anatomy to a more abstract approach examining different forces acting on the respiratory system.

1.1 HISTORICAL BACKGROUND

Many well renowned scientists have helped to expand and deepen our insight into respiratory mechanics throughout the centuries. Naturally it all began with the Greeks and Erasistratus, ca 300 B.C., regarded by some as “the founder of physiology”, who described the diaphragm’s role in breathing. 500 years later, Galen described the importance of intercostal and accessory muscles in addition to the diaphragm and realized that the lung is moved by the actions of the chest wall rather than the opposite, as had been previously believed. The next major advancement in the understanding of respiratory mechanics was during the Renaissance with the publication of Leonardo da Vinci and Andreas Vesalius’ anatomical charts. Vesalius also published his theories regarding the action of the diaphragm to elevate and extend the lower ribs. In the 17$^{th}$ century, René Descartes, Giovanni Alfonso Borelli and John Mayow pointed out the similarities between the properties of mechanical systems and motions, such as breathing, in living subjects. In the 19$^{th}$ century Francois Magendi and Guillaume Duchenne discussed the influence of the abdomen and its contents on respiratory mechanics. Also in the 1800s scientists such as James Carson, Donders, Heynsius, van der Brugh and Cloetta contributed to the knowledge of elastic forces of the respiratory system and their relation to lung volume. In 1878 Heinrich Quincke published the first report of direct measurements of intrapleural pressure in humans, which to this day remains an elusive concept. The relationship between pressure and volume were among others studied by Hutchinson, Bernoulli and von Recklinghausen. In the early stages of last century the foundation of modern respiratory mechanics was laid through work by Fritz Rohrer, Karl Wirz and Kurt von Neergaard who undertook important studies on lung elasticity and flow.
resistance. This leads us to the verge of contemporary, ongoing search for ways to accurately describe the different aspects of respiratory mechanics, new discoveries mixed with the old ones in a new perspective.

1.2 CONTEMPORARY BACKGROUND

Respiratory failure is a common symptom in the critically ill patient and mechanical ventilation is a routine intervention in intensive care units. Despite this, it remains a significant challenge for the physician to use artificial tools in order to provide the best means for recovery from potentially reversible conditions.

Ventilatory assistance was initially provided using negative pressure ventilators, “tank ventilators” or “iron lungs”. Positive-pressure invasive mechanical ventilation was not introduced until in the 1940s. A concept called “respirator lung” was described by pathologists twenty years later. The acute respiratory distress syndrome (ARDS) was first described in 1967 by Ashbaugh et al as a cohort of patients characterized by refractory hypoxemia, tachypnea, bilateral pulmonary infiltrates on chest X-ray and decreased compliance of the respiratory system. More detailed definitions were proposed during the following years.

An attempt to grade the degree of lung injury was made by Murray et al, in 1988, who introduced a lung injury scoring system (LISS). Apart from identification of trigger factors and dividing the disease process in acute or chronic, four parameters were assessed to create LISS; \( \frac{\text{PaO}_2}{\text{FiO}_2} \), PEEP, chest X-ray and compliance. A score between 1 and 2.5 indicated mild to moderate lung injury and a higher score indicated ARDS.

In 1994 the conclusions of an American-European consensus conference were published where acute lung injury (ALI) and ARDS were defined as follows; 1) acute onset of respiratory distress, 2) bilateral infiltrates on chest X-ray, 3) pulmonary capillary wedge pressure less than 18 mm Hg or absence of clinical signs of left ventricular failure, 4) \( \frac{\text{PaO}_2}{\text{FiO}_2} \leq 300 \text{ mmHg (} \approx 40 \text{ kPa)} \) for ALI and \( \leq 200 \text{ mmHg (} \approx 27 \text{ kPa)} \) for ARDS.

A revised definition denoted “the Berlin Definition for ARDS” was published in 2012; 1) debut within a week from known insult or new or worsening respiratory symptoms, 2) bilateral opacities on chest X-ray or CT, 3) origin of edema not fully explained by cardiac failure or fluid overload, 4) PEEP \( \geq 5 \text{ cmH}_2\text{O} \) and \( \frac{\text{PaO}_2}{\text{FiO}_2} \) between 200 and 300 mmHg (\( \approx 27 \text{ and } 40 \text{ kPa)\) for mild ARDS, between 100 and
200 mmHg (≈ 14 and 27 kPa) for moderate ARDS and < 100 mmHg (≈ 14 kPa) for severe ARDS.\textsuperscript{9,10} The recognition of different trigger factors for ARDS has resulted in the concepts “pulmonary and extrapulmonary ARDS”, discussed by Gattinoni et al in 1998\textsuperscript{11}, characterizing the insult to the lungs as being direct or indirect. On a microscopic level this could be illustrated as primarily damage to the alveolar epithelium or pulmonary capillary endothelium resulting in diffuse alveolar damage, increased pulmonary vascular permeability and pulmonary edema.\textsuperscript{12} The inflammatory process in the lung parenchyma starts with an exudative phase which progresses to fibrosing alveolitis. In at least the early phases of ARDS the extent of the inflammation is heterogeneous, leaving parts of the lung more functionally normal, the “baby lung concept”.\textsuperscript{13} Lung injury can also be iatrogenic depending on ventilator settings, i.e. ventilator induced lung injury.\textsuperscript{14,15} Inappropriate combinations of delivered volumes and end-inspiratory as well as end-expiratory pressures, which lead to regional alveolar overdistention and/or repetitive opening and closing of lung sections, are deleterious. This applies to both previously healthy lungs and the more susceptible ones already exposed to harmful effects of endotoxins or inflammatory mediators, locally produced or coming from the systemic circulation. Ventilator induced lung injury could be the effect of systemic inflammation or perhaps even the cause.\textsuperscript{16} The nomenclature associated with ventilator induced lung injury illustrates the multifaceted actions of damage; “barotrauma”, “volutrauma”, “atelectrauma”, “biotrauma”.

This knowledge has led to the pursuit of lung protective ventilation. The “open lung” concept pointed out the need for overcoming high opening pressures in partially collapsed lung and subsequent sufficiently high PEEP to keep these sections aerated.\textsuperscript{17} For a long time the only guidelines were the ones published in 1998 by the second American-European Consensus Conference on ARDS.\textsuperscript{18} It consisted mainly of general advice but stated that maximal transalveolar pressure should not exceed 25-30 cmH\textsubscript{2}O, usually corresponding to end-inspiratory plateau pressure of 30-40 cmH\textsubscript{2}O, depending on lung and chest wall compliance.\textsuperscript{19} The study by the ARDS Network published in 2000, showed improved survival using ventilation with tidal volumes of 6 ml per kg of predicted body weight and a maximum plateau pressure of 30 cmH\textsubscript{2}O.\textsuperscript{20} Since then the use of low tidal volumes is widely accepted. The recommendations on lung protective ventilation were initially directed towards patients with established lung injuries,
but the concept has expanded to also include patients without lung injuries.\textsuperscript{21-23} The enigma of optimal PEEP has not yet been solved.\textsuperscript{24-27} PEEP can be protective except when it contributes to overinflation. The challenge is to identify those patients that benefit from higher levels of PEEP.\textsuperscript{28} Pulmonary inhomogeneity can be decreased both by higher PEEP levels and prone positioning and in this way it could be possible to decrease focal forces in the lung.\textsuperscript{29} The global force acting on the lung is the transpulmonary pressure which is defined as the pressure difference between the alveoli and the pleural surface. An approximation of the alveoli pressure is the airway pressure during an end-inspiratory occlusion. Measurement of pleural pressure is not feasible in clinical practice but esophageal pressure is used as a substitute. The effect of transpulmonary pressure on the lung is deformation which could result in volume changes but also structural damage.\textsuperscript{30} The risk factors for ventilator induced lung injury are overdistention and excessive transpulmonary pressure. The applied airway pressure during mechanical ventilation results in very different transpulmonary pressure depending on the absolute and relative values of the elastance of the lung and the chest wall complex (rib cage, diaphragm and abdomen). Partitioning respiratory mechanics in its components, lung and chest wall complex elastance, could help identify patients who benefit from higher PEEP levels (extra-pulmonary ARDS). Equally important is to identify patients where seemingly “acceptable” airway pressures lead to high transpulmonary pressure and/or alveolar overdistention (pulmonary ARDS). The reported mortality rate of ARDS has decreased from approximately 60\% to 35-45\% over the years.\textsuperscript{31} One of the reasons for this is growing insight in how to perform lung protective ventilation. A crucial point is how well current praxis in mechanical ventilation is consistent with this.\textsuperscript{32-34} Determination of the transpulmonary pressure in the individual patient could be one way to make further progress in treating or preventing lung injury. It would be a great advantage if a simpler method could be developed, than the use of esophageal pressure, for determining lung elastance and hence transpulmonary pressure.
2. AIM OF THIS THESIS

- To describe current clinical practice on the daily management of ventilated patients regarding aerosol therapy, endotracheal suctioning and recruitment maneuvers.

- To develop a bedside tool for determining lung volume changes induced by changes in positive end-expiratory pressure (PEEP).

- To investigate the impact of a PEEP increase on changes in airway and esophageal pressure and in lung volume.

- To compare the measured changes in lung volume, induced by a PEEP change, and the predicted changes calculated as the change in PEEP divided by lung elastance, determined by esophageal pressure measurements.

- To investigate whether transpulmonary pressure can be determined without esophageal pressure measurements.
3. METHODS

3.1 ETHICAL ISSUES

Study protocols on patients (paper I, II and IV) were approved by the Local Ethics Committee in Gothenburg. Informed consent was obtained from next of kin (not applicable in paper I in accordance to the decision of the Ethics Committee because of the character of the study).

The study on animals (paper III) was approved by the Committee for Ethical Review of Animal Experiments at Gothenburg University and performed in accordance with National Institute of Health guidelines for the use of laboratory animals.

3.2 PATIENTS (PAPER I, II AND IV)

Patients with acute respiratory failure treated in ICU-settings were studied. In Paper I the only criteria for inclusion was mechanical ventilation for the last 24 hours. In Papers II and IV altogether 24 patients were studied. They were ventilated with a Servo-i ventilator (Maquet Critical Care, Solna, Sweden). Before the start of protocol, sedation was deepened and muscle relaxant was given to prevent spontaneous breathing efforts. For details on demographics and baseline data, see respective Paper.

3.3 MECHANICAL LUNG MODEL (PAPER II)

A U-pipe filled with water was intubated with an endotracheal tube, 8 mm ID, and ventilated with a Servo 300 ventilator (Maquet Ltd, Solna, Sweden). The compliance of the lung model was 40 ml/cmH$_2$O. The volume above the surface (distal from the ventilator) represented end-expiratory lung volume, which could be measured using a scale on the water pipe. A side stream spirometer was connected between the ventilator and the endotracheal tube.

Fig. 1 Lung model
3.4 EX VIVO LUNG MODEL (PAPER III)

Thirteen pigs were pre-medicated and anaesthetized, placed in supine position and intubated with an endotracheal tube, 8 mm ID. A Servo 300 ventilator (Siemens-Elema, Solna, Sweden) was used for mechanical ventilation. To eliminate cardiac-related variations in the esophageal pressure circulatory arrest was accomplished by an overdose of pentobarbital prior to measurements.

3.5 MEASUREMENTS, MONITORING EQUIPMENT AND DATA COLLECTIONS

3.5.1 Pressure and Volume measurements

Ventilatory flow was measured at the Y-piece with a D-lite side stream spirometer (GE Healthcare, Helsinki, Finland).\(^{35}\) In the monitoring system, volume is calculated by integration of flow over time. Tidal volume measurement, by this technique, is affected by differences in flow profile as well as in gas conditions (temperature, humidity, O\(_2\)/CO\(_2\)-concentrations). The errors for tidal volume are reported within a range of ± 5%.\(^{36}\)

Tracheal pressure was measured via a pressure line (GE Healthcare Finland Oy, Helsinki, Finland) introduced through the endotracheal tube and placed with the tip at the distal end of the tube.

Esophageal pressure was measured, in the patients, with a balloon catheter (Nutrivent™, SIDAM S.R.L., Mirandola, Italy), which has been validated by Chiumello et al.\(^{37}\) The length of the balloon was 10 cm. Correct positioning was verified according to a modified occlusion test\(^{38}\), where the rib cage was compressed during occlusion of the airway.\(^{39-41}\) Pressure variations in tracheal and esophageal tracings were compared and catheter position was adjusted to “best fit”. The aim was to identify a position where the tracings were of equal size. In paper IV Pes/Paw at the occlusion test was 0,96±0,16 (range 0,69 – 1,25).

A standard pressure transducer (DTXPlus, Argon Medical Devices Inc, Plano, TX, USA) was used both for tracheal pressure and esophageal pressure. According to the manufacturer the range for the transducer is -30 to 300 mmHg with an accuracy of 2% or ± 1 mmHg (whichever is greater).
3.5.2 Electrical Impedance Tomography

Impedance describes a measure of opposition to alternating current. The reciprocal entity is admittance which describes the ability to conduct an electrical current. The admittance of a tissue depends on the electrical conductivity and on geometric dimensions. Impedance is strain dependent. The tissues in the thorax act as a strain gauge, more strain results in higher impedance. At higher lung volumes the pulmonary tissues are more extended, more strain is induced which results in higher impedance. Impedance changes during ventilation are possible to monitor. The impedance of lung tissue also varies with air/tissue/fluid content.

A distensible belt containing 16 electrodes is placed around the chest wall at mid-thoracic level. In a sequential rotating manner a small alternating current (5mA, 50 kHz) is applied to two of the 16 electrodes at a time. This generates voltage differences at the remaining 13 electrode pairs. Each complete rotation results in 208 voltage values, the sizes of which are depending on impedance. By measuring induced voltage differences every 20 ms (50 Hz), the EIT device (EIT Evaluation Kit 2, Dräger Medical, Lübeck, Germany) creates a lens-shaped scan slice of impedance variations.\(^{42}\)

By comparing the global tidal impedance change (\(\Delta Z\)) with the tidal volume measured by spirometry, a calibration factor for impedance change per ml was calculated. Since the amount of stress/strain in the tissue influence admittance, a calibration factor for every PEEP level was calculated (\(\Delta Z_{\text{PEEP}}/\text{ml}\)).\(^{43}\)

3.5.3 FRC measurement

A modified nitrogen wash-out/wash-in technique was used for FRC measurements in paper IV.\(^{44}\)

3.5.4 Data collection

Data from the monitoring system (AS/3, Datex-Ohmeda, Helsinki, Finland) were collected by using S/5 Collect™ software, Datex-Ohmeda, with the possibility to analyze both trends and waveform signals (sampling frequency 1 and 100 Hz) from flow, volume and pressure.
3.6 CALCULATIONS

3.6.1 Lung volume changes determined by cumulated tidal volume difference and impedance changes.

In paper II we validated a method where the lung volume change was determined by calculating the sum of the differences between inspiratory and expiratory tidal volumes for the first 10 breaths following a change in PEEP. When the respiratory quotient is below 1.0 the sizes of tidal volumes at inspiration and expiration are not equal even at steady state, since the volume of O₂ consumption then exceeds the volume of CO₂ production. The differences in flow profile also affect the measurements of tidal volumes. In paper II this discrepancy, at steady state, was denoted tidal volume offset (VToffset). The VToffset was calculated at each PEEP level when there was a period of steady state, which was when there were more than 10 breaths per PEEP level. A linear interpolation between VToffset determined at the lowest and highest PEEP levels showed good correlation with specifically calculated VToffset at each PEEP level. When, according to protocol, only 10 breaths per PEEP level were applied, the linear interpolation method was used for estimation of the VToffset for the intermediate PEEP levels.

To estimate the induced lung volume change by a change in PEEP, the differences of the inspiratory and expiratory tidal volumes for the first ten breaths were studied, using the trend signals recorded by S/5 Collect™ software analyzed by a specially designed MATLAB application (The Mathworks Inc., Natick, MA, USA). The PEEP-specific VToffset was subtracted from each difference and the resulting values were added, the sum being a measure of change in end-expiratory lung volume; “cumulative inspiratory-expiratory tidal volume difference”. In paper III, instead of the D-lite spirometer, the flow meter of the Servo 300 was used and in paper IV the flow meter of the Servo-i was used.

For the electrical impedance tomography the global tidal impedance change, at each PEEP level, was compared with the measured tidal volume by spirometry. In this way, a PEEP-related calibration factor for impedance change per milliliter (ΔZPEEP/ml) was calculated. After ten breaths, at every change in PEEP level, the difference in end-expiratory impedance between the two PEEP levels was calculated. These changes in end-expiratory impedance were divided by the mean value of ΔZPEEP/ml of the two compared PEEP levels. The ratio was denoted ΔEELV_{EIT}. 
3.6.2 Driving pressures

The inspiratory driving pressure of the total respiratory system can be estimated by the difference between end-inspiratory airway plateau pressure and end-expiratory airway pressure (\(\Delta P_{aw} = P_{awEI} - P_{awEE}\)). In paper III a correction factor of 0,9 was used on the measured values of \(P_{awEI}\), this was not used in paper IV. (See comments under “Methodological considerations” section 5.2.3.a.)

The inspiratory driving pressure of the chest wall complex can in a similar way be estimated by the difference between end-inspiratory esophageal pressure and end-expiratory esophageal pressure (\(\Delta P_{es} = P_{esEI} - P_{esEE}\)). The chest wall complex consists of the thoracic cage, the diaphragm and the abdomen. The inspiratory driving pressure of the lung is the tidal transpulmonary pressure, which is the difference between the driving pressure of the total respiratory system and the driving pressure of the chest wall complex (\(\Delta P_{tp} = \Delta P_{aw} - \Delta P_{es}\)).

3.6.3 Elastance and compliance

Elastance is the inverse ratio of compliance, see table 1. Serial elastance are additive in their absolute numbers and hence used in the following discussion.
The elastance of the total respiratory system is the ratio of the inspiratory driving pressure of the total respiratory system and the tidal volume \( \text{ETOT} = \Delta \text{Paw}/V_T \). The elastance of the chest wall complex is the ratio of the tidal esophageal pressure variation and the tidal volume \( \text{ECW} = \Delta \text{Pes}/V_T \). Lung elastance is the difference between elastance in the total respiratory system and the chest wall complex.

**Table 1 Conversion table for elastance and compliance.**

<table>
<thead>
<tr>
<th>Elastance, cm H₂O/l</th>
<th>Compliance, ml/cm H₂O</th>
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<td>100</td>
<td>10</td>
</tr>
</tbody>
</table>

3.6.4 Two ways to determine change in transpulmonary pressure; a conventional approach and a new concept.

Transpulmonary pressure is conventionally determined by subtracting tidal difference in esophageal pressure \( \Delta \text{Pes} \) from tidal difference in airway pressure \( \Delta \text{Paw} \). See section 5.2.3 for further discussion.

As the transpulmonary pressure is the driving pressure of the lung, a change in lung volume, of the same size, induced either by a tidal breath or by a change in PEEP, is regarded as created by the same size of change in transpulmonary pressure.

With the new concept introduced in paper III and IV, it is possible to calculate the change in transpulmonary pressure at end-expiration, induced by a PEEP change, in the following way:

First the change in lung volume following a PEEP increase is determined. PEEP is then returned to baseline level and a tidal breath is applied, of the same size as the PEEP induced change in lung volume. See figure 3.
The resulting pressures can be used to calculate the elastance of the total respiratory system (ETOT) and the elastance of the chest wall complex (ECW) (conventionally derived via the esophageal pressure measurements) and hence the lung elastance (EL). The product of lung elastance and change in end-expiratory lung volume is the change in end-expiratory transpulmonary pressure after a change in PEEP.

The corresponding end-inspiratory transpulmonary pressure, at the higher PEEP level, is calculated as \[ [(EL \cdot \Delta EELV) + (\Delta Paw - \Delta Pes)] \].

Based on the new concept presented in paper III, change in end-expiratory transpulmonary pressure equals \( \Delta \text{PEEP} \) and the end-inspiratory transpulmonary pressure is calculated as \[ \Delta \text{PEEP} + (EL \cdot V_t) \], where \( EL = \Delta \text{PEEP} / \Delta \text{EELV} \).

In paper IV the new concept also is applied on an incremental PEEP-step maneuver. On the highest PEEP level (16 cm H\(_2\)O) lung elastance was determined as \( \Delta \text{Paw}_{\text{EIP}} / \Delta \text{EELV} \), where \( \Delta \text{Paw}_{\text{EIP}} \) is the difference in end-inspiratory airway plateau pressure between the second highest and the highest PEEP level. The rationale behind this is that the elastance of the chest wall complex is almost constant with increasing lung volume and PEEP.\(^{11,45,46}\)
3.6.5 Transpulmonary pressure based on esophageal pressure measurements.

In paper IV calculation of conventional transpulmonary pressure, at incremental PEEP steps, based on esophageal pressure measurements was based on the following:

Fig. 4 The red arrows illustrate tidal breaths at four different PEEP levels; 0, 4, 8, 12 and 16 cmH₂O.

\[ \Delta EELV = \text{Change in end-expiratory lung volume.} \]

Note the larger lung volume changes at the higher equally large PEEP steps.

At a PEEP level of 0 cm H₂O (ZEEP), lung elastance (EL₁) can be determined as the difference between tidal airway pressure and tidal esophageal pressure divided by the tidal volume (ΔPaw-ΔPes)/VT. End-inspiratory transpulmonary pressure was calculated as the product of lung elastance at ZEEP and tidal volume (EL₁ x VT).

At the second PEEP level end-expiratory transpulmonary pressure was calculated as the product of lung elastance at the first PEEP level (=ZEEP) and the change in end-expiratory lung volume between the first and the second PEEP level (EL₁ x ΔEELV₁→₂). End-inspiratory transpulmonary pressure at the second PEEP level was calculated as the sum of the end-expiratory transpulmonary pressure of this PEEP level and the product of lung elastance at the second PEEP level and the tidal volume [(EL₁ x ΔEELV₁→₂) + (EL₂ x VT)].

Further PEEP steps were calculated in analogy with the two first PEEP steps.
3.7 STUDY DESIGN

3.7.1 Paper I – Web-based survey

161 intensive care units in the Nordic countries were identified by contacting the societies of anesthesiology and intensive care medicine, via internet and personal contacts within the SSAI network. The units were invited to participate in a web-based survey with questions on procedures concerning mechanical ventilation, such as use of heated humidification, drug administration through inhalation, endotracheal suctioning and lung recruitment including prone position. One part of the survey was a 24 hour point prevalence study to describe how these interventions were used in patients. The patient data were anonymous. Values of highest PaO\textsubscript{2} with corresponding lowest FiO\textsubscript{2} and lowest PaO\textsubscript{2} with corresponding highest FiO\textsubscript{2} during the last 24 hours were reported. Two PaO\textsubscript{2}/FiO\textsubscript{2} ratios per patient were calculated. The PaO\textsubscript{2}/FiO\textsubscript{2} ratios were used to categorize patients according to the oxygenation criteria for acute respiratory failure (ARF), acute lung injury (ALI) and acute respiratory distress syndrome (ARDS); PaO\textsubscript{2}/FiO\textsubscript{2} ratio > 40 kPa, PaO\textsubscript{2}/FiO\textsubscript{2} ratio < 40 kPa and > 27 kPa respectively PaO\textsubscript{2}/FiO\textsubscript{2} ratio < 27 kPa (40 kPa \(\approx\) 300 mmHg, 27 kPa \(\approx\) 200 mmHg). In the cases where the PaO\textsubscript{2}/FiO\textsubscript{2} ratios for a patient were in two different oxygenation groups, a mean value was calculated to categorize the patient to the group most probable to be of clinical relevance.

3.7.2 Paper II – Estimation of changes in end-expiratory lung volume

Changes in end-expiratory lung volume were achieved by changes in PEEP. In the lung model PEEP changes were between 0 cm H\textsubscript{2}O and levels 1 to 18 cm H\textsubscript{2}O in a random order, both in volume and pressure controlled modes. Volume changes read from the scale on the lung model were regarded as “true” values and they were compared to the calculated values derived from the spirometry, “cumulative inspiratory-expiratory tidal volume difference”.
In the patients, changes in PEEP were performed in an incremental followed by a decremental maneuver. Volume changes were determined by spirometry, “cumulative inspiratory-expiratory tidal volume difference”, and by impedance changes using electrical impedance tomography. The maneuver was performed in volume and pressure control modes with 10 breaths at each PEEP level and a third time in volume control mode with 40 breaths at each PEEP level.

![Graph](image)

**Fig. 5** Changes in lung volume measured by the spirometric method, “cumulative inspiratory-expiratory tidal volume difference” (upper panel in red), and by impedance changes (lower panel in green).

### 3.7.3 Paper III – Lung elastance and transpulmonary pressure in an ex vivo lung model

Ventilation was set to volume control mode, tidal volume 10-12 ml/kg, respiratory rate 10 and inspiratory time 30% with an end-inspiratory pause of 10%.

Changes in end-expiratory lung volume were achieved by changes in PEEP between 0 – 4 – 0 – 8 – 0 – 12 – 0 cmH₂O in horizontal supine position, with and without abdominal loading of 8 kg and in reverse Trendelenburg position.
At 0 cmH$_2$O of PEEP alterations of tidal volumes between 100(150) and 700 ml were performed with increments of 100 ml. The duration of the procedure was approximately 120 minutes.

![Graph showing PEEP levels and corresponding pressure changes](Image)

**Fig. 6** Illustration of one part of the study protocol in paper III. Supine position. Airway (red) and esophageal (green) pressure. Impedance changes (black) in the lower panel.
The black dotted line illustrates where the zero level would be if end-expiratory esophageal pressure was $-5$ cm H$_2$O at PEEP 0 cmH$_2$O.
PAW; airway pressure (from the trachea), PES; esophageal pressure, EIT; Electrical Impedance Tomography, $\Delta Z$; Impedance change

### 3.7.4 Paper IV – Lung elastance and transpulmonary pressure in patients

Ventilation was set to volume-control mode, tidal volume 6 - 7 ml/kg ideal body weight, respiratory rate 20 breaths/minute and inspiratory time 30% with an inspiratory pause of 10%. Patients were in horizontal supine position. Changes in end-expiratory lung volume were achieved by PEEP-step maneuvers; 0 – 10 – 0 cmH$_2$O with 5 minutes at each PEEP level, 0 – 4 – 8 – 12 – 16 – 0 cmH$_2$O twice and then 0 – 4 – 8 – 12 – 16 – 12 – 8 – 4 – 0 cmH$_2$O with 2 minutes at each PEEP level. Correct positioning of the esophageal balloon catheter was verified at start and end of the protocol and between the PEEP maneuvers to minimize measurement errors.
To obtain a reference level of absolute esophageal pressure at FRC, zero PEEP was used as initial PEEP level and FRC-measurement was performed during start of each PEEP step maneuver to ensure that baseline conditions were re-established. At zero PEEP alterations of VT between 150 ml to 500 or 600 ml were performed with incremental steps of 50 ml up to a peak pressure of 40 cmH$_2$O.

**Fig. 7** Single PEEP step from zero to 10 cmH$_2$O during 5 minutes and back to zero. Airway (blue) and esophageal (red) pressure in the upper and middle panel. The grey dashed line is the zero line if end-expiratory esophageal pressure is transposed to − 5 cmH$_2$O. The black dashed line depicts the initial level of the end-expiratory esophageal pressure.

In the lower panel is the change in end-expiratory lung volume illustrated by the impedance change.

PAW; airway pressure (from the trachea), PES; esophageal pressure, EIT; Electrical Impedance Tomography

**Fig. 8** Incremental and decremental PEEP step maneuver. Airway (blue) and esophageal (red) pressure in the two upper panels. Impedance changes in black in the third panel and lung volume changes according to the spirometric method, “cumulative inspiratory-expiratory tidal volume difference”, in the lower panel.

PAW; airway pressure (from the trachea), PES; esophageal pressure, EIT; Electrical Impedance Tomography, ΔZ; Impedance change, ΔEELV; change in end-expiratory lung volume
3.8 STATISTICAL ANALYSES

3.8.1 Paper I

Paired or unpaired t-tests as appropriate were used to analyze changes in PaO$_2$/FiO$_2$ ratio, PEEP level and frequency of endotracheal suctioning grouped for airway access (Mann-Whitney). One-way ANOVA was used to analyze differences in adjunct therapies categorized by PaO$_2$/FiO$_2$ ratio or duration of ventilator treatment (Kruskal-Wallis test followed by Dunn’s multiple comparison test). A p-value less than 0.05 was considered statistically significant.

All statistical analyses were performed using Graph Pad Prism 5.0a for Mac OS X (GraphPad Software, Inc., San Diego, CA, USA).

3.8.2 Paper II

Data are presented as mean ± standard deviation. The data from the lung model was assessed by using descriptive statistics and linear correlation analysis. The patient data consist of replicated data in pairs, where the underlying true value changes from pair to pair. By performing two-way analysis of variance, the correlation coefficient within subjects, the within-subject variance and between-subject variance was calculated.\(^{47-49}\) In this way, several observations per patient could be handled statistically. The mean bias was calculated according to Bland and Altman, taken into account the fact that repeated measurements on the same subject were performed \(\left(\frac{\sum m_i \times d_i}{\sum m_i}\right)\), where \(m_i\) is the number of observations for subject \(i\) and \(d_i\) is the mean difference for subject \(i\).\(^ {50}\) Limits of agreement were calculated from the standard deviation derived from the analysis of variances.\(^ {51}\) By doing this, both the variations within a subject and between subjects were taken into account. The 95% confidence interval for the limits of agreement was calculated. One-way t-test was performed on the correlation factor for the line of regression of \(\Delta Z_{\text{PEEP}}/\text{ml}\) versus PEEP level, to explore whether there was any individual relation between \(\Delta Z_{\text{PEEP}}/\text{ml}\) and change in PEEP. A p value less than 0.05 was considered statistically significant. All statistical analyses were performed using StatView for Windows, version 5.0.1 (SAS Institute Inc Copyright©).

A power analysis was performed using a web-based statistical tool (www.quantitativeskills.com). To detect a 10% mean difference between lung volume changes measured with EIT vs spirometry, with a standard deviation for the difference of 10%, a sample size of at least 10 patients were needed for a
power of 80% and p < 0.05. To allow for missing data 12 patients were included in the study.

3.8.3 Paper III

Linear regression was used for the correlation analysis of measured and calculated changes in end-expiratory lung volume. Analysis of variance followed by paired Student t-tests with Bonferroni correction for multiple comparisons were used on the changes in measured parameters of respiratory mechanics.

As in paper II a power analysis was performed using the same web-based statistical tool. To detect a 50% difference between observed vs. predicted increase in end-expiratory esophageal pressure following a PEEP increase, with a standard deviation for the difference of 50%, 10 animals were needed for a power of 80% and p < 0.05. To allow for missing values 13 animals were included in the study.

3.8.4 Paper IV

The same power analysis as in paper III was performed. To allow for missing values 12 patients were included in the study.

The change in end-expiratory esophageal pressure and lung volume from 0.5 to 5 minutes after the PEEP increase, in the single PEEP-step maneuver, was analyzed by one-way t-test.

Data from the incremental PEEP steps were analyzed using mean values from three maneuvers. Correlations between measured changes in end-expiratory lung volume using spirometry and predicted changes in end-expiratory lung volume, calculated from lung-, chest wall complex- or total respiratory system - elastance and PEEP change, were analyzed using linear regression analysis. Data consist of replicated data in pairs, where the underlying true value changes from pair to pair. By performing two-way analysis of variance, the correlation coefficient within subjects was calculated.47,48

Statistical analyses were performed using StatView for Windows, version 5.0.1 (SAS Institute Inc Copyright©) and Prism 6 for Windows, version 6.02 (GraphPad Software Inc ©)
4. MAIN RESULTS

4.1 PAPER I

The web-based survey on adjunct therapies to mechanical ventilation was answered by 97 intensive care units and data from 186 patients were reported. Large variations in the individual maximum and minimum oxygenation ratios (PaO₂/FiO₂) were observed during the 24 hours studied.

Fig. 9 Two reported PaO₂/FiO₂ ratios were used for categorization of the patients due to the oxygenation criteria for acute respiratory failure (ARF), acute lung injury (ALI) and acute respiratory distress (ARDS).

A; remained within the same oxygenation group (88 patients), B; varied between “ARF” and “ARDS” (15 patients), C; varied between “ARF” and “ALI” (31 patients), D; varied between “ALI” and “ARDS” (47 patients). Five patients did not have two values of PaO₂ and FiO₂ reported.

Due to drug administration through inhalation and endotracheal suctioning, 60% of the patients were disconnected from the ventilator more than seven times during the 24 hours studied. One third of these patients had more than twelve disconnections. 55% of the patients had the suction system device set at more negative vacuum levels than 20 kPa (150 mmHg).

Fig. 10 Adjunct therapies within each oxygenation group (see Fig. 9).
*Statistically significant difference (p<0.05).
4.2 PAPER II

In paper II we describe a spirometric method for determining lung volume changes induced by a change in PEEP. We validated this method in a lung model and evaluated it in twelve patients. Comparisons were made with simultaneously measured changes in impedance, by electrical impedance tomography (EIT), enabled through calibration of tidal impedance changes at different PEEP levels with tidal volume.

In the lung model, irrespective of ventilator mode, there was good correlation \( (R^2 = 0.98) \) between volume changes obtained by spirometry, \( \Delta EELV_{VT(i-e)} \) and “true” volume changes in the lung model, \( \Delta EELV_{LM} \) and the equation for the trend line was \( y=0.99x+9 \). The deviation of \( \Delta EELV_{VT(i-e)} \) from \( \Delta EELV_{LM} \) was \( -4\pm10\% \), calculated as \( \left[ (\Delta EELV_{LM} - \Delta EELV_{VT(i-e)}) / \Delta EELV_{LM} \right] \).

![Fig. 11 Bland-Altman plot of the data from the lung model. Bias -4 ml, limits of agreement 42 and -50 ml.](image)

In the patients the correlation coefficient within subjects was 0.92, between changes obtained by spirometry, \( \Delta EELV_{VT(i-e)} \) and end-expiratory lung volume determined by electrical impedance tomography, \( \Delta EELV_{EIT} \). The difference between \( \Delta EELV_{EIT} \) and \( \Delta EELV_{VT(i-e)} \) within subjects was 14±7\%, calculated as \( \left[ (\Delta EELV_{EIT} - \Delta EELV_{VT(i-e)}) / \text{mean value of } \Delta EELV_{EIT} \text{ and } \Delta EELV_{VT(i-e)} \right] \). A trend line on all patient data could be described by the equation \( y=0.8x+23 \).
4.3 PAPER III

In this study we used an animal model to investigate the impact of a PEEP increase on changes in esophageal pressure and lung volume. We compared the measured changes in lung volumes with calculated volumes, derived from values of lung elastance. The aim was to investigate whether transpulmonary pressure can be determined without esophageal pressure measurements.

The different body positions or loading or unloading the abdomen changed both lung elastance and the elastance of the chest wall complex but did not change the ratio of lung elastance and total respiratory elastance (EL/E\text{TOT} \approx 0,7).

A PEEP induced increase in lung volume resulted in less increase in esophageal pressure than a tidal volume of the same size did. The increase in esophageal pressure was prompt and did not progress, although the lung volume continued to increase over several breaths.

It was possible to partition the elastance of the respiratory system, by studying a tidal volume of the similar size as the PEEP induced lung volume change. A predicted change in lung volume was calculated by taking the ratio of the PEEP step and the calculated lung elastance. There was good correlation between the predicted and the measured change in lung volume. The PEEP induced lung volume change could not be predicted by similar calculations using the elastance of the total respiratory system or the chest wall complex.

Fig. 12 Correlation between changes in lung volume measured by spirometry (Δ\text{EELV}_{\text{VT}(i+\text{a})}) and electrical impedance tomography (Δ\text{EELV}_{\text{ETT}}).
Fig. 13 Correlation plots between measured lung volume changes by spirometry and predicted lung volume changes by the ratio of the PEEP change and the elastance of the lung, the total respiratory system or the chest wall complex.
Blue diamonds: Supine position; Green triangles: Supine position with abdominal load; Red dots: Reverse Trendelenburg position

There was close correlation between the size of the increase in end-expiratory lung volume after the first breath and the ratio of change in PEEP and the elastance of the total respiratory system, derived from esophageal measurements with tidal volumes of similar sizes as the final changes in lung volume. This is in agreement with previous studies. 49±10% of the final change in lung volume was achieved after the first breath.
When comparing a tidal volume of the similar size as the change in lung volume induced by a PEEP change, the tidal change in transpulmonary pressure was close to the size of the change in PEEP.

The results from this study imply that lung elastance can be calculated from the ratio of change in PEEP and the induced change in end-expiratory lung volume (\(\Delta\text{PEEP}/\Delta\text{EELV}\)) and that a change in PEEP leads to a similar size of change in transpulmonary pressure.

**Fig. 14** Correlation between the change in end-expiratory lung volume after the first breath and the ratio between PEEP change and elastance of the total respiratory system, derived from a tidal volume of the similar size as the final change in end-expiratory lung volume.

*Blue diamonds: Supine position; Green triangles: Supine position with abdominal load; Red dots: Reverse Trendelenburg position*

**Fig. 15** Comparison, at three PEEP levels, of end-expiratory airway pressure (PawEE) and the tidal change in transpulmonary pressure of a tidal volume similar to the PEEP induced change in lung volume (VT\text{cal}).
4.4 PAPER IV

In this study we explored the changes in lung volume and the tidal changes of esophageal pressure, both during a single PEEP step and incremental PEEP changes in twelve mechanically ventilated patients. We aimed to see if the results from the animal study in paper III could be repeated in patients; if it was possible to determine transpulmonary pressure without esophageal pressure measurements.

During the single PEEP-step maneuver, 0 – 10 – 0 cmH\textsubscript{2}O, there was an initial increase in end-expiratory esophageal pressure which subsided significantly over the following five minutes. Concomitantly lung volume increased from 299 ± 142 ml, measured directly after the first breath at 10 cmH\textsubscript{2}O PEEP, to 597 ± 353 ml five minutes later. See also figure 7.

![Figure 16](image1.png)

**Fig. 16** Single PEEP step, 0 – 10 – 0 cmH\textsubscript{2}O.
Pes EI= end-inspiratory esophageal pressure
Pes EE= end-expiratory esophageal pressure
\(\Delta\)EELV= change in end-expiratory lung volume.

There was close correlation between measured, PEEP induced, changes in lung volume and calculated volumes derived by values on lung elastance from esophageal pressure measurements.

![Figure 17](image2.png)

**Fig. 17** Left panel shows correlation plot from the single PEEP step. Right panel is the results from the incremental PEEP steps, within subject correlation 0,95.
We then investigated the correlation between lung elastance derived from esophageal pressure measurements and the elastance calculated from PEEP induced changes in lung volume ($\Delta$PEEP/$\Delta$EELV). According to the results in figure 17 and 18, lung elastance could be predicted by dividing the change in PEEP with the change in end-expiratory lung volume.

![Graph](image)

Fig. 18 Values from the single PEEP step. See section 5.2.5 for further discussion.

Similar to the results in paper III, there were close correlations between observed changes in transpulmonary pressure (conventionally calculated from esophageal pressure measurements) and changes in PEEP.

![Graph](image)

Fig. 19 End-expiratory transpulmonary pressure ($P_{tp\text{EE~conv}}$) conventionally calculated as described in section 3.6.5 for the incremental PEEP steps (4 – 8 – 12 – 16 cmH₂O) and as described in section 3.6.4 for the single PEEP step (0 – 10 – 0 cmH₂O).
The result is illustrated in figure 20, by individual transpulmonary pressure/volume curves based on conventional calculation, from esophageal pressure measurements, and the corresponding pressure/volume curves based on cumulated change in end expiratory lung volume versus end expiratory airway pressure.

Fig. 20 Transpulmonary pressure/volume curves based on conventional calculation from esophageal pressure measurements (blue diamonds). See section 3.6.5 for details on calculation. The red dots are cumulated change in end-expiratory volumes versus end-expiratory pressure, except for the last dot on every curve which is calculated from the lung elastance on the highest PEEP level multiplied with the tidal volume (see section 3.6.4 for details). Lung compliances varied between 27 and 90 ml/cmH2O.

The close correlations imply that it is possible to estimate transpulmonary pressure during mechanical ventilation without esophageal pressure measurements. Lung elastance can be assessed by performing a PEEP change and measure the change in end-expiratory volume. Tidal change in transpulmonary pressure during mechanical ventilation can be calculated by multiplying lung elastance and tidal volume. The absolute value on transpulmonary pressure is calculated by adding the PEEP-level (PEEP + EL·Vt).
5. DISCUSSION

5.1 MAIN FINDINGS

- The survey on the use of adjunct therapies in mechanically ventilated patients in Nordic ICUs in 2007, showed frequent use of aerosol therapy in conjunction with endotracheal suctioning with high vacuum levels. The reported large variations in PaO$_2$/FiO$_2$ ratios were probably a reflection of recruitment and derecruitment of the lungs, at least partly due to frequent disconnections of the ventilator circuit.

- It is possible, with high precision, to measure changes in lung volume ($\Delta$EELV) after a change in positive end-expiratory pressure ($\Delta$PEEP) by spirometric determination of the cumulative difference between inspiratory and expiratory tidal volumes.

- A change in lung volume of a similar size as the tidal volume induces less change in the end-expiratory esophageal pressure than the pressure change seen during tidal ventilation.

- The change in transpulmonary pressure following a PEEP increase is of a similar size as the $\Delta$PEEP.

- Lung elastance can be derived, without esophageal measurements, through a PEEP-step by dividing $\Delta$PEEP with $\Delta$EELV.
5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 The survey on the use of adjunct therapies to mechanical ventilation

The aim of the study in paper I was to describe current clinical practice regarding the use of aerosol therapy, heated humidification and routines concerning endotracheal suctioning and recruitment maneuvers in Nordic ICUs.

The method used in paper I was an observational, cross-sectional descriptive study distributed via a web-based questionnaire. The problems associated with this type of study are for one the selection and the representativeness of the sample. Another bias is the response rate which in this study varied between 45% (Norway and Finland) and 78% (Sweden). Efforts were made to maximize the response rate with up to three reminders to those that failed to respond. There was a predominance of answers from Swedish ICUs. There is no obvious reason to expect nation-bound differences in treatment policies. The study does not have the power to address this question. The overall answering rate was considered sufficiently high to draw some conclusions about the use of adjunct therapies in the surveyed intensive care units.

Our subdivision of the patients, based on oxygenation ratio (PaO$_2$/FiO$_2$), was denoted “ARF” (Acute Respiratory Failure), “ALI” (Acute Lung Injury) and “ARDS” (Acute Respiratory Distress Syndrome). Since the American-European Consensus Conference defined ARDS as a subset of ALI, perhaps a better choice of nomenclature would have been “ARF without ALI”, “ALI without ARDS” and “ARDS”, thus illustrating the wide spectra of impaired gas exchange. No questions were asked concerning the patients’ chest X-rays due to the presumed difficulties in correct interpretation of the answers.$^{53}$ An improved patient categorization would have been possible if we had requested information regarding the respiratory system compliance and the mean airway pressure at the time for the reported values of PaO$_2$ and FiO$_2$. The latter data would have enabled calculation of the oxygenation index, defined as mean airway pressure*100*FiO$_2$/PaO$_2$. The oxygenation index has been used as one of several parameters to assess the degree of lung disease.$^{25,27}$
5.2.2 How to monitor lung volume changes during mechanical ventilation

Our aim was to develop bedside tools for continuous assessment of respiratory mechanics. The first step was to decide how to monitor lung volume changes induced by PEEP changes.

One way to accomplish this would have been to measure the absolute lung volume at different PEEP levels. CT scan has been taken as the gold standard for lung volume determination, but the negative effects of repeated radiation exposure and lack of bedside equipment, limits its clinical use for this purpose. Another method described in the literature is body plethysmography but for obvious reasons it is poorly suited in the intensive care setting. Helium dilution technique is an established method but it is time consuming, requires special equipment and cannot be used for continuous measurements. Neither of these methods can be used as bedside tools in daily care.

The nitrogen wash-out/wash-in technique, modified by Olegård et al, is well suited for bedside determination of absolute lung volumes but with an accuracy that limits its use when smaller changes in lung volume are assessed. According to Olegård et al there was a bias of 149 ml with limits of agreement of -93 ml to 391 ml when comparing the wash-in with the wash-out procedures, in patients, using a FiO₂ step of 0.1. In a study by Chiumello et al the corresponding results were a bias of 48 ml with limits of agreement of -117 ml to 213 ml. This accuracy could be adequate for evaluating absolute lung volumes but for assessment of smaller changes in lung volume, for example similar to the size of a tidal volume, the limits of agreement are too wide.

If a difference in end-expiratory lung volume is determined indirectly by subtraction of the absolute end-expiratory lung volume at the lower PEEP level from the absolute end-expiratory lung volume at the higher PEEP level, with a true change in lung volume of 300 ml (for instance from 1800 ml to 2100 ml) the resulting measured change in volume could vary within the range from 105 ml to 495 ml.

The same is true when oxygen is used as a tracer gas. For measurements of small lung volumes tracer gases such as sulfur hexafluoride (SF₆) and heptafluoropropane have been described, but again these methods require special equipment and measure absolute lung volumes.
Spirometric methods have been described in the literature. Falke et al described a PEEP-release method, where the change in lung volume by a PEEP step was calculated as the difference between the last inspired tidal volume with PEEP and the first expired tidal volume after discontinuation of PEEP.\(^{63}\) This method is not acceptable in clinical practice with current knowledge of ventilator induced lung injury, as it causes derecruitment. Katz et al observed the cumulative net loss or gain of expired tidal volumes of the first twenty breaths after a PEEP change, using the following ten to twenty breaths for establishing a steady state of expired tidal volumes.\(^{52}\) Putensen et al used a similar method observing the expired tidal volumes of at least three breaths after a PEEP change.\(^{64}\) Fretschner et al described a method similar to the method “cumulative inspiratory-expiratory tidal volume difference” described in paper II, where the differences between inspiratory and expiratory volumes were calculated breath by breath.\(^{65}\) Stahl et al used a different approach by continuous integration of flow at the y-piece, taking the average relationship between inspiratory and expiratory volume during steady state and multiplying the following expiratory volumes with this quotient.\(^{66}\)

We decided to evaluate a spirometric method for direct determination of changes in end-expiratory lung volume, where sizes of tidal volumes following a change in PEEP reflect the change in lung volume. A direct measurement method with a variation of 10% applied in the example above, where a difference of 300 ml between 2100 and 1800 ml was to be determined, would result in a value between 270 ml and 330 ml, showing the superiority of direct measurements of lung volume changes.

We hypothesized that the cumulative difference of the inspiratory and expiratory tidal volumes of the first ten breaths after a PEEP change, accurately reflects the change in lung volume following a PEEP alteration.

The accuracy of the tidal volume measurement is an important factor. There is a well-known difference between inspiratory and expiratory volumes during stable ventilation. We denoted this difference the “\(V_{\text{Toffset}}\)”. Since the flow profile can affect the tidal volume measurement, it is possible that a difference in mean airway pressure could have an additional effect. Therefore it was important to determine the \(V_{\text{Toffset}}\) at every PEEP level in order to minimize systematic error.
A small change of the offset value induces a duration-dependent proportional bias. To minimize this effect, measurements were limited to the first ten breaths after a PEEP change, during which the major differences in inspiratory-expiratory tidal volumes \((V_{T(i-e)})\) occur.\(^{52,64}\) The result from the lung model indicates that inspiratory-expiratory tidal volume offset calibration, at each PEEP level, can be applied to minimize the offset bias and ensure that the spirometric method, “cumulative inspiratory-expiratory tidal volume difference” \((\Delta EELV_{VT(i-e)})\), can be used to accurately determine changes in lung volume.

Since the inspiratory and expiratory tidal volumes are not equal, it is important that the system which collects data from the flow signal resets to zero before the next inspiration to avoid additional drift in the measurements.

In our study in paper II we used a flow and airway pressure sensor with reported errors for tidal volume within a range of ±5%. The principle of the D-lite sensor is that of a Pitot-tube type. Another way to measure tidal volumes is with a pneumotachograph, where a resistance is introduced into the gas pathway, designed to produce a laminar flow so that the flow rate is directly proportional to the measured pressure drop over the resistance. The device is usually heated to prevent condensation which could introduce turbulent flow. The accuracy of these devices is within the same range as the D-lite. Modern ventilators are equipped with flow transducers with the ability to calculate flow rate, and thus tidal volumes, with a high degree of accuracy. A thin metal disc on a flexible pin is bent backwards by the gas flow. A strain gauge is compressed, as the pin is bent, with a force dependent on the flow. The resulting electrical signal is processed to calculate the flow rate. In paper III and IV we used the flow transducer in the ventilators instead of the D-lite spirometer for determining lung volume changes with the spirometric method, “cumulative inspiratory-expiratory tidal volume difference”.

We used a lung model to validate our spirometric method. The reason for this was the lack of a gold standard for measuring lung volume changes in patients. Which other methods are described for repeated determinations of lung volume changes?

Changes in end-expiratory lung volume can be monitored by a method called respiratory inductive plethysmography. It requires a calibration procedure versus spirometry and has a baseline drift due to thermal instability, which limits its use.\(^{67}\) Respiratory inductive plethysmography has been used in studies in the
pediatric intensive care setting in connection with high-frequency oscillatory ventilation.\textsuperscript{68} The calibration includes partitioning of the tidal volume between rib cage and abdomen. If this relationship changes at different lung volumes over time, it could be an explanation for time-dependent baseline drift.

Electrical impedance tomography (EIT) is another way to assess changes in lung volume. This technique has been compared with several other techniques, such as CT, SPECT (single photon emission computer tomography), respiratory inductive plethysmography and the multibreath nitrogen wash-out maneuver.\textsuperscript{42,69,70} Impedance is affected by changes in gas/fluid composition. Impedance changes ($\Delta Z$) can be calibrated with different tidal volumes but may also be affected by PEEP changes due to changes in tissue properties. In this way a correlation factor can be calculated, between changes in impedance and corresponding changes in lung volume measured by spirometry, specific for each studied PEEP level. We denoted this correlation factor $\Delta Z_{\text{PEEP}}/\text{ml}$.

In our study where the spirometric method was compared with electrical impedance tomography, individual $\Delta Z_{\text{PEEP}}/\text{ml}$ varied between different PEEP levels, although the differences were not statistically significant.

**Fig. 21** This x-y plot shows the correlation between tidal changes in impedance and tidal changes in ml depending on the level of PEEP. Individual mean values for the twelve patients.

We based the calculation of changes in lung volume, due to a change in PEEP ($\Delta\text{EELV}_{\text{EIT}}$), on the mean value for $\Delta Z_{\text{PEEP}}/\text{ml}$ at the adjacent higher and lower PEEP level. The end-expiratory change in impedance after a PEEP change was divided with the corresponding mean value of the correlation factor $\Delta Z_{\text{PEEP}}/\text{ml}$. This resulted in estimations of lung volume changes that exceeded the spirometric method, “cumulative inspiratory-expiratory tidal volume difference”. It is not surprising that the two methods differ to some degree. The spirometric method is
a global method, even if the measured changes are not necessarily equivalent to absolute changes in gas exchanging capacity. That is, we cannot with this method alone distinguish between newly recruited alveoli and overdistention. Electrical impedance tomography measures impedance changes within a cross section of the thorax. It has been questioned how much of the lung that is actually measured with the EIT-technique. The measurement field has been described as a lens-shaped disc with a thickness that depends on the radius of the thorax. Thickness values between 5 and 20 cm have been reported.\textsuperscript{71-73} If the tidal images of electrical impedance tomography represent different proportions of the true tidal volume at different lung volumes, this could yield a proportional bias. (See below under “Method comparison”, section 5.2.4.b). Another possibility is if the EIT-“slice” represents different lung units at different lung volumes due to relative “movements” with lung inflation between anatomical structures and the electrode belt which could yield a systematic bias. Electrical impedance tomography makes it possible to illustrate changes in regional ventilation as well as regional intra-tidal gas distribution.\textsuperscript{74-76} This could be a potential tool to enable discrimination between recruitable and non-recruitable lung.

In paper III and IV we used the spirometric method, “cumulative inspiratory-expiratory tidal volume difference” for the majority of measurements of changes in end-expiratory lung volume. Electrical impedance tomography was used for illustration and in paper IV, for determining lung volume changes during the single PEEP step, with duration of 5 minutes.
5.2.3 How to monitor transpulmonary pressure during mechanical ventilation

A bedside tool for assessment of respiratory mechanics must include means for partitioning the driving pressure of the lung and chest wall complex (rib cage, diaphragm and abdomen). The definition of the driving pressure over the lung is the difference between the alveolar pressure and the pleural pressure; the transpulmonary pressure.

5.2.3.a How to monitor alveolar pressure

Our first consideration is how to monitor the alveolar pressure. Since two open-connected compartments of gas have the same pressure when there is no gas flow between them, alveolar pressure can be estimated by pressure at the airway opening during no-flow conditions. During mechanical ventilation this can be accomplished by an end-inspiratory occlusion. In the literature the duration of this occlusion varies from 2 to 6 seconds.\(^\text{77,78}\)

Using volume controlled ventilation with constant flow and an inspiratory pause, the end-inspiratory pressure reaches a peak followed by a plateau. The initial decrease in pressure is more rapid than the following decrease. Depending on the length of the inspiratory pause the plateau pressure is used as an approximation of alveolar pressure.

The pressure, where the slope of the decline clearly changes, is used for calculation of the dynamic elastance, by subtracting PEEP and dividing by the tidal volume. In a similar way, the plateau pressure is used for calculation of the static elastance. When tracheal pressures are measured, the initial pressure drop is a reflection of the resistance in the conducting airways. The more slowly declining pressure is a reflection of the viscoelastic properties of the tissues and inhomogeneity of time constants within the lung.

The question is how long the inspiratory pause should be? For the reasons mentioned above it is intuitive that the more inhomogeneous the pulmonary condition that is present, the more important the inspiratory pause becomes. The same applies for a respiratory system with a substantial component of viscoelastic influence.

In a study by Barberis et al\(^\text{79}\) the difference in plateau pressures, measured at 0,5 second versus 5 seconds, were 11%±3% in patients with ARDS. In the ex-vivo
model in paper III we used an end-inspiratory pause of 0.6 second and used a correction factor of 0.9 for the values of tidal airway pressure (ΔP_{AW}). Since we changed PEEP from ZEEP in this protocol, in reality the correction factor only had impact on the end-inspiratory plateau pressure. The ex vivo model had no intrinsic PEEP.

The study by Barberis showed that an end-inspiratory pause of 3 seconds probably is sufficient for approximation of alveolar pressure from measurements of airway plateau pressures. In our study on patients in paper IV the ventilator settings led to an end-inspiratory pause of 0.3 second. We performed prolonged end-expiratory and end-inspiratory occlusions with a duration of 3 seconds, and could see that the difference in airway plateau pressure was approximately 10% at any PEEP level in all patients. However in this study we did not use any correction factor, which may have affected the calculations of the transpulmonary pressure.

### 5.2.3.b How to monitor pleural pressure

The next pressure to assess is the pleural pressure. The pleural space is exposed to opposing forces; the recoil of the lung and the spring out force of the rib cage. Direct measurements of pleural pressure are not available in clinical practice, instead indirect determination of pleural pressure is obtained from the esophageal pressure. This is done by placing an air-containing balloon in the lower third of the esophagus. The pressure within the balloon will approximate local pleural pressure under certain circumstances. The pressure difference must be zero across all intervening structures, such as balloon wall, esophageal wall and mediastinal tissues. A thorough review of the possibilities and pitfalls of this technique is published by Hedenstierna.\(^80\)

The volume of air introduced into the balloon is of great importance and can easily affect the pressure readings, at least that of the absolute esophageal pressure. In our study on patients in paper IV this was evident. The recommendations from the manufacturer of the esophageal balloon we used were to empty the balloon from all the air using a syringe and then insufflate an air volume of 4 ml. This process was to be repeated every hour. Our experience was that the amount of air needed varied from patient to patient, often with less than 4 ml required to obtain a stable baseline reading and that the procedure needed to be repeated more often than recommended, sometimes every half hour. There could be a number of explanations for this. The balloon could be twisted round the attached catheter and thus behave differently over time depending on air distribution within the
balloon. The pressure in the esophagus may not be uniform over the length of the balloon. Since our protocol meant incremental and decremental PEEP steps and thus different lung volumes applied during a relatively short interval, this could change the relationship between the location of the balloon in the esophagus and the surrounding mediastinal structures, such as the heart.

The recommendation in the literature is to place the esophageal balloon in the lower third of the esophagus to avoid the maximum effect of the weight of the heart. This position is approximately 40-45 cm from the nasal opening in adults. An additional estimation of the depth was to multiply height by 0.288 according to the manufacturer. To ascertain optimal position of the balloon, a tracing of the pressure amplitude of an inspiration against an occluded airway should be equal when measured in both the airway and the esophageal balloon. Since the patients we studied were sedated and not able to cooperate to perform a maneuver like this, we used a different method to identify optimal balloon position. We compressed the thorax against an occluded airway and recorded the resulting amplitude of the pressure trace from the airway and from the esophagus. We considered the position of the balloon and the filling of the balloon to be optimal in the case of equal amplitudes. This was not possible to achieve in every patient, probably due to habitus, but at least this was a way to try to optimize the conditions for measurement. A similar method has been described in an abstract by Ducros et al. and used in a study by Albaiceta et al. To ascertain equal conditions during our protocol we repeated the maneuver of compressing the thorax between every completed PEEP trial. The baseline of the esophageal pressure recording was very sensitive to how much air the balloon was filled with, the tidal amplitude was less sensitive.

With respect to all these interacting parameters influencing how well the esophageal pressure approximates pleural pressure we decided not to use the correction factor of 0.9 for the plateau pressure, see above.
5.2.4 How to compare methods

In paper II we compared methods to determine changes in lung volume. Data from the spirometric method (“cumulative inspiratory-expiratory tidal volume difference”) were compared with data from a lung model and data derived from impedance differences.

When two methods are compared there are several aspects that should be accounted for. One aspect is to assess the degree of agreement between the methods.

5.2.4.a Association between two methods

Association between methods can be illustrated by an $x/y$-plot and by performing a linear regression analysis. The (Pearson) correlation coefficient ($r$) measures the degree of “straight-line” association. The value of $r$ is between -1 and 1 where 0 is no correlation. The correlation coefficient has to do with the scatter around the line and not agreement. There is of course a good agreement if the data lie along the line of equality.

When variables are compared it could be considered to be a strength of the study if data are within a wide range, but a high correlation coefficient can be obtained just because the fact that there is large variation between data. The Pearson correlation coefficient is calculated by the least squares approach and considers variability only in the “$y$”-direction. The square of the correlation coefficient is called the coefficient of determination and estimates how much of the variability in $y$ is explained by the variation in $x$. By performing a Deming regression or a Passing-Bablok regression variability both in $y$ and $x$ are accounted for. Our data on lung volume changes by spirometry compared to the lung model were practically along the line of equality and there was no need for using another regression model than the ordinary linear regression.

5.2.4.b Agreement between methods

We used the Bland Altman difference plot to illustrate agreement between the two studied methods in paper II. On the $y$-axis the differences between the methods are displayed and on the $x$-axis the corresponding mean value. When we compared the spirometric method, the “cumulative inspiratory-expiratory tidal volume difference”, with the volumes derived from the lung model we chose to display data from the lung model on the $x$-axis (and not the mean values) since
these were regarded as “true” values. When electrical impedance tomography and the spirometric method were compared we used the mean value on the x-axis.

The mean difference is the bias and the 95% confidence interval is depicted by the “limits of agreement”, which equal two standard deviations of the bias. The standard deviation was calculated according to Bland et al\cite{49,50}, taking into account the fact that the data consist of replicated data in pairs where the underlying true value changes from pair to pair and that the data are independent, the differences normally distributed and the within-subject variance is constant. The standard deviation used in the paper (40,5 ml) was derived from the total variance. This includes differences between subjects. A more relevant approach would perhaps be to use the within-subject variance, since serial measurements of lung volume changes only are of interest in the individual patient and not between patients. This would yield a standard deviation of 28,5 ml and more narrow limits of agreement.

If proportional bias is suspected the recommendation in the literature is to convert the data to logarithms. If the calculation of the 95% confidence interval of the log data bias includes zero one could argue that the slope could be $10^{0} = 1$ and therefore without proportional bias, with the presumption of Gaussian distribution of data.\cite{83,84} When reviewing our data we did not find any support for proportional bias in the data from the spirometric method but there was a tendency towards proportional bias in the method of electrical impedance tomography.

In the studies in paper III and IV we aimed to investigate whether transpulmonary pressure during mechanical ventilation can be estimated without esophageal pressure measurements and to illustrate the close correlation between lung elastance and PEEP induced lung volume changes. The “gold standard” for partitioning total respiratory system in lung and chest wall complex elastance is esophageal pressure measurements. This is a method with many limitations, as discussed in section 5.2.3.b. The problem is when a new method is introduced and the only way to compare it is with an old one with apparent low precision and accuracy. Under these circumstances, the new method is at risk to be rejected due to low degree of agreement with an old imprecise method. The Bland Altman difference plot is in this case not applicable.
5.2.4.c Repeatability

Another aspect when comparing methods are the repeatability within methods. According to Bland et al\textsuperscript{51} this can be described by a coefficient of repeatability. It is calculated in the following way: take the sum of the square of all repeated measurements, divide it by the number of measurements and then take the square root to get the standard deviation of the differences. The coefficient of repeatability is twice this standard deviation. When reviewing our data in paper II the coefficient of repeatability was 80 ml for the method of electrical impedance tomography and 62 ml for the “cumulative inspiratory-expiratory tidal volume difference”, based on measurements with equal changes in end-expiratory pressures in the volume controlled mode. The two series of measurements in volume controlled mode are not exactly the same since we used two minutes per PEEP level the second time compared to one minute the first time. This could have an impact on the size of the following lung volume change. Another study design would have provided more reliable data on repeatability.

The study design in paper III was not suited for assessment of repeatability. In paper IV we decided to use three PEEP trials, a decision based on current praxis regarding cardiac output measurements to perform at least three maneuvers to increase the precision in the assessed value.

5.2.4.d Errors between methods

A third parameter of interest when comparing methods is the percentage error, calculated as two standard deviations of the bias divided by the mean. The percentage error for the spirometric method, “cumulative inspiratory-expiratory tidal volume difference”, in the lung model was 12% and the between methods percentage error in the studied patients were between 18 and 26% depending on which value of standard deviation being used. The standard deviation derived from the total variance on different patients yields the higher percentage. This includes differences between the two methods that actually exist between subjects. Since the clinical application of determining lung volume changes is serial measurements within the same subject, it is more relevant to calculate on the standard deviation derived from the within-subject variance which yields the lower percentage. The percentages we reported in paper II were the relative error.
Based on a percentage error of 12% in the spirometric method, “cumulative inspiratory-expiratory tidal volume difference”, our result in the studied patients would allow a percentage error in the electrical impedance tomography method between approximately 12 to 22%, according to the error-gram by Critchley et al 1999.85

5.2.5 Possible improvements of study design

A more appropriate study design for evaluation of repeatability would have improved the study in paper II, for instance repeated measurements between PEEP levels of 5 and 10 cmH₂O.

In paper III, the ex-vivo model, it would have been an advantage if we had made tidal variations with smaller increments than 100 – 200 ml, since the lung volume changes induced by a PEEP change were compared to tidal volumes of similar size for calculation of lung elastance. In some cases the differences between the compared volumes were more than 20% and this may have contributed to some of the variability in our results.

In the patient study in paper IV, it would have been advantageous if the chosen size of the single PEEP step maneuver had resulted in lung volume changes in the range of a tidal volume or larger. We know from other studies75 that the first part of a tidal breath is distributed to non-dependent parts of the lung. If the size of the tidal volume is very small, this volume is only distributed to the non-dependent region and this leads to very small (if any) tidal variation in pleural pressure in the proximity of the zone where it can be reflected by the esophageal pressure. In this case the conventional method to calculate transpulmonary pressure by measurement of esophageal pressure is not optimal.

In our data, two of the patients (patient nr 3 and 12) only increased their lung volume by 110 and 80 ml when increasing PEEP from 0 to 10 cmH₂O. Calculation of lung elastance by the conventional method was 68 and 102 cmH₂O/L and by our method 88 and 125 cmH₂O/L (see Fig. 18). Although the data are reasonably matched, the magnitudes of lung elastance are unlikely considering the patients’ status. Out of protocol a PEEP step of 16 cmH₂O was applied to these patients, which resulted in lung volume changes of 420 and 190 ml respectively. Calculation of lung elastance by the conventional method was then 48 and 82 cmH₂O/L and by our method 38 and 84 cmH₂O/L.
The crucial point in mechanical ventilation is how to individualize the ventilator settings in a way that does not induce, or aggravate already existing, lung injury. In order to identify the risk of ventilator induced lung injury Gattinoni and co-workers use the concept of stress and strain.\textsuperscript{2,30,86} Strain has been defined as the ratio of volume variation to lung resting volume (i.e. tidal volume/functional residual capacity at 0 cmH\textsubscript{2}O end-expiratory pressure). Stress is defined as the transpulmonary pressure. Excessive strain (overdistention) and stress (high transpulmonary pressure) are of overriding importance when considering ventilator induced lung injury. According to Gattinoni\textsuperscript{30} the upper (maximum) limit for strain, in a previously healthy lung, could be set at 2 and for tidal transpulmonary pressure 22-23 cmH\textsubscript{2}O.

When the lung is inhomogeneous, local stress and strain are of greater proportions and more complex according to a theoretical model by Mead et al\textsuperscript{87}, often cited in the literature. In such cases perhaps a different upper limit for “global” transpulmonary pressure should be set.

There is consensus in the scientific community of the importance of partitioning respiratory mechanics of the total respiratory system into its components; lung and chest wall complex (rib cage, diaphragm and abdomen).\textsuperscript{1,80,88-90} Tidal airway pressure is the inspiratory driving pressure of the total respiratory system. The same end-inspiratory airway pressure can have very different effects on the transpulmonary pressure, depending on how the elastance of the total respiratory system is divided between the elastance of the chest wall complex and that of the lung.

For instance, in a condition where the main pathophysiology results in increased elastance of the chest wall complex (for example secondary to increased intra-abdominal pressure) and the elastance of the lung is near normal, a larger part of the end-inspiratory airway pressure will be distributed to the chest wall complex and less to the change in transpulmonary pressure. The end-expiratory pressure, in this example, has the obvious effect of keeping the chest wall complex “out of the way” (mainly pushing the abdomen caudally since the rib cage has an inherited outward striving force) and allowing the lung to stay inflated.

On the other hand if the main pathophysiology results in increased elastance of the lung (for example pneumonia) and the elastance of the chest wall complex is near normal, a larger part of the end-inspiratory airway pressure will be
distributed to the change in transpulmonary pressure, that is force per unit area of the pulmonary structure.

In the critically ill patient the clinical reality is often a mixture of these two scenarios.

**Fig 22** A schematic tidal breath illustrated by the red line, in three different conditions. In the two right panels the inspiratory pressure is elevated compared to the left panel. To enable illustration of elastance, volume is on the x-axis instead of pressure, in contrast to the conventional way of illustrating P/V-curves.

The slope of the red line is the elastance of the total respiratory system. The slopes of the blue and green lines represent the lung elastance and the chest wall complex elastance, respectively. The dotted line shows the resulting transpulmonary pressure under the different conditions.

**Note,** that with increasing intra-abdominal pressure, the lung volume decreases. As lung elastance is inversely proportional to lung volume, the transpulmonary pressure increases in spite of the lung being healthy.

It is the size of the transpulmonary pressure we should be conscious of during mechanical ventilation of a patient with respiratory failure.

### 5.3.1 Chest wall complex and the effect of driving pressures

An increase in lung volume induced by an increase in PEEP will lead to a displacement of the chest wall complex (rib cage, diaphragm and abdomen) until a new pressure-volume equilibrium has been established. The majority of these changes occur within a few breaths but the presence of “slow compartments” and stress adaptation slow down the process. Our opinion is that these “slow compartments” can be explained mainly by the fluid-like characteristics of the abdomen.

In our study in paper III, the ex-vivo model, the increase in lung volume achieved by the first breath, after an increase in PEEP, was closely related to the ratio
between change in PEEP and the elastance of the total respiratory system, ΔPEEP/ETOT. This has also been shown by Katz et al.\textsuperscript{52} The extra driving pressure applied to the respiratory system by the increase in PEEP, is to a large extent in this first breath, “absorbed” by the chest wall complex and has the effect of moving the chest wall complex outwards. We could show that when a new pressure-volume equilibrium had been established, the achieved increase in lung volume was largely dependent on pulmonary characteristics. At 0 cmH\textsubscript{2}O of PEEP, we applied a tidal volume of the same size as the previously achieved lung volume increase by a single PEEP step. We could then determine the elastance of the total respiratory system, of the chest wall complex and of the lung (ETOT, ECW and EL), for this individual breath. If the lung volume change induced by a single PEEP step mainly is dependent on pulmonary characteristics it would be possible to predict its size by dividing the change in PEEP by the elastance of the lung obtained by esophageal pressure measurements (ΔPEEP/EL). We could show a close correlation between predicted and measured lung volume change although there was a wide variation.

In paper III we could show that the pressure/volume curve of the chest wall complex is successively left- and parallel shifted with increasing PEEP. This means that the elastance of the chest wall complex remains largely unchanged with increasing PEEP. Similar findings have been published by others.\textsuperscript{46,91}

Fig. 23 Pressure/volume curves of tidal breaths at different PEEP levels. The right panel shows data from a pig where the lungs play a major role for the mechanical behavior of the respiratory system, the ratio between lung elastance and total respiratory system elastance was 0,89. The left panel shows data from a pig where there is a substantial influence from the chest wall complex on the total respiratory system, the ratio between lung elastance and total respiratory system elastance was 0,69.
In a study by Lu et al, with the aim to validate a technique for measuring the inflation pressure/volume curve, they used a constant inspiratory flow of 3 and 9 l/min.\textsuperscript{92} With this slow inspiratory flow the influence of the resistive properties of the respiratory system is minimized. The method was validated against the super-syringe method and an inspiratory occlusion method.\textsuperscript{93,94} All three methods showed a very steep, linear pressure/volume curve for the chest wall complex, similar to our findings (see figure 23).

A PEEP-induced increase in end-expiratory lung volume will increase the diameter of the caudal part of the rib cage which results in the diaphragm being stretched and moved in a caudal direction. This acts to reduce the amount of pressure transmitted from the abdominal cavity to the thoracic cavity, thus changing the trans-diaphragmatic pressure.

The position of the diaphragm at equilibrium in end-expiration is determined by the balance between three forces; the rib cage spring out force, the abdominal pressure against the diaphragm and the recoil force of the lung.

5.3.2 Esophageal pressure as a reflection of pleural pressure

The question of how accurately esophageal pressure reflects pleural pressure has been extensively discussed in the literature. The esophageal pressure has been shown to reflect the pleural pressure at a certain thoracic level. Apart from all the technical difficulties with the esophageal pressure measurements, the pleural pressure is not uniform over the entire pulmonary surface. It must be considered a relatively large approximation to use the absolute value from a single measure point (=esophageal pressure) for calculation of the transpulmonary pressure of the whole lung. The tidal variations of esophageal pressure have been shown to reflect the tidal variations in pleural pressure.\textsuperscript{95}
In a study by Pelosi et al\textsuperscript{96} in dogs with oleic-acid respiratory failure they showed that the vertical gradient of pleural pressure is inversely proportional to the airway pressure. They showed that esophageal pressure correlates with the lateral lung surface pressure but overestimates pleural pressure in nondependent lung and underestimates it in dependent lung areas with a proportional bias depending on airway pressure. However the changes of esophageal pressure in response to airway pressure approximate the changes of pleural pressure in all regions according to this study.

5.3.3 The influence of PEEP on esophageal pressure

We have showed that increasing PEEP only leads to a minor increase in esophageal pressure. The absolute increase in esophageal pressure was limited to the first breath after a PEEP increase even when the lung volume continued to increase. We believe that this supports our theory of the chest wall complex behaving more like a weight, with hydraulic properties, which can be displaced by PEEP, rather than a pure elastic structure that is expanded by PEEP.

The minor influence of a PEEP increase on esophageal pressure has also been shown in a study by de Leon et al.\textsuperscript{97} They used a multi-tip manometer, with the ability to measure over a distance of 36 cm along the esophagus. They showed that the end-expiratory esophageal pressure, in the lower part of the esophagus, only increased by 2 cmH\textsubscript{2}O when PEEP was increased by 10 cmH\textsubscript{2}O.

\textbf{Fig 24} This figure shows a CT-image at the lower thoracic level, in the area of where an esophageal balloon would be placed. The arrow points at the esophagus.
Since the end-expiratory esophageal pressure changes minimally with PEEP, this implies that the pleural pressure change is also minimal. This leads to the conclusion that transpulmonary pressure will increase in close relation to the change in PEEP.

5.3.4 Transpulmonary pressure during mechanical ventilation

The results in paper III and IV show that the end-expiratory esophageal pressure changes minimally with PEEP. This leads to the conclusion that transpulmonary pressure will increase as much as PEEP and lung elastance can be calculated as the ratio of the change in PEEP and the change in end-expiratory lung volume (\(\Delta\text{PEEP}/\Delta\text{EELV}\)). The pressure/volume curves in figure 25 are based on the mean values from the 12 studied patients in paper IV. The conventional transpulmonary pressure/volume curve, based on data from the esophageal pressures, is closely related to the end-expiratory airway pressure/volume curve. For details on calculation, see section 3.6.4 and 3.6.5.

![Data based on mean values of twelve patients. The conventional esophageal pressure measurements are connected to form a mean transpulmonary pressure/volume curve (black triangles). The end-inspiratory airway pressure/volume points (blue diamonds) are connected to form an inspiratory pressure/volume curve. The end-expiratory airway pressure/volume points (red dots) are connected to form an expiratory pressure/volume curve. PAW_{EE}, End-Inspiratory Airway Pressure; PAW_{EE}, End-Expiratory Airway Pressure; PTP_{conv}, Conventional Transpulmonary Pressure.](image-url)
5.3.5 Theoretical model of the respiratory system

The findings in our studies in papers III and IV underline the viscoelastic properties of the respiratory system. Schematic models of the respiratory system use different springs to illustrate the respiratory mechanics. We propose a model where the abdomen is depicted as liquid-filled compartments with different time constants ("slow compartments").

The pleural space is delineated by two pistons (equivalent to the visceral pleura and the parietal pleura), each of them attached to springs that work in opposite directions, thereby resulting in negative pleural pressure. One spring belongs to the lung compartment and illustrates the lung recoil force. The other spring illustrates the spring out force of the rib cage and its close connection to the mechanical properties of the abdominal compartment, which in turn acts as a weight on the rib cage piston. The balance between the opposing forces determines the position of the two pistons.

The abdominal compartment has a volume of ≈ 10 liters and the ventral surface area is ≈ 1000 cm². An increase in end-expiratory lung volume is equally distributed to the thoracic wall and the diaphragm and an increase of 1 liter will lead to an intrusion by 500 ml of the diaphragm into the abdomen, increasing the vertical height of the abdominal container by ≈ 0.5 cm, influencing abdominal gravitational pressure minimally. There are previously presented data to support the view that the rib cage accounts for a larger portion of the volume change than the abdomen and in this case an even minor influence on the abdominal gravitational pressure would be the result. Thus, a PEEP increase results in a caudal displacement of the diaphragm, opening the thoracic cavity for the lung to expand.
In this model of the respiratory system, lung and chest wall elastance both are 10 cmH\textsubscript{2}O/L, resulting in a total respiratory system elastance of 20 cmH\textsubscript{2}O/L.

A tidal inflation of 500 ml will raise end-inspiratory airway pressure by 10 cmH\textsubscript{2}O and pleural pressure by 5 cmH\textsubscript{2}O to 0 cmH\textsubscript{2}O and the transpulmonary pressure with 10 − 5 = 5 cmH\textsubscript{2}O from +5 to 10 cmH\textsubscript{2}O.

If PEEP is raised by 5 cmH\textsubscript{2}O, the system will be inflated breath by breath and a new pressure/volume equilibrium will be reached when the end-expiratory lung volume is increased by 500 ml. During this PEEP induced inflation the two linked pistons will gradually move towards the abdominal compartment.

This model emphasizes the important effect of the spring out force of the rib cage and how a PEEP induced increase in lung volume can appear, without raising pleural pressure.

\textit{Fig. 26 Model of the respiratory system.}
5.3.6 Current praxis in the daily care of mechanically ventilated patients

When the survey in paper I was performed in 2007, there was no consensus on which ventilator settings to use when oxygenation ratios (PaO$_2$/FiO$_2$) were assessed. Two oxygenation ratios per patient were reported during the investigated 24 hours; highest PaO$_2$ with corresponding lowest FiO$_2$ and lowest PaO$_2$ with corresponding highest FiO$_2$. Our study showed large individual variations in reported oxygenation ratios. According to the definition by the American-European Consensus Conference on ARDS in 1994 any one of these oxygenation ratios could have been chosen to categorize the patient, with obvious risk for false assessment. Factors such as the degree of true shunt, arterio-venous differences as well as FiO$_2$ and PEEP have an impact on the oxygenation ratio. The effect of a changing FiO$_2$ on the oxygenation ratio depends on the degree of shunt and arterio-venous difference. The arterio-venous difference varies depending on oxygen consumption and cardiac output. The level of FiO$_2$ and PEEP can also interact and influence the oxygenation ratio in various ways. At high FiO$_2$, lung sections with low ventilation-perfusion ratios are at risk for resorption atelectasis, which to some extent could be prevented by PEEP. Villar et al have addressed this question and in a study published 2007 they used a standardized protocol for how to set the ventilator during assessment of the patients which illustrated the impact of PEEP and FiO$_2$ on the oxygenation ratio. They showed that a combination of PEEP $\geq$ 10 cmH$_2$O and FiO$_2$ $\geq$ 0.5 with a tidal volume of 7 ml/kg (predicted body weight) applied 24 hours after classification as ARDS, according to the definition from the American-European Consensus Conference, separates patients into three groups with markedly different mortalities. The latest definition of ARDS includes a PEEP criterion of 5 cm H$_2$O, but not a specific level of FiO$_2$. The risk for false assessment of a patient with regard to the oxygenation ratio is still present.

Aerosol therapy with $\beta$-adrenergic agonists and mucolytica are widely used in mechanically ventilated patients. The rational for using $\beta$-adrenergic agonists in patients without obvious signs of obstructivity, could be to improve respiratory mechanics, mucociliary clearance and to facilitate clearance of pulmonary edema (BALTI-study). Two large multicenter, randomized placebo-controlled studies, on mechanically ventilated patients with ARDS receiving $\beta$-adrenergic agonists either by inhalation or intravenously (BALTI-2), have been published.
in the last two years, which do not support routine use of these agents. Clearance of airway secretions are supposed to be facilitated by mucolytica but the scientific evidence for extensive use in mechanically ventilated patients is scarce. Guidelines on endotracheal suctioning recommend a negative pressure of less than -150 mm Hg (= -20 kPa = -200 cm H₂O) in adults.¹¹⁹ The data in our study in paper I indicate the common use of much higher levels of negative pressure. Endotracheal suctioning is known to cause a transient reduction in lung volume due to derecruitment, closed suction systems to a lesser degree. The efficacy of closed suction systems for evacuation of tracheal aspirate has been shown to be lower, which could lead to the use of higher levels of negative pressure.¹²⁰,¹²¹ The use of recruitment maneuvers post-suctioning has been proposed, but due to the diverging effects on patients with lung injury no universal recommendation has been published.¹²² Neither the optimal technique, timing or frequency of recruitment maneuvers has been established, nor the patient category likely to benefit from such interventions.²⁸,¹²³

Prone positioning has been regarded as a rescue strategy in patients with severe refractory hypoxemia. Recently the results of a prospective, multicenter, randomized controlled trial were published, that showed improved survival in patients with severe ARDS when prolonged periods of prone position were used during a 28 day period.²⁹ The proposed mechanisms behind the positive effects of prone position are multifactorial; 1) redistribution of ventilation to a more uniform pattern while pulmonary perfusion is not altered, results in improved matching between ventilation and perfusion, 2) reduced pleural pressure gradient due to “unloading” of the pressure caused by the mediastinal contents, thus making the transpulmonary pressure gradient more homogeneously distributed, 3) reduced effects of the abdominal pressure on the thoracic cavity and altered mobility in the rib cage leading to changes in compliance of the chest wall complex. A combination of these factors could lead to higher end-expiratory lung volume without the enhanced element of overdistention, thus explaining the improved oxygenation and possibly lesser degree of ventilator induced lung injury. It has been shown by Pelosi et al, that an increased global end-expiratory lung volume is not necessary to improve gas exchange.¹²⁴-¹²⁷ The benefit of prone positioning has been shown to be time-dependent, supporting the theory of existing slow compartments.¹²⁴
6. CONCLUSIONS

Our routines in the daily care of mechanically ventilated patients risk repeated derecruitment episodes, which could thwart the quest of lung protective ventilation. Easily accessible data on individual respiratory mechanics would be helpful in optimizing ventilator settings in the critically ill patients.

We have shown that it is possible to use a spirometric method, measuring cumulative inspiratory-expiratory tidal volume difference, to assess changes in end-expiratory lung volume. In addition, there was an excellent correlation and a reasonable bias and limits of agreement between lung volume changes obtained with spirometry, $\Delta EELV_{VT(i-e)}$, compared to lung volume changes determined by electrical impedance tomography, $\Delta EELV_{EIT}$, indicating that electrical impedance tomography calibrated with spirometry can be used for assessing changes in end-expiratory lung volume. Measurements of lung volume changes obtained with spirometry, $\Delta EELV_{VT(i-e)}$, require only simple technology and no extra equipment. It can be implemented as software in any ICU ventilator. Such a feature in a ventilator would improve selection of appropriate and individualized ventilator strategies at the bedside.

It is obvious that it is not enough only to set goals for volumes and pressures relating to the whole respiratory system without regarding the characteristics of the individual lung and chest wall complex (rib cage, diaphragm and abdomen). The question of how the forces applied to the respiratory system are distributed between the lung and chest wall complex needs to be answered, preferably by easily managed bedside tools.

In the ex-vivo model we showed that the pressure/volume curve for the chest wall complex is left- and parallel shifted with increasing PEEP. This means that with increasing PEEP the elastance of the chest wall complex only changes to a minor extent. In both the ex-vivo model and the patient study we showed that end-expiratory esophageal pressure increases only minimally with increasing PEEP. This could be explained by two mechanisms; 1) the abdominal compartment adapts to the change in position of the diaphragm and 2) the spring out force of the rib cage is active and is striving to expand the rib cage and tense the diaphragm.
We have also shown in the patient study that the pressure/volume curve of transpulmonary pressure, derived conventionally by esophageal pressure measurements, is closely related to the end-expiratory airway pressure/volume curve. This can be explained by the fact that the chest wall complex has only minor influence on the expiratory behavior of the respiratory system. This makes it possible to determine transpulmonary pressure without esophageal pressure. With regular assessment of respiratory mechanics, especially lung elastance and transpulmonary pressure, it is likely that we could improve our management of mechanically ventilated patients.
FUTURE PERSPECTIVES

Since it is possible to measure lung volume changes induced by a PEEP step in a simple way by data from the ventilator flow meter, this could be implemented as software in an ICU ventilator. Our work implies that by performing a PEEP step maneuver and measuring the resulting lung volume change, it is possible to get information on pulmonary characteristics (compliance=$\frac{\Delta EELV}{\Delta PEEP}$ and elastance=$\frac{\Delta PEEP}{\Delta EELV}$). This would make it possible to acquire important information on lung mechanics and enable calculation of the transpulmonary pressure without the need for esophageal pressures. In fact no extra equipment is needed – only additional software in the ventilator.

The optimal way to perform the PEEP step maneuver remains to be studied. Changing the PEEP ± 5 cmH$_2$O from the PEEP level set by the attending physician could be a solution, providing no contraindications are present. Probably it is best to repeat measurements at least 3 times to get a mean value, in the same way as many measurements of cardiac output are performed.

With an easy accessible bedside tool to estimate transpulmonary pressure we may well have taken a step towards optimization of ventilator support for many critically ill patients. It remains to be studied if this method also can be applied to patients with severe pulmonary or extrapulmonary ARDS.
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However, there is another person without whose help I would have been unable to complete this. Words are not enough…
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“The more I read, the more I acquire, 
the more certain I am that I know nothing.”

Voltaire (1694-1778)