Lung and chest wall properties during mechanical ventilation

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Abstract

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Background: Mechanical ventilation causes injury to the lungs due to high pressures and high volumes. Pressure affecting the lungs, the transpulmonary pressure, needs to be monitored to minimise harmful side effects but then lung and chest wall mechanics need to be separately considered. The conventional method is based on measurement of esophageal pressures but the interpretation of these pressures is debated. A non-invasive "PEEP-step method" for calculation of transpulmonary pressure has been introduced and tested in pigs and in patients in the ICU but still it has not been generally accepted. The aim of this thesis was to (1) validate the PEEP-step method in patients, (2) assess factors influencing the conventional method using esophageal pressure measurements and (3) evaluate lung and chest wall mechanics during mechanical ventilation.

Methods: In a mechanical model, based on the classical description of the respiratory system with a recoiling lung and an expanding chest wall, the theoretical explanation for the PEEP-step method was tested. The PEEP-step method, involving changes of PEEP and calculation of changes in end-expiratory lung volume, was further evaluated by comparison with the conventional method, based on esophageal pressure, in 24 patients undergoing general anaesthesia. In the third study esophageal pressures were evaluated with an advanced High Resolution Manometry (HRM) catheter in 20 mechanically ventilated patients in the ICU and Operating theatre as well as in 17 awake spontaneous breathing patients in sitting and supine positions. HRM permits simultaneous measurements of pressure at all levels in esophagus. Finally chest wall mechanics during mechanical ventilation were studied in pigs using electric impedance tomography, esophageal pressures and measurement of the recoiling pressure after pneumothorax and of the thoracic volume before and after pneumothorax (determined with computer tomography).

Results: The respiratory system model with a recoiling lung inside an expanding chest wall connected to an abdomen with high plasticity behaved similarly to patients during tidal and PEEP-induced inflation. The change in end-expiratory lung volume after an increase in PEEP was determined by the elastance of the lung and the size of the PEEP-change. Elastance of the lung and transpulmonary pressure could be calculated from a PEEP-step manoeuvre. In patients, transpulmonary driving pressure calculated with the PEEP-step method and the conventional method showed good agreement (mean difference < 0.2 cmH_2O). The calculated change in end-expiratory pleural pressure was -0.1 cmH_2O after an increase of PEEP. When esophageal pressures were measured with HRM, there was a substantial variation within individual patients (mean difference between highest and lowest esophageal pressures within a patient was 23.7 cmH_2O) as well as a significantly higher mean pressure in supine compared to sitting position (mean difference 12.3 cmH_2O). In the supine position, larger cardiac artefacts were seen as well as simultaneous increases and decreases in esophageal pressures within a patient. In pigs, the distribution of a tidal inflation and a PEEP-induced inflation within the lung was similar. The recoiling pressure of the lung at functional residual capacity was 3.9 cmH_2O. Calculated end-expiratory chest wall elastance was low (0.6-2.3 cmH_2O/L) compared to tidal chest wall elastance (10.0-13.6 cmH_2O/L).

Conclusions: The PEEP-step method accurately measures transpulmonary driving pressure. After an increase of PEEP the chest wall expands and restores the negative pleural pressure at end-expiration and the change in end-expiratory lung volume is dependent on lung elastance. Esophageal pressures are affected by many factors and vary substantially within individual patients. An equally large tidal and PEEP-induced inflation have similar distributions within the lung and necessitates an equally large change in transpulmonary pressure. The chest wall exerts an expanding force on the lung at end-expiration, which causes the end-expiratory pleural pressure to remain negative also at higher PEEP levels.

Keywords: Mechanical ventilation, Respiratory mechanics, Ventilator induced lung injury, Esophageal pressure, Positive end-expiratory pressure

Sammanfattning på svenska

Respiratorbehandling under intensivvård är livräddande i många situationer. Men det övertryck som används för att skapa ett andetag har visat sig kunna vara skadligt för lungorna. För att minska skadorna av respiratorbehandling är det viktigt att övervaka de tryck och volymer som respiratorn utsätter lungan för. Trycket som respiratorn åstadkommer tänjer i olika grad ut lungan beroende på lungans och bröstkorgens egenskaper och variationerna är stora särskilt bland patienter inom intensivvården. För att kunna utvärdera lungornas och bröstkorgens mekaniska egenskaper vill man mäta trycket i lungsäcken vilket dock är riskfyllt. Istället används tryck uppmätta i matstrupen som ett substitut då man för mer än 60 år sedan visade att tryckförändringar i matstrupen i hög utsträckning motsvarar tryckförändringar i lungsäcken. Tryckmätning i matstrupen, vilket kräver nedläggning av en sond med ballong på, påverkas av många faktorer och det är oklart hur de uppmätta trycken ska tolkas. För ca 6 år sedan visade vår forskningsgrupp att man genom en ny metod kan beräkna lungans och bröstkorgens egenskaper utan tryckmätning i matstrupen. ”PEEP-stegs metoden” baseras på att trycket i slutet på utandningen (PEEP) ändras samtidigt som den efterföljande volymförändringen i lungan beräknas. Med standardformler inom lungmekanik kan man utifrån dessa data beräkna lungans och bröstkorgens egenskaper. Metoden baseras på basal lungmekanik beskriven i läroböcker men har ändå haft svårt att nå acceptans hittills.

Den första studien i denna avhandling innebar att vi skapade en mekanisk modell av lungan, bröstkorgen och buken för att utröna om den teoretiska förklaringsmodellen för PEEP-stegs metoden kunde efterliknas i en modell byggd utifrån läroböckernas beskrivning av lungans och bröstkorgens mekanik. Detta visade sig vara möjligt och även när lungans och bröstkorgens egenskaper förändrades betedde sig modellen som lungan och bröstkorgen hos en patient. I den andra studien gjordes mätningar på patienter på operation för att jämföra beräkningar av trycken i lungan utförda med PEEP-stegs metoden och med den hittills använda metoden med tryckmätning i matstrupen. PEEP-stegsmetoden visade sig vara pålitlig och ha god träffsäkerhet. I den tredje studien fokuserade vi på alla de frågetecken som fanns beträffande tryckmätning i matstrupen. Med hjälp av mätningar med en i sammanhanget ny avancerad kateter kunde trycket mätas på alla nivåer i matstrupen samtidigt. Genomförda mät-

ningar på vakna lungfriska patienter, på patienter på intensivvården och under sövning i samband med operation visade att trycket i matstrupen varierar mycket beroende på var i matstrupen man mäter och vilket kroppsläge patienten har. Med hjälp av den nya metoden kunde vi också beskriva hur trycket i matstrupen påverkas av hjärtats tyngd och slagvolym. Den fjärde studien gjordes på grisar och målet var att öka kunskapen om bröstkorgen betydelse under olika delar av respiratorns andetag. På grisarna utfördes tryckmätningar i lungan och matstrupen, mätningar av andetagens volym och fördelning inom lungan liksom mätningar av bröstkorgens rörelse när den kopplas loss från lungan. Utifrån resultaten kunde vi påvisa hur bröstkorgen i slutet av andetaget håller lungan öppen medan den under inblåsning av andetagsvolymen verkar som ett motstånd. Dessa fynd i grisar bekräftade ytterligare förklaringsmodellen för PEEP-stegsmetoden.

Sammanfattningsvis har studierna i avhandlingen visat (1) att PEEP-stegs metoden fungerar väl för att beräkna de tryck respiratorn utsätter lungan för hos sövda patienter, (2) hur den bakomliggande fysiologin fungerar och (3) att det finns påtagliga osäkerheter med den vanliga metoden (baserad på tryckmätning i matstrupen) för att beräkna lungornas och bröstkorgens egenskaper.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Persson P., Lundin S., Stenqvist O.

Transpulmonary and pleural pressure in a respiratory system model with an elastic recoiling lung and an expanding chest wall

Intensive Care Medicine Experimental 2016 Dec; 4(1): 26.

II. Persson P., Stenqvist O., Lundin S.

Evaluation of lung and chest wall mechanics during anaesthesia using the PEEP-step method

British Journal of Anaesthesia, 2018 Apr; 120(4): 860-867

III. Persson P., Ahlstrand R., Gudmundsson M., de Leon A., Stenqvist O., Lundin S.

Detailed measurement of esophageal pressure during mechanical ventilation with an advanced high-resolution manometry catheter

Submitted

IV. Persson P., Stenqvist O., Lundin S.

The chest wall during mechanical ventilation – an experimental study in a pig model

In manuscript

Content

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
CCW	Compliance of the Chest Wall
CL	Compliance of the Lung
CO_2	Carbondioxid
COPD	Chronic Obstructive Pulmonary Disease
CRS	Compliance of the Respiratory System
CT	Computer Tomography
ECMO	Extracorporeal Membrane Oxygenation
ECW	Elastance of the Chest Wall
EELV	End-Expiratory Lung Volume
EIT	Electric Impedance Tomography
EL	Elastance of the Lung
ERS	Elastance of the Respiratory System
FiO_2	Fraction of Inspired Oxygen
FRC	Functional Residual Capacity
HRM	High Resolution Manometry
IBW	Ideal Body Weight
ICU	Intensive Care Unit
P/V	Pressure/Volume
PaO2	Partial pressure of Oxygen in Arterial blood
PEEP	Positive End-Expiratory Pressure
PES_{EE}	End-Expiratory Esophageal Pressure
PES_{EI}	End-Inspiratory Esophageal Pressure
VILI	Ventilator-Induced Lung Injury
VT	Tidal Volume
ZEEP	Zero End-expiratory Pressure
ΔPAW	Change in Airway Pressure
ΔPES	Change in Esophageal pressure
ΔV	Change in Volume

Introduction

Although life-saving in many situations mechanical ventilation is not without complications. Shortly after the introduction of positive pressure ventilation in the treatment of respiratory failure during the polio epidemic in Copenhagen in 1952[1] side effects of mechanical ventilation became obvious[2]. Complications due to positive pressure ventilation such as pneumothorax, pneumomediastinum and subcutaneous emphysema were recognized[3] and initially included in the concept of barotrauma[4]. In addition to the often obvious sign of air leakage, post mortem examinations showed macro- and microscopic lung injuries in mechanically ventilated patients, summarized in the "respirator lung syndrome" [5]. During the following decades, research focused on lung injury induced by the ventilator, which eventually led us to the modern concept now named VILI, ventilator induced lung injury.

Ventilator-induced lung injury and lung protective ventilation

Ventilator-induced lung injury - Experimental research

In 1974 Webb and Tierney showed rapid development of pulmonary oedema in rats during mechanical ventilation with high airway pressures [6] and a similar picture was seen in sheep after 48 hours of mechanical ventilation[7]. These findings suggested that high pressure in the lungs caused more complex injuries than the air leakage traditionally included in the term barotrauma. The pulmonary oedema observed in the lungs proved to a large extent to be caused by increased capillary permeability[8-10]. Further experimental research questioned the role of high pressure as the sole determinant of ventilator induced lung injury. When high airway pressures were used in combination with low tidal volumes (achieved by strapping of the chest wall) no sign of pulmonary oedema was seen in contrast to when large tidal volumes were used [8, 10]. The harmful effect was

instead attributed to high volumes distending the lung and the term volutrauma suggested to replace barotrauma[11]. In addition to limiting the airway pressures and tidal volumes experimental studies also suggested that maintained end-expiratory lung volume by application of PEEP decreased ventilator induced lung injury [6, 10, 12]. As the protective effect of PEEP seen in these studies was thought to be due to prevention of cyclic opening and closing of alveoli and airways during each inflation/deflation, the term atelectotrauma was added to the determinants of VILI. Many of these studies included animal models with healthy lungs, which are seldom seen in ventilated patients in the ICU. In order to mimic lung properties of patients with severe respiratory failure, animal models with oleic acid-injured lungs were used[13, 14] and the previously described detrimental effect on the lung by mechanical ventilation was even more pronounced in already injured lungs.

A few years later it was shown that mechanical ventilation with high volumes also increased the release of inflammatory markers into the lungs of ventilated rats[15]. The term biotrauma was coined by Tremblay and Slutsky in 1998 [16] to describe this inflammatory response to mechanical forces and suggested that it may represent a connection between ventilator induced lung injury and multi-system organ failure[17]. The correlation between release of inflammatory markers into the lungs and blood circulation and ventilation with high volumes was later confirmed in patients in 1999 and 2002[18, 19].

Decades of experimental research in animal models focused on ventilator induced lung injury has demonstrated a correlation between positive pressure ventilation with high volumes/pressures and low PEEP, cellular injuries in the lungs and an inflammatory response.

Acute respiratory distress syndrome, ARDS

The first description of ARDS is usually ascribed to Ashbaugh in 1967 [20] who coined the term adult respiratory distress syndrome in contrast to infant respiratory distress syndrome seen in premature babies with surfactant depleted lungs. There has been an extensive amount of research about the syndrome later named

"Acute Respiratory Distress Syndrome". The definition has changed over the years eventually leading up to the current "Berlin definition" defined in 2012 through an American-European consensus process. In short, the syndrome is defined as a hypoxic respiratory failure, with acute onset (within 1 week), not fully explained by cardiac failure or fluid overload and radiologically characterised by bilateral opacities not fully explained by effusions, collapse or nodules. Depending on the ratio between arterial oxygen tension and fraction of inspired oxygen (PaO2/FiO2-ratio) the syndrome is classified as mild, moderate or severe ARDS[21]. The high airway pressure required during mechanical ventilation because of the low respiratory system compliance was noted already in early descriptions of ARDS[20] and was thought be due to a homogenous oedema in the lungs. The introduction of computer tomography in ARDS research in the 1980s challenged this view by showing a pronounced non-homogenous aeration of the lungs in patients with ARDS[22]. In the lungs there were areas, mostly in dependent regions, that were collapsed or consolidated and thereby non-aerated. Other areas were poorly aerated and some non-dependent parts of the lungs were often normally aerated. The revelation that the volume of the normally aerated part of the lungs corresponded to the normal lung volume of a ≈5 years old child led to the well-known "Concept of the Baby Lung" introduced by Gattinoni and Pesenti[23]. The correlation between the amount of non-aerated lung and the degree of hypoxemia, likely due to shunt, and between the size of the normally aerated lung and compliance of the respiratory system[24] increased the understanding of ARDS. The low compliance was not caused by a homogenously stiff lung but instead caused by only a small portion of the lung being aerated and available for ventilation. The compliance of the normally aerated lung actually showed to be within the normal range[24]. In an attempt to decrease the shunt, prone positioning of patients was introduced. The aim was to move lung perfusion from the dependent regions of the lungs to the aerated non-dependent regions in order to improve oxygenation. Oxygenation did improve but CT-scans revealed that densities were redistributed from the dorsal to the ventral part of the lung, now being dependent [25, 26]. Later animal studies discovered that lung perfusion does not follow gravitation but instead remains primarily in the dorsal region also in prone position[27]. The improved oxygenation that was seen in patients in prone position in the study by Langer et al[25] was probably to a large part caused by improved matching of ventilation and perfusion. But instead of moving lung

perfusion to the aerated parts of the lung it was the aerated part of the lung that was redistributed to the better perfused dorsal part [28].

Ventilation of patients with ARDS – historical perspective

Extensive research aimed at finding effective medical treatments for established ARDS have often failed and promising medications, several listed in the review by Yadav et al[29], have turned out to be ineffective. But the evolving knowledge about ventilator-induced lung injury and ARDS resulted in awareness of the importance of optimal ventilator settings when dealing with severely injured lungs. During the first decades after Ashbaugh's description of ARDS in 1967[20] patients were ventilated with high tidal volumes of 10-15 ml/kg or even higher (up to 24 ml/kg in the study by Falke)[30-33] to maintain normal arterial levels of CO_2. The basis for high tidal volumes were the findings by Bendixen et al that development of atelectasis and shunt during anaesthesia was minimized by larger-than-physiological tidal volumes[34].

The use of positive end-expiratory pressure (PEEP) was introduced already in the original description of ARDS and since it seemed to have a positive effect on oxygenation[20] it soon became more widely studied. The main reason for the use of higher PEEP during the following 20 years was the desire to lower the fraction of inspired O_2 (FiO_2) to a safe level and avoid oxygen toxicity [35]. The main concern was the negative effect on circulation and risk of barotrauma. Most often PEEP levels between 5-20 cmH_2O were applied [33, 36, 37] but sometimes much higher levels were used (25-43 cmH_2O in the study by Kirby)[32]. Among the patients included in the studies, the stated incidence of pneumothorax and pneumomediastinum during this time period was often between 10-15%. Although in the study with high PEEP by Kirby it was also stated "subcutaneous emphysema was a common finding".

Lung protective ventilation in patients with ARDS

In 1990 Hickling et al published a study where they incorporated knowledge about ventilator-induced lung injury in animal studies into the management of patients with ARDS[38]. Instead of the conventional approach with high tidal volumes and PEEP depending on FiO_2 they limited the peak inspiratory airway pressure to < 30 cmH_2O when possible and otherwise < 40 cmH_2O. In order to achieve these aims they introduced permissive hypercapnia as the tidal volumes were decreased and arterial CO_2 levels were allowed to increase. Without having a control group they stated that mortality was lower than expected compared to similarly ill patients in other studies. The study was a starting point for the development of what we today refer to as lung-protective ventilation. During the following 10 years several studies investigated the effect of smaller tidal volumes and lower plateau pressures (often together with higher PEEP) in the management of ARDS[39-43] but results were conflicting. Then in 2000 the ARDS network published a study often cited when discussing lung protective ventilation[44]. In this multicentre randomized trial patients with ARDS were either ventilated conventionally with tidal volumes 12 ml/kg calculated from ideal body weight (IBW) and plateau pressures of <50 cmH_2O or with a lung protective approach with tidal volumes 6 ml/kg (IBW) and plateau pressures < 30 cmH2O. The lower mortality in the lung protective group is the basis for the current recommendation to use lower tidal volumes in management of ARDS. Adjusting tidal volumes according to ideal body weight, which today is standard practice in many Intensive Care Units (ICUs), was based on research within lung physiology showing that lung volumes are best predicted from sex and length[45, 46].
Lower tidal volumes than 6 ml/kg IBW in combination with extracorporeal CO_2-removal, have been evaluated and shown to be feasible even if there were no differences in ventilator-free days which was the primary outcome[47]. Adapting tidal volumes to the patient's lung volume was improved by the calculations using ideal body weight. Still one major feature of ARDS is the small portion of the lung that is well aerated and open for ventilation, "the concept of the baby lung" described by Gattinoni et al[23] (se above). The low compliance of the respiratory system in ARDS is correlated to the size of the "baby lung"[24] which makes it possible to adapt the tidal volume to the functional part of the lung by

looking at the airway driving pressure. The airway driving pressure (ΔPAW), which is the difference between plateau pressure and PEEP, is equal to the ratio between tidal volume and respiratory system compliance ($\Delta PAW=VT/C_{RS}$). Based on the hypothesis that the airway driving pressure is more strongly related to outcome in ARDS than the tidal volume Amato et al performed a retrospective analysis including >3500 patients with ARDS and found that airway driving pressure was the ventilation variable that correlated best with survival[48]. In contrast to the recommendation to limit tidal volumes and airway plateau pressures the optimal setting of PEEP has been much harder to establish[49]. In the latest definition of ARDS a PEEP of 5 cmH_2O is needed to fulfil the criteria[21] and PEEP is recommended in management of patient with ARDS[49]. Several studies have addressed the subject and compared different methods for finding the optimal PEEP-level[50-52] but how to set the optimal PEEP still remains unknown. In a sub-group analysis included in an individual patient data meta-analysis of these three studies (ALVEOLI[50], LOVS[51], EXPRESS[52]) a higher PEEP (15 compared to 9 cmH_2O at day 1) was associated with lower mortality in patients with moderate and severe ARDS[53]. The results from this meta-analysis are the basis for current recommendation to use a higher PEEP-level in these groups of patients[49].

Lung protective ventilation in patients without ARDS

The concept of lung-protective ventilation with lower tidal volumes has evolved from research in patients with ARDS based on experimental studies on animals, but it has also been evaluated in other groups of patients. The use of low tidal volumes in patients without ARDS has been shown to prevent development of ARDS [54-56]. Conclusions in these studies are supported by a meta-analysis of 20 studies on patients without ARDS showing a benefit from lung protective ventilation with lower tidal volumes[57]. In contrast, a recent trial comparing tidal volumes of 4-6 ml/kg IBW to 8-10 ml/kg IBW in patients in the ICU without ARDS did not show any differences in ventilator-free days, ICU-stay or 28 day mortality[58]. Every year a large number of patients are subject to mechanical ven-

tilation outside the ICU during general anaesthesia. According to a 16-year old systematic review the incidence of postoperative pulmonary complications varied from 2-19% depending on the definition of complications and type of surgery[59] but a much higher incidence was noted after cardiac and thoracic surgery in a later study[60]. Several attempts, including a Cochrane analysis, have been made to evaluate the effect of low tidal volume ventilation perioperatively[61-65]. Results are not homogenous, which in part might be explained by differences in the use of PEEP in the included studies, but strongly indicates that low tidal volume ventilation perioperatively has a positive effect on postoperative pulmonary complications. As in patients with ARDS the optimal PEEP-level during general anaesthesia has been hard to define[66, 67]. When lung protective ventilation was evaluated in potential organ donors the use of lower tidal volumes increased the numbers of eligible and harvested lungs[68].

Lung and chest wall mechanics

The components of the respiratory system

Lung protective ventilation as described above involves restricting airway plateau pressures and airway driving pressures. One limitation of using airway pressures when aiming at lung protective ventilation is that they not only distend the lung but act on the whole respiratory system. The lungs constitute only one part of the respiratory system, which also includes the chest wall complex comprising both the thoracic wall and the diaphragm in contact with the abdominal content. The term "chest wall" in this thesis refers to the chest wall complex including the diaphragm connected to the abdominal content if not otherwise stated. The chest wall and the lungs are mechanically connected in series and the pressure difference between the airway and body surface is the sum of the pressure over the lung and the pressure over the chest wall[69]. With the development of esophageal pressure measurements mainly during the 1950s, see below, it became possible to separately determine the contribution to total respiratory system compliance from the lung and chest wall in mechanically ventilated patients[70, 71]. These studies focused mainly on how lung and chest wall compliance were affected by anaesthesia, different levels of PEEP and different sizes of tidal volumes. Later there was an increasing interest in characterising patients due to differences in properties of the lung and chest wall. When studying respiratory system mechanics in patients requiring mechanical ventilation for acute respiratory failure, Katz et al stated that "patients did vary as to the proportions of pulmonary and chest wall contributions"[72]. They also argued for the use of elastance instead of compliance when evaluating lung and chest wall mechanics, which today is routine in most studies within this field of research.

Elastance vs. Compliance

Elastance, which is the inverse of compliance (=1/Compliance), of the respiratory system (ERS) is equal to the sum of elastance of the lung (EL) and elastance of the chest wall (ECW). ERS = EL + ECW.

Using compliance (CRS, CL, CCW) instead complicates calculations since 1/CRS = 1/CL + 1/CCW.

In this thesis elastance will be preferably used when mechanics of the respiratory system, lung and chest wall are described.

Lung and chest wall elastance and transpulmonary pressure

Among patients in the study by Katz et al, the contribution of lung elastance to total respiratory system elastance ranged from 55-78%. Within these patients it was possible to identify two groups with different mechanical characteristics. Three patients treated for respiratory failure after "abdominal aortic aneurysmectomy" were noted to have a much larger contribution from the chest wall compared to patients with pulmonary contusions. When the same airway driving pressure is applied in patients with similar respiratory system elastance (ERS) their lungs will suffer different levels of barotrauma depending on the mechanical properties of the lung and chest wall. This was clearly stated by Jardin et al who found that increased lung stiffness decreased the corresponding change in pleural pressure when airway pressure was increased[73]. The described variations in lung and chest wall mechanics between patients highlights the limitations of using airway pressure as a guide for lung protective ventilation. The actual pressure distending the lung for a given airway pressure, the transpulmonary pressure, can vary depending on the ratio between elastance of the lung and elastance of the respiratory system (EL/ERS), **Fig 1**. The need for evaluation of lung and chest wall mechanics was further emphasized when Gattinoni et al published the well-known milestone description of pulmonary and extrapulmonary ARDS in 1998[74] . They not only identified the differences in lung and chest wall mechan-

ics between patients with ARDS of pulmonary or extrapulmonary origin but also noted that an increase of PEEP had different effects on respiratory system elastance in these two groups. In several other non-ARDS scenarios such as pneumoperitoneum during laparoscopic surgery[75] and obesity[76] the E_L/E_{RS}-ratio is affected. However there can be large differences in E_L/E_{RS} ratio in mechanically ventilated patients without ARDS[77] or other lung pathology (II), which makes it difficult to distinguish the distending pressure of the lung from the airway pressure. The ratio, which tells us how much of the airway driving pressure is propagated to the lungs, ranged from 0.5-0.95 in our study of patients with healthy lungs (II), 0.33-0.92 in patients with ARDS and 0.36-0.95 in a group of mixed surgical and medical ICU patients without ARDS in the study by Chiumello[77]. If we recall some of the experimental studies on animals, mentioned in the section about VILI, there was a relation between the transpulmonary pressure, the difference between airway pressure and pleural pressure, and ventilator-induced lung injury. When strapping of the chest wall was performed to increase the airway pressure [8, 9] chest wall elastance was increased and a low E_L/E_{RS} ratio was achieved. Despite high airway pressures the transpulmonary pressure remained low and the lungs were ventilated with both low tidal volumes and low transpulmonary pressures and no pulmonary oedema developed. The initial interpretation of those studies was that volume rather than pressure was dangerous. But drawing these conclusions from the airway pressure could be misleading since it is a poor surrogate for the pressure over the lung.

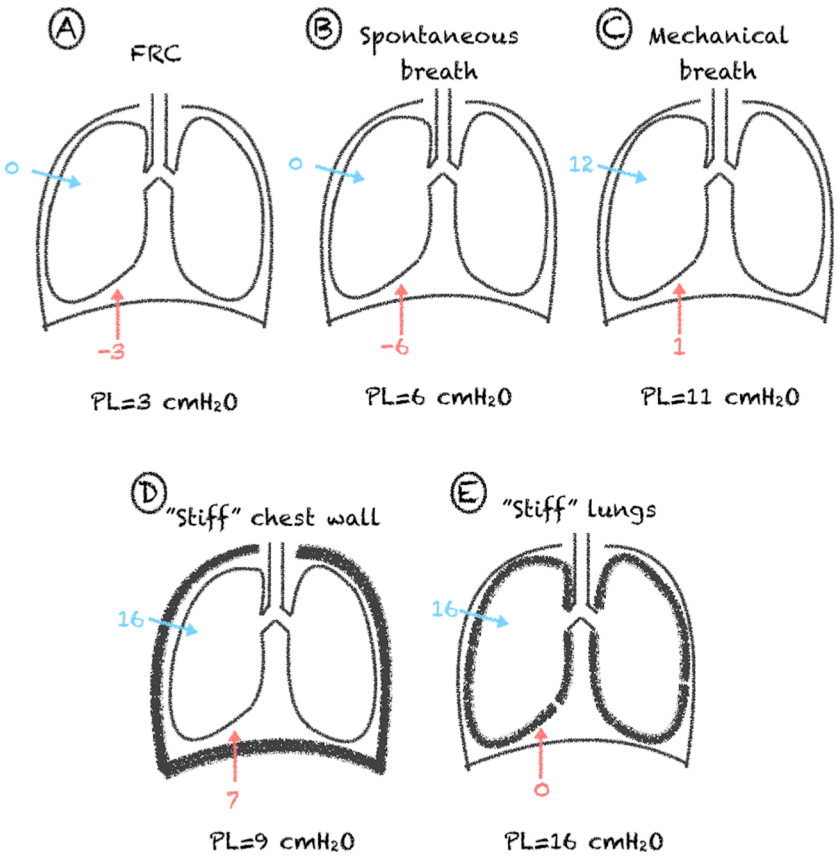


Fig 1 A: Pressure in the lung and pleura at functional residual capacity (FRC). The negative pleural pressure causes the transpulmonary pressure(P_L) to be positive at end-expiration. (P_L=3 cmH_2O) **B:** The pressure in the lung and pleura at end-inspiration in spontaneously breathing patient. (P_L= 6 cmH_2O) **C:** Pressure in lung and pleura at end-inspiration in mechanically ventilated patient with normal chest wall. (Tidal volume ≈ 500 ml and P_L=11 cmH_2O) **D:** Pressure in lung and pleura at end-inspiration in mechanically ventilated patient with a "stiff" chest wall (Tidal volume ≈ 500 ml and P_L=9 cmH_2O) **E:** Pressure in lung and pleura at end-inspiration in mechanically ventilated patient with "stiff" lungs (Tidal volume ≈ 500 ml and P_L=16 cmH_2O)

Stress, strain and mechanical power

To better understand the influence of pressure and volume in the development of VILI two terms borrowed from bioengineering are used, *stress* and *strain*[77-79]. Within lung mechanics, stress is the pressure distending the lung, the transpulmonary pressure, and strain is the associated deformation defined as the change in volume (ΔV) related to volume at start, the functional residual capacity (ΔV/FRC). In these studies[77-79] they showed that plateau pressure and tidal volume calculated according to ideal body weight were inadequate surrogates for stress and strain because of variation in FRC and chest wall properties. Using similar tidal volumes, the strain was higher in patients with ARDS compared to postoperative surgical patients and medical ICU patients due to a lower FRC. The stress varied among patients with ARDS because of differences in EL/ERS ratio. Measurements in animals suggest that the relation between stress and strain and ventilator induced lung injury is a threshold phenomenon[80]. When a certain limit (still poorly defined in humans) is reached, lung injury develops. However there also seems to be a difference in how a certain limit of strain is reached. Dynamic strain (tidal ventilation) appears more damaging to the lungs than static strain (inflation with PEEP)[81]. When using the concept of stress and strain, the applied pressures and volumes during mechanical ventilation are individualized according to properties of the patient's lung and chest wall. In 2016 Gattinoni et al argued that it was not only stress and strain that were important determinants of ventilator induced lung injury, but also the respiratory rate and airflow[82]. Instead of focusing on a single parameter such as tidal volume or transpulmonary pressure, the total energy load delivered to the lung during a time unit need to be taken into account. In an attempt to summarize the different factors into one formula the concept of mechanical power was introduced, which also included airflow and respiratory rate into the calculations. A central part in the discussion regarding energy delivered to the lung is the transpulmonary pressure. This is sometimes defined as the pressure difference between the alveoli and the pleura, but generally as the difference between airway pressure and pleural pressure[83]. The latter definition is used in this thesis and it requires estimation of pleural pressure.

Pleural pressure

The pleural space is very thin, 5-35 micrometers[84] and contains small amounts of fluid (≈0,3 ml/kg)[85, 86]. Measurement of the pleural pressure is difficult. As described in textbooks, the pleura is affected by two forces acting in the opposing directions: the recoiling force of the lung and the expanding force of the chest wall. When these forces are in balance we obtain the functional residual capacity[87]. The extent of these opposing forces is determined by the resting volume of the chest wall and lung. The resting volume is the volume the chest wall and the lung are striving against. The resting volume of the thorax and lungs were described as early as 1946 by Rahn et al, who showed that the chest wall tends to expand until it reaches it's resting volume of approximately 75-80% of the total lung capacity and the lung recoils until it collapses at a volume below residual volume[88]. Below its resting volume, the chest wall strives outwards and the opposing forces acting on the parietal and visceral pleura create a negative pleural pressure (see below). The pleural pressure is a regional phenomenon with a normal vertical gradient of 0,2-0,9 cmH_2O/cm (depending on measurement technique), with an increasing pressure down the vertical axis. Within the pleura, two different types of pressures exist with different vertical gradients, the more subatmospheric pleural liquid pressure and the pleural surface pressure[89]. The higher gradient measured with fluid-filled catheters and needles introduced into the pleura without air in the pleural space refer to the pleura liquid pressure, [90] which is thought to be related to the small amounts of fluid within the pleura and involved in the circulation of that fluid. Pleural surface pressure on the other hand, is related to the mechanical forces from the lung and chest wall acting on the pleura. Henceforth the term "pleural pressure" refers to pleural surface pressure.

Measurement of pleural pressure

Several different techniques with their different advantages and disadvantages have historically been used for estimations of pleural pressure. For estimation of the mean overall pleural pressure, measurements of the pressure inside a large pneumothorax[91, 92] have been used since the air surrounding the lung diminishes the vertical gradient. Compensation has to be made for the change in lung volume since it affects the lung recoil. An alternative method, introduced by Carson in 1820[93], is to measure the mean pleural pressure by letting air into the pleural space through an opening of the chest wall while measuring the recoil pressure of the lung against a closed airway, a method used in our study on pigs (IV). With this method there is a risk of overestimation of the recoiling pressure due to the gravitational forces acting on the lungs after the visceral pleura is separated from parietal pleura. The regional pleural pressure may be directly measured by pressure measurement inside a small pneumothorax, obtained by introduction of a small quantity of air[92, 94]or through surgically implanted pleural balloons[95, 96]. Pleura pressures at end-expiration measured in large pneumothorax [91, 97-99], in small pneumothorax [100] and pleural balloons (in dogs)[95] show sub-atmospheric values ranging from 0 to -10 cmH_2O. Gillespie et al on the other hand found positive pleural pressures in mid-lung region in dogs[101] and in two studies both positive and negative pleural pressures were seen dependent on where the pressure was measured[96, 102].

A common problem for many of the techniques for direct measurement of the pleural pressure, is that the measurement procedure affects pleural mechanics. Techniques with minimal distortion of the pleural space have been developed but mainly measure the pleural liquid pressure. With all the direct measurement techniques the risk of pneumothorax associated with puncture of the pleura remains. Instead, an indirect method for estimation of the regional pleural pressure by esophageal pressure measurements is the only technique currently used in humans.

Esophageal pressures – in research and in the clinic

Historical perspective

Esophageal pressure measurements were introduced 140 years ago[103] but became more widely used in calculations of respiratory mechanics in the 1950s after the work of Buytendijk[104] and the introduction of the balloon catheter. Due to the difficulties and risk of complications associated with pleural pressure measurements many studies were performed in order to develop the technique for indirect pressure measurements. Several researchers have compared esophageal and direct pleural pressure measurements [70, 91, 98, 100, 105-108]. The agreement between pleural and esophageal pressure in these studies varied between patients and also depending on where pleural pressure was measured as it is affected by gravity (see above). Pressure variations during breathing on the other hand were quite similar in the esophagus and the pleural space. Most measurements were performed in spontaneously breathing patients. After these "validation studies" esophageal pressure replaced directly measured pleural pressure in calculations of respiratory mechanics. As the knowledge regarding esophageal pressure measurement increased, several factors influencing the pressures became obvious such as patient positioning[109-111], balloon position in the esophagus[111-113], size of the balloon[111, 114], filling volume of the balloon[114-116] and cardiac artefacts[109, 117-119]. Factors influencing esophageal pressures will be discussed in more detail below. In an attempt to optimize pressure recordings, the lower two thirds of the esophagus was suggested as optimal balloon position, 5-10 cm as optimal balloon length and small volumes of air inside as optimal filling volume[116], **Fig 2**. Despite attempts to optimize measurement techniques there were still uncertainties regarding the relation between absolute esophageal pressure and absolute pleural pressure[111].

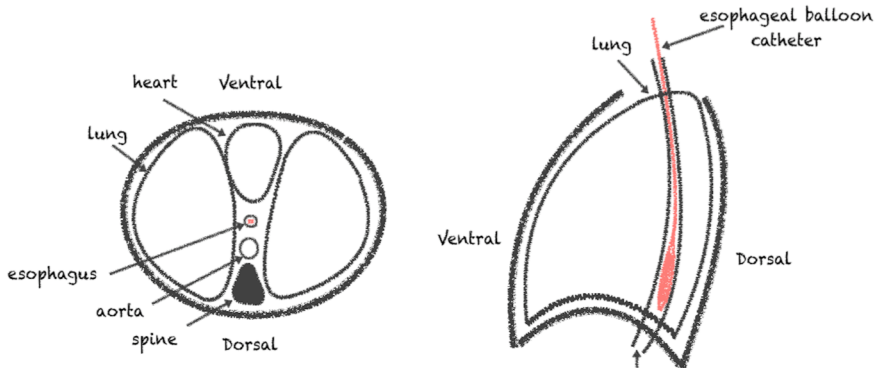


Figure 2 Esophageal balloon catheter in esophagus. **Left panel**: Transversal plane. Note the close proximity between the esophagus and the heart. **Right panel:** Mid-sagittal plane with the esophageal balloon in the lower third of the esophagus

Esophageal pressure and mechanical ventilation

Under general anaesthesia it was noted that respiratory system mechanics changed with a decrease in FRC and compliance. By introducing esophageal pressure measurements in anesthetized patients it became possible to separately determine the effect of general anaesthesia on the lung and chest wall[70, 119-124]. Esophageal pressures measured in supine, anesthetized and paralyzed patients were often positive and generally higher than in sitting patients[122, 123]. With the availability of esophageal pressures the separate pressure-volume curves for the lung and chest wall was determined, as previously done without esophageal pressures by Rahn et al[88]. When measuring esophageal pressure, the chest wall resting volume, which is the volume at which the chest wall changes from being an expanding force on the lung to compressing the lung, was lower in awake patients in sitting position[110] and even lower in anesthetized and paralysed patients[121]. In the last reference, the authors suggested that the right shift of the chest wall pressure-volume curve might be due to inaccurately elevated esophageal pressure caused by the supine position of the patient.
An occlusion test, which had been described for spontaneously breathing patients, [117] was further developed for use during muscle paralysis[125]. The last reference is an animal experiment and describes the positive pressure occlusion

test, which was adopted and used in humans but evaluated systematically much later[126]. The method consists of a compression of the chest wall during an end-expiratory pause while determining the ratio between the pressure change in the airway and the esophagus. A ratio close to one suggests that the measured changes in pressure inside the balloon are an acceptable substitute for changes in pleural pressures.
Even if the interest for esophageal pressures somewhat declined for a few decades, the measurements were used for research purposes in lung and chest wall mechanics as described, and gradually introduced in the management of critically ill patients[72, 73, 127].

Esophageal pressure in acute respiratory failure

In 1995 Pelosi published a study where they showed that ARDS affects both the lung and the chest wall[128]. Chest wall and lung mechanics were separated using esophageal pressure measurements. Further studies confirmed the findings and discovered that patients with ARDS could be divided in groups according to the mechanical properties of their lung and chest wall, which in turn was associated with the cause initiating ARDS [74, 129]. Groups of patients with different lung and chest wall mechanics also responded differently to increase of PEEP[74] and prone positioning[130]. These studies underline the value of separate measurement of lung and chest wall mechanics in patients with respiratory failure and since esophageal pressure measurements were the only clinically available method it gained an increased interest. Still there were discussions about the usefulness of esophageal pressure measurements due to the uncertainty concerning how well it reflected pleural pressure in acutely ill patients[131]. In the studies previously mentioned, esophageal pressure was used in different ways. Gattinoni et al[74] and Ranieri et al[129] used esophageal pressure variations to avoid the uncertainties associated with absolute values in supine position, while Pelosi et al[128] used the absolute pressure. In 2006 Talmor et al further evaluated the absolute esophageal pressures in patients with acute respiratory failure[132]. In a group of 70 patients

the mean end-expiratory esophageal pressure was ≈17 cmH_2O but in some patients end-expiratory esophageal pressures exceeded 30 cmH_2O. End-expiratory esophageal pressures were used as surrogates for pleural pressure in calculation of transpulmonary pressure (the difference between airway and pleural pressure) resulting in low and even negative transpulmonary pressures at end-expiration. An important detail in the study by Talmor et al is that end-expiratory esophageal pressure was corrected for supine position and a higher balloon volume by subtracting 5 cmH_2O. This correction was based on a study of 10 healthy subjects where the calculated increase in esophageal pressure caused by changing to supine position was ≈3 cmH_2O (range 0-7 cmH_2O)[133]. Two years later Talmor et al published a study in New England Journal of Medicine where PEEP set to achieve an end-expiratory transpulmonary pressure of 0-10 cmH_2O (depended on FiO_2) improved oxygenation in patients with ARDS compared to PEEP set directly according to FiO_2[134]. Transpulmonary pressure was calculated as the difference between airway and esophageal pressures. This study has influenced the discussion of esophageal pressure for the last 10 years. An interesting detail is that end-expiratory esophageal pressure was not corrected for supine position as in the previous study, which lead to the esophageal pressure-guided patient group receiving a mean PEEP of 17 cmH_2O compared to 10 cmH_2O in the control group. If esophageal pressure had been corrected as in the previous study, the difference in PEEP between groups would have decreased to 2 cmH_2O. In 2012 during the H1N1 influenza epidemic, esophageal pressure was used to evaluate lung and chest wall mechanics in patients who fulfilled the criteria for extracorporeal oxygenation (ECMO). By identifying patients with low transpulmonary pressures despite high airway pressures, ECMO was avoided by optimizing ventilator setting based on transpulmonary pressures[135]. These studies by Talmor and Grasso indicated that ventilator settings based on transpulmonary pressures further contributed to lung protective ventilation.

Still, there was a lack of consensus regarding the interpretation of absolute esophageal pressures. Talmor and colleagues argued for the use of the absolute end-expiratory esophageal pressure while others argued that these are not reliable as estimates of the pleural pressure[136]. In order to avoid the uncertainties with absolute pressure in supine patients, the transpulmonary pressure could instead be estimated from lung elastance calculated based on tidal variations in esophageal pressure[77, 137-139]. Calculations by this method had been used as the basis for

ventilator settings in a pig study with promising results[140]. Both methods calculate transpulmonary pressure and lung and chest wall elastance, but if applied in the same patients the results are often incompatible[141] and thus the debate concerning interpretation of esophageal pressure continues[142-144]. (For description of calculations se below) In 2018 Yoshida et al presented a study comparing transpulmonary pressure calculated by the two methods with transpulmonary pressure derived from pleural pressure measured with wafers (flat balloons) inserted in different parts of the pleura[96]. Results from measurements in pigs with induced lung injury and three human cadavers indicated that calculation from absolute esophageal pressure corresponded to transpulmonary pressure in the mid/dorsal-lung region while calculations from tidal changes in esophageal pressure (elastance-derived method) corresponded to transpulmonary pressure in the ventral part of the lung.

***Calculations from absolute esophageal pressure**:*

End-expiratory transpulmonary pressure = End-expiratory airway pressure (PEEP) – End-expiratory esophageal pressure (PES_{EE})

End-inspiratory transpulmonary pressure = Airway plateau pressure – End-inspiratory esophageal pressure (PES_{EI})

Calculations using tidal changes in esophageal pressure (elastance-derived method):

Respiratory system elastance = (Airway plateau pressure – PEEP)/Tidal volume (=ΔPAW/VT)

Chest wall elastance = Tidal variation in esophageal pressure (ΔPES) / Tidal volume (=ΔPES/VT)

Lung elastance = (ΔPAW- ΔPES) / Tidal volume

Transpulmonary pressure at end-expiration = PEEP x (EL/ERS)

Transpulmonary pressure at end-inspiration = Airway plateau pressure x (EL/ERS)

Lung and chest wall properties during mechanical ventilation

Is the study by Yoshida et al the "landmark physiological study", as described in an editorial by Grasso[145], that finally ends the debate and validates esophageal pressure for calculation of transpulmonary pressure? Quite a few uncertainties still remain to be addressed and the main question concerns basic lung and chest wall mechanics during mechanical ventilation. Based on centuries of research in respiratory mechanics, textbooks describe the respiratory system as a recoiling lung inside an expanding chest wall[69, 146, 147]. The interaction between the lung and the chest wall creates a negative pleural pressure at functional residual capacity, which has been confirmed by previously mentioned measurements of pleural pressures in patients. Still, end-expiratory esophageal pressure is often positive not only in patients with ARDS but also in lung healthy mechanically ventilated patients at end-expiration. If end-expiratory esophageal pressure is a valid substitute for pleural pressure, the transpulmonary pressure becomes negative at zero PEEP. According to Loring et al there is nothing that prevents the relaxed chest wall from applying a positive pressure on the outside of the lung[144]. Is a higher pressure on the outside of the lung compared to the inside (= negative transpulmonary pressure) compatible with an open lung? In previous publications from our research group, a non-invasive method for determination of transpulmonary pressure had been introduced, the PEEP-step method[148, 149]. The basis for this method is an expanding chest wall that keeps the pleural pressure negative at end-expiration also at high lung volumes.

This discussion reveals opposing views on the role of the chest wall and how it interacts with the lung. When aiming at optimal ventilator settings and lung protective ventilation, an understanding of lung and chest wall mechanics is fundamental. An in-depth knowledge of "Lung and chest wall properties during mechanical ventilation" is of interest not only for researchers within the field, but also for clinicians caring for mechanically ventilated patients.

Main aim and description of included studies

The overall aim of this thesis was to study the mechanical properties of the lung and chest wall during mechanical ventilation and to evaluate the methods, PEEP-step method and conventional method with esophageal pressure measurements, used to determine these properties.

The included studies in this thesis are referenced by roman numerals I-IV.

I. Evaluation of the physiology behind the PEEP-step method in a mechanical model of the respiratory system including a recoiling lung and an expanding chest wall connected to an abdomen with high plasticity
II. Evaluation of lung and chest wall mechanics during a PEEP-induced inflation and comparison of transpulmonary driving pressures measured with the PEEP-step method and the conventional method using esophageal pressures. Measurements performed in patients under general anaesthesia
III. Evaluation of factors influencing esophageal pressure in mechanically ventilated patients in the ICU and operating room as well as in awake spontaneously breathing patients. Measurements performed with an advanced High Resolution Manometry catheter and a regular balloon catheter.
IV. Evaluation of the role of the chest wall during mechanical ventilation with a focus on differences in end-expiratory and tidal chest wall elastance. Measurements performed on pigs.

Main areas in the thesis

Results from studies I-IV will not be discussed in order but instead included in a broader discussion concerning three main areas:

1. Esophageal pressure
2. The physiology of a PEEP-step
3. The chest wall during mechanical ventilation

The final sections include a condensed description of the respiratory system from a mechanical model followed by clinical implications and future perspectives. Methodological considerations and included studies with supplemental material are found in “Appendix”.

Esophageal pressure

Aim

To determine what factors influence measured esophageal pressures and explore the role of esophageal pressures in determination of lung and chest wall properties

End-expiratory esophageal pressure

End-expiratory esophageal pressure and the chest wall

In the early studies of esophageal pressure measurements during mechanical ventilation the pressure was often within 3-6 cmH_2O[122, 123]. In more recent studies the mean end-expiratory esophageal pressure often ranges from 10-13 cmH_2O [126, 137, 150-152](patients both with and without ARDS) but in the two studies by Talmor it was higher, ≈17 cmH_2O[132, 134]. Similar mean levels were seen at zero PEEP in our lung healthy patients during general anaesthesia, 11.2 cmH_2O (suppl. material in II) and in patients in the ICU with respiratory failure, 11.3 cmH_2O (III, measured with High Resolution Manometry, se below). In most studies the levels of end-expiratory esophageal pressure is fairly similar despite being measured in patients with ARDS as well as in lung healthy patients. An interesting finding is that the levels of end-expiratory esophageal pressure are not correlated to chest wall elastance measured during tidal ventilation[132, 137, 153].

The level of end-expiratory esophageal pressure is also not affected by increased chest wall elastance through elevated abdominal pressure from pneumoperitoneum during laparoscopic surgery[154] and there is no clear correlation with gastric pressure[132, 137]. In obesity, mean end-expiratory esophageal pressure may be increased[152] but there is little or no correlation between BMI and end-expiratory esophageal pressure[137, 155]. From these studies we may conclude that end-expiratory esophageal pressure does not seem to provide reliable information concerning the properties of the chest wall. When end-expiratory esophageal pressure is used as basis for PEEP-selection, the lack of correlation with chest wall elastance means that "appropriate PEEP-level" is set without regard to chest wall properties. This is in contrast to the findings that the effect of PEEP varies due to chest wall properties in patients with ARDS[74].

Factors influencing end-expiratory esophageal pressure

Even if changes in chest wall elastance do not affect end-expiratory esophageal pressure there are many other factors influencing the pressure. Two important factors, which have to do with the measurement technique when using a balloon catheter, are the position and the filling volume of the balloon. Mojoli et al has published studies looking at optimal volume of the esophageal balloon and found that a higher volume of air inside the balloon increases end-expiratory esophageal pressure[156]. They also concluded that the optimal volume inside the balloon, determined from tidal changes in esophageal pressure, was different for each patient and has to be titrated in order to obtain correct measurements. When using a short balloon to compare the pressure in different parts of the esophagus the results are conflicting regarding variation in pressure along the esophagus[111, 114]. With High Resolution Manometry (HRM) (III) the esophageal pressure is measured separately at each centimetre along the length of esophagus and no balloon is involved, **Fig 3**.

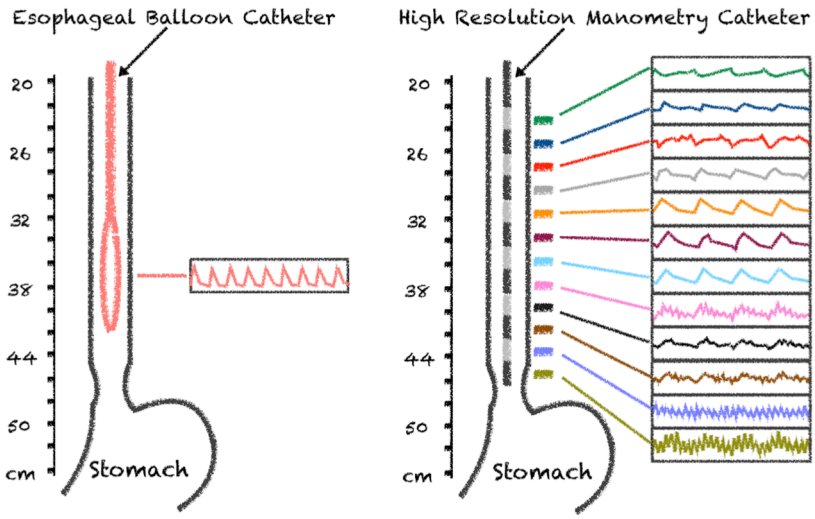


Figure 3 Left panel: Measurements with an esophageal balloon catheter, normally placed in the part of the esophagus between 30-42 cm from the nostril. A single pressure is measured. Curve next to the esophagus show typical esophageal swings during tidal inflations. **Right panel:** Esophageal pressure measured with an advanced High-Resolution Manometry catheter. Pressures are measured at 36 different levels 1 cm apart with 12 circumferential pressure sensors at each level, altogether 432 pressure sensors. In the software it is possible to analyse 12 levels at the same time. If including every second level, 22 cm of esophagus is included in analysis (III). Curves next to the esophagus shows tidal changes in esophageal pressure at 12 different levels 2 cm apart. At the lowest levels cardiac artefacts are clearly visible. Distance shown on the left in each panel represents centimetres from nostril.

Study III shows that the end-expiratory esophageal pressure varies substantially along the esophagus, **Fig 4** (Fig 1 and Suppl. Fig 2 in III). Within the area where the balloon is normally located the mean difference between the highest and lowest pressure was ≈13 cmH_20. When PEEP is increased the end-expiratory lung volume and the end-expiratory esophageal pressure increases [126] (II) but the change in end-expiratory esophageal pressure varies substantially along the esophagus (Suppl. figure in III). In some patients the end-expiratory esophageal pressure decreases in some parts of the esophagus and increases in other parts when PEEP is changed (Fig 2 in III). The pressure measured with the balloon catheter only reflects a mean of several sometimes very different pressures and the variation in pressures are not revealed.

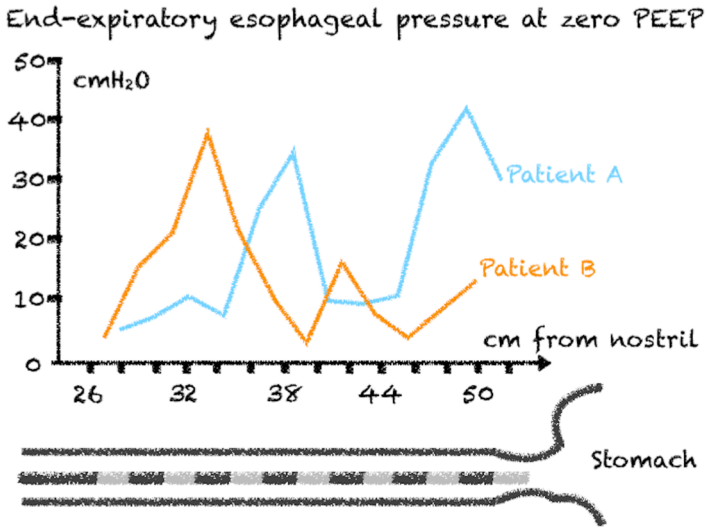


Figure 4 End-expiratory esophageal pressure measured with High Resolution Manometry catheter in two representative patients. Large variations in pressure are seen along the esophagus (III).

One reason for the large variation in end-expiratory esophageal pressure is revealed in the measurements in spontaneously breathing patients with the HRM-catheter (III). In supine position, the esophageal pressure is significantly higher than in sitting position, which has been known since the 1950s [109, 111] (mean difference =12.3 cmH_2O), **Fig 5** (Fig 4 in III). The variation in esophageal pressure also increases in supine position as do visible cardiac artefacts (Suppl. figure 9 in III), previously described by Baydur et al[118]. The larger variation in end-expiratory esophageal pressure and more pronounced cardiac artefacts in supine position suggest that the increase in pressure is in part due to compression of the esophagus from the heart and possibly also from the great vessels (aortic arch). The decrease in esophageal pressure after an increase of PEEP is mainly seen in areas with large cardiac artefacts, (Suppl. figure 6 in III) which further suggest a significant effect on esophageal pressure from the cardiovascular system.

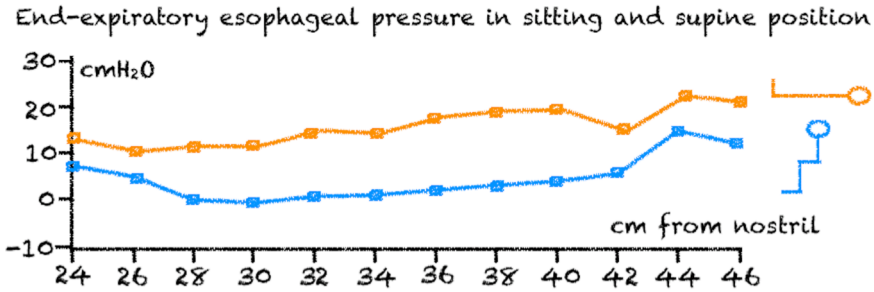


Figure 5 End-expiratory esophageal pressure measured with High Resolution Manometry catheter in awake spontaneously breathing patients in sitting and supine positions. Curves represent mean pressure from 17 patients (III)

Transpulmonary pressure and end-expiratory esophageal pressure

In a correspondence regarding esophageal pressure and pleural pressure it is stated that airway pressure "often must be raised until it exceeds esophageal pressure (PES) before air begins to inflate the lungs"[144] with reference to a study by Behazin et al[155]. In this study the airway pressure, when air begins to inflate the lungs, was seen as an indirect measure of the lowest pleural pressure surrounding the lung since a positive transpulmonary pressure (higher pressure in the airways compared to in the pleura surrounding the lungs) is needed in order to inflate the lung. If the pleural pressure was sub-atmospheric at FRC then air would inflate the lungs as soon as the airway pressure exceeds zero, since the transpulmonary pressure is positive. In the study a cut off of 1,3 cmH_2O was used in order to compensate for pulmonary resistance. In all of the patients with normal BMI the airflow begun at an airway pressure <1 cmH2O despite a end-expiratory esophageal pressure ranging from 0.7-12.2 cmH2O (mean 6.9 cmH2O). In the group with obese patients, the airway pressure needed to start inflation of the lung ranged from 0.6-14 cmH_2O while esophageal pressure was between 3.0-25.7 cmH_2O (mean 12.5 cmH_2O). There was no correlation between airway pressure at start of inflation and esophageal pressure at end-expiration (r^2=0.16). But since esophageal pressure measurements is an indirect method for regional pleural pressure as described previously, the lack of correlation could be due to dif-

ferences in the vertical pleural pressure gradient within the patients. The vertical gradient may cause the transpulmonary pressure to be positive in ventral areas while negative in dorsal areas. When similar measurements were conducted in pigs (IV) inflation of the lungs begun as soon as airway pressure exceeded zero (<0.2 cmH2O in all pigs) despite an esophageal pressure of 2.0-8,6 cmH_2O. Filling volume of the balloon was kept low in order to avoid overestimation of the end-expiratory esophageal pressure. With electrical impedance tomography, which analyses distribution of inflated air using changes in impedance, inflation also started in the most dorsal region of the lung surrounding the esophagus as soon as airway pressure exceeded zero (Fig 4 in IV). This finding questions the notion of end-expiratory esophageal pressure being equal to the pleural pressure even in the dorsal regions since expansion of the lungs caused by inflation of air then occurs against a higher surrounding pressure (= negative transpulmonary pressure). These results are in contrast with the findings by Yoshida et al[96] and by Pelosi et al (in dogs)[102] who compared esophageal pressure to directly measured pleural pressure and found that end-expiratory esophageal pressure correlated with pleural pressure at the mid/dorsal part of the lung.

Esophageal pressure at increased PEEP

Increase of PEEP causes end-expiratory esophageal pressure to increase (II)[96, 126]. This is also true of average end-expiratory esophageal pressure measured with High-Resolution manometry (III). The total increase in end-expiratory esophageal and airway pressure occurs simultaneously during the first breath (Suppl. Fig. 5 in III), which suggests that the end-expiratory transpulmonary pressure is unchanged after the first breath following an increase of PEEP. Still there is a continuous increase in end-expiratory lung volume during several breaths corresponding to ≈30% of the increase in EELV despite an absence of a pressure gradient creating the flow of air.

Positive pleural and end-expiratory esophageal pressure

Instead of the chest wall compressing the lung at functional residual capacity an increased pleural pressure in the dorsal regions could be caused by an increased vertical pressure gradient due to increased lung density, for example in ARDS[157]. The heavy lung then rests on the dorsal chest wall and creates a positive pleural pressure and a negative transpulmonary pressure and possibly also the positive end-expiratory esophageal pressure. On the other hand, lung weight calculated from computer tomography is not correlated to end-expiratory esophageal pressure and neither is the amount of non-aerated lung tissue[137].

Tidal variations in esophageal pressure.

As previously described, tidal changes in esophageal pressure have been used in calculation of lung and chest wall mechanics in order to avoid the uncertainties associated with absolute esophageal pressures[77, 137, 138]. The use of tidal changes in esophageal pressure is based upon previously cited article comparing esophageal and pleural pressures[100]. Separation of total respiratory system elastance into lung and chest wall elastance is achieved by measurement of tidal changes in esophageal pressure[158]. After classification of patients with ARDS into groups based on the clinical presentation and assumed cause of ARDS, tidal changes in esophageal pressure confirmed differences in lung and chest wall properties between groups [74, 129]. Measurement of tidal changes in esophageal pressure must today be considered the gold standard for estimation of lung and chest wall mechanics.

Factors influencing tidal changes in esophageal pressure

The volume of the esophageal balloon affects not only the absolute end-expiratory esophageal pressure but also the tidal changes[156]. Increasing the volume of the balloon leads to a higher end-expiratory esophageal pressure but with tidal changes that is not always true. Mojoli et al stated that the optimal volume of air inside the balloon was the one that led to the largest tidal changes in esophageal pressure and this optimal volume ranged from 0.5-6 ml in different patients. If 4 ml was used as recommended by the manufacturer of the esophageal balloon and used in (II), the tidal changes was on average 7% smaller than at the optimal filling volume.

When tidal changes in esophageal pressure were measured with the HRM catheter, large variations within individual patients were revealed (III), **Fig 6**. The mean difference between the highest and lowest value in the area where the balloon is normally positioned was 5.5 cmH_2O. This variation is concealed when measurements are performed with balloon catheters. In > 50% of the patients in (III) both negative and positive tidal changes in esophageal pressure were seen simultaneously in different part of the esophagus. The negative tidal changes in esophageal pressure (=decrease in esophageal pressure when intrathoracic pressure and lung volume is increased by a tidal inflation) appeared mostly in areas with obvious cardiac artefacts (Fig 2 in III). This indicates an influence from the cardiovascular system on tidal variations in esophageal pressure. The balloon on the catheters used for esophageal pressure measurements in (II, III and IV) is 10 cm long and is consequently affected by a large variation in tidal changes in pressure and provides an average of the change in esophageal pressure within the examined part of the esophagus.

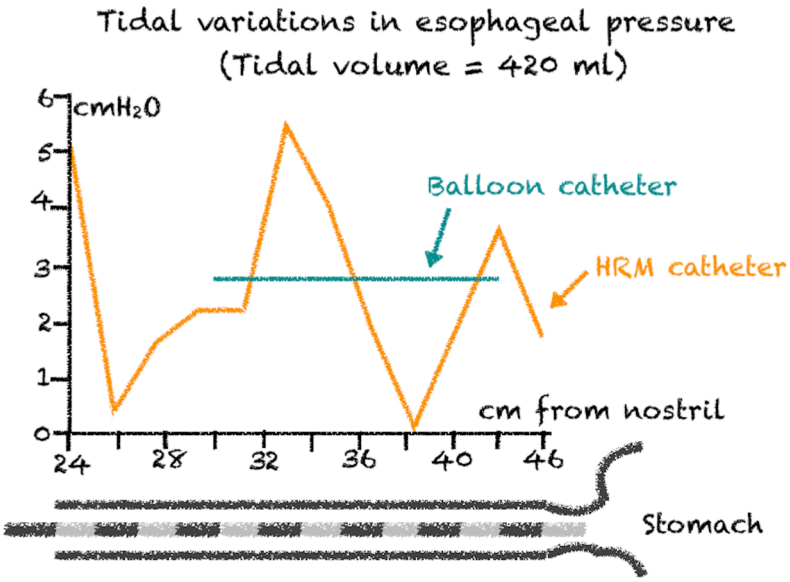


Figure 6 Tidal variations in esophageal pressure measured with a High Resolution Manometry (HRM) catheter and a conventional balloon catheter. With the HRM catheter large differences in pressure variations are seen within the esophagus. The balloon catheter, placed in esophagus between 30-42 cm from nostril, only presents a single pressure variation.

Transpulmonary pressure and tidal changes in esophageal pressure

Transpulmonary driving pressure, the pressure distending the lung during each tidal inflation, may be calculated as the difference between the tidal change in airway and esophageal pressures[158]. Based on the data from Amato et al concerning airway driving pressure and the outcome in patients with ARDS,[48] it is appealing to measure to what extent the airway driving pressure actually distends the lung (=transpulmonary driving pressure). As described earlier, tidal changes in esophageal pressure have despite all the uncertainties proven to be useful in identifying differences in lung and chest wall mechanics among patients with ARDS from different causes[74]. But due to the factors that influence tidal changes in esophageal pressure, the method will seldom accurately represent tidal changes in pleural pressure. If used as a reference when a new method for calculation

of transpulmonary driving pressure is introduced there will always be variability between measurements (II).

When the total transpulmonary pressure is calculated from tidal changes in esophageal pressure, some assumptions are made. Since only changes in esophageal and airway pressures are used in calculations it assumes the transpulmonary pressure at FRC (zero airway pressure =ZEEP) to be zero[137, 140]. In other words pleural pressure is also zero. This assumption is necessarily not true, which has been pointed out both by those who believe pleural pressure to be negative at FRC[159] and by those who consider a positive pleural pressure at FRC to be possible[144]. Calculations of transpulmonary pressure from lung elastance, the elastance-derived method (see descriptions of calculations earlier) necessitate that the change in pressure due to the total increase in volume above FRC (PEEP-induced and tidal inflation) is estimated from pressure/volume changes during tidal inflation. This assumes that the chest wall behaves similarly during an increase of PEEP, as it would during tidal inflation. When comparing changes in esophageal pressure after an equally large PEEP-induced and tidal inflation, changes are found to be smaller after a PEEP-induced inflation (IV). This indicates a difference in end-expiratory and tidal chest wall behaviour[160]. If such a difference in chest wall behaviour exists, the elastance-derived method underestimates the end-inspiratory transpulmonary pressure.

Conclusion - Esophageal pressure

With the data presented above it is difficult to look at the end-expiratory esophageal pressure as a valid substitute of absolute pleural pressure despite the findings by Yoshida and Pelosi. The end-expiratory esophageal pressure varies substantially along the esophagus, is poorly correlated to chest wall properties and is affected by several factors, which make interpretation of the measured pressure complicated. A respiratory system with an inflated lung despite a higher pressure outside compared to inside the lung instinctively contradicts basic physical laws[161]. The functionality of such a system still needs to be proven.
Tidal changes in esophageal pressure most probably estimate tidal changes in pleural pressure accurately enough to be used in evaluation of lung and chest wall mechanics. But the measured tidal changes in pressure varies within a patient and is influenced by several factors to such a degree that it cannot be seen as a precise representation of changes in pleural pressure.

The physiology of a PEEP-step

Aim

To determine how a change of PEEP affects the lung and chest wall and explore the role of the PEEP-step method in determination of lung and chest wall properties.

Positive end-expiratory pressure (PEEP)

As previously described, it has been difficult to find the optimal method for selecting PEEP in patients with ARDS. The decrease in functional residual capacity (FRC) seen in ARDS was established decades ago as was the correlation between the level of decrease in FRC and degree of shunt[162]. In order to improve oxygenation, PEEP was applied to restore FRC and decrease the venous admixture of blood from the part of the lung previously not ventilated[163]. With the increasing knowledge of ventilator induced lung injury and atelecttrauma, PEEP setting was adjusted according to the mechanical properties of the respiratory system, instead of focusing only on oxygenation. In a classic editorial in 1992 Lachmann suggested that mechanical ventilation should aim to "Open up the lung and keep the lung open"[164]. This approach, involving recruitment manoeuvres and application of PEEP to keep the recruited lung open, has shown sufficient to decrease atelectasis in morbidly obese patients during general anaesthesia[165] and decrease pulmonary complications after cardiac surgery[166]. On the other hand, in a study of patients with ARDS, an approach with recruitment manoeuvres and PEEP adjusted to the best respiratory system compliance increased mortality[167]. Several studies have evaluated PEEP set according to the

pressure volume curve of the respiratory system in comparison to PEEP set according to FiO_2[18, 41, 168]. In these studies PEEP was set higher than the lower inflection point of the pressure volume curve for the respiratory system, which often has been interpreted as the point where the applied airway pressure open up closed alveoli[169]. But the view of the lower inflection point as a measure of alveolar recruitment has been questioned, as other investigations have proposed that recruitment and derecruitment occur along the full P/V curve[170, 171]. In order to further understand the discussion about PEEP and recruitment we first need to define the term recruitment and then look closer at the PEEP-induced change in end-expiratory lung volume and its similarities and differences with tidal inflation.

Recruitment

There are several methods for determination of alveolar recruitment and also different definitions of the term "recruitment". Computer tomography is the golden standard to assess recruitment and Gattinoni et al defines the CT verified recruitment as inflation of previously non-aerated parts of the lung, which means opening of previously collapsed (non-aerated) alveoli [172]. Classification of lung tissue into non-aerated, poorly aerated and normally aerated is made radiologically from tissue density measured with Hounsfield units. In another study with computer tomography, the increase in gas volume into the poorly aerated areas was included, indicating that distension of already open but poorly aerated areas are included in the term recruitment[173]. When recruited volume was assessed from pressure volume curves at the bedside, the difference between the total and expected increase in end-expiratory lung volume after an increase of PEEP (see below) was ascribed to recruitment without knowledge about which parts of the lung had increased their gas content[174, 175]. The calculated increase in end-expiratory lung volume from pressure volume curves was thought to be due to opening of previously collapsed alveoli, but was later shown to occur almost totally in already aerated parts of the lung[176]. When the term recruitment is used in this thesis it refers to the definition by Gattinoni, opening of previously closed alveoli.

Measurement and time-course of PEEP-induced inflation

An increase in the end-expiratory airway pressure (PEEP) induces an increase in end-expiratory lung volume (EELV). In lung healthy patients undergoing general anaesthesia (II) the mean change in end-expiratory lung volume was ≈ 440 ml after PEEP was increased 5 cmH_2O but much lower changes in volumes was seen among patients in the ICU with low PaO_2/FiO_2-ratio (lowest increase in EELV was 158 ml after a PEEP-step of 4.9 cmH_2O) (III). The change in end-expiratory lung volume from functional residual capacity can be estimated with different methods as for example a disconnection of the patient from the breathing circuit while measuring the exhaled volume down to zero airway pressure[128] or repeated measurement of EELV with the nitrogen washin/washout method at different PEEP[177]. Fretschner et al introduced a method where changes in end-expiratory lung volume were calculated from changes in inspiratory and expiratory lung tidal volumes[178]. The method that was further developed and validated in a lung-model and in patients by Grivans et al[179] makes it possible to continuously monitor the increase in end-expiratory lung volume breath-by-breath after a change of PEEP. After an increase in PEEP the change in end-expiratory lung volume happens over several breaths, mean seven breaths in lung healthy patients (II). This slow increase in end-expiratory lung volume was first described by Katz et al who noticed that only 66% of the total increase in EELV occurred during the first breath after an increase of PEEP and that the remaining increase in volume happened during several breaths[180]. Studies with electrical impedance tomography (EIT) has also shown the slow time-course of the change in end-expiratory lung volume after a change in PEEP[148, 181] which earlier was ascribed to "slowly distensible compartments of the respiratory system"[178]. In the experimental study on pigs EIT monitoring identified a long time course (often more than 15 breathes) of PEEP-induced inflation after larger changes of PEEP (≈ 8 and 12 cmH_2O respectively) (IV), **Fig 7**.

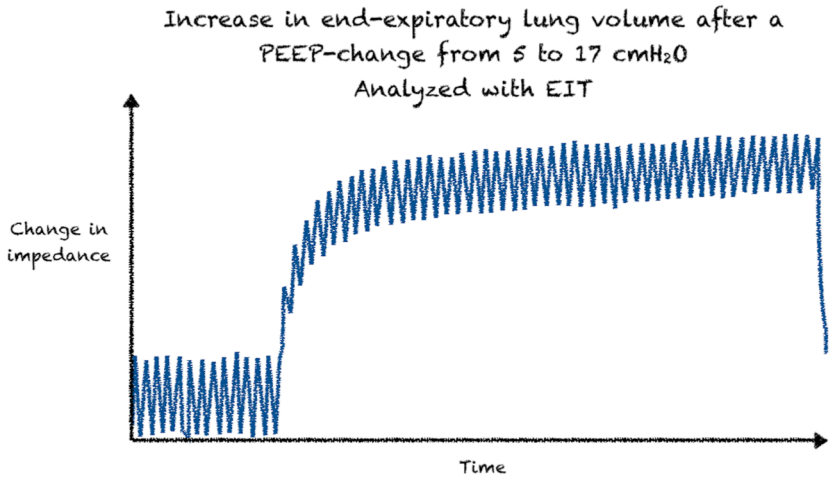


Figure 7 Increase in end-expiratory lung volume during >40 breaths in a pig after PEEP was increased from 5 to 17 cmH_2O. Increase in end-expiratory lung volume analyzed from changes in impedance using electric impedance tomography.

PEEP-induced increase in end-expiratory lung volume

The change in end-expiratory lung volume during the first breath after an increase of PEEP was similar in the lung healthy patients (68% of total change in EELV) (II) as in the study by Katz[180]. The increase in volume during the first breath followed the pressure volume curve of the respiratory system determined during tidal inflation, **Fig 8 and 9**. This means that the increase in end-expiratory lung volume after the first breath was dependent on the elastance of the respiratory system and the size of the PEEP change (Suppl. Fig 2 in II). This is logical since it can be compared to a pressure-controlled breath where the ventilator closes the expiratory valve at a new pressure level and causes a certain volume from the tidal inflation to stay within the lungs. The following slow change in end-expiratory lung volume is an "unexpected" change since it deviates from the expected, calculated from the pressure volume curve of the respiratory system. This slow increase in volume at a constant end-expiratory airway pressure (PEEP) moves the pressure/volume curve in a vertical direction (sometimes described as a left shift of the P/V curve) to a higher volume for the same

airway pressure compared to the pressure volume curve on initial PEEP-level[175, 182] (I, II), **Fig 8 and 9**. The unexpected change in end-expiratory lung volume after a change of PEEP has often been assigned to recruitment (when PEEP is increased) or derecruitment (when PEEP is decreased)[170, 171] and methods for bedside estimation of the "recruited" volume have been developed[175]. An interesting phenomenon concerning this "recruited volume" is that it is higher in lung healthy patients compared to patients with ARDS [182] and higher in patients with better compliance of the respiratory system[175]. This is opposite to corresponding findings with computer tomography, where the amount of recruitable tissue is close to zero in lung healthy patients and positively correlated to severity of disease and decrease in respiratory system compliance[172].

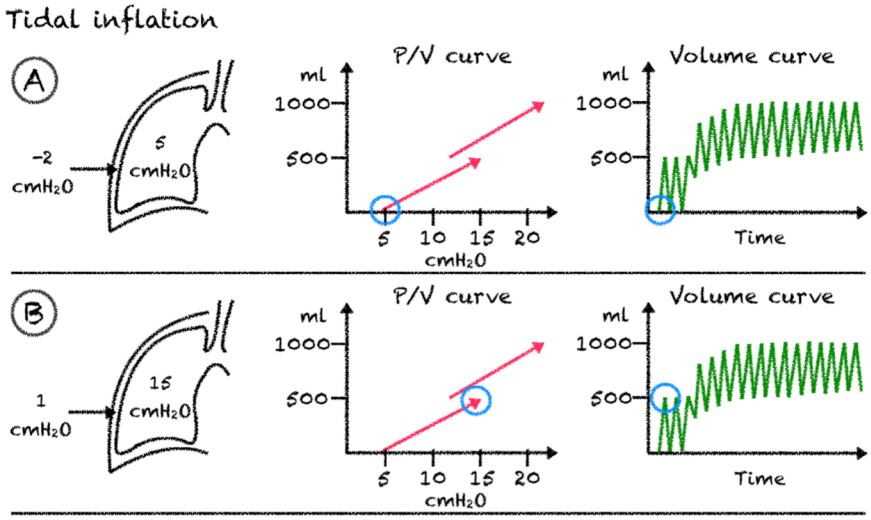
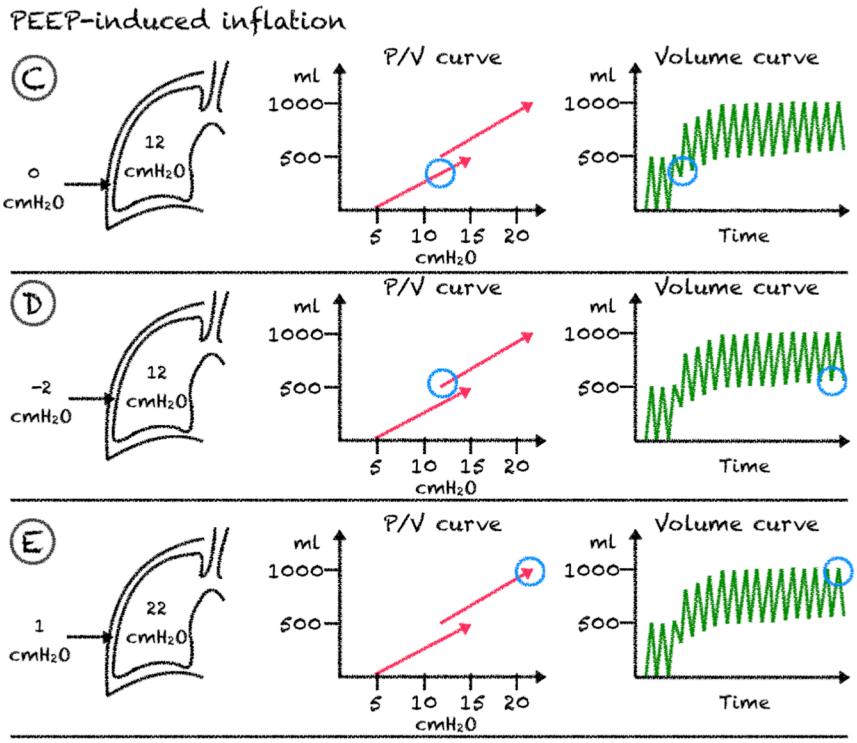


Figure 8 Tidal inflation
A: End-expiration at baseline PEEP of 5 cmH_2O. Lung volume at baseline PEEP = 0 ml in P/V curve and volume curve. Pleural pressure ≈ -2 cmH_2O and the transpulmonary pressure at end-expiration is 7 cmH_2O.
B: End-inspiration after inflation of 500 ml. Airway plateau pressure is 15 cmH_2O and pleural pressure has increased to 1 cmH_2O. Transpulmonary pressure at end-inspiration is 14 cmH_2O.



F**igure 9** PEEP-induced inflation

C: End-expiration after the first breath at the new PEEP-level =12 cmH_2O. End-expiratory lung volume has increased with 370 ml and pleural pressure has increased to 0 cmH_2O.

D: During the following breaths the chest wall complex slowly expands and the end-expiratory lung volume increases to 530 ml despite a constant end-expiratory airway pressure (=12 cmH_2O). The expanding chest wall restores the end-expiratory pleural pressure and the slow inflation of the lungs is caused by the slow increase in transpulmonary pressure.

E: End-inspiration after inflation of a tidal volume ≈500 ml starting from the new PEEP-level.

Tidal inflation and PEEP-induced inflation

When inflating an equally large volume with PEEP and tidal inflation, the mean change of PEEP is only ≈70% of the airway driving pressure (II), which means that the end-expiratory compliance is much higher than the tidal compliance as shown almost 40 years ago[180]. It has been shown that PEEP-induced inflation in patients with ARDS mainly occurs in the non-dependent region[183], which is similar to the distribution of tidal inflation in mechanically ventilated patients[184]. In ARDS, the oedema in the lung causes an increased hydrostatic pressure gradient in a vertical direction due to the weight of the lung[185]. The pressure gradient causes lung inflation to start in the non-dependant region and in order in inflate more dorsal lung regions this "superimposed hydrostatic pressure" needs to be overcome by the airway pressure. When tidal inflation and PEEP-induced inflation were analysed with electric impedance tomography in pigs, the distribution of the inflated air within the lung was almost identical (IV), **Fig 10.** The small differences seen suggested that PEEP-inflation occurred slightly more ventrally compared to tidal inflation. In 2015 Chiumello et al evaluated distribution of PEEP-induced inflation with computer tomography and concluded that the increase in end-expiratory lung volume from a change of PEEP from 5 to 15 cmH_2O almost completely appeared in already aerated parts of the lung and was proportional to the amount of well-inflated lung[176]. From these studies we can conclude that despite the fact that we inflate equally large volumes (tidal and PEEP-induced inflation) with a similar distribution within mainly non-dependant areas, the pressure required is different.

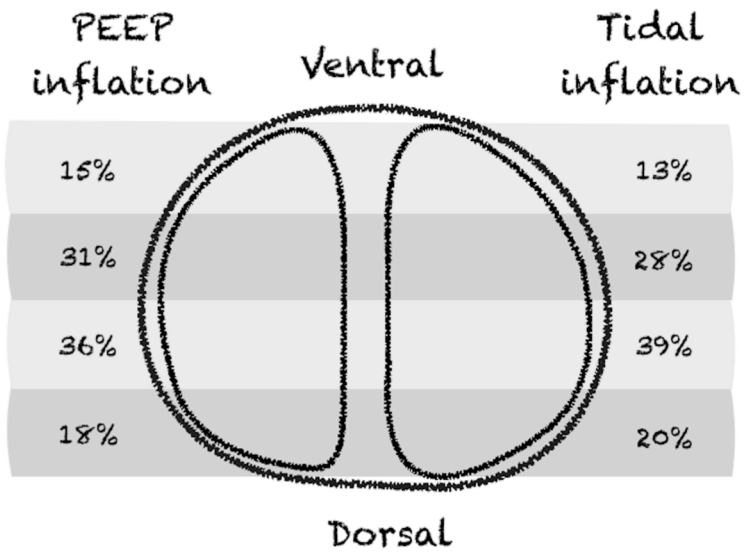


Figure 10 Distribution of air after en equally large PEEP-induced inflation and tidal inflation. Distribution analysed with electric impedance tomography in pigs. Numbers are mean values of 14 animals.

What determines the change in end-expiratory lung volume?

The change in end-expiratory lung volume during the first breath after a change of PEEP was determined by the size of the PEEP change and the elastance of the respiratory system (II). In 2012, Stenqvist et al showed that the total change in end-expiratory lung volume could be predicted by the elastance of the lung and the size of the PEEP increase[148]. This indicates that the total inflation with PEEP is not influenced by the chest wall in contrast to tidal inflation, where the airway driving pressure not only expands the lung but also pushes the chest wall complex outwards. It also means that the change in PEEP and the change in end-expiratory transpulmonary pressure are equal, which was also confirmed by Lundin et al in patients with acute respiratory failure[149]. Measurements in lung healthy patients confirmed that it was possible to predict the change in end-expiratory lung volume after a change in PEEP using lung elastance, calculated from airway and esophageal pressure changes during tidal inflation (Fig 2 in II).

Transpulmonary pressure calculated from a PEEP-step

If the total PEEP-induced increase in end-expiratory lung volume follows the pressure volume curve of the lung, the end-expiratory transpulmonary pressure increases as much as PEEP and the pleural pressure remains unchanged after a PEEP-induced inflation. In the lung healthy patients (II) and in pigs (IV), the calculated change in pleural pressure was close to zero, **Fig 11** (Suppl. Fig 4 in II and Fig 3 in IV). The change in PEEP and the change in transpulmonary pressure correlated well (Fig 3 in II). As a consequence, lung elastance may be calculated from a change in PEEP and the change in end-expiratory lung volume and used in calculations of the transpulmonary driving pressure during tidal inflation (II). Transpulmonary driving pressure calculated with the PEEP-step method correlated well with transpulmonary driving pressure determined with the conventional method (II).

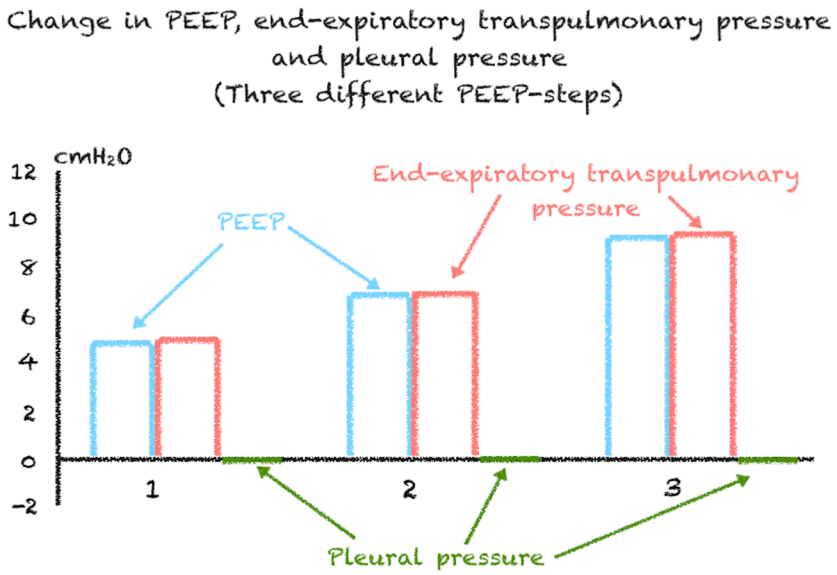


Fig 11 Comparison of the change in PEEP, the change in end-expiratory transpulmonary pressure determined from lung elastance and the calculated change in end-expiratory pleural pressure in lung healthy patients. Mean values from 24 patients. Numbers 1-3 represents three PEEP-steps of different sizes.

Conclusion - The physiology of a PEEP-step

The difference between PEEP-induced inflation and tidal inflation is well established, but often referred to as opening of previously collapsed alveoli when PEEP is increased. However PEEP-induced inflation occurs mainly in the non-dependant lung regions while collapse is seen in dependant lung regions. Regarding the results from the studies included in this thesis and from other studies referenced in the text, the view of recruitment as the primary explanation is questioned. Instead, the difference seems to be explained by chest wall mechanics, which causes PEEP-induced inflation to be dependent on the elastance of the lung while tidal inflation is dependent on elastance of the respiratory system. This means that the chest wall does not affect the total increase in end-expiratory lung volume but is off-loaded from the lung at end-expiration, see below. As a consequence it is possible to determine lung elastance and the transpulmonary pressure from a PEEP-step manoeuvre if the change in end-expiratory lung volume is calculated.

The chest wall during mechanical ventilation

Aim

To determine the role of the chest wall during mechanical ventilation and explore differences in chest wall behaviour at end-inspiration and end-expiration

The chest wall and lung inflation

It seems logical that there is a similar change in transpulmonary pressure when an equally large volume with similar distribution is inflated into the lungs regardless of inflation mode (tidal inflation or PEEP-induced inflation), **Fig 11**. According to this reasoning, the difference between the pressure needed for an equally large tidal inflation and PEEP-induced inflation is because of a difference in chest wall behaviour. The inflation of the lungs during the first breath after an increase of PEEP seems to be affected by the chest wall in a similar manner as during tidal inflation but the total PEEP-induced inflation seems unaffected by the chest wall. This indicates a difference in chest wall behaviour during tidal inflation and at end-expiration.

The chest wall at functional residual capacity

Previously the interaction between the lung and the chest wall has been described in the familiar textbooks explanation of a chest wall striving towards its high resting volume connected to a lung that recoils towards a low resting volume, with the functional residual capacity (FRC) as the volume of the lungs when these opposing forces are in balance [146, 147]. When properties of the lung and/or chest wall are altered, the FRC is affected and consequently if one of the opposing forces are lowered FRC will change towards the resting volume of the element applying the counteracting force.

In patients with Chronic Obstructive Pulmonary Disease (COPD) chronic hyperinflation, defined as increase of functional residual capacity, is common and caused by a combination of static and dynamic effects. Static hyperinflation occurs because of a decrease in lung elastic properties with a decrease in lung recoiling pressure allowing the chest wall to pull the volume equilibrium (FRC) further towards its high resting volume[186, 187]. When lung recoil is increased in these patients through lung-reduction surgery, the chest wall is pulled inwards and the lung volume decreases[188]. An opposite change in FRC is seen in patients during general anaesthesia. When the diaphragm relaxes, it is pushed in a cranial direction by the abdominal content and the ribcage is drawn inwards[189]. These factors affecting the chest wall, together with the recoiling force of the lung, move the volume equilibrium inwards and correspondingly FRC decreases. As in spontaneous breathing at rest, the expiration in mechanical ventilation is a passive process. At zero end-expiratory airway pressure, expiration ends when the recoiling force of the lung is balanced by the expanding chest wall. In pigs (IV) at zero end-expiratory airway pressure (ZEEP), a pneumothorax created by incision of the thoracic wall released the lung from the chest wall and caused the lung to recoil freely. The mean increase in pressure measured in the airways when the lung recoiled against a closed endotracheal tube was ≈ 4 cmH_2O, which is indirect measurement of the mean pleural pressure before pneumothorax was induced, ≈ -4 cmH_2O.

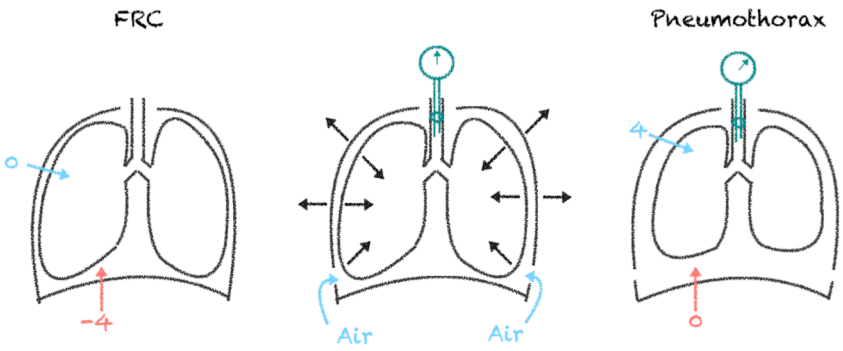


Fig 12 Measurement of the recoiling pressure of the lung. At functional residual capacity the pleural pressure is negative. When air enters the pleural space and the lung is free to recoil towards a closed airway the airway pressure increases. The increase in airway pressure (lung recoiling pressure) represents the mean pleural pressure before pneumothorax was induced, ≈ 4 cmH_2O.

The chest wall at increased end-expiratory lung volume

An important question concerns the chest wall at higher end-expiratory pressure and consequently higher end-expiratory lung volume. According to the elastance-derived method (see "Esophageal pressure in acute respiratory failure"), the chest wall resists PEEP-induced inflation and tidal inflation equally and pleural pressure increases when PEEP is increased. Still, according to textbook physiology the resting volume of the chest wall is far higher than the highest lung volumes during mechanical ventilation. When does the chest wall change from being an expanding force to become an elastic entity resisting end-expiratory inflation?

In the lung healthy patients (II), the increase in end-expiratory lung volume after the largest PEEP-step (≈900 ml) was still well predicted by the elastance of the lung (Fig 2 in II). The baseline PEEP of 5-6 cmH2O increased the end-expiratory lung volume ≈ 450 ml. This indicates that in these patients, the chest wall had minimal influence on an end-expiratory inflation ≈1350 ml above FRC and continued to be an expanding force at end-expiration even at high PEEP (mean 14.5 cmH2O).

From previous description we know that the increase in end-expiratory lung volume during the first breath is dependent on elastance of the total respiratory sys-

tem, but that the total increase in end-expiratory volume is dependent on elastance of the lung. From the first breath and onwards after an increase of PEEP, the end-expiratory inflation continues breath by breath despite a constant end-expiratory airway pressure. In order to create a flow, we need a difference in pressure between the airway and the lungs. If the influence of the chest wall on end-expiratory inflation gradually decreases, the negative pleural pressure is gradually restored and the transpulmonary pressure slowly increases. In pigs (IV) at the highest PEEP-level (17 cmH2O), the PEEP-induced inflation continued for many breaths, which indicates that the chest wall still expands at this high PEEP-level and is off-loaded from the lungs at end-expiration, **Fig 13**.

Adaptation of the chest wall complex – an expiratory phenomenon

Lundin et al[149] describe the increase in end-expiratory lung volume as an expiratory phenomenon. In pressure curves and volume curves derived from pigs (IV), there was no change in volume or airway pressure when an end-expiratory pause was performed during the first breaths after an increase of PEEP. This indicates that there is no change in volume of the chest wall complex or lung at end-expiration during the period of increasing end-expiratory lung volume. But after the next inspiration, the expiration stops at a higher volume as seen on volume curves (Supplemental material in II, III). In pigs (IV), the volume of the thorax was measured with computer tomography and comparisons were made between the volume at zero airway pressure before and after a pneumothorax. Computer tomography examinations were performed after cardiac arrest with the ventilator disconnected from the endotracheal tube. The mean increase in thoracic volume was 8% when the lung recoiling pressure was removed from the chest wall.

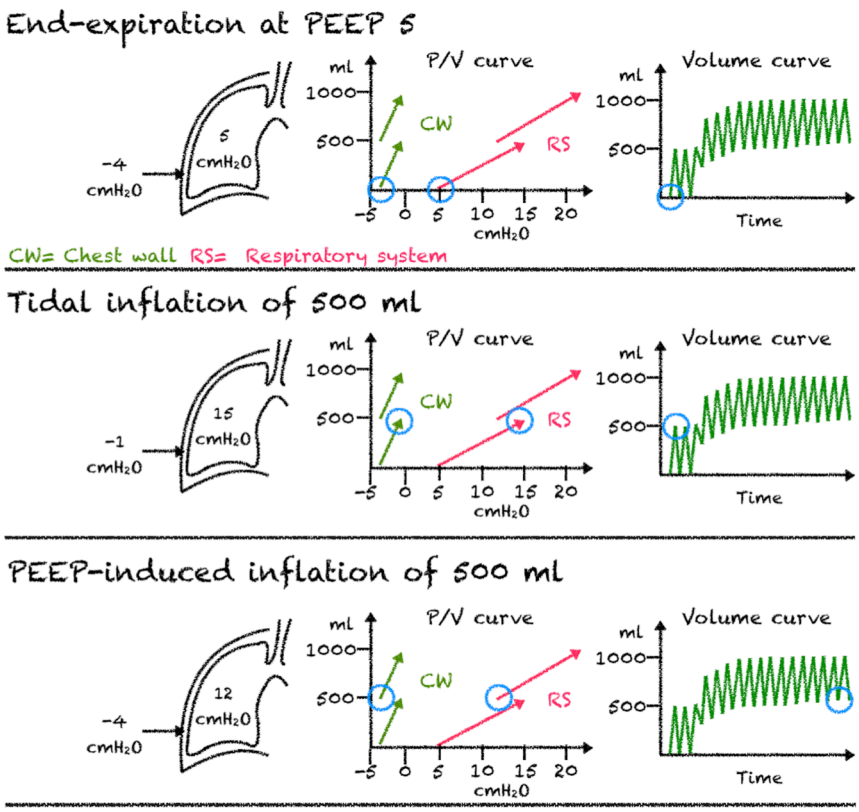


Fig 13 Comparison between a similarly large (≈500 ml) tidal inflation and PEEP-induced inflation. Note the vertical displacement of the green pressure volume curve of the chest wall after PEEP-induced inflation. The expanding chest wall restores the negative pleural pressure at end-expiration after a PEEP-induced inflation. Consequently the end-expiratory chest wall elastance is =0.

Chest wall elastance and the abdomen

Several studies have shown that the chest wall complex does not behave as an elastic entity but that chest wall elastance during tidal inflation is constant or sometimes even decreases minimally when PEEP is increased[74, 128, 149]. Part of the inspiration is directed towards the abdomen, which similar to the chest wall complex, does not normally behave as an elastic compartment. When PEEP is increased and the volume of the thorax is increased, the abdominal pressure is affected minimally[190], indicating that the abdominal container has high plasticity and can harbour a change in volume with minimal change in pressure. The abdomen mechanically behaves as a liquid-filled container[69] instead of an elastic entity and the chest wall complex in total as a load that must be displaced during tidal inspiration as described by Hedenstierna[191]. An abdomen with these properties was one of the components in the model of the respiratory system (I), which described the behaviour of the lung and chest wall during tidal and PEEP-induced inflation, see below.

The chest wall during tidal and PEEP-induced inflation

If we use esophageal pressure to determine the role of the chest wall, there is a difference between tidal inflation and PEEP-induced inflation. When a similar volume of air was inflated with PEEP and tidal inflation in pigs (IV), the change in end-expiratory esophageal pressure was on average 62% of the tidal change in esophageal pressure. If lung elastance (calculated using tidal changes in esophageal pressure) is used to determine the change in transpulmonary pressure of a PEEP-induced inflation, the calculated change in end-expiratory pleural pressure is close to zero (II, IV), **Fig 11**. This implies a fundamental difference in chest wall elastance during tidal inflation and PEEP-induced inflation. The end-expiratory chest wall elastance is zero while the chest wall elastance during tidal inspiration is on average ≈30% of the elastance of the respiratory system. The chest wall elastance did not change significantly when different sizes of tidal volumes were used or when an equal tidal volume was inflated from different

PEEP. When PEEP is decreased the end-expiratory lung volume decreases during several breaths as shown in Supplemental Fig. 1 (II), which is in contrast to tidal expiration. This slow PEEP-induced expiration indicates a force counteracting the recoiling force of the lung.

Conclusion - The chest wall during mechanical ventilation

The difference between PEEP-induced inflation and tidal inflation seems to be explained by differences in chest wall influence. In the absence of reliable pleural pressure measurements, the behaviour of the chest wall is determined from esophageal and airway pressure and lung volumes. It is problematic to make assumptions about the pleural pressure and the chest wall based on indirect measurements. Still, with the available information it is reasonable to conclude that the textbook description of the respiratory system with an expanding chest wall complex, a recoiling lung and a negative pleural pressure is valid during mechanical ventilation even at higher end-expiratory pressure. This view is strengthened by the fact that a model of the respiratory system based on the textbook description mechanically behaves almost identically to patients during mechanical ventilation (I), see below.

A respiratory system model to understand lung and chest wall mechanics

Earlier findings in pigs and patients that PEEP-induced inflation was not influenced by the chest wall in contrast to tidal inflation, was theoretically explained by the mechanical properties of and interaction between the different parts of the respiratory system [148, 149]. Included in this theoretical model was an elastic recoiling lung situated inside an expanding chest wall connected to the diaphragm, which in turn was in contact with the "fluid-filled" abdominal compartment with high plasticity. The model of the respiratory system (I) was built based on these different components to see if such a model behaved similarly to the respiratory system in patients. The slow PEEP-induced inflation was achieved in the mechanical model by an "expanding chest wall" connected to a time-dependent "abdominal compartment" with high plasticity, which slowly adapted to the new pressure/volume state. When inflating the recoiling lung connected to the expanding chest wall and slow abdominal compartment there were similar differences between tidal inflation and PEEP-induced inflation as were seen in patients (II). In the model (I), both lung and chest wall elastance could be changed. Differences in lung elastance caused the PEEP-induced inflation to differ in a similar fashion to that seen by Stahl[182] (Fig 5 in I). Despite the changes in lung and chest wall elastance, the pressure/volume curve of the lung coincided with the end-expiratory pressure/volume curve of the respiratory system. As a consequence, PEEP-induced inflation was determined by the lung pressure/volume curve whilst tidal inflation was determined by the respiratory system pressure/volume curve. This is identical to the later findings in lung healthy patients, **Fig 14** (and also Fig 6 in Suppl. material in II).

The “pleural pressure” in the model initially increased when PEEP was increased but then returned to its initial level (Fig 3 in I) as also suggested by calculations in patients (II) and pigs (IV). The result from the model are no valid proof of how the respiratory system works, but show that the theoretical explanation of the findings in patients and pigs are plausible from a mechanical point of view.

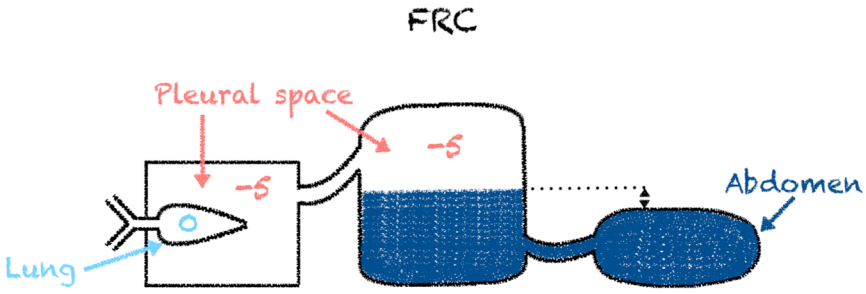


Figure 14 Schematic drawing of the mechanical model of the respiratory system used in study I. At functional residual capacity (FRC) the airway pressure is 0 and the recoiling lung is surrounded by a negative “pleural pressure” (-5 cmH_2O). The negative “pleural pressure” and expanding force of the “chest wall complex” is achieved by evacuation of air, which causes the water level in the plastic container to rise above the level of the abdomen.

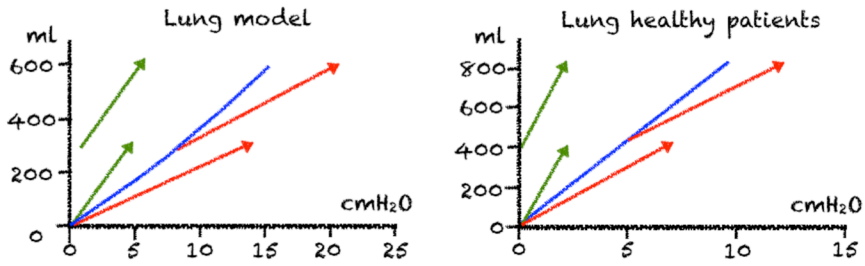


Figure 15 Pressure/volume curve of the respiratory system (red) and the chest wall (green). The pressure volume curve of the lung (blue) (calculated from changes in “pleural pressure” in model and esophageal pressure in patients) coincides with the end-expiratory pressure/volume curve of the respiratory system. **Left panel** represents measurements in the mechanical lung model. **Right panel** represents mean values from the smallest PEEP-step in 24 lung healthy patients during general anaesthesia. Curves in figure represents changes in pressures and volumes and therefore start from zero irrespective of the actual pressures and volumes at start.

Clinical implications and future perspective

Decreasing ventilator induced lung injury in patients is of fundamental importance both in the intensive care unit and in the operating theatre. Lung protective ventilation based on tidal volumes and plateau pressure, as is standard practice, is not sufficient in all patients due to differences in lung and chest wall mechanics. In the future we need to individualize ventilator settings especially in the critically ill, which requires better monitoring of the total amount of energy applied to the lung. Stress and strain need to be determined and considered, possibly together with other parameters such as respiratory rate and airflow. Furthermore, an understanding of lung and chest wall mechanics as well as bedside methods to evaluate the mechanical properties of the different components of the respiratory system are of fundamental importance.

The PEEP-step method

The most obvious clinical implication of the included studies is the "PEEP-step method" to determine lung elastance and transpulmonary pressure. This non-invasive method to determine transpulmonary driving pressure during mechanical ventilation could, if incorporated in the ventilators, provide the clinician with crucial information when aiming for optimal ventilator settings in the ICU and operating theatre. This research project was initiated in order to evaluate the PEEP-step method described in the studies included in the thesis by Grivans[148, 149, 192]. In the included studies we have validated the PEEP-step method and shown that transpulmonary driving pressure can be calculated from a PEEP-step manoeuvre if the change in end-expiratory lung volume is calculated. Still the method has not reached widespread acceptance, to a large degree because of the

physiological explanation behind the method. Even if the PEEP-step method is based on textbook physiology, it challenges some prevailing views on lung and chest wall mechanics, which to a large extent is based on esophageal pressure measurements. Hopefully the method will receive more interest in the future.

Esophageal pressure measurements

Esophageal pressure measurements are used increasingly and within the research field of respiratory mechanics there has been a lot of optimism surrounding the use of the technique. It remains primarily a tool for respiratory research, but an introduction into clinical practice is often encouraged despite the debate concerning interpretation of the measured pressure. The results from studies in this thesis add important information to the discussion concerning the clinical interpretation and usefulness of esophageal pressure measurements. When esophageal pressure measurements are used in the clinical setting, they may have a large impact on ventilator settings and therefore reliability of the measured pressures is of great concern. The study with HRM (III) constitutes one of the most comprehensive evaluations of factors influencing esophageal pressures in mechanically ventilated patients. I believe esophageal pressures need further critical evaluation and that this might perhaps be achieved in the future with technologies such as High-Resolution Manometry. There are areas where esophageal pressure measurements provide useful information and hopefully it will become clearer in the future when to and when not to use the method.

Final remarks

For me an important insight from conducting this research is the lack of consensus regarding basic physiological concepts. Does the chest wall compress or expand the lung? Is the pleural pressure negative or positive? The partly prevailing knowledge gap is obvious when a similar method was used in study IV as that

employed by Carson 1820 with a similar goal: To understand lung and chest wall properties. The studies in this thesis have already contributed to the scientific discussion[160, 193] and hopefully they will in the long run make a small but important contribution to close the knowledge gap.

As a reflection of my experiences during these years concerning research and scientific discussion, I will borrow the terms finite and infinite games from game theory. In finite games you play to defeat your opponent within predetermined boundaries. You rely on power and focus on short-term gains. In infinite games you play with the boundaries, embrace the unpredictable and invite anyone who wants to participate. The goal in infinite games is not to win but to keep the game going. Power is not important but strength is. Surprise causes finite games to end but keeps infinite games going. In infinite games the focus is the direction of the play in the long run even if it means losing in the short run.

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References

1 Lassen HC. The epidemic of poliomyelitis in Copenhagen, 1952. *Proceedings of the Royal Society of Medicine* 1954; **47**: 67-71

2 Avignon PD, Hedenstrom G, Hedman C. Pulmonary complications in respirator patients. *Acta medica Scandinavica Supplementum* 1956; **316**: 86-90

3 Nennhaus HP, Javid H, Julian OC. Alveolar and pleural rupture. Hazards of positive pressure respiration. *Archives of surgery* 1967; **94**: 136-41

4 Kumar A, Pontoppidan H, Falke KJ, Wilson RS, Laver MB. Pulmonary barotrauma during mechanical ventilation. *Critical care medicine* 1973; **1**: 181-6

5 Nash GB, JB.; Pontopiddan H. Respirator lung syndrome. *Canadian Family Physician* 1967: 57-8

6 Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end expiratory pressure. *The American review of respiratory disease* 1974; **110**: 556-65

7 Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *The American review of respiratory disease* 1987; **135**: 312-5

8 Hernandez LA, Peevy KJ, Moise AA, Parker JC. Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *Journal of applied physiology (Bethesda, Md : 1985)* 1989; **66**: 2364-8

9 Carlton DP, Cummings JJ, Scheerer RG, Poulain FR, Bland RD. Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. *Journal of applied physiology (Bethesda, Md : 1985)* 1990; **69**: 577-83

10 Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *The American review of respiratory disease* 1988; **137**: 1159-64

11 Dreyfuss D, Saumon G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive care medicine* 1992; **18**: 139-41

12 Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *American journal of respiratory and critical care medicine* 1994; **149**: 1327-34

13 Bowton DL, Kong DL. High tidal volume ventilation produces increased lung water in oleic acid-injured rabbit lungs. *Critical care medicine* 1989; **17**: 908-11

14 Hernandez LA, Coker PJ, May S, Thompson AL, Parker JC. Mechanical ventilation increases microvascular permeability in oleic acid-injured lungs. *Journal of applied physiology (Bethesda, Md : 1985)* 1990; **69**: 2057-61

15 Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *The Journal of clinical investigation* 1997; **99**: 944-52

16 Tremblay LN, Slutsky AS. Ventilator-induced injury: from barotrauma to biotrauma. *Proceedings of the Association of American Physicians* 1998; **110**: 482-8

17 Slutsky AS, Tremblay LN. Multiple system organ failure. Is mechanical ventilation a contributing factor? *American journal of respiratory and critical care medicine* 1998; **157**: 1721-5

18 Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA : Journal of the American Medical Association* 1999; **282**: 54-61

19 Stuber F, Wrigge H, Schroeder S, et al. Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. *Intensive care medicine* 2002; **28**: 834-41

20 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319-23

21 Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA : Journal of the American Medical Association* 2012; **307**: 2526-33

22 Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? *American journal of respiratory and critical care medicine* 2001; **164**: 1701-11

23 Gattinoni L, Pesenti A. The concept of "baby lung". *Intensive care medicine* 2005; **31**: 776-84

24 Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *The American review of respiratory disease* 1987; **136**: 730-6

25 Langer M, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients. A clinical study. *Chest* 1988; **94**: 103-7

26 Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure. *Anesthesiology* 1991; **74**: 15-23

27 Richard JC, Janier M, Lavenne F, et al. Effect of position, nitric oxide, and almitrine on lung perfusion in a porcine model of acute lung injury. *Journal of applied physiology (Bethesda, Md : 1985)* 2002; **93**: 2181-91

28 Guerin C, Baboi L, Richard JC. Mechanisms of the effects of prone positioning in acute respiratory distress syndrome. *Intensive care medicine* 2014; **40**: 1634-42

29 Yadav H, Thompson BT, Gajic O. Fifty Years of Research in ARDS. Is Acute Respiratory Distress Syndrome a Preventable Disease? *American journal of respiratory and critical care medicine* 2017; **195**: 725-36

30 Petty TL, Newman JH. Adult respiratory distress syndrome. *The Western journal of medicine* 1978; **128**: 399-407

31 Falke KJ, Pontoppidan H, Kumar A, Leith DE, Geffin B, Laver MB. Ventilation with end-expiratory pressure in acute lung disease. *The Journal of clinical investigation* 1972; **51**: 2315-23

32 Kirby RR, Downs JB, Civetta JM, et al. High level positive end expiratory pressure (PEEP) in acute respiratory insufficiency. *Chest* 1975; **67**: 156-63

33 Kuckelt W, Scharfenberg J, Mrochen H, et al. Effect of PEEP on gas exchange, pulmonary mechanics, and hemodynamics in adult respiratory distress syndrome (ARDS). *Intensive care medicine* 1981; **7**: 177-85

34 Bendixen HH, Hedley-Whyte J, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. *The New England journal of medicine* 1963; **269**: 991-6

35 Pierson DJ. Oxygen in respiratory care: a personal perspective from 40 years in the field. *Respiratory care* 2013; **58**: 196-204

36 Ashbaugh DG, Petty TL, Bigelow DB, Harris TM. Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. *The Journal of thoracic and cardiovascular surgery* 1969; **57**: 31-41

37 Sugerman HJ, Rogers RM, Miller LD. Positive end-expiratory pressure (PEEP); indications and physiologic considerations. *Chest* 1972; **62**: Suppl:86S-94S

38 Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive care medicine* 1990; **16**: 372-7

39 Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Critical care medicine* 1994; **22**: 1568-78

40 Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *American journal of respiratory and critical care medicine* 1995; **152**: 1835-46

41 Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *The New England journal of medicine* 1998; **338**: 347-54

42 Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *American journal of respiratory and critical care medicine* 1998; **158**: 1831-8

43 Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Critical care medicine* 1999; **27**: 1492-8

44 Network ARDS, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *New England Journal of Medicine* 2000; **342**: 1301-8

45 Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *The American review of respiratory disease* 1981; **123**: 659-64

46 Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bulletin europeen de physiopathologie respiratoire* 1982; **18**: 419-25

47 Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive care medicine* 2013; **39**: 847-56

48 Amato MB, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. *The New England journal of medicine* 2015; **372**: 747-55

49 Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *American journal of respiratory and critical care medicine* 2017; **195**: 1253-63

50 Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *New England Journal of Medicine* 2004; **351**: 327-36+411

51 Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA : Journal of the American Medical Association* 2008; **299**: 637-45

52 Mercat A, Richard JCM, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA - Journal of the American Medical Association* 2008; **299**: 646-55

53 Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA - Journal of the American Medical Association* 2010; **303**: 865-73

54 Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Critical care medicine* 2004; **32**: 1817-24

55 Gajic O, Frutos-Vivar F, Esteban A, Hubmayr RD, Anzueto A. Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. *Intensive care medicine* 2005; **31**: 922-6

56 Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: A preventive randomized controlled trial. *Critical care* 2010; **14**

57 Neto AS, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without

acute respiratory distress syndrome: A meta-analysis. *JAMA - Journal of the American Medical Association* 2012; **308**: 1651-9

58 Writing Group for the PI. Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ards: A randomized clinical trial. *JAMA : Journal of the American Medical Association* 2018

59 Fisher BW, Majumdar SR, McAlister FA. Predicting pulmonary complications after nonthoracic surgery: A systematic review of blinded studies. *American Journal of Medicine* 2002; **112**: 219-25

60 Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010; **113**: 1338-50

61 Futier E, Constantin JM, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *New England Journal of Medicine* 2013; **369**: 428-37

62 Severgnini P, Selmo G, Lanza C, et al. Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. *Anesthesiology* 2013; **118**: 1307-21

63 Ladha K, Vidal Melo MF, McLean DJ, et al. Intraoperative protective mechanical ventilation and risk of postoperative respiratory complications: hospital based registry study. *Bmj* 2015; **351**: h3646

64 Guay J, Ochroch EA. Intraoperative use of low volume ventilation to decrease postoperative mortality, mechanical ventilation, lengths of stay and lung injury in patients without acute lung injury. *The Cochrane database of systematic reviews* 2015; **12**: CD011151

65 Levin MA, McCormick PJ, Lin HM, Hosseinian L, Fischer GW. Low intraoperative tidal volume ventilation with minimal PEEP is associated with increased mortality. *British journal of anaesthesia* 2014; **113**: 97-108

66 Investigators TPN, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014; **384**: 495-503

67 Barbosa FT, Castro AA, de Sousa-Rodrigues CF. Positive end-expiratory pressure (PEEP) during anaesthesia for prevention of mortality and postoperative pulmonary complications. *Cochrane Database Syst Rev* 2014: Cd007922

68 Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA : Journal of the American Medical Association* 2010; **304**: 2620-7

69 Agostoni E, Hyatt R. The respiratory system. Mechanics of breathing. *Handbook of Physiology*. Bethesda: American Physiological Society, 1986; 113-30

70 Howell JB, Peckett BW. Studies of the elastic properties of the thorax of supine anaesthetized paralysed human subjects. *The Journal of physiology* 1957; **136**: 1-19

71 Suter PM, Fairley HB, Isenberg MD. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. *Chest* 1978; **73**: 158-62

72 Katz JA, Zinn SE, Ozanne GM, Fairley HB. Pulmonary, chest wall, and lung-thorax elastances in acute respiratory failure. *Chest* 1981; **80**: 304-11

73 Jardin F, Genevray B, Brun-Ney D, Bourdarias JP. Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. *Chest* 1985; **88**: 653-8

74 Gattinoni L, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *American journal of respiratory and critical care medicine* 1998; **158**: 3-11

75 Cinnella G, Grasso S, Spadaro S, et al. Effects of recruitment maneuver and positive end-expiratory pressure on respiratory mechanics and transpulmonary pressure during laparoscopic surgery. *Anesthesiology* 2013; **118**: 114-22

76 Pelosi P, Croci M, Ravagnan I, Vicardi P, Gattinoni L. Total Respiratory System, Lung, and Chest Wall Mechanics in Sedated-Paralyzed Postoperative Morbidly Obese Patients. *Chest* 1996; **109**: 144-51

77 Chiumello D, Carlesso E, Cadringher P, et al. Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. *American journal of respiratory and critical care medicine* 2008; **178**: 346-55

78 Gattinoni L, Carlesso E, Cadringher P, Valenza F, Vagginelli F, Chiumello D. Physical and biological triggers of ventilator-induced lung injury and its prevention. *The European respiratory journal Supplement* 2003; **47**: 15s-25s

79 Wilson TA. Solid Mechanics. *American Physiological Society, ed Handbook of Physiology: a Critical, Comprehensive Presentation of Physiological Knowledge and Concepts*: Bethesda, MD, Waverly Press, Inc, 1986; 35–9

80 Protti A, Cressoni M, Santini A, et al. Lung stress and strain during mechanical ventilation: any safe threshold? *American journal of respiratory and critical care medicine* 2011; **183**: 1354-62

81 Protti A, Andreis DT, Monti M, et al. Lung stress and strain during mechanical ventilation: any difference between statics and dynamics? *Critical care medicine* 2013; **41**: 1046-55

82 Gattinoni L, Tonetti T, Cressoni M, et al. Ventilator-related causes of lung injury: the mechanical power. *Intensive care medicine* 2016; **42**: 1567-75

83 Loring SH, Topulos GP, Hubmayr RD. Transpulmonary Pressure: The Importance of Precise Definitions and Limiting Assumptions. *American journal of respiratory and critical care medicine* 2016

84 Agostoni E, Miserocchi G, Bonanni MV. Thickness and pressure of the pleural liquid in some mammals. *Respiration physiology* 1969; **6**: 245-56

85 Miserocchi G, Agostoni E. Contents of the pleural space. *Journal of applied physiology* 1971; **30**: 208-13

86 Noppen M, De Waele M, Li R, et al. Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. *American journal of respiratory and critical care medicine* 2000; **162**: 1023-6

87 Nunn J. Elastic forces and lung volumes. In: JF N, ed. *Nunn´s applied respiratory physiology*. Oxford: Butterworth-Heinemann, 1995; 36 - 52

88 Rahn H, Otis AB, et al. The pressure-volume diagram of the thorax and lung. *The American journal of physiology* 1946; **146**: 161-78

89 Miserocchi G, Agostoni E. Pleural liquid and surface pressures at various lung volumes. *Respiration physiology* 1980; **39**: 315-26

90 Lai-Fook SJ. Pleural Mechanics and Fluid Exchange. *Physiological Reviews* 2004; **84**: 385-410

91 Mead J, Gaensler EA. Esophageal and pleural pressures in man, upright and supine. *Journal of applied physiology* 1959; **14**: 81-3

92 Agostoni E. Mechanics of the pleural space. *Physiological Reviews* 1972; **52**: 57-128

93 Carson J. On the elasticity of the lungs. *Philosophical Transactions of the Royal Society of London* 1820; **110**: 29-44

94 Mead J, Whittenberger JL. Physical Properties of Human Lungs Measured During Spontaneous Respiration. *Journal of applied physiology* 1953; **5**: 779-96

95 McMahon SM, Proctor DF, Permutt S. Pleural surface pressure in dogs. *Journal of applied physiology* 1969; **27**: 881-5

96 Yoshida T, Amato MBP, Grieco DL, et al. Esophageal manometry and regional transpulmonary pressure in lung injury. *American journal of respiratory and critical care medicine* 2018; **197**: 1018-26

97 Herrejon A, Inchaurraga I, Vivas C, Custardoy J, Marin J. Initial pleural pressure measurement in spontaneous pneumothorax. *Lung* 2000; **178**: 309-16

98 Fry DL, Stead WW, Ebert RV, Lubin RI, Wells HS. The measurement of intraesophageal pressure and its relationship to intrathoracic pressure. *The Journal of laboratory and clinical medicine* 1952; **40**: 664-73

99 Christie RV, McIntosh CA. The Measurement of the Intrapleural Pressure in Man and Its Significance. *The Journal of clinical investigation* 1934; **13**: 279-94

100 Cherniack RM, Farhi LE, Armstrong BW, Proctor DF. A comparison of esophageal and intrapleural pressure in man. *Journal of applied physiology* 1955; **8**: 203-11

101 Gillespie DJ, Lai YL, Hyatt RE. Comparison of esophageal and pleural pressures in the anesthetized dog. *Journal of applied physiology* 1973; **35**: 709-13

102 Pelosi P, Goldner M, McKibben A, et al. Recruitment and derecruitment during acute respiratory failure: an experimental study. *American journal of respiratory and critical care medicine* 2001; **164**: 122-30

103 Luciani L. Delle oscillazioni della pressione intratoracica intrab- dominale. Studio sperimentale. *Arch Sci Med* 1878; **2**: 177-224

104 Buytendijk HJ. Oesophagusdruck em Longelasticiteit. University Groningen, 1949

105 Dornhorst AC, Leathart GL. A method of assessing the mechanical properties of lungs and air-passages. *The Lancet* 1952; **260**: 109-11

106 Attinger EO, Monroe RG, Segal MS. The mechanics of breathing in different body positions. I. In normal subjects. *The Journal of clinical investigation* 1956; **35**: 904-11

107 Butler J, White HC, Arnott WM. The pulmonary compliance in normal subjects. *Clin Sci* 1957; **16**: 709-29

108 Daly WJ, Biondurant S. Direct measurements of respiratory pleural pressure changes in normal man. *Journal of applied physiology* 1963; **18**: 513-8

109 Ferris BG, Mead J, Frank N. Effect of body position on esophageal pressure and measurement of pulmonary compliance. *Journal of applied physiology* 1959; **14**: 521-4

110 Knowles JH, Hong SK, Rahn H. Possible errors using esophageal balloon in determination of pressure-volume characteristics of the lung and thoracic cage. *Journal of applied physiology* 1959; **14**: 525-30

111 Milic-Emili J, Mead J, Turner JM. Topography of Esophageal Pressure as a Function of Posture in Man. *Journal of applied physiology* 1964; **19**: 212-6

112 Mead J, Whittenberger JL. Physical properties of the human lungs during spontaneous respiration. *Journal of applied physiology* 1953: 779-96

113 Frank NR, Mead J, Siebens AA, Storey CF. Measurements of pulmonary compliance in seventy healthy young adults. *Journal of applied physiology* 1956; **9**: 38-42

114 Mead J, Mc IM, Selverstone NJ, Kriete BC. Measurement of intraesophageal pressure. *Journal of applied physiology* 1955; **7**: 491-5

115 Petit JM, Milic-Emili G. Measurement of endoesophageal pressure. *Journal of applied physiology* 1958; **13**: 481-5

116 Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved Technique for Estimating Pleural Pressure from Esophageal Balloons. *Journal of applied physiology* 1964; **19**: 207-11

117 Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. *The American review of respiratory disease* 1982; **126**: 788-91

118 Baydur A, Cha EJ, Sassoon CS. Validation of esophageal balloon technique at different lung volumes and postures. *Journal of applied physiology (Bethesda, Md : 1985)* 1987; **62**: 315-21

119 Higgs BD, Behrakis PK, Bevan DR, Milic-Emili J. Measurement of pleural pressure with esophageal balloon in anesthetized humans. *Anesthesiology* 1983; **59**: 340-3

120 Gold MI, Han YH, Helrich M. Pulmonary mechanics during anesthesia. 3. Influence of intermittent positive pressure and relation to blood gases. *Anesthesia and analgesia* 1966; **45**: 631-41

121 Van Lith P, Johnson FN, Sharp JT. Respiratory elastances in relaxed and paralyzed states in normal and abnormal men. *Journal of applied physiology* 1967; **23**: 475-86

122 Westbrook PR, Stubbs SE, Sessler AD, Rehder K, Hyatt RE. Effects of anesthesia and muscle paralysis on respiratory mechanics in normal man. *Journal of applied physiology* 1973; **34**: 81-6

123 Rehder K, Mallow JE, Fibuch EE, Krabill DR, Sessler AD. Effects of isoflurane anesthesia and muscle paralysis on respiratory mechanics in normal man. *Anesthesiology* 1974; **41**: 477-85

124 D'Angelo E, Robatto FM, Calderini E, et al. Pulmonary and chest wall mechanics in anesthetized paralyzed humans. *Journal of applied physiology (Bethesda, Md : 1985)* 1991; **70**: 2602-10

125 Lanteri CJ, Kano S, Sly PD. Validation of esophageal pressure occlusion test after paralysis. *Pediatric pulmonology* 1994; **17**: 56-62

126 Chiumello D, Consonni D, Coppola S, Froio S, Crimella F, Colombo A. The occlusion tests and end-expiratory esophageal pressure: measurements and comparison in controlled and assisted ventilation. *Annals of intensive care* 2016; **6**: 1-10

127 Peters RM, Hilberman M, Hogan JS, Crawford DA. Objective indications for respirator therapy in post-trauma and postoperative patients. *American journal of surgery* 1972; **124**: 262-9

128 Pelosi P, Cereda M, Foti G, Giacomini M, Pesenti A. Alterations of lung and chest wall mechanics in patients with acute lung injury: effects of positive end-expiratory pressure. *American journal of respiratory and critical care medicine* 1995; **152**: 531-7

129 Ranieri VM, Brienza N, Santostasi S, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. *American journal of respiratory and critical care medicine* 1997; **156**: 1082-91

130 Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. *American journal of respiratory and critical care medicine* 1998; **157**: 387-93

131 de Chazal I, Hubmayr RD. Novel aspects of pulmonary mechanics in intensive care. *British journal of anaesthesia* 2003; **91**: 81-91

132 Talmor D, Sarge T, O'Donnell CR, et al. Esophageal and transpulmonary pressures in acute respiratory failure. *Critical care medicine* 2006; **34**: 1389-94

133 Washko GR, O'Donnell CR, Loring SH. Volume-related and volume-independent effects of posture on esophageal and transpulmonary pressures in healthy subjects. *Journal of applied physiology (Bethesda, Md : 1985)* 2006; **100**: 753-8

134 Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *The New England journal of medicine* 2008; **359**: 2095-104

135 Grasso S, Terragni P, Birocco A, et al. ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure. *Intensive care medicine* 2012; **38**: 395-403

136 Hager DN, Brower RG. Customizing lung-protective mechanical ventilation strategies. *Critical care medicine* 2006; **34**: 1554-5

137 Chiumello D, Cressoni M, Colombo A, et al. The assessment of transpulmonary pressure in mechanically ventilated ARDS patients. *Intensive care medicine* 2014; **40**: 1670-8

138 Gattinoni L, Chiumello D, Carlesso E, Valenza F. Bench-to-bedside review: chest wall elastance in acute lung injury/acute respiratory distress syndrome patients. *Critical care* 2004; **8**: 350-5

139 Gattinoni L, Vagginelli F, Chiumello D, Taccone P, Carlesso E. Physiologic rationale for ventilator setting in acute lung injury/acute respiratory distress syndrome patients. *Critical care medicine* 2003; **31**: S300-4

140 Staffieri F, Stripoli T, De Monte V, et al. Physiological effects of an open lung ventilatory strategy titrated on elastance-derived end-inspiratory transpulmonary pressure: study in a pig model*. *Critical care medicine* 2012; **40**: 2124-31

141 Gulati G, Novero A, Loring SH, Talmor D. Pleural pressure and optimal positive end-expiratory pressure based on esophageal pressure versus chest wall elastance: incompatible results*. *Critical care medicine* 2013; **41**: 1951-7

142 Akoumianaki E, Maggiore SM, Valenza F, et al. The application of esophageal pressure measurement in patients with respiratory failure. *American journal of respiratory and critical care medicine* 2014; **189**: 520-31

143 Gattinoni L, Cressoni M, Chiumello D, Marini JJ. Transpulmonary Pressure Meaning: Babel or Conceptual Evolution? *American journal of respiratory and critical care medicine* 2017; **195**: 1404-5

144 Loring SH, Topulos GP, Hubmayr RD. Reply: Transpulmonary Pressure Meaning: Babel or Conceptual Evolution? *American journal of respiratory and critical care medicine* 2017; **195**: 1405-6

145 Grasso S, Stripoli T. Transpulmonary Pressure-based Mechanical Ventilation in Acute Respiratory Distress Syndrome. From Theory to Practice? *American journal of respiratory and critical care medicine* 2018; **197**: 977-8

146 Lumb AB. *Nunn's Applied Respiratory Physiology*. 8 Edn.: Elsevier, 2016

147 West JB. Mechanics of breathing. In: West JB, ed. *Respiratory physiology*. Baltimore, Hong Kong, London, Sydney: Williams & Wilkins, 1985; 85-111

148 Stenqvist O, Grivans C, Andersson B, Lundin S. Lung elastance and transpulmonary pressure can be determined without using oesophageal pressure measurements. *Acta anaesthesiologica Scandinavica* 2012; **56**: 738-47

149 Lundin S, Grivans C, Stenqvist O. Transpulmonary pressure and lung elastance can be estimated by a PEEP-step manoeuvre. *Acta anaesthesiologica Scandinavica* 2015; **59**: 185-96

150 Chiumello D, Cressoni M, Carlesso E, et al. Bedside selection of positive end-expiratory pressure in mild, moderate, and severe acute respiratory distress syndrome. *Critical care medicine* 2014; **42**: 252-64

151 Chiumello D, Gallazzi E, Marino A, et al. A validation study of a new nasogastric polyfunctional catheter. *Intensive care medicine* 2011; **37**: 791-5

152 Chiumello D, Colombo A, Algieri I, et al. Effect of body mass index in acute respiratory distress syndrome. *British journal of anaesthesia* 2016; **116**: 113-21

153 Loring SH, O'Donnell CR, Behazin N, et al. Esophageal pressures in acute lung injury: do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? *Journal of applied physiology* 2010; **108**: 515-22

154 Loring SH, Behazin N, Novero A, et al. Respiratory mechanical effects of surgical pneumoperitoneum in humans. *Journal of applied physiology (Bethesda, Md : 1985)* 2014; **117**: 1074-9

155 Behazin N, Jones SB, Cohen RI, Loring SH. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. *Journal of applied physiology (Bethesda, Md : 1985)* 2010; **108**: 212-8

156 Mojoli F, Iotti GA, Torriglia F, et al. In vivo calibration of esophageal pressure in the mechanically ventilated patient makes measurements reliable. *Critical care* 2016; **20**: 98

157 Stenqvist O, Gattinoni L, Hedenstierna G. What's new in respiratory physiology? The expanding chest wall revisited! *Intensive care medicine* 2015; **41**: 1110-3

158 Chiumello D, Carlesso E, Brioni M, Cressoni M. Airway driving pressure and lung stress in ARDS patients. *Critical care* 2016; **20**: 276

159 Pesenti A, Bellani G, Mauri T. Transpulmonary pressure at functional residual capacity. *Critical care medicine* 2013; **41**: e9

160 Stenqvist O, Persson P, Stahl C, Lundin S. Monitoring transpulmonary pressure during anaesthesia using the PEEP-step method. *British journal of anaesthesia* 2018

161 Newton I. *The mathematical principles of natural philosophy*. 1687, 1729

162 Powers SR, Jr., Burdge R, Leather R, et al. Studies of pulmonary insufficiency in non-thoracic trauma. *The Journal of trauma* 1972; **12**: 1-14

163 Powers SR, Jr., Mannal R, Neclerio M, et al. Physiologic consequences of positive end-expiratory pressure (PEEP) ventilation. *Annals of surgery* 1973; **178**: 265-72

164 Lachmann B. Open up the lung and keep the lung open. *Intensive care medicine* 1992; **18**: 319-21

165 Reinius H, Jonsson L, Gustafsson S, et al. Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. *Anesthesiology* 2009; **111**: 979-87

166 Costa Leme A, Hajjar LA, Volpe MS, et al. Effect of Intensive vs Moderate Alveolar Recruitment Strategies Added to Lung-Protective Ventilation on Postoperative Pulmonary Complications: A Randomized Clinical Trial. *JAMA : the journal of the American Medical Association* 2017; **317**: 1422-32

167 Cavalcanti AB, Suzumura EA, Laranjeira LN, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. *JAMA : Journal of the American Medical Association* 2017; **318**: 1335-45

168 Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Critical care medicine* 2006; **34**: 1311-8

169 Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, Atlan G. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest* 1984; **86**: 58-66

170 Maggiore SM, Jonson B, Richard JC, Jaber S, Lemaire F, Brochard L. Alveolar derecruitment at decremental positive end-expiratory pressure levels in acute lung injury: comparison with the lower inflection point, oxygenation, and compliance. *American journal of respiratory and critical care medicine* 2001; **164**: 795-801

171 Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L. Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *American journal of respiratory and critical care medicine* 1999; **159**: 1172-8

172 Gattinoni L, Caironi P, Cressoni M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *The New England journal of medicine* 2006; **354**: 1775-86

173 Malbouisson LM, Muller JC, Constantin JM, et al. Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome. *American journal of respiratory and critical care medicine* 2001; **163**: 1444-50

174 Ranieri VM, Eissa NT, Corbeil C, et al. Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. *The American review of respiratory disease* 1991; **144**: 544-51

175 Dellamonica J, Lerolle N, Sargentini C, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. *Intensive care medicine* 2011; **37**: 1595-604

176 Chiumello D, Marino A, Brioni M, et al. Lung Recruitment Assessed by Respiratory Mechanics and by CT Scan: What is the Relationship? *American journal of respiratory and critical care medicine* 2015

177 Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O. Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. *Anesthesia and analgesia* 2005; **101**: 206-12, table of contents

178 Fretschner R, Laubscher TP, Brunner JX. New aspects of pulmonary mechanics: "slowly" distensible compartments of the respiratory system, identified by a PEEP step maneuver. *Intensive care medicine* 1996; **22**: 1328-34

179 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. *Acta anaesthesiologica Scandinavica* 2011; **55**: 1068-77

180 Katz JA, Ozanne GM, Zinn SE, Fairley HB. Time course and mechanisms of lung-volume increase with PEEP in acute pulmonary failure. *Anesthesiology* 1981; **54**: 9-16

181 Erlandsson K, Odenstedt H, Lundin S, Stenqvist O. Positive end-expiratory pressure optimization using electric impedance tomography in morbidly obese patients during laparoscopic gastric bypass surgery. *Acta anaesthesiologica Scandinavica* 2006; **50**: 833-9

182 Stahl CA, Moller K, Steinmann D, Henzler D, Lundin S, Stenqvist O. Determination of 'recruited volume' following a PEEP step is not a measure of lung recruitability. *Acta anaesthesiologica Scandinavica* 2015; **59**: 35-46

183 Lowhagen K, Lundin S, Stenqvist O. Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. *Minerva anestesiologica* 2010; **76**: 1024-35

184 Victorino JA, Borges JB, Okamoto VN, et al. Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *American journal of respiratory and critical care medicine* 2004; **169**: 791-800

185 Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA : Journal of the American Medical Association* 1993; **269**: 2122-7

186 Christie RV. The Elastic Properties of the Emphysematous Lung and Their Clinical Significance. *The Journal of clinical investigation* 1934; **13**: 295-321

187 Ferguson GT. Why does the lung hyperinflate? *Proceedings of the American Thoracic Society* 2006; **3**: 176-9

188 Sciurba FC, Rogers RM, Keenan RJ, et al. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *The New England journal of medicine* 1996; **334**: 1095-9

189 Hedenstierna G, Strandberg A, Brismar B, Lundquist H, Svensson L, Tokics L. Functional residual capacity, thoracoabdominal dimensions, and central blood volume during general anesthesia with muscle paralysis and mechanical ventilation. *Anesthesiology* 1985; **62**: 247-54

190 Jakob SM, Knuesel R, Tenhunen JJ, Pradl R, Takala J. Increasing abdominal pressure with and without PEEP: effects on intra-peritoneal, intra-organ and intra-vascular pressures. *BMC gastroenterology* 2010; **10**: 70

191 Hedenstierna G. Esophageal pressure: benefit and limitations. *Minerva anestesiologica* 2012; **78**: 959-66

192 Grivans C. Transpulmonary pressure during mechanical ventilation. 2013, Doctoral Thesis

193 Grieco DL, Anzellotti GM, Dell'Anna AM, Russo A, Bongiovanni F, Antonelli M. PEEP-induced changes in lung volume to estimate transpulmonary pressure: the role of alveolar recruitment. *British journal of anaesthesia* 2018

194 Mojoli F, Chiumello D, Pozzi M, et al. Esophageal pressure measurements under different conditions of intrathoracic pressure. An in vitro study of second generation balloon catheters. *Minerva anestesiologica* 2015; **81**: 855-64

195 Lamvik K, Guiu Hernandez E, Jones R, Huckabee ML. Characterization and correction of pressure drift in the ManoScan() high-resolution manometry system: In

vitro and in vivo. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 2016; **28**: 732-42

196 Adler A, Amyot R, Guardo R, Bates JH, Berthiaume Y. Monitoring changes in lung air and liquid volumes with electrical impedance tomography. *Journal of applied physiology (Bethesda, Md : 1985)* 1997; **83**: 1762-7

197 El-Dash SA, Borges JB, Costa EL, et al. There is no cephalocaudal gradient of computed tomography densities or lung behavior in supine patients with acute respiratory distress syndrome. *Acta anaesthesiologica Scandinavica* 2016; **60**: 767-79

Appendix

Methodological considerations

Standard pressure, flow and volume measurements

Airway pressure, flow and volume were measured by the Flow-I anaesthesia machine or Servo-I ventilator and presented by a dedicated software developed by Maquet for this purpose. Airway pressure was also measured at the Y-piece with standard pressure transducers, also used in measurements of the pressure inside the esophageal balloon and "pleural space" in the model.

Esophageal pressure with a balloon catheter

The balloon catheter (Nutrivent™, SIDAM, Mirandola, Italy) used in II, III and IV for esophageal pressure measurements has previously been validated for esophageal pressure measurements[151, 156, 194]. The distal end of the 10 cm long balloon should, according to manufacturer, be placed 40-42 cm from nostril, which was used as an initial landmark. Adjustment of depth was made until typical tidal pressure changes were seen and then a correct position was confirmed with a positive pressure occlusion test[126]. By using 4 ml of air inside the balloon in all patients a small potential error in pressure measurements was introduced since 4 ml has been shown not to be optimal in every patient (underestimating the tidal changes with 7% on average). A titration procedure was not possible due to time factors especially when measurements were performed in the operating room. In pigs the lowest volume of air with an acceptable positive occlusion test was used (1-2 ml). This approach was chosen in order to avoid overestima-

tion of the end-expiratory esophageal pressure since it increases with increasing balloon volume[156]. In a few patients in study II a slow decrease in end-expiratory esophageal pressure was seen over time as a sign of a small leakage from the system. Since only tidal changes of esophageal pressures were used and the range of acceptable balloon volume is large[156] measurements were considered accurate as long as the size of the tidal variations at baseline tidal volume and PEEP did not decrease. One patient was excluded due to leakage from the system.

Esophageal pressure with High-Resolution Manometry

The High-Resolution catheter used for measurements was calibrated before each measurement inside a chamber with a known pressure. Still pressure drift during measurements is a concern with the HRM catheter as described in III. The drift is partly due to a thermal effect that causes an initial change in pressure that stabilizes within 2 minutes after insertion of the catheter into the esophagus. During measurements there is also a slower time-dependent drift[195]. The amount of pressure drift is different between sensors but can be estimated by measurements of the pressure while holding the catheter in the air after it is removed from the patient. The mean pressure drift in the study (III) before compensation was estimated to 9 cmH_2O but to what extent it was due to the faster temperature dependent drift or the slow time-dependent is unclear. The used correction method compensates quite well for the thermal effect but not for the time-dependent drift. This causes an underestimation of the pressures in the beginning of the examination equal to the time-dependent drift, which according to manufacturer is low (<3 cmH_2O during shorter examinations).

Estimation of change in end-expiratory lung volume

The method used for estimation of change in end-expiratory lung volume (ΔEELV) from differences in inspiratory and expiratory tidal volumes has previously been validated with electric impedance tomography[179] and used in studies both in patients[149] and in pigs[148]. In the study in pigs (IV) ΔEELV calculated from computer tomography was on average 18% higher than calculated with the method based on tidal volumes (CT performed in 4 pigs only). This difference can to a large degree be explained by the continuous increase in end-expiratory lung volume after 15 breaths as seen with EIT after a similar size of PEEP-change (IV). The was no significant differences in impedance changes during inflation of a tidal volume 8 ml/kg and an equally large PEEP-induced inflation (IV). The mean coefficient of variation when comparing calculated ΔEELV from an increase and a decrease of PEEP was 3.5% (II). Calculations of ΔEELV are based on differences between inspiratory and expiratory tidal volumes. The mean coefficient of variation for inspiratory and expiratory tidal volumes at steady state was 0.2 and 0.8 % respectively (II). The conclusion from these numbers is that the method for calculations of ΔEELV is based on precise measurements of inspiratory and expiratory tidal volumes, shows good repeatability and also reasonable agreement with other methods.

Nevertheless two issues regarding the method need to be addressed. Including only 15 breaths for calculation of ΔEELV is not sufficient after larger PEEP-changes but limits the risk of multiplication of small errors. After the larger PEEP-steps in pigs the end-expiratory lung volume increased approximately 5% after breath 15, which still has to be regarded as a small deviation from the calculated value.

Secondly the offset at the new PEEP level is calculated during breath 16-20. If EELV is still increasing at this time the offset will be overestimated and the already underestimated change in end-expiratory lung volume will be lowered even further. One way to avoid the multiplication of small errors and the overestimation of the offset is to calculate the change in end-expiratory lung volume during breath 1-15 but the offset at breath 25-30 when the new steady state is probably reached. Also only changes in end-expiratory lung volume from the decrease in PEEP could be used, especially after large changes of PEEP since

the decrease in lung volume theoretically occurs during fewer breaths. After the largest PEEP-step in lung healthy patients (II) the change in end-expiratory lung volume was on average 4% higher when PEEP was decreased compared to when PEEP was increased.

Electric impedance tomography (EIT)

EIT was used in the study in pigs to compare the distribution of air during a PEEP-induced inflation and a tidal inflation and to assess when and in what part of the lung inflation starts during a slow inflation. EIT analyses changes in impedance with the use of electrodes around the thorax and thereby makes it possible to verify the distribution of the inflated air in real-time. The belt surrounding the thorax only covers a slice of the lungs but due to the pattern of the current between the electrodes the thickness of the slice is approximately 50% of the diameter of the thorax[196], representing ≈10 cm in pigs. Since this covers a large part of the thorax of the animal it provides a good estimate of the vertical distribution of air within the lung. Distribution of air in the cephalocaudal axis is less well estimated but in patients with ARDS no cephalocaudal gradient in lung densities or collapse have been found[197]. The ratio between changes in impedance per ml inflated air during tidal inflation (ΔZ/ml) is altered when PEEP is increased an in order to evaluate the change in end-expiratory lung volume ΔZ/ml has to be "calibrated". During inflation of the same tidal volume at PEEP 5 and PEEP 9 the difference in ΔZ/ml was only 2.5% (95% CI 0.9-4.1%). Changes in end-expiratory lung volume between these PEEP-levels calculated from EIT were therefore used without "calibration" in comparison with calculations from inspiratory and expiratory tidal volumes.

Statistical methods

	Study	I	II	III	IV
Descriptive statistics	Average and distribution measurements	X	X	X	X
	Within subject standard deviation			X	
	Coefficient of variation		X		X
	95% confidence interval of the mean			X	
Comparison of mean / median	Confidence interval of mean differences			X	X
	Limits of agreement		X		
	Wilcoxon Signed rank test		X		
Linear regression	Linear regression analysis	X			
Comparison of methods	Intraclass Correlation Coefficient (ICC)		X		
	Bland Altman plot		X		

Table 1 Statistical methods used in studies I-IV

Paper I-IV with supplemental material