ASPECTS OF LUNG MECHANICS DURING MECHANICAL VENTILATION

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“Lærdómsgyðju greiddi skatt

glöggur, klár og natinn

lífið við þig leiki glatt

læknakandidatinn.”

Dr. Pétur Pétursson

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ABSTRACT

Background: One of the most common diagnoses in the intensive care unit is acute respiratory failure. In its most severe form it is called acute respiratory distress syndrome and often requires mechanical ventilation. The main challenge for physicians is to provide mechanical ventilation that treats the patient´s hypoxia, which can be due to a variety of causes, without damaging the lung.

Method: In paper I computed tomography scans were acquired in ten anesthetized surfactant depleted pigs. The volume of gas and atelectasis were correlated with transpulmonary pressure as the pressure support and PEEP were lowered. In paper II a non-invasive method for measuring transpulmonary driving pressure was validated in 31 mechanically ventilated intensive care patients. In paper III external expiratory resistors were added to the expiratory limb of the ventilator while calculating expiratory time constant, respiratory compliance, driving pressure and intrinsic PEEP in 12 anesthetized pigs. In paper IV transpulmonary pressure was calculated from esophageal pressure in supine and prone position in 10 anesthetized lung healthy patients.

Results: Gradual decrease in transpulmonary pressure causes a proportional increase in atelectasis and decrease in gas content while the work of breathing increases. There is a good statistical agreement between the conventional and the non-invasive method for measuring transpulmonary driving pressure. Increasing the expiratory resistance increases the expiratory time constant and increases intrinsic PEEP in healthy lungs. There is a great variability in esophageal pressure in the part of the esophagus 22 – 44cm from the nostrils in both supine and prone position. Depending on method the transpulmonary

pressure either increases or decreases when patients are turned in prone position.

Conclusion: There is no transpulmonary pressure threshold, where atelectasis with desaturation or cyclic collapse suddenly occurs during gradual decrease in the ventilator support. The PEEP-step method is comparable to the traditional esophageal balloon method for measuring transpulmonary driving pressure. The application of expiratory resistors could be useful during weaning from mechanical ventilation. The mean end-expiratory esophageal pressure changes which affect the calculation of transpulmonary pressure but uncertainties about the use of absolute esophageal pressure remains.

Keywords: Acute respiratory failure, Acute respiratory distress syndrome, Mechanical ventilation, Transpulmonary pressure, Expiratory time constant, Esophageal pressure

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SAMMANFATTNING PÅ SVENSKA

En av de vanligaste orsakerna till att man hamnar på en intensivvårdsavdelning är sviktande andningsfunktion. Det kan vara olika orsaker som ligger bakom, till exempel lunginflammation, trauma mot bröstkorgen eller blodpropp i lungan, bara för att nämna några. I de svåraste fallen behöver patienterna läggas i en respirator, d.v.s. en maskin som hjälper till med andningen. Hur man ställer in respirator beror bland annat på patientens storlek, orsaken till respiratorvård och hur länge patienten har varit i respiratorn. Om respiratorn inte är inställd på ett rätt sätt, kan lungan ta skada om till exempel trycket inne i lungan blir för högt eller om volymerna i lungan blir för stora. Det är därför viktigt att ställa in den rätt så att lungan kan bli bättre, men samtidigt ta hänsyn till underliggande sjukdomar och framför allt utan att skada lungan.

Lungan är omgiven av bröstkorgen och diafragman och det är revbensbågens utåtriktade kraft och diafragmans förmåga att stå emot bukens tryck mot brösthålan som håller lungan utspänd. Respiratorn trycker ner luft i lungan för att hjälpa till med andningen och skapar då så kallat transpulmonellt tryck d.v.s tryck som påverkar lungan. Om bröstkorgen är styv då blir transpulmonella trycket lågt. Om bröstkorgen däremot är mjuk blir transpulmonella trycket högt, trots att respiratorn ger samma tryck ner i lungan. Ett för högt transpulmonellt tryck kan ge skador på lungvävnaden och därför är det av stor vikt att kunna mäta det transpulmonella trycket och förstå hur vi kan använda det för att kunna göra respiratorvård säkrare.

Denna avhandling som består av fyra forskningsstudier har för syfte att undersöka mekaniken i lungan vid olika tillfällen på både sjuka och friska lungor. I första studien undersöktes sambandet mellan transpulmonellt tryck och hur lungan faller samman när man successivt minskar trycket som respiratorn ger när man försöker få patienterna ur respiratorn. I studie två validerades ett nytt sätt att mäta transpulmonellt tryck på patienter i respirator på intensivvårdsavdelningar. Det nya sättet är skonsammare för patienterna, då man inte behöver föra ner en slang i matstrupen. I studie tre undersöktes vad som händer i friska lungor om man lägger till ett motstånd på utandningsdelen på respiratorn. Man har tidigare kunnat visa att det kan vara fördelaktigt att göra det på lungsjuka patienter, men hur det påverkar friska lungor var oklart. I fjärde studien undersöktes hur det transpulmonella trycket ändras i friska lungor när man flyttar sig från att ligga på rygg till att ligga på mage när man är i respirator.

Sammanfattningsvis har den här avhandlingen gett oss mer insyn i hur lungans mekanik fungerar och gett oss flera verktyg för att kunna bedriva respiratorvård på ett säkrare sätt.

LIST OF PAPERS

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

I. Gudmundsson M, Perchiazzi G, Pellegrini M, Vena A, Hedenstierna G, Rylander C.

Atelectasis is inversely proportional to transpulmonary pressure during weaning from ventilator support in a large animal model.
Acta Anaesthesiol Scand 2018; 62: 94-104.

II. Gudmundsson M, Persson P, Perchiazzi G, Lundin S, Rylander C.

Transpulmonary driving pressure during mechanical ventilation-validation of a non-invasive measurement method.
Acta Anaesthesiol Scand 2020; 64: 211-215.

III. Gudmundsson M, Pellegrini M, Perchiazzi G, Hedenstierna G, Benzce R, Rylander C.

Increasing the time constant by applying expiratory resistance – an experimental feasibility study.

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IV. Gudmundsson M, Erbring V, Lundin S, Rylander C, Persson P.

The effect of prone position on transpulmonary pressure measured with high-resolution manometry catheter.

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CONTENT

ABBREVIATIONS IV
1 INTRODUCTION 1
1.1 Acute respiratory failure 1
1.2 Mechanical ventilation 2
1.3 Lung protective ventilation 3
1.4 lung imaging 3
1.5 lung mechanics 4
1.6 Weaning 5
1.7 Transpulmonary driving pressure 6
1.8 External expiratory resistance 7
1.9 prone positioning 8
2 AIM 9
3 PATIENTS AND METHODS 10
3.1 Ethical issues 10
3.2 Patients 10
3.3 Measurements, monitoring equipment and data acquisition 11
3.4 Calculations 11
3.4.1 Paper I 11
3.4.2 Paper I, II and IV 12
3.4.3 Paper III 13
3.5 Study protocols 14
3.5.1 Paper I 14
3.5.2 Paper II 16
3.5.3 Paper III 17
3.5.4 Paper IV 18
3.6 Statistical analysis 19
4 RESULTS 20
5 DISCUSSION 30

5.1 Main findings 30
5.2 Methodological considerations 30
5.2.1 Paper I 30
5.2.2 Paper II 31
5.2.3 Paper III 32
5.2.4 Paper IV 33
5.3 General discussion 34
6 CONCLUSION 39
7 FUTURE PERSPECTIVES 40
ACKNOWLEDGEMENT 41
REFERENCES 43

ABBREVIATIONS

AECC	American-European consensus conference
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BG	Blood gas
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CV	Coefficient of variation
EE	End-expiratory
EELV	End-expiratory lung volume
EI	End-inspiratory
ERS	Respiratory system elastance
ER	Elastance ratio
ES	Esophageal
ExpR	External expiratory resistor
FiO_2	Inspiratory fraction of oxygen
FRC	Functional residual capacity
HD	Hemodynamic measurement
HU	Hounsfield unit
ICC	Intraclass correlation
ICU	Intensive care unit

PaO_2	Partial pressure of oxygen
PAW	Airway pressure
ΔPAW	Driving pressure of the total respiratory system
PEEP	Positive end expiratory pressure
PES	Esophageal pressure
ΔPES	Tidal difference in esophageal pressure
PES_{EE}	End-expiratory esophageal pressure
PES_{EI}	End-inspiratory esophageal pressure
Pexp	Pressure at end expiration
Pins	Pressure at end inspiration
PL_{ER}	Transpulmonary pressure from elastance ratio
PL_{ES}	Transpulmonary pressure from absolute esophageal pressure
Pplat	Plateau pressure
PSM	PEEP-step method
Ptp	Transpulmonary driving pressure
ΔPtp_{conv}	Transpulmonary driving pressure from the conventional method
ΔPtp_{PSM}	Transpulmonary driving pressure from the PEEP-step method
ROI	Region of interest
SD	Standard deviation
τ_{exp}	Expiratory time constant

Vate	Volume of atelectasis
Vgas	Volume of gas
VILI	Ventilator induced lung injury
VT (Vt)	Tidal volume
WOB	Work of breathing

1 INTRODUCTION

One of the most common diagnosis in the intensive care unit (ICU) is Acute Respiratory Failure(ARF)[1, 2]. The most severe form of acute respiratory failure is acute respiratory distress syndrome (ARDS) and although great progress has been made in ICU care in recent decades there is still a high mortality[2]. The main treatment is mechanical ventilation[3] which is used on a daily basis in ICU´s around the world. Despite this, setting the respirator in the most optimal way is still a great challenge to the physician. The acute phase with hypoxia and often hypercapnia has to be treated and at the same time there is often an underlying disease that has to be taken into account[4]. This has to be done without damaging the lung[5-7] and prepare them for weaning as soon as possible[8].

1.1 ACUTE RESPIRATORY FAILURE

Acute respiratory failure is one of the main reasons for admission to the ICU and is associated with significant mortality[2]. In up to 75% of patients ARF progresses into ARDS[9] and these patients often need mechanical ventilation. ARDS is not a disease in itself but a clinical syndrome with large variety of clinical conditions. These conditions can include pneumonia, extrapulmonary sepsis, trauma, pulmonary embolism and aspiration to name some, so treatment of the underlying disease is crucial when managing ARDS.

ARDS was first described by Ashbaugh and colleagues in 1697, their original description of twelve adult patients shows that there is a dramatic decrease in compliance of the respiratory system[10]. A series of more detailed definitions have been made during the years but in 1994 the American-European consensus conference (AECC) published a definition that is the basis of what is still used today.

The AECC criteria for ARDS:[11]

1. Acute onset of hypoxemia
2. Presence of bilateral infiltrates on chest X-ray
3. $PaO_2/FiO_2 \leq 200$ mmHg regardless of PEEP level
4. Pulmonary artery wedge pressure ≤ 18 mmHg or no clinical signs of cardiogenic pulmonary edema

In 2012, the adoption of the Berlin definition addressed limitations of the AECC criteria and classified patients according to the severity of the ARDS. This is the ARDS definition most commonly used today.

The Berlin definition:[12, 13]

1. Onset within a week from known insult or new or worsening respiratory symptoms
2. Bilateral opacities on chest X-ray or Computed Tomography
3. Origin of edema not fully explained by cardiac failure or fluid overload
4. PEEP $\geq$ 5 cm H_2O and PaO_2/FiO_2 between 200mmHg and 300mmHg for mild ARDS, between 100mmHg and 200mmHg for moderate ARDS and $\leq$ 100mmHg for severe ARDS

ARDS is characterized by a significant reduction in compliance[10] and this is related to diffuse alveolar damage which is considered the morphological hallmark of the lung in ARDS[14]. Diffuse alveolar damage is defined as the presence of hyaline membranes associated with interstitial edema, cell necrosis and proliferation and fibrosis often at a later stage[14].

By comparing measurements of compliance with the distribution of lung aeration compartments on Computed Tomography (CT) scans it has been found that compliance correlated with the normally aerated lung and that the specific compliance was actually normal. This has led to the concept of *baby lung*, that is the ARDS lung is not stiff (high elasticity) but instead small with nearly normal elasticity[15].

Several mechanisms can cause hypoxemia in ARDS but it is primarily caused by the loss of lung volume due to alveolar edema and collapse leading to intrapulmonary shunt and alteration in ventilation to perfusion distribution.

1.2 MECHANICAL VENTILATION

From the mid 19th century, negative pressure ventilators were available, one of the first to describe one was John Dalziel in 1838, it was an air tight box with negative pressure established by manually pumping air in and out of the box[16]. In the years to come numerous different machines were developed[17] and in 1904 German surgeon Ferdinand Sauerbruch even developed a negative pressure operating chamber[16]. During the polio

epidemic in Copenhagen Ibsen and colleagues performed a tracheostomy and ventilated their patients with positive pressure ventilation performed by over 1500 medical students, nurses and volunteers[18], the same procedure had been done by Lassen in treating tetanus patients[19]. This helped to start the modern day ICU[20, 21]. Initially ventilators only provided volume control ventilation and it was not until the late 1960´s that positive end-expiratory pressure (PEEP) was incorporated[3]. Today mechanical ventilation is used on a daily basis and there are numerous different ventilator modes available.

1.3 LUNG PROTECTIVE VENTILATION

The primary goal of mechanical ventilation is to maintain oxygenation without causing harm to the lung. In recent years iatrogenic lung injury due to mechanical ventilation i.e. Ventilator Induced Lung Injury (VILI) has become increasingly more recognized[6, 7, 22]. VILI has three main components, number one is the excess in end-inspiratory lung volume and is named volutrauma[23]. The ratio of the Tidal Volume (VT) to the end-expiratory lung volume (including that due to PEEP) is the so called strain. The excess in strain results from the amount of non-aerated lung in association with high VT and/or high PEEP and brings the end-expiratory lung volume close to the total lung capacity. The second component is barotrauma, there is a linear relationship between strain and the resulting stress which is the transpulmonary pressure[24-26]. The third component is atelectrauma which is due to repeated opening and closing of small airways during the breathing cycle[27]. The ventilator setting should be adjusted to avoid VILI and the two main factors are 1). Hyperinflation during inspiration induced by large VT and high end-inspiratory pressures. 2). Alveolar collapse during expiration and cyclic opening and closing during each breath promoted by low pressures during expiration.

1.4 LUNG IMAGING

One method for measuring the volume of air in the lung is using Computed Tomography (CT). It is important to note however that the term lung volume can be used differently in physiology compared to radiology. In physiology, lung volume is defined as the volume of gas contained within the lung. In radiology, lung volume may refer to the entire volume of the lung as an organ defined by its outer margins[28]. To be able to divide the total volume of the lung into gas and tissue, intervals of radiographic attenuation is used[29]. The minimum element of volume resolution in a scanned plane is called a voxel. Every voxel is assigned a specific value or a CT number. The scale used in

most modern CT systems is the Hounsfield scale[30]. A voxel with the attenuation identical to that of water is assigned the value of 0 Hounsfield Units (HU). A voxel with the attenuation identical to that of air is assigned the value -1000 HU. Between these points the scale is linear and extrapolated to positive values for voxels attenuating more than water. For analysis a Region Of Interest (ROI) can be manually traced and shaped to fit the purpose of the analysis. Manual ROI tracing can be expected to be reproducible within ±2% with regards to their area[31]. If the CT covers the entire lung and the ROI of every transverse section delineates its outer limits, the volume of the organ can be determined. By varying the limits of attenuation, subdivisions of the entire volume of the lung according to specific attenuation interval can be determined.

1.5 LUNG MECHANICS

The lung is an elastic structure connected to the chest cage only at its hilum. It collapses like a balloon and expels all its air when there is no force to keep it inflated. It floats in the thoracic cavity surrounded by a thin layer of pleural fluid and is kept open by the willingness of the thoracic cage to expand. The pleural pressure is therefore negative, otherwise the lung collapses. The alveolar pressure is the pressure inside the lung alveoli and when the glottis is open and no air is flowing the pressure in the alveoli is equal to atmospheric pressure. The transpulmonary pressure is the difference between the alveolar pressure and the pleural pressure and measures the elastic forces of the lung[32].

Before going further some definitions must be clear:

- *Driving pressure: Difference between end-inspiratory and end-expiratory pressure.*
- *Compliance: Change in lung volume produced by a unit change in transpulmonary pressure.*
- *Elastance: The reciprocal of compliance, the pressure required to inflate the lungs.*
- *Resistance: Change in pressure per unit flow, usually in cmH_2O.*
- *Time Constant: The quotient between the lung resistance to airflow and its elastance[33, 34].*

In clinical practice, these measures are applied to the entire respiratory system because isolated lung mechanics are difficult to measure. To be able to provide mechanical ventilation with minimal risk of VILI one needs to understand the

mechanics of the respiratory system. It is important to have in mind that it is based on two parts, the chest wall (which includes the thoracic wall and the diaphragm in contact with the abdominal content) and the lung. The chest wall and lung 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[35]. By using esophageal pressure measurements it is possible to separate the mechanics of the lung from the whole respiratory system in mechanically ventilated patients[36]. Lung mechanics can be divided into two parts. One is static which includes the forces acting on the lung and affects volumes and elastic behavior. The other is dynamic which involves the forces that moves air and addresses flow patterns and resistance[37]. In studies of the contribution of lung elastance to total respiratory system elastance, the contribution ranged from 55-78%[38]. Within these patients it was possible to identify two groups of patients with very different mechanical characteristics depending on the basis of their respiratory failure. Further studies showed that increased lung stiffness decreased the corresponding change in pleural pressure when airway pressure was increased[39]. There can be a considerable variation in the transpulmonary pressure depending on the ratio between elastance of the lung end the elastance of the respiratory system. The importance of separating these two was further highlighted in a study by Gattinoni where he described pulmonary and extrapulmonary ARDS with different lung and chest wall elastances depending on the origin of the ARDS[40]. This is also true in other instances like laparoscopic surgery[41] and obesity[42]. Consequently, without considering the lung and chest wall elastance, it is not possible to estimate the transpulmonary pressure and consequently to assess the possible risks of lung overdistension or collapse[26, 43].

1.6 WEANING

Weaning is defined as the process of liberating the patient from mechanical support and the endotracheal tube. The process starts when the underlying illness that led to mechanical ventilation has resolved to a degree that the patients can breathe by themselves. Readiness to wean should be evaluated early in the course of mechanical ventilation and the discontinuation should be rapid to minimize ventilator induced lung injury and other complications[8]. When decision to wean has been taken a gradual decrease in inspiratory and end-expiratory pressures are performed whereas the patient increases the spontaneous breathing effort. If the patient has no spontaneous breathing effort, decreasing the PEEP lowers transpulmonary pressure and may lead to a rapid decrease in arterial saturation because of derecruitment of the lung and

shunt[44]. When the patient is considered to be able to breath on his own, extubation is performed. Extubation failure occurs in 10 – 20% of patients and is associated with poor outcome[45]. It is therefore of great interest to be able to wean the patient effectively but with a good safety margin against reintubation.

Work of breathing is the work that the respiratory muscles do to maintain ventilation. In quiet breathing, the work is exerted during inspiration while expiration is passive. During mechanical ventilation the patient performs almost no work but during weaning the patient is required to do increasingly more work by himself until he can breathe on his own. The work of breathing can be divided into three components, one is to expand the lung against the lung and chest wall elastic forces, the second is to overcome the viscosity of the lung and chest wall and the third is to overcome airway resistance during movement of air into the lung[32].

1.7 TRANSPULMONARY DRIVING PRESSURE

The driving pressure which is the difference between end-inspiratory pressure and end-expiratory pressure, represents the force that distends the entire respiratory system during mechanical positive pressure ventilation[46]. The transpulmonary pressure is the difference between airway pressure and pleural pressure and reflects the force exerted on the lung surface at any given moment[47]. Consequently, the transpulmonary driving pressure represents the force that distends the lung during mechanical ventilation. As mentioned previously VILI is associated with several mechanisms where uptake of mechanical energy causes injury to the lung structure. VILI has been associated with large driving pressure as measured at the airway opening[46]. Increased amplitudes of transpulmonary pressure swings distending the lung are injurious and therefore it has been advocated for several years that clinical measurements of the transpulmonary pressure are important [48, 49].

As will be discussed later in this thesis, calculating transpulmonary pressure from esophageal pressure measurements is no easy task. Finding a method that would make this easier and less invasive would be of great interest and perhaps get physicians to use transpulmonary pressure more in clinical practice. Furthermore, there is an alternative non-invasive method for calculating transpulmonary pressure available that is based on the stepwise changes of PEEP with increased end-expiratory lung volume (EELV)[50] that needs to be validated in the ICU.

1.8 EXTERNAL EXPIRATORY RESISTANCE

Much of the research in mechanical ventilation has been about the inspiratory phase, believing the expiratory phase is passive and trouble-free[20]. Recently though experiments studying the expiratory phase have shown some interesting features. One for example demonstrated an important role of the diaphragm in attenuating the expiration time[51]. To retain more control over the degree of lung inflation over the entire tidal cycle, expiration can be actively modulated in a relatively new ventilator modality, the "Flow Controlled Ventilation"[52, 53]. This ventilator mode was proposed quite recently[54] and requires special experimental or patented commercial equipment including feedback loops with computed monitor data and a special ancillary endotracheal tube inserted into the ordinary endotracheal tube[53, 55].

In ARDS the expiratory phase can be prolonged because of outflow obstruction[56] but the dominant effect is a shortened expiratory time in an edematous lung with increased elastance[57]. A simple and physiological method for keeping the injured lung open is to increase the shortened expiratory time by adding a variable expiratory resistor to the ventilator circuit[58]. The resistor increases the expiratory time constant which normally is defined as one third of the time it takes the lung to passively exhale 95% of the maximum inspiratory volume. To increase the end-expiratory lung volume (EELV) increasing the PEEP is the most common method. But increasing the PEEP comes with the risk of hyperinflating the lung at inspiration and decreasing compliance[59]. Reversing the inspiratory vs. expiratory (I:E) quotient has been suggested so that the inspiratory phase will be longer than the expiratory phase[60], but this too comes with increased risk of intrinsic PEEP and hyperinflation. Increasing the respiratory frequency (RF) increases the absolute time that the lung is open but it exposes the fine lung structures to more energy uptake which in recent years have been shown to be correlated with increased risk of VILI[61, 62]. Recent studies have shown that by applying resistance to the expiratory limb of the mechanical ventilator circuit, it is possible to increase the time constant, thereby increasing the time during which the lung in inflated above EELV without the risk of hyperinflation and intrinsic PEEP[63, 64]. Knowing that increased PEEP increases the risk of hyperinflation in healthy lung, the question remains as to how the external expiratory resistance would affect healthy lung in terms of time constant, driving pressure, respiratory compliance and intrinsic PEEP.

1.9 PRONE POSITIONING

For decades prone position has been used as a treatment in severe hypoxemia in ARDS[65, 66], it has even been shown that it reduces mortality in mechanically ventilated patients with ARDS[67, 68]. Prone position improves ventilation-perfusion matching and prevents VILI by affecting lung and chest wall mechanics[69]. A part of the effect comes from the weight of the heart being lifted from the lung in prone position and thus decreasing the relative compression volume of the lung by the heart and mediastinum[70, 71]. Esophageal pressure measurements have been used in several studies aiming to optimize mechanical ventilation in ARDS[49, 72-74] and in recent years even in prone position on both animals and humans[75-79]. There seem to be an increase in end-expiratory transpulmonary pressure in prone position through a decrease in end-expiratory esophageal pressure[76, 77, 79] and an increased chest wall elastance[75, 80]. Recently though a study has shown that the relation between esophageal pressure and directly measured pleural pressure is different in prone compared to supine position[81].

2 AIM

The main aim of this thesis is to study how the mechanical properties of the lung can be managed by applying transpulmonary pressure measurements and adding expiratory resistance.

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

I. Determine the relationship between transpulmonary pressure and the volume of atelectasis and gas in the lung in a situation resembling weaning from mechanical ventilation

II. Validate a non-invasive method based on the PEEP-step method for assessing transpulmonary driving pressure in mechanically ventilated patients during intensive care

III. Assess how respiratory mechanics in healthy lungs react to increased external expiratory resistance by measuring time constant, driving pressure, respiratory compliance and intrinsic PEEP

IV. Describe the distribution of pressure in the esophagus of healthy anesthetized patients and to measure the effect of prone position on transpulmonary pressure

3 PATIENTS AND METHODS

3.1 ETHICAL ISSUES

Study protocols on patients in paper II (Dnr 615-13) were approved by the Regional Research Ethics Committee of Gothenburg. The patients in paper II were often sedated and mechanically ventilated and therefore getting informed consent from the patients was sometimes impossible. Instead next of kin was informed of the study protocol and could give informed consent. The study protocols on patients in paper IV (Ref 2019-06583) were approved by The Swedish Ethical Review Authority. Informed consent was obtained from the patient before surgery. All the studies on humans were minimally invasive and did not affect the clinical therapy provided by the attending physician. The ethical concern was mainly about patient integrity while working with the sampled data.

The studies on animals (papers I (Dnr C335-9) and III (No 5.8.18-20174) were approved by the Regional Animal Ethics Committee in Uppsala. All animals were treated in adherence with the European Union Directive 2010/63/EU for animal experiments and according to the National Institute of Health Guidelines and the Helsinki Conventions for the use and care of animals. All the studies on animals were supervised by specialists in animal anesthesia to guarantee appropriate sedation and analgesia. In paper I radiological imaging with CT scans was important for the understanding of the pathophysiology of the lung injury but the quantity of radiation needed made it impossible to do the study on humans.

3.2 PATIENTS

In paper II the inclusion criteria was positive pressure mechanical ventilation in the ICU. Contraindications were damage to the lung or thoracic wall (i.e. pneumothorax or pleural drainage) and diseases of the esophagus that contraindicated the use of an esophageal balloon catheter. In paper IV the inclusion criteria was lung healthy adults undergoing spinal surgery requiring prone position.

3.3 MEASUREMENTS, MONITORING EQUIPMENT AND DATA ACQUISITION

CT scans in paper I were taken at the mid thoracic level. Images were then analysed by a dedicated software to find the maximum inspiration and maximum expiration. The Region of interest (ROI) was identified and calculations were made for different Hounsfield Units (HU).

Airway pressure was measured at the proximal end of the endotracheal tube via a side-mounted, small bore, stiff plastic catheter. Readings of ventilation volumes were imported in real-time from the Servo I/U or Flow I ventilator into a personal computer and processed using a dedicated software (Maquet Critical Care, Solna, Sweden).

Esophageal pressure in papers I and II was measured with an esophageal balloon catheter. Correct positioning was verified according to a modified occlusion test[82], were the rib cage was compressed during occlusion of the airway[83]. Pressure variations in tracheal and esophageal tracings were compared and catheter position was adjusted to get the best fit.

A standard pressure transducer was used for tracheal and esophageal pressure tracing.

In paper IV esophageal pressure was measured with high resolution esophageal manometry catheter which has 36 pressure channels 1cm apart.

In paper III readings of airway pressure, flow and volume were acquired using a ventilator specific software (ServoAnalysisTool, Maquet-Getinge Critical Care, Solna, Sweden).

3.4 CALCULATIONS

3.4.1 PAPER I

In the CT images the volume of atelectasis within each ROI was calculated as the aggregated volume of voxels attenuating from -100 to 100 HU. The total volume of gas within the ROI was calculated according to the formula[84]

$$V=\sum_{i=1}^{n}\left[V_{vox}\times\left(\frac{-HU}{1000}\right)\right]$$

In which HU is the single voxel attenuation and V_{vox} is the single voxel volume of *n* voxels within the ROI.

Work of breathing was defined as the respiratory work generated by the animal regardless of the contribution from the mechanical support[85]. It was calculated as the integrated area of the pressure/volume loops registered from esophageal pressure and VT in parallel to the dynamic CT images[86]. Using the Campbell diagram two breath loops were analysed for each ventilator setting and the mean WOB values were divided by the corresponding tidal volume and expressed as ml/L[87].

3.4.2 PAPER I, II AND IV

There are two different methods for measuring transpulmonary pressure using esophageal pressure. One is calculating transpulmonary pressure as the difference between the airway pressure and the absolute esophageal pressure[72]. The other is calculating the transpulmonary pressure from lung elastance based on tidal variations in the esophageal pressure[26, 88-90], (calculations are seen below). Which method better describes the pressure relationship in the lungs is difficult to say. A study in 2018 compared these two methods to transpulmonary pressure derived from pleural pressure measured with flat balloons within the pleural space. The results indicated that calculation from absolute esophageal pressure corresponds to transpulmonary pressure in the mid/dorsal lung region while calculations from tidal changes in esophageal pressure corresponds to transpulmonary pressure in the ventral part of the lung[91]. This may be true in the supine position but the relationship is more unclear in the prone position[81].

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 plateu pressure – End-inspiratory esophageal pressure (PES_{EI})

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

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

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

Lung elastance (EL) = (ΔPAW – ΔPES)/VT

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

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

3.4.3 PAPER III

To achieve increased expiratory resistance, external expiratory resistors were applied to the expiratory limb of the ventilator. To avoid the potential flaw of nonlinearities, the measures of the different expiratory resistors were reported at a reference flow of 0,8L/s (table 1).

Table 1. Characteristics of the external resistors. Resistance measured at a reference flow of 0.8L/s. ExpR 0 = Expiratory circuit of the ventilator without any added resistor. ExpR 1-3 = Resistors added to the expiratory circuit of the ventilator.

Resistor	**Inner diameter** (mm)	**Resistance** ($cmH_2O/L/s$)
ExpR 0 (Baseline)	N/A	15,4
ExpR 1	5.0	31,1
ExpR 2	4.5	53,9
ExpR 3	4.0	76,5

The expiratory time constant is defined as the time it takes to passively exhale the lungs, with 3τ the time it takes to reach at least 95% exhalation. Because the onset of exhalation in mechanically ventilated patients is mainly dominated by inertial effects the analyses starts at 75% of breath-wise maximum and skips the first part of the exhalation curve[58, 92]. 3τ was measured as the time in seconds it took to passively exhale the volume from the point where 75% of the end inspiratory lung volume was left till the point where 5% of the end inspiratory lung volume was left, and then divided by three to get the expiratory time constant (Figure 1).

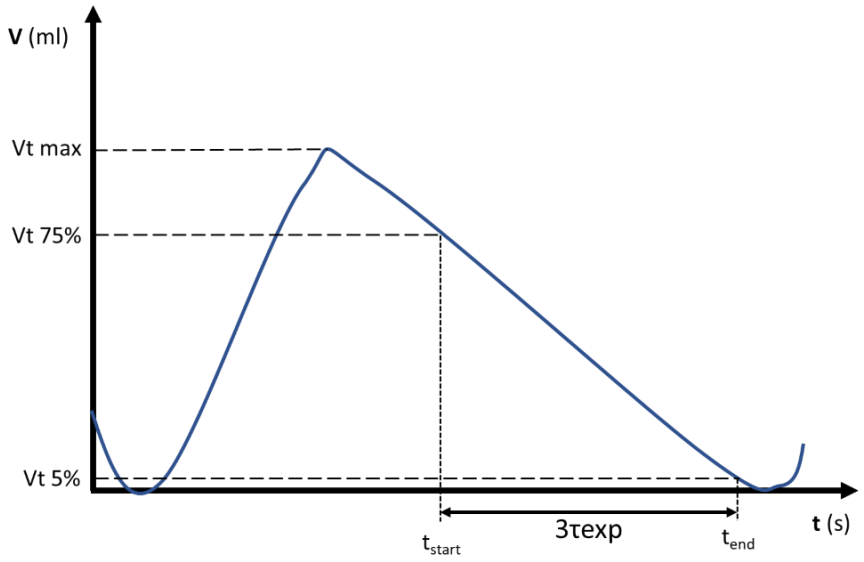

Figure 1. Determination of the expiratory time constant (τexp) from the volume curve.

Principle for determining the expiratory time constant from the expiratory volume curve. τstart is the time at 75% of breath wise maximum tidal volume (Vt). τend is the time at 5% if breath wise maximum tidal volume (Vt). τexp is the expiratory time constant in seconds. 3 τexp was defined as the period between τstart and τend.

3.5 STUDY PROTOCOLS

3.5.1 PAPER I

Relationship between changes in transpulmonary pressure and development of lung atelectasis during weaning.

Ten anaesthetized pigs were surfactant depleted by performing whole lung lavage. With preserved spontaneous breathing, mechanical ventilation was supplied with pressure support. A protocol with a stepwise decrease in pressure support and eventually negative pressure setting was followed. (Figure 2) At every step a juxtadiaphragmatic dynamic CT scan was performed while measuring esophageal pressure with esophageal balloon catheter. Transpulmonary pressure was calculated as Paw – Pes, with Pes used as a substitute for pleural pressure[48]. For each pressure level of the ramp, the two images representing maximum inspiration and maximum expiration were identified and region of interest (ROI) was manually traced. The volume of atelectasis within the ROI was calculated as the aggregated volume of voxels attenuating from -100 to 100 Hounsfield Units (HU) as previously described. (Figure 3)

CT	top	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn	dyn
Pins	0	8	6	4	2	0	0	0	0	0	0	0	-4	-8	-12	-16	-20	-24	0
Pexp	0	12	12	12	12	12	10	8	6	4	2	0	-4	-8	-12	-16	-20	-24	0
	BG HD Pre-ramp											BG HD Mid-ramp							BG HD Post-ramp

Figure 2. Protocol with ventilator support/negative pressure setting (cm H_2O)

During preserved spontaneous breathing, first inspiratory pressure support then PEEP from the ventilator were deceased in steps down to zero, followed by application of increasingly negative pressure from thoracic drainage unit connected to the breathing circuit. At each level of the ramp procedure, dynamic transverse 5mm CT scans were acquired at a fixed mid-thoracic level. Hemodynamic measurements and blood gas samples were acquired at specific protocol positions with no external pressure applied. CT = Computed Tomography, Pins = Pressure at end inspiration (pressure support above PEEP when applicable in cm H_2O), Pexp = Pressure at end-expiration (PEEP when applicable in cm H_2O), BG = Blood Gas Sampling, HD = Hemodynamic Measurements.

3.5.2 PAPER II

Validation of a non-invasive method to calculate transpulmonary driving pressure.

31 patients undergoing mechanical ventilation in an ICU were included. Measurements of transpulmonary driving pressure were performed with both esophageal balloon catheter (conventional method) and with a non-invasive method based on the PEEP step (PEEP-step method)[50]. In the conventional method the transpulmonary driving pressure was calculated as ΔPaw-ΔPes where the ΔPaw is Paw_{ei}-Paw_{ee} and ΔPes is Pes_{ei}-Pes_{ee}, ei and ee representing end-inspiratory and end-expiratory positions respectively, in the tidal cycle. In the PEEP-step method the transpulmonary pressure is calculated as Elung x Vt, where Elung is lung elastance calculated as ΔPEEP/ΔEELV[93]. ΔEELV is the difference between end-expiratory lung volume at the different PEEP levels. The EELV was measured with a dedicated software as the accumulated difference between inspired and expired gas volumes during 15 breaths after the PEEP change. The patients were ventilated with volume-control mode with PEEP set by the attending physician. After muscle relaxation a PEEP increase that yielded an increase of EELV equal to one actual tidal volume was performed[94]. (Figure 4) For the comparison to the esophageal method the PEEP was increased and after a period of at least 20 breaths the PEEP was decreased to baseline again, the procedure was repeated twice and the mean of triplicate EELV measurements and esophageal pressure measurements were used to calculate transpulmonary driving pressure.

3.5.3 PAPER III

Investigating the effect of increased expiratory resistance on respiratory mechanics.

Twelve pigs were anesthetized and ventilated with volume control ventilation. Airway pressure and flow were continuously acquired at the airway opening and analyzed with a software where pressure and volume curves were built. A combination of three consecutive PEEP levels (0, 6 and 12) and four respiratory resistances were tested, by adding three constant time-invariant expiratory resistors to the expiratory limb of the ventilator. Time constant, respiratory compliance, driving pressure and intrinsic PEEP were achieved at every PEEP level and at every resistance.

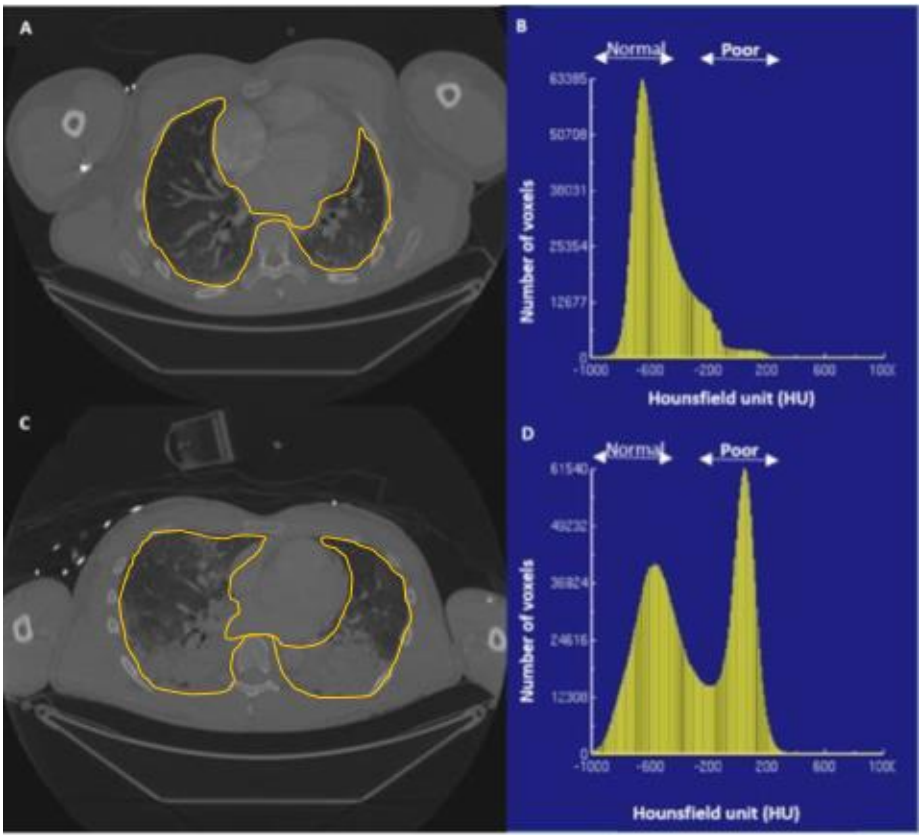

Figure 3. Juxtadiaphragmatic dynamic CT scans at maximum inspiration (A) and maximum expiration (C). Region of interest are manually traced on both images (yellow lines). The number of voxels with Hounsfield units between -1000 and 1000 within the region of interest are counted and the results are shown in diagram B for maximum inspiration and in diagram D for maximum expiration.

3.5.4 PAPER IV

Investigating the effect of prone positioning on transpulmonary pressure.

10 lung healthy subjects undergoing spine surgery were included. The subjects were anesthetized, pharmacologically paralyzed, and mechanically ventilated. At baseline the patients were in the supine position and ventilated in with volume control, PEEP 5 cmH_2O with tidal volumes of 6ml/kg ideal body weight and respiratory rate of 15. After insertion of the high resolution manometry catheter, continuous recording of esophageal pressure, airway pressure and tidal volume was initiated. Pressure sensors spaced 2cm apart inside 22cm of the esophagus (22 to 44 cm from the nostril) were used for registration of esophageal pressure at the end of expiration (PES_{EE}). Transpulmonary pressure was then calculated for every segment of the esophagus as the difference between airway pressure and esophageal pressure (Transpulmonary pressure=PAW-PES). End inspiratory transpulmonary pressure was also calculated from the airway plateau pressure (P_{PLAT}).

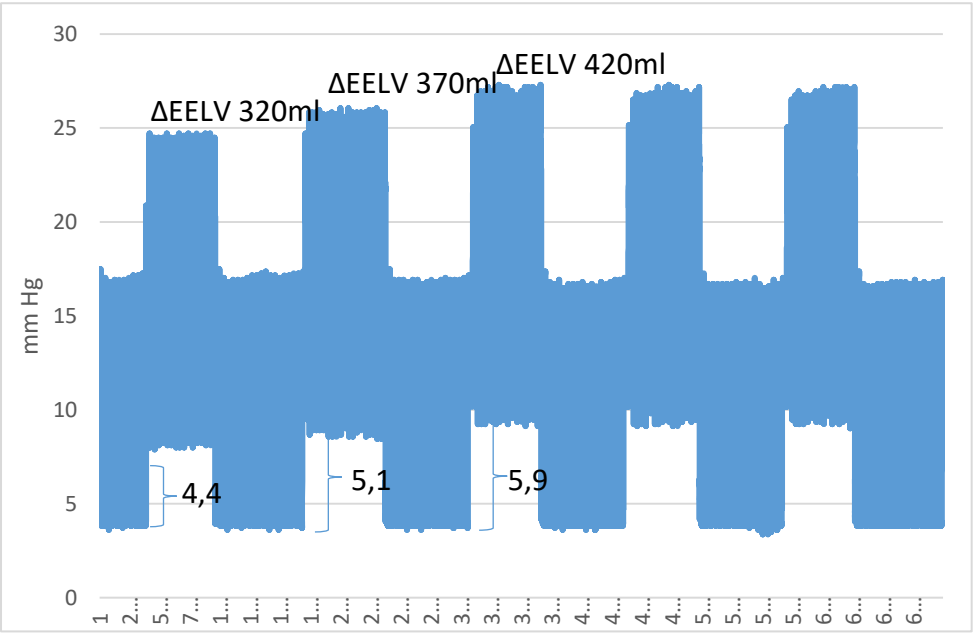

Figure 4. Airway pressure depicting how increasing PEEP increases end-expiratory lung volume (EELV) until it reaches the same volume as the tidal volume and then increasing and decreasing it three times for the measurement. The first PEEP step is 4.4mm Hg which equals 6cm H_2O increasing the EELV by 320ml. The next PEEP step is 5.1 mm hg which equals 7cm H_2O increasing the EELV by 370ml. the third PEEP step is 5.9mm Hg which equals 7cm H_2O increasing the EELV by 420ml which is the same volume as the tidal volume (Vt=420ml).

3.6 STATISTICAL ANALYSIS

Paper I

Data were presented as mean (SD) and $p<0,05$ was chosen as the level of significance. Wilcoxon signed-rank test was applied to repeated measurements. A linear mixed model with autoregressive correlation matrix was used to evaluate the correlation between transpulmonary pressure and gas/atelectasis volume with repeated measures defined by the different steps of the protocol[95].

Paper II

For this study a sample size of 27 patients was deemed necessary to detect an intraclass correlation coefficient (ICC) of 0,6 assuming an inherent ICC of 0,2 for measurements with the two methods with 95% probability and 80% power[96]. The agreement between the esophageal and the non-invasive methods was assessed according to Bland and Altman. The coefficient of variation for triplicate measurements was calculated as the standard deviation of the difference divided by the mean of all measurements.

Paper III and IV

Comparing different expiratory resistances in paper III and supine versus prone position in paper IV we used Wilcoxon signed-rank test with $p<0,05$ chosen as level of significance.

4 RESULTS

Paper I

In paper 1 were we analyzed the relationship between transpulmonary pressure and atelectasis we found that most of the animals were fully recruited at the start of the ramp procedure and atelectasis did not occur until PEEP was decreased to about 4 cm H_2O. The changes in gas and atelectasis volumes during the ramp procedure are presented in figure 5. The mixed model analysis showed significant linear correlations with equations. Correlation coefficients are displayed in table 2. In parallel with first pressure support and then PEEP being reduced to zero, end-inspiratory esophageal pressure and transpulmonary pressure gradually decreased and the total work of breathing gradually increased (figure 6).

Table 2. Linear equations expressing the volume (y) indicated in the head of the column as a function of transpulmonary pressure (x) as found applying linear mixed model with an autoregressive correlation matrix to the respective x/y plots.

	End-expiration		End-inspiration	
	Vgas	Vate	Vgas	Vate
Correlation	y=31+0.91x	y=11.7-0.62x	y=26.4+0.88x	y=16.2-0.59x
p-value	<0.001	<0.001	<0.001	<0.001

Paper II

Out of around 180 patients that were screened for participation in the study 31 patients were enrolled and studied. The patients had been submitted to mechanical ventilation for a median (range) of 2 (1-27) days. The coefficient of variation for the repeated measurements was 6,5% for EELV, 4,3% for transpulmonary driving pressure measured with the PEEP-step method and 9,2% for transpulmonary driving pressure calculated with the conventional method. Data are listed in table 3. The ICC of 0,864 and the Bland-Altman plot with all measurements within ±2 SD (figure 7) indicated good agreement between the two methods.

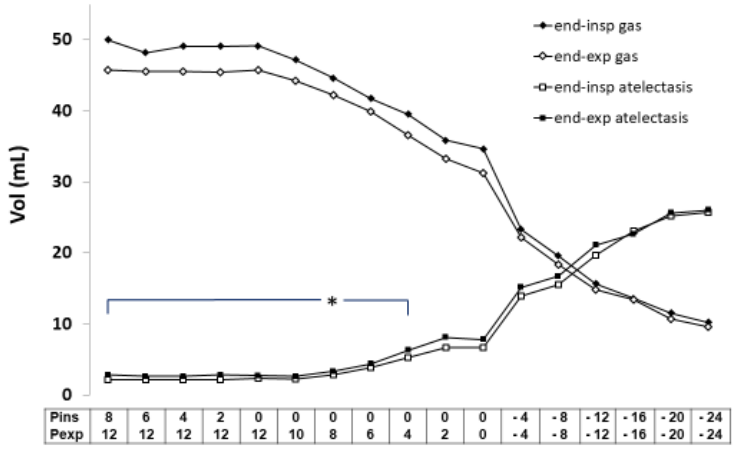

Figure 5. Atelectasis and gas volumes

*End-inspiratory and end-expiratory volumes of atelectasis and gas within dynamic transverse 5 mm CT scans acquired during assisted spontaneous ventilation at different ventilation settings, decreasing first pressure support, the PEEP, followed by increasingly negative airway pressure. Cyclic collapse, represented by the space between the plots of atelectasis at end-inspiration and end-expiration did not change significantly during the ramp procedure. Pins = Pressure at end-inspiration (pressure support above PEEP when applicable in cm H_2O), Pexp = Pressure at end-expiration (PEEP when applicable in cm H_2O), * = first significant increase of end-inspiratory as well as end-expiratory atelectasis volume ($p<0,05$), Wilcoxon signed rank test.*

Table 3. Data are expressed as median (min-max). Pressures are expressed as cmH_2O. Pressure measurements with the conventional method were measured with the same tidal volume as the difference in end-expiratory lung volume in the PEEP-step method and from the same initial PEEP.

Mechanical ventilation characteristics	
ΔPEEP	6 (4-10)
End-inspiratory pressure at baseline	17.1 (13.6-25.4)
Airway driving pressure	9.1 (5.6-19.1)
FiO_2	45 (25-80)
P/F ratio	0.33 (0.1-0.62)
Esophageal pressure measurements	
End-expiratory esophageal pressure	9 (-0.7-21.7)
End-inspiratory esophageal pressure	12.4 (3.7-23.8)
End-expiratory transpulmonary pressure	0 (-13.3-7.8)
End-inspiratory transpulmonary pressure	5 (-7.3-20.9)
Transpulmonary driving pressure	5.9 (2.4-14.4)
PEEP-step mesaurements	
ΔEELV (ml)	484 (231-687)
Transpulmonary driving pressure	6.7 (4.1-12.3)

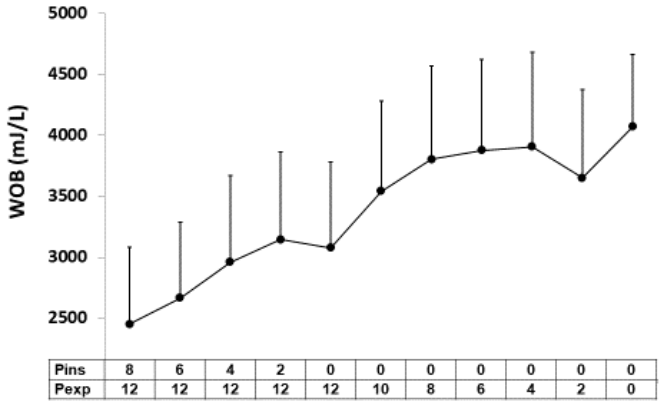

Figure 6. Total work of breathing derived from Campbell diagrams obtained during assisted spontaneous ventilation at the different ventilator settings, decreasing pressure support first, then PEEP. Pins = Pressure at end inspiration (pressure support above PEEP in cm H_2O. Pexp = Pressure at end expiration (PEEP in cm H_2O). Error bars are standard errors of plotted mean values.

Paper III

With added expiratory resistance the time constant increased significantly at all the PEEP levels. It also increased at every PEEP level irrespective of expiratory resistance. The respiratory compliance increased significantly with increased expiratory resistance at PEEP 0, it was relatively unchanged at PEEP 6, but decreased at PEEP 12. Driving pressure decreased significantly with increased expiratory resistance at PEEP 0, at PEEP 6 and PEEP 12 it increased slightly but the difference was not significant. Intrinsic PEEP increased significantly at every PEEP level. Results can be seen in table 4.

*Table 4. Time constant (s) at three levels of PEEP and expiratory resistance. Measurements acquired at the airway opening. PEEPi; intrinsic PEEP, ExpR0; Baseline without any added resistor to the expiratory circuit, ExpR1-3; Different expiratory resistors decreasing in diameter. Data presentet as median (IQR). Time constant was measured in seconds. *p<0,05 according to Wilcoxon signed-rank test compared to baseline.*

	PPEP (cmH_2O)	**ExpR 0**	**ExpR 1**	**ExpR 2**	**ExpR 3**
Time constant (s)	PEEP 0	0.18 (0.03)	0.21* (0.051)	0.24* (0.05)	0.25* (0.029)
	PEEP 6	0.18 (0.049)	0.25* (0.072)	0.28* (0.031)	0.29* (0.036)
	PEEP 12	0.22 (0.024)	0.31* (0.027)	0.32* (0.040)	0.36* (0.047)
Compliance (ml/cmH_2O)	PEEP 0	29 (7.8)	34* (6.0)	37* (6.4)	38* (2.5)
	PEEP 6	37 (5.2)	38 (5.9)	39 (7.9)	37 (11.5)
	PEEP 12	36 (7.6)	32 (6.0)	32 (8.8)	30* (6.3)
Driving pressure (cmH_2O)	PEEP 0	8.1 (0,95)	6.7* (1.15)	6.0* (1.48)	6.3* (1.0)
	PEEP 6	6.4 (0.65)	6.3 (1.08)	6,3 (2.63)	7.2 (2.43)
	PEEP 12	7.1 (2.33)	7.9 (1.63)	8.1* (1.68)	8.6 (2.05)
PEEPi (cmH_2O)	PEEP 0	0.6 (0.35)	3.7* (1.93)	5.4* (2.34)	7.0* (1.05)
	PEEP 6	6.3 (0.35)	8.5* (1.35)	9.5* (1.55)	10.6* (1.45)
	PEEP 12	12.2 (0.2)	13* (1.05)	14.2* (0.98)	15.3* (1.15)

Paper IV

There is a great variability in end-expiratory esophageal pressure in the part of the esophagus 22-44cm from the nostrils in both the supine and prone position, figure 8. End-expiratory esophageal pressure measurements for the part of the esophagus 22- 44cm from nostrils is depicted in table 5. On average the end-expiratory esophageal pressure was 4.5cmH_2O higher in supine position compared to prone position. Mean end-inspiratory transpulmonary pressure was negative in supine and prone position when calculated as the difference between airway and esophageal pressure but when calculated from elastance ratio, end-inspiratory transpulmonary pressure was positive in both supine and

prone position as can be seen in table 6. The difference between end-inspiratory transpulmonary pressure calculated with the two methods was statistically significant. The difference in transpulmonary pressure between supine and prone position with both aforementioned methods is depicted in figure 9.

*Table 5. Esophageal pressure. End-expiratory esophageal pressure (PES_{EE}) and tidal variation in esophageal pressure (ΔPES) in supine and prone position. Data are presented as Median (min;max). * Statistical significant difference ($p<0,05$) according to Wilcoxon signed-rank test.*

Part of esophagus	Patient mean PES_{EE} Supine	Patient mean PES_{EE} Prone	Difference Patient mean PES_{EE} Supine-Prone
22-44cm	14.5 (9.9;29.1)	11.0 (0.8;19.7)	3.5 (-6.5;20.3)
22-30cm	17.1 (4.6;29.8)	9.5 (2.1;22.3)	2.1 (-11.2;17.7)
30-42cm	16.6 (8.8;32.2)	12.1 (0.2;26.1)	2.2 (-9.2;26.7)
Part of esophagus	Patient mean ΔPES Supine	Patient mean ΔPES Prone	Difference Patient mean ΔPES Supine-Prone
22-44cm	0.7 (0.0;3.3)	2.3 (0.7;3.5)	1.2 (-0.7;2.9)*
22-30cm	0.3 (-2.0;1.8)	0.2 (-0.5;1.5)	0.3 (-2.0;0.7)
30-42cm	1.2 (-0.3;4.6)	3.2 (1.1;4.7)	1.3 (-0.8;4.2)

*Table 6. Transpulmonary pressure. End-inspiratory transpulmonary pressure calculated as PAW-PES (PL_{ES}) and from elastance ratio (PL_{ER}). Data are presented as Median (min;max). * Statistical difference ($p<0,05$) according to Wilcoxon signed-rank test.*

Part of esophagus	End-insp PL_{ES} ($PEEP-PES_{EE}$) Supine	End-insp PL_{ES} ($PEEP-PES_{EE}$) Prone	Difference Mean Prone-Supine
22-44cm	-4.0 (-27.8;1.5)	-0.8 (-27.1;8.7)	4.5 (-7.8;21.4)*
22-30cm	-4.6 (-23.1;0.1)	-2.2 (-27.6;9.4)	3.5 (-5.7;20.7)
30-42cm	-6.0 (-31.6;4.5)	-1.8 (-28.9;8.1)	2.7 (-10.7;27.2)
Part of esophagus	End-insp PL_{ES} (P_{PLAT}*EL/ERS) Supine	End-insp PL_{ES} (P_{PLAT}*EL/ERS) Prone	Difference Mean Prone-Supine
22-44cm	10.4 (7.0;13.0)	8.3 (7.3;13.9)	-0.8 (-3.1;2.3)
22-30cm	11.7 (7.6;15.7)	12.3 (9.2;16.6)	1.0 (-4.5;4.7)
30-42cm	9.5 (6.0;13.6)	7.7 (4.6;13.3)	-1.4 (-4.7;2.8)

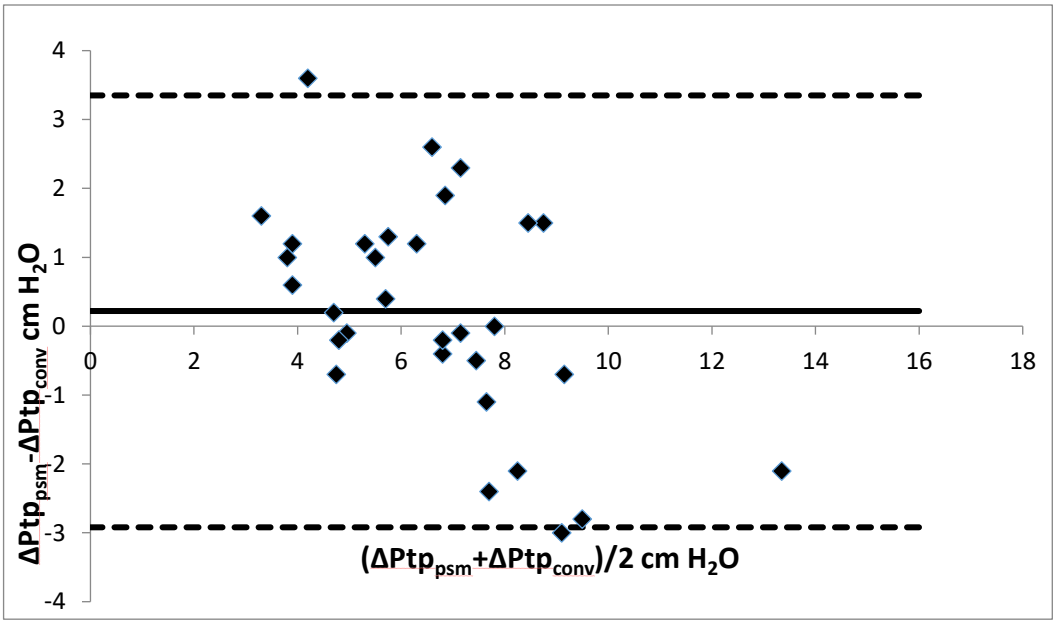

Figure 7. Bland-Altman plot. Difference between the transpulmonary driving pressure calculated by the conventional method ($\Delta Ptp_{conv}=\Delta PAW-\Delta PES$) and the PEEP step method ($\Delta Ptp_{psm}=EL*VT$) plotted against their average according to Bland and Altman. Mean difference (bias) indicated with a solid line and limits of agreement (±1.96 SD) with dashed lines.

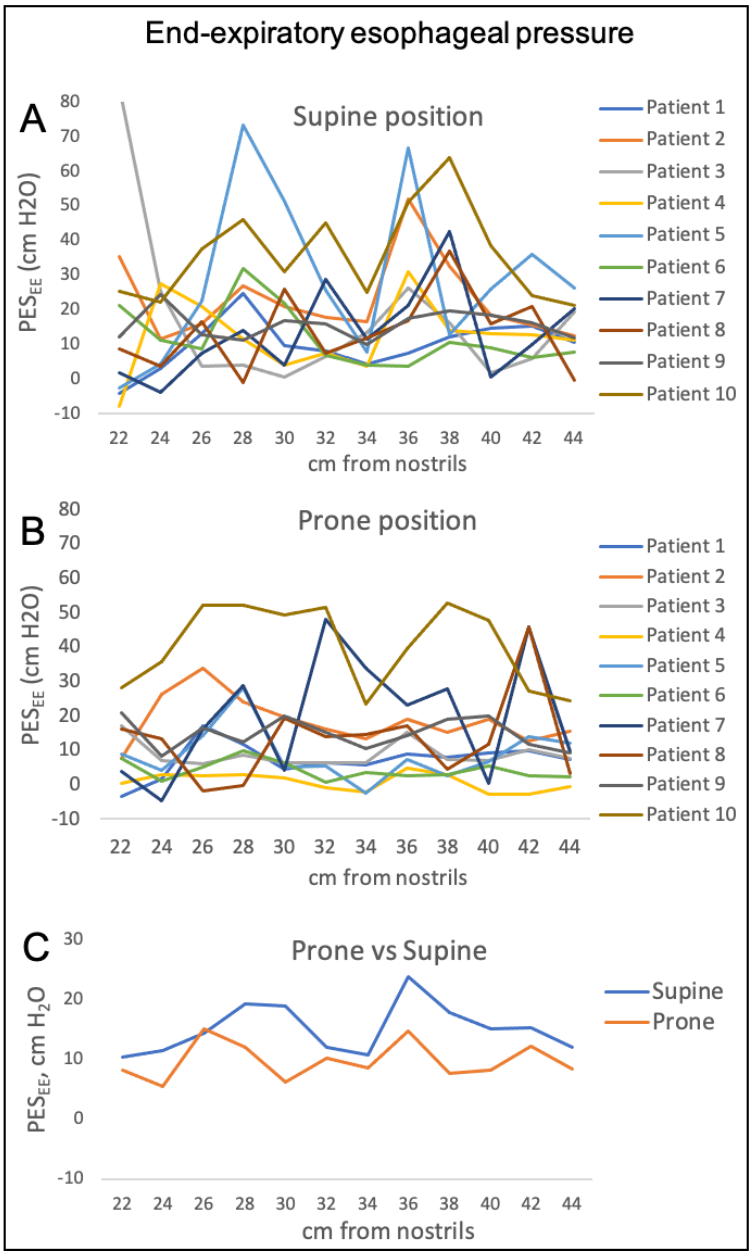

Figure 8. End-expiratory esophageal pressure (PES_{EE}) along the esophagus 22-44cm from the nostrils. A is supine position, all 10 patients shown, B is prone position, all 10 patients shown, C is a comparison of supine and prone position, median of all 10 patients shown.

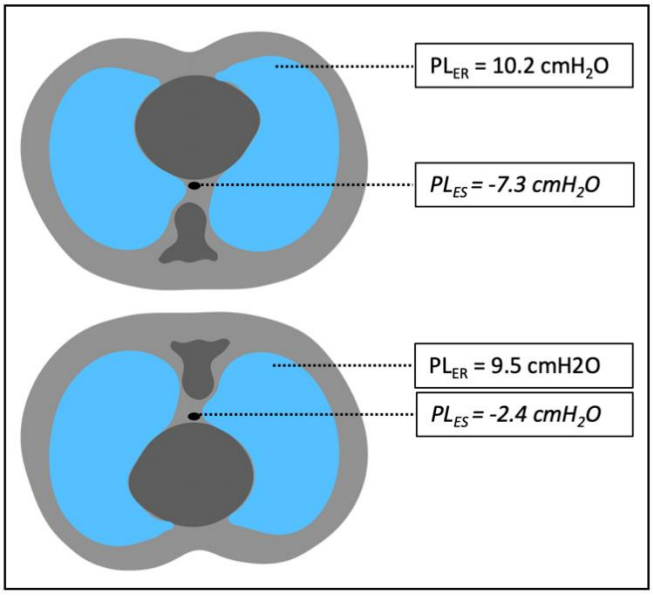

Figure 9. End-inspiratory transpulmonary pressure (PL_{ES}) calculated as PAW-PES where PAW is airway pressure and PES is esophageal pressure and from elastance ratio (PL_{ER}) presented and correlated anatomically according to previously published data (91). The image at the top depicting a patient in supine position, the image at the bottom depicting a patient in prone position. Mean within-patient SD defined as mean variation.

5 DISCUSSION

5.1 MAIN FINDINGS

There is a linear and inversely proportional relationship between transpulmonary pressure and atelectasis in moderately injured lungs during gradual decrease in ventilator support.

It is possible to use a non-invasive PEEP step method during intensive care to assess transpulmonary driving pressure in mechanically ventilated patients with a wide range of diagnoses.

Applying external expiratory resistance on healthy lung in pigs increases the time constant but also increases the intrinsic PEEP at three different PEEP levels.

The large variability in end-expiratory esophageal pressure within a patient and between otherwise healthy patients as well as the unexplained large end-inspiratory "pleural pressure" gradient indicates that absolute values of esophageal pressure is a questionable substitute for pleural pressure.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 PAPER I

This study used an animal model to allow radiation from repeated dynamic CT exposures which would have been impossible in a human study. The radiographical method has been developed and previously used by our group where dynamic CT exposures have been needed to analyze gas distribution during ongoing ventilation[97]. This approach has the limitation of having a single plane of exposure that may not be representative of the entire lung[98]. On the other hand, the juxtadiaphragmatic plane has been shown to best represent the lung tissue structure[99] and the content of one single plane on CT is mirrored by adjacent planes[100]. The goal of the lavage was to create a moderate lung injury that would be stable during the entire protocol and this goal was achieved as shown by hemodynamic and respiratory data. There is however a weakness of the model and which is that it has not been shown to mimic older lung injury during healing. In fact, it may induce an inflammatory

defense reaction in itself[101]. As the focus of the study was on the pathophysiological interplay between lung collapse and different ventilator conditions and the lavage model promotes that, this method of lavage is acceptable. The effect of PEEP on atelectasis and cyclic collapse during weaning from respiratory support is a complex matter. This study examined only the relation between mechanical parameters (pressure, work) and the entity of atelectasis that is, the direct mechanical aspects. During weaning the status of lung patency modulates the braking activity of the diaphragm and is an additional mechanism that has been described at the same PEEP levels than controlled ventilation but disappears when muscle relaxants are given[51]. The pressure settings of the protocol were chosen to ensure that the lung would start from full recruitment and end with full derecruitment so it would be possible to analyze all the dynamic changes of the dependent variables in between these end points. It was supposed to illustrate clinical practice during the weaning process by sequentially decreasing the ventilator pressure. Because of the absence of randomized application of transpulmonary pressure, its correlation with the dependent variables cannot be generalized to other situations. This study did not study the potential injurious effect of high transpulmonary pressure regardless of whether it is generated mainly by ventilator pressure or by muscular force during the weaning process[102]. Absolute esophageal pressure was used to calculate transpulmonary pressure in this study. As has been previously mentioned there are two methods for calculating transpulmonary pressure, one using absolute esophageal pressure[72] and one using delta esophageal pressure[88]. As we have learned more about lung mechanics in recent years it would have been interesting to have calculated the transpulmonary pressure with both methods for comparison. According to Yoshida[91] they represent different areas of the lung and it would have been valuable to know if the same applies in spontaneous breathing with different ventilator support.

5.2.2 PAPER II

The aim was to validate the non-invasive PEEP step method to calculate transpulmonary driving pressure in the ICU setting. The reason for using transpulmonary driving pressure is because it plays an important role in understanding the underlying mechanisms of VILI[103]. Previously this method has been validated in a lung model[104], in patients with acute lung injury[93] and in lung healthy subjects undergoing elective surgery[94]. The improvement in this study to the study by Lundin et.al is that we used a more physiological PEEP step that is more applicable to clinical practice in contrast

to a PEEP ladder from PEEP 0 to PEEP 16, and we had more patients (31 vs 12). One limitation is that we validated the measurements of transpulmonary driving pressure during mechanical ventilation only within a certain range of pressure and volume. To reflect clinical practice a PEEP step that increased EELV by one tidal volume was chosen. This rendered the patients an end-inspiratory lung volume corresponding to that of a physiological sigh to the baseline EELV.

To illustrate agreement between the two studied methods we used Bland Altman plot[105]. On the y axis the difference between the methods is displayed and on the x axis the corresponding average. The mean difference is the bias and the 95% confidence interval is depicted by the limits of agreement, which is equal two standard deviations of the bias. The standard deviation was calculated according to Bland et.al[106, 107]. To account for repeatability we used coefficient of variation (CV), it was calculated as the standard deviation of the difference divided by the mean of all measurements[108]. Interestingly the repeatability of the conventional method was slightly lesser than the repeatability of the PEEP step-method 9.2% and 4.3% respectively. As will be discussed in further detail later, it is difficult to use esophageal pressure to calculate transpulmonary pressure and there are many pitfalls. There are always difficulties involved in validating new methods when the method that is considered the gold standard is not so accurate but by using triplicate measurements we increased the precision in the assessed value.

5.2.3 PAPER III

This study sought to ascertain how healthy lung would react to external expiratory resistance. In ARDS lung there is regional heterogeneity which causes regional airway closure phenomena throughout the expiration[109, 110]. Each group of alveoli has its own expiratory time constant and inflates and deflates at volumes that are different from other neighboring groups of alveoli[111]. Applying a single, specific PEEP value to overcome the main opening pressure is quite an oversimplification[20]. It is known from COPD patients that they purse their lips during expiration to increase expiratory resistance and decrease airway collapse[112]. By applying resistance to the expiratory limb of the ventilator circuit we tried to mimic that effect, keeping the lung inflated for a longer period over the tidal cycle. It must be mentioned though that in intubated COPD patients being weaned from the ventilator, application of an external resistance did not have the same beneficial effect as pursed lip breathing[113]. High PEEP levels have been known to increase the

risk for hyperinflation in healthy lung[59]. Conversely applying external expiratory resistance has not been shown to increase that risk in injured lung[64]. To identify expiratory time constant it was measured from the time/volume curve extracted from the ventilator, that is the actual time it takes for 95% exhalation. Most often it is calculated from the evaluation of the slope of the expiratory flow-volume curve[92, 114]. Time constant calculated from the last 75% of the expiratory flow-volume curve relates well to the actual time needed for complete expiration[92] so using that method in healthy lung was considered applicable. By using actual time instead of curve fitting, one could argue that it should be called expiratory time instead of expiratory time constant. Notwithstanding, the purpose of the study being to show relative changes makes the result less sensible to these methodological limitations. Some authors have even said that calculating expiratory time constant from the slope of the expiratory flow-volume curve is inappropriate for evaluating lung mechanics, claiming direct measurement is much more accurate[115].

5.2.4 PAPER IV

In order to get a clearer picture of what happens in the esophagus during prone positioning a more accurate measurement of the esophageal pressure than has been done previously is needed. In previous studies of transpulmonary pressure in prone position esophageal balloon catheter has been used[77]. This is the conventional method, however it has certain difficulties. It is clear that the esophageal pressure is different in different regions of the esophagus and a balloon measures a mean pressure over a certain area[116, 117]. It is also clear that the higher the filling volume of air is in the esophageal balloon the higher the end-expiratory esophageal pressure will be[118]. To exclude this variables and get better measurements the research team used a high resolution manometry catheter that measures the pressure directly and not via a balloon. By using this technique it is possible to get separate measurements for every centimeter of the esophagus without worrying about balloon placement or filling volume. One can see in more detail the effect of offloading the heart and mediastinal organs from the lung in prone position. One limit of this method remains and that is that we only measure the pressure at one level in the lung which according to some authors corresponds to the mid/dorsal part of the lung[91, 119]. Others question the notion that end-expiratory esophageal pressure being equal to the pleural pressure even in the dorsal region[120]. It would have been interesting to have complemented the measurements with electric impedance tomography to see how the whole lung would be affected.

5.3 GENERAL DISCUSSION

During mechanical ventilation it is of utmost importance not to induce or aggravate existing lung injury while promoting reversal of the underlying cause of the respiratory failure. Stress (transpulmonary pressure) and strain (tidal volume / functional residual capacity at zero PEEP) are two concepts that have been used to identify the risk of VILI[24-26]. Excessive stress (high transpulmonary pressure) and strain (overdistension) are along with atelectotrauma (cyclic collapse of the alveoli during tidal ventilation) important factors in promoting VILI. To be able to individualize the ventilation therapy the different parts of the respiratory system must be identified and isolated. When the ventilator introduces air into the patient it is important to know how much of the pressure affects the lung and how much affects the chest wall complex (rib cage, diaphragm and abdomen)[88, 121-124]. The effect on the transpulmonary pressure can be very different depending on how the elastance is divided between the elastance of the chest wall complex and that of the lung[125]. For example, in a patient with increased chest wall elastance because of increased abdominal pressure, but exhibiting near-normal lung elastance, a larger part of the end-inspiratory airway pressure will be distributed to the chest wall complex with only limited influence upon the transpulmonary pressure. If on the other hand the patient has increased lung elastance because of lung fibrosis and a normal chest wall elastance, the end-inspiratory pressure will affect the transpulmonary pressure considerably more and increase the force per unit area of the pulmonary structure.

To assess lung and chest wall mechanics separately it would be ideal to be able to measure pleural pressure. In clinical work that is not possible so instead esophageal pressure is used as a surrogate for pleural pressure[48, 126, 127]. Esophageal pressure has been used in several studies aiming to optimize mechanical ventilation in patients with ARDS[49, 72-74] and in the weaning process[128]. As has been addressed previously there are two methods for calculating transpulmonary pressure, by using absolute esophageal pressure and using tidal difference in esophageal pressure and both seem to be true according to Yoshida et.al[91]. Using the absolute Pes has many pitfalls as the esophageal pressure can be effected by many things. Two of the most important factors have to do with the measurement technique and they are the position and the filling volume of the esophageal balloon. It has been shown that a higher volume of air inside the balloon increases the end-expiratory Pes[118].The position is also important as studies have shown that the pressure

difference along the esophagus can be very large in any individual[117]. Tidal difference in Pes has been used to avoid the uncertainties associated with absolute esophageal pressure[26, 88, 90]. When using tidal changes to calculate transpulmonary pressure, the assumption is made that the transpulmonary pressure at FRC (zero airway pressure) is zero, which means that the pleural pressure is zero[90, 129]. This assumption is not always true as has been pointed out by several researchers[130, 131]. 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[120]. This indicates difference in end-expiratory and tidal chest wall behavior[132]. If such a difference exists the tidal change method underestimates the end-inspiratory transpulmonary pressure[120].

As was apparent in paper IV the transpulmonary pressure calculated from absolute values increased from supine to prone position, it became less negative. Whereas the transpulmonary pressure calculated from tidal changes decreased from supine to prone position. We know that prone positioning can reduce mortality[67] so it would be logical that the transpulmonary pressure decreases when in prone position and by that reducing the stress of the lung. We can also see in paper IV that when in prone position the weight of the heart[70, 133] is offloaded from the lung and the esophageal pressure decreases substantially, but the tidal cycle amplitudes remain almost unchanged.

All things considered, using the tidal change to calculate transpulmonary pressure is more accurate than using the absolute esophageal pressure[120, 127] although it cannot precisely represent the pleural pressure. This is especially true in prone position as has been shown in both paper IV and in a recent article by Terzi et.al[81].

Although the traditional way of calculating transpulmonary pressure from airway and esophageal pressure has been available for several years, it is rarely used in the clinic[126]. The main reasons for this is that the method is cumbersome, time consuming[134-136] and challenging for physicians. So a non-invasive method would be of great importance. By validating the PEEP-step method[50] clinicians have a non-invasive method to be used bedside in the operating theatre and the ICU.

In the weaning process the ventilator support is gradually decreased and the patient has to take over and breathe on his own. The underlying question in paper I was whether a gradual decrease in in ventilator support would induce a sudden formation of atelectasis with shunt and hypoxemia, increase cyclic

collapse and a sudden increase in WOB. On the contrary we saw a linear and inverse relationship between transpulmonary pressure and atelectasis. Because the diaphragm contracts in a braking fashion during expiration[51] it may partly explain the increase in WOB during the down-titration of PEEP. We also found that the gas content of the lung decreased proportionately to transpulmonary pressure. From the respiratory mechanics perspective our results do not raise concerns about shifting WOB from the ventilator to the patient by gradually lowering pressure support and PEEP during weaning. Many studies have shown that assisted spontaneous ventilation attributes to a more homogenous distribution of ventilation and a better matching of ventilation/perfusion when compared to controlled ventilation in both clinical[137] and experimental[138, 139] settings. There is also evidence for that spontaneous breathing through an endotracheal tube at atmospheric pressure induces WOB more similar to post-extubation situation than can be achieved with pressure support breathing[140]. Also, chest radiographs from cardiac surgery patients comparing T-piece to pressure support during weaning found no difference in atelectasis[141]. But spontaneous breathing can also cause lung injury. It can do so by having large negative swings in Pes causing high transpulmonary pressure, often as high as in controlled mechanical ventilation[142]. Another mechanism is increased cyclic collapse when ventilator support is decreased during assisted spontaneous ventilation[143]. In paper I we observed increased mean values of tidal variation in atelectasis at low PEEP levels but it was not significant. It is possible that by using five mm thick CT slices to increase resolution and accuracy within the cut, only a small fraction of the lung is represented. That may explain why others using CT and electric impedance tomography have detected differences in cyclic collapse[144]. Our results regarding the relation between the volume of atelectasis and transpulmonary pressure are in line with other results that have shown that transpulmonary pressure is inversely proportional to the amount of non- aerated lung tissue in spontaneously breathing pigs[145]. In severe experimental lung injury, this relation has not been observed[102], so it may be that this only applies to less severe injury or lung injury that is partly healed. In ARDS patients the PEEP level at which arterial oxygen tension starts to fall during a PEEP down-titration is indicative of the transpulmonary pressure at which significant lung derecruitment and shunt occurs[44]. This derecruitment corresponds, in some patients, to a lower inflection point on the expiratory limb of the pressure/volume curve of the respiratory system[146]. However, alveolar derecruitment can be observed during the entire expiration by analyzing the pressure/volume curve in muscle relaxed ARDS patients[147]. It has even been shown that the volumes of gas and atelectasis are proportional to the transpulmonary pressure both during inspiration and expiration[148]. As these results are partly conflicting it may be desirable to use transpulmonary

pressure to guide individual ventilator setting during mechanical ventilation. As the load on the lung from the chest wall and abdomen is taken as similar at the beginning and the end of a breath[50], this study supports the idea that the degree of expansion of acutely injured lung is proportional to transpulmonary pressure within some upper and lower limits. In paper I full recruitment was observed at transpulmonary pressure above 20cmH_2O and full derecruitment with maximum volume of atelectasis at a transpulmonary pressure below -15cmH_2O. These transpulmonary pressure interval must be interpreted with caution though, as the interval for linear relationship can vary dependent on the constitution of the patient and the origin and the state of the lung injury.

When applying expiratory resistance to ARDS lungs the time constant increases without increasing the risk for intrinsic PEEP[63, 64]. It can give the lungs more time for gas exchange during exhalation without increasing the respiratory rate or the airway pressure. In paper III we found that by applying respiratory resistance the time constant increased but so did the intrinsic PEEP. This is in coherence with previous studies that have shown that increased resistance in healthy lungs increases time constant, induces hyperinflation[149-151], increases carbon dioxide and decreases cardiac output[149, 152]. Increasing PEEP irrespective of resistance increases the time constant too. In healthy lungs this increase is not confined to early or late time constant segments but is constant throughout the expiratory phase[153]. In injured lungs the PEEP increase changes the mechanical properties of the respiratory system fast-emptying compartments[57].

Mechanical ventilation at PEEP 0 is associated with high compliance in healthy lungs[154]. Adding an expiratory resistance can be expected to move the respiratory system up the P/V curve where it is even steeper and thereby compliance increases. By increasing the PEEP and consequently the intrinsic PEEP, the EELV increases to a point that the lungs are being ventilated above the upper inflection point and are being overdistended with lower compliance[155, 156]. Several investigator have found that there is no exact point where the lung is fully recruited and the expansion is isotropic[157]. They suggest that there is a continuous recruitment up to the maximum pressure to inflate the lung. Others have found that there is a clear lower and higher inflection point[119, 148, 158] and the lung should be ventilated in the deflation limb of the pressure/volume curve to avoid VILI[159]. In paper III the lung seem to be ventilated at the upper flattened slope of the pressure/volume curve when higher levels of PEEP and external expiratory resistances are applied. It is important to remember that in paper III the lungs are healthy and not subjected to lung injury. Therefore PEEP 12 is quite high, in injured lungs as in ARDS patients who are benefitted from higher PEEP

levels this transformation from increased to decreased respiratory compliance would materialize at a higher PEEP level[64]. Other studies, albeit in spontaneously breathing patients, have shown that expiratory resistance increased the EELV in both healthy and injured lungs without the risk of intrinsic PEEP. However, the results are difficult to compare as that study used an indirect technique to measure intrinsic PEEP by esophageal gradients during the early phase of inspiration whereas in paper III airway pressure was registered during an end-expiratory occlusion.

6 CONCLUSION

In an animal model there is a proportional relationship between transpulmonary pressure and the amounts of atelectasis and gas in the lung during pressure supported spontaneous breathing. There is no transpulmonary pressure threshold, where atelectasis with desaturation or cyclic collapse suddenly occurs during gradual decrease in the ventilator support, but an insidious increase in atelectasis, however, with no increase in cyclic collapse.

The PEEP-step method, a non-invasive method to measure transpulmonary driving pressure can be applied in mechanically ventilated patients with an accuracy comparable to the traditional esophageal balloon method.

The application of external resistors could be particularly useful during weaning from mechanical ventilation to attenuate work of breathing and avoid patient self-inflicted lung injury during spontaneous ventilation.

Prone position increases chest wall elastance as noted by increased ΔPES during tidal ventilation. The mean end-expiratory esophageal pressure changes, which affects the calculations of transpulmonary pressure but uncertainties about the use of absolute esophageal pressure remains.

7 FUTURE PERSPECTIVES

To be able to provide mechanical ventilation in a safe way while promote healing of the underlying disease a more individualized approach would be desirable. One step in achieving that is to deepen our understanding in lung mechanics and use that knowledge when setting the ventilator mode. The conclusions from this thesis can hopefully help physicians choose the appropriate ventilator mode and aid in setting the best pressure and or volume settings depending on the patient, the underlying disease, the time of mechanical ventilation and posture.

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