Regional Lung Mechanics and Influence of an Active Diaphragm in Experimental Lung Injury

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Abstract


Despite being an essential life-support strategy in severe respiratory failure, mechanical ventilation can, if not optimally set and monitored, lead to injury of the lung parenchyma and diaphragm. These conditions are called ventilator-induced lung injury and ventilator-induced diaphragmatic dysfunction (VIDD), respectively. Although substantial progress has been made in the ventilator management of severely lung-injured patients, we are still far from a fully protective mechanical ventilation. In consideration of this gap of knowledge, this doctoral thesis aimed at investigating regional lung mechanics during both inspiration and expiration, in both controlled and assisted ventilation. Particular emphasis was placed on the expiratory phase, which is involved in expiratory flow limitation, airway closure and atelectasis formation, although commonly considered non-harmful.

A novel methodological approach has been the fundamental basis for this research project. The combination of respiratory mechanics, diaphragmatic electromyographic activity and lung imaging enabled a breath-by-breath analysis at high temporal and spatial resolution.

In Study I, the gravitational field affected the distribution of gas and transpulmonary pressures, as previously shown. This effect differed between healthy and injured lungs. Moreover, lung injury induced a heterogeneous distribution of gas within the lungs, as well as an increased gravitational gradient in transpulmonary pressure. Study I was mainly aimed at testing the new methodological approach centred on the investigation of regional lung mechanics.

In Study II, the focus was on assisted ventilation and the phenomenon of gas redistribution within the lungs. Large pendelluft events had been demonstrated in disproportionate inspiratory efforts. In Study II, we showed that large pendelluft resulting from pathological respiratory drive could be attenuated by high positive end expiratory pressure (PEEP). Moreover, we showed that transient and widespread small gas redistribution events occur at all times during inspiration. Assisted ventilation and high PEEP reduced the size of gas redistribution as compared with controlled ventilation and low PEEP.

In Study III, we demonstrated a diaphragmatic expiratory contraction in lungs prone to collapse, serving to brake the expiratory flow. It preserved end expiratory lung volume (EELV) and counteracted tidal atelectasis. However, the expiratory brake induced by diaphragmatic contraction is a known cause of VIDD.

In Study IV, we tested the effects of external expiratory resistances (ExpR). We showed that, by applying ExpR, an expiratory brake was induced. The beneficial effects on EELV were retained, while the diaphragm could quickly relax during the expiration, thus reducing the risk of VIDD.

Keywords: acute respiratory distress syndrome, artificial respiration, diaphragm, pulmonary atelectasis, lung imaging, respiratory system, animal model

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To my parents.
To all of you who encourage my dreams.
List of Papers

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


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Abbreviations

ARDS: acute respiratory distress syndrome
AreaSq: mean areas of the squares obtained from quadtree decomposition analysis
COPD: chronic obstructive pulmonary disease
CPAP: continuous positive airway pressure
CT: computed tomography
CTim\textsubscript{i}: a sequence of \textit{i} CT images
$\Delta P_{\text{TP,MAP}}$: maps of transpulmonary pressure
$\Delta V_{\text{map}}$: volume maps
$\Delta \text{Vol}$: delta volume images
$\Delta P_{\text{TP}}$: delta transpulmonary pressure
EAdi: electrical activity of the diaphragm
EAdi\textsubscript{exp}: expiratory electrical activity of the diaphragm
EAdi\textsubscript{min}: minimum electrical diaphragmatic activity
eALI: experimental acute lung injury conditions
EDC: eccentric diaphragmatic contraction
EELV: end expiratory lung volume
EFL: expiratory flow limitation
End Insp: end of inspiration
ExpR: external expiratory resistances
F\textsubscript{i}O\textsubscript{2}: fraction of inspired oxygen
FRC: functional residual capacity
HL: healthy lungs
HU: Hounsfield units
IC: inspiratory capacity
I:E: inspiratory-to-expiratory ratio
IHM: inspiratory hold manoeuvre
IL: injured lung
iPEEP: intrinsic PEEP
IR: image registration
L1 – L4: cranio-caudal levels 1 – 4
MV: controlled mechanical ventilation
NegΔV: negative delta volume
NumSq: numerosity of the squares
PA: pulmonary artery
PaCO₂: partial pressure of arterial carbon dioxide
PaO₂/FI₂: partial pressure of arterial oxygen to inspired oxygen fraction ratio
Paw: pressure at the airway opening
Paw,EE: Paw at the end of expiration
Paw,plat: Paw during IHM
PCV: pressure controlled ventilation
Pdi: trans-diaphragmatic pressure
Pdi,exp: expiratory trans-diaphragmatic pressure
Pes: oesophageal pressure
Pes,EE: Pes at the end of expiration
Pes,plat: Pes during IHM
Pga: gastric pressure
PEEP: positive end-expiratory pressure
PIIA: post-inspiratory inspiratory diaphragmatic electrical activity
Pinsp: inspiratory pressure above PEEP
PosΔV: positive delta volume
P-SILI: patient self-induced lung injury
PSV: pressure support ventilation
P_{TP}: transpulmonary pressure
PTP,REG: regional transpulmonary pressure
QtD: quadtree decomposition
Q1EAdi\textsubscript{exp} – Q4EAdi\textsubscript{exp}: EAdi\textsubscript{exp} quartiles 1 – 4
Q1Pdi\textsubscript{exp} – Q4Pdi\textsubscript{exp}: Pdi\textsubscript{exp} quartiles 1 – 4
RM: recruitment manoeuvre
ROI: region of interest
RR: respiratory rate
R0 – R3: external expiratory resistances 0 – 3
SB: spontaneous breathing
SB-HighR: high external resistance during spontaneous breathing
SB-LowR: low external resistance during spontaneous breathing
SpO\textsubscript{2}: oxyhaemoglobin peripheral saturation
TAC: tomografia assiale computerizzata
T\textsubscript{exp}: expiratory time constant
T\textsubscript{long}: expiratory time constant of the slow compartment
T\textsubscript{short}: expiratory time constant of the rapid compartment
Tot\Delta V: total delta volume
V: tidal volume
V': flow at the airway opening
V\textsubscript{gas}: volume of gas
VIDD: ventilator-induced diaphragmatic dysfunction
VILI: ventilator-induced lung injury
V\textsubscript{REG}: regional volume
V\textsubscript{tissue}: volume of tissue contained in a voxel
V\textsubscript{vox}: volume of the voxel
xRaw: external resistance
1/4 Exp – 4/4 Exp: expiratory quartiles 1 – 4
Introduction

“I will argue that many controversies about ventilation strategy can be traced to uncertainties in the interpretation of data on regional lung function. I will emphasize the remaining gaps in our understanding of lung deformation at the acinar scale.”

Hubmayr RD. Am J Respir Crit Care Med, 2002

Background

Nothing in nature can be fully understood through external observation alone: nature is a complex hierarchical structure built in accordance with fundamental laws. At each level of complexity, new proprieties, laws and behaviours appear (1). Emergent phenomena dominating nature lead to a spontaneous self-organised order among its parts (2). The aim of physiology is not merely a description of what is directly evident in nature. Physiology must provide understanding of emergent phenomena and explore deeper levels of natural organisation. As regards respiratory physiology and mechanical ventilation of heterogeneously injured lungs, only a deeper knowledge of the complex regional behaviours regulating unstable airways and lung units – not merely an investigation of length of stay and mortality (3) – can lead to significant improvements of therapeutic strategies and individualised respiratory care (4).

The last decades have brought important insights into the mechanisms of lung injury. Substantial progress has been made in the ventilator management of severely lung-injured patients (5). However, the recognition that further injury can result from incongruous ventilatory settings leading to ventilator-induced lung injury (VILI) has opened a vast area of research, which still encompasses many unexplored and controversial issues (6).

Randomised controlled trials have confirmed that large tidal volumes and high driving pressures are among the main determinants of VILI (7, 8). Moreover, assisted ventilation is one of the more complex and unpredictable ventilatory conditions. In this case, VILI is called patient self-induced lung injury – P-SILI (9). Studying the interaction between lung mechanics and diaphragm function during assisted ventilation is extremely important for understanding
mechanical ventilation in patients who preserve their own respiratory drive. Unfortunately, complex patient-ventilator interactions during assisted ventilation are still largely unexplored.

Despite a clear improvement in ventilatory strategies brought about through large randomised trials, we still lack knowledge that could make mechanical ventilation fully protective. The insufficiency of information regarding regional lung mechanics and deformation at the acinar level is likely the main determinant of these unresolved issues (10).

The present research project is based on a robust and novel methodological approach characterised by a simultaneous recording of respiratory mechanics, electrical activity of the diaphragm (EAdi) and lung computed tomography (CT) scans, leading to high temporal and spatial resolution, and investigation of complex regional behaviours characterising unstable airways and lung units under various ventilatory conditions.

Mechanical ventilation and VILI
Mechanical ventilation is intended as supportive treatment of the respiratory function, ensuring gas exchange while allowing the respiratory muscles to rest. Ventilatory support was first introduced during the polio epidemic in Copenhagen 1952, decreasing mortality from over 80% to 40% (11). Despite the clear benefits and a normalised gas exchange, many patients still died. Among all the possible causal factors, direct complications of mechanical ventilation, such as barotrauma due to structural damage of the lung, could be observed (12). Lung damage as a consequence of mechanical ventilation is now referred to as ventilator-induced lung injury (VILI) (13). The recognition of the importance of VILI has led to considerable changes in ventilatory strategy. The main target was initially related to gas exchange optimisation, but now a new target has been introduced: minimising VILI, even if this means accepting a higher partial pressure of arterial carbon dioxide (PaCO₂). Controlled randomised trials have clearly shown that large tidal volumes and/or high driving pressures are among the main determinants of VILI (7, 8, 14, 15). Thus, a ventilation strategy characterised by low tidal volume, high PEEP and low driving pressure is now considered state of the art in terms of protective ventilation. However, fully protective mechanical ventilation is still far from being reality.

P-SILI and assisted ventilation
Assisted ventilatory modalities have been developed with the purpose of optimising the interface between mechanical ventilation and a patient’s pattern of spontaneous breathing (SB), thus enhancing the comfort of the patient during the weaning phase. SB during mechanical ventilation has been proven to
be beneficial in those subjects who have a partially preserved respiratory capacity (16–18). Theoretically, optimally ventilated healthy lungs would expand isotropically, having nearly homogenous time constants and being exposed only to equally distributed distending pressures (19, 20). However, unpredictable phenomena of local overstretch have been demonstrated to characterise some SB settings under mechanical ventilation (21–23), mainly in injured lungs (9, 24–26), but also in healthy ones (27). To this day, very little is known about regional mechanics and lung-diaphragm interaction in spontaneously breathing patients.

In recent years, experts in the field of lung injury and mechanical ventilation have expressed their concerns regarding SB, discouraging it in patients with acute respiratory distress syndrome (ARDS) because of the risk for P-SILI (9, 26). Controlled mechanical ventilation (MV) under deep sedation and muscle paralysis is encouraged instead. The main reason behind concerns regarding SB is the unpredictability of injurious events due to a lack of monitoring ensuring safe SB ventilation. By introducing monitoring tools based on a deeper physio-pathological understanding of patient-ventilator interaction, a safe control of SB could be reached. SB could, if optimised, be a viable and safe alternative to passive MV.

While the importance of lung-protective ventilation is now well-established, the concept of diaphragm-protective ventilation has recently been introduced and scientific evidence related thereto is currently being gathered. The diaphragm plays a crucial role during the weaning phase, enabling patients to gradually take full control of ventilation. Controlled ventilation, as well as over-assistance during SB, combined with critical illness such as polyeuromyopathy and/or systemic inflammatory cascades, can lead to diaphragmatic weakness and, consequently, to substantial morbidity and mortality in ventilated patients (28, 29). Several pathophysiological mechanisms have been indicated as possible causes leading to four different forms of ventilator-induced diaphragm dysfunction (VIDD): 1. cross-sectional atrophy due to excessive support and over-assistance, 2. longitudinal atrophy due to excessive PEEP, 3. concentric loading, which occurs when the muscle contracts against an excessive load during the contraction phase, e.g., in case of insufficient support, and 4. eccentric loading, which occurs when the muscle contracts against an excessive load during the relaxing phase. This last phenomenon is at hand in patient-ventilator asynchronies and expiratory brake (shown for the first time by us in Studies III and IV) (30, 31).

Lung mechanics and pulmonary heterogeneity

Respiratory mechanics measured at the airway opening constitute a simplified parameter that does not necessarily reflect regional lung properties (32). A simplistic visualisation of acute lung injury, at least its early phases, could be
based on an elastic sponge: following injury, an excessive tissue mass, equally distributed in all lung regions, is exposed to the combined action of a gravitational field and to an increased superimposed hydrostatic pressure due to lung oedema (33, 34). Intrinsic proprieties of the pulmonary structures, such as alveolar interdependency and gravitational forces (35, 36), as well as the structural heterogeneity characterising a lung injury, contribute to uneven regional distribution of gas and pressures (37). An excessive heterogeneity of regional lung properties is one of the factors seen as a potential source for VILI(38).

Recently, local force gradients, resulting from vigorous inspiratory efforts and/or unsuitable ventilator settings (25, 39), have been shown to generate large gas displacement among lung regions, independent of the flow at the airway opening. This dynamic gas redistribution has been named pendelluft, even if it does not occurs under static conditions. Dynamic pendelluft could be a cause of unpredictable overstretch in mechanically ventilated heterogeneous lungs, activating an inflammatory cascade (26, 40).

The prevalence and impact of dynamic pendelluft in clinical settings remain uncertain. Furthermore, the micromechanics behind regional gas redistribution have neither been investigated nor quantified before.

The expiratory phase

The progress in mechanical ventilation within the last decades has caused researchers to focus their attention almost exclusively on the regulation and control of the inspiratory phase, e.g., trans-pulmonary pressure reached at the end of inspiration, plateau pressure, driving pressure and inspiratory assistance. The assumption that expiration is a passive and non-harmful phase of the ventilation, together with the evidence that incongruous inspiratory settings can cause VILI, led to an almost complete disregard of the expiratory phase. With the exception of positive end-expiratory pressure (PEEP), the expiratory phase is largely overlooked during mechanical ventilation.

“During expiration, the diaphragm simply relaxes, and the elastic recoil of the lungs, chest wall, and abdominal structures compresses the lungs and expels the air.” (41)

We learn from classical physiology that the diaphragm simply relaxes during expiration and passively expels the air, profiting off the elastic recoil of lungs, chest wall and abdominal structures. It is not known if there is any reason to question this assumption. There is some evidence that the diaphragm is not completely passive during expiration. Since the 70s, studies based on the electromyography of respiratory muscles have documented a “post-inspiratory
neural respiratory activity” (42) followed by a “post-inspiratory inspiratory diaphragmatic electrical activity” (PIIA) (43). PIIA is better defined as a residue inspiratory EAdi that lasts throughout expiration. PIIA has been demonstrated under both healthy and pathological conditions (e.g., healthy infants, asthma, ARDS) (44–46). It has never been demonstrated or visualised if the described expiratory EAdi has an effect on the actual diaphragmatic contraction (in terms of changes in trans-diaphragmatic pressure, Pdi) and if this could translate into changes in expiratory lung volume and expiratory atelectasis formation. The possibility that a PIIA could shield end expiratory lung volume from decreasing during expiration has only been hypothesised.

Expiratory flow limitation

The patency of distal airways during expiration is of crucial importance in injured heterogeneous lungs, with cyclical airway closure and atelectasis being among the main factors worsening lung injury. However, in all conditions that promote lung collapse, peripheral airways gradually compress and close throughout the expiration. This phenomenon is known as expiratory flow limitation (EFL).

The equal point theory (47) explains EFL and is based on the idea that there is a point along the airways at which the delta pressure across the wall is zero during expiration. Distally of this point of equal pressure, the extraluminal pressure exceeds the intraluminal one, leading to airway compression. Both forced expiration and lung injury shift this point of equal pressure towards more distal, collapsible airways and make EFL more likely.

In case of heterogeneous injury, the lung is comparable to a multi-compartmental system composed of several areas differing in their elastic and resistive properties and, therefore, showing different time constants. Analysis of the volume-flow loop enables visualisation of different lung compartments that empty sequentially during expiration: “rapid compartments” characterised by a short expiratory time constant ($\tau_{\text{exp}}$), followed by “slow compartments” characterised by longer $\tau_{\text{exp}}$. EFL is suspected if a downward concavity in the expiratory portion of the flow-volume curve is observed during tidal breathing. The $\tau_{\text{exp}}$ for a defined time in the expiration corresponds to the slope of the flow-volume curve at that time (48).

EFL is considered one of the major factors determining dynamic hyperinflation and intrinsic PEEP, which result in over-distention and worsening of lung injury. Dynamic hyperinflation significantly increases the effort of breathing, reduces respiratory efficiency, delays reinflation during the subsequent inspiratory phase and impairs gas exchange (49). Haemodynamics are also compromised by the effects on intrathoracic pressures.

While EFL is well-known in lung pathologies such as chronic obstructive pulmonary disease (COPD) and asthma (50), it has also been recently noted
in mechanically ventilated patients with ARDS (51, 52) and recognised as an important cause of major respiratory symptoms and complications (51). In ARDS patients, 40% of lung parenchyma appear to be aerated but not ventilated, as a consequence of EFL (53). EFL in ARDS is commonly described as a consequence of suboptimal PEEP (7, 54). However, because of the regional heterogeneity characterising ARDS lungs (55, 56), widespread regional airway closure phenomena occur throughout the expiration. Each small group of alveoli has its own time constant, inflates at a specific speed and maintains specific volumes that are different from those of other neighbouring groups of alveoli (57). Thus, choosing a single, specific optimal PEEP value to overcome the main airway opening pressure can be considered an oversimplification (58).

Some COPD patients counteract dyspnoea by pursing their lips during expiration; it is thought that this increases expiratory resistances and consequently decreases airway collapse (59). During both SB and MV, the introduction of an external expiratory resistance could reduce EFL in ARDS subjects (aim of Study IV).

Lung computed tomography

Lung imaging plays a key role in the diagnosis and monitoring of mechanically ventilated critically ill patients. CT of the lungs is considered the gold standard imaging strategy in case of heterogeneous lung injury, allowing both a qualitative and a quantitative evaluation of regional distribution of aeration (60). The first reports on lung CT examination appeared only in the 80s (61, 62), when CT drastically changed the view of acute lung injury, showing for the first time the regional distribution of aeration. This contributed greatly to the understanding of ARDS pathophysiology, diagnosis and management (63). CT is based on x-rays and creates image in which each volume element (the voxel) is characterised by a specific x-ray’s attenuation number. This is expressed using a normalised scale (Hounsfield scale), on which −1000 Hounsfield units (HU) corresponds to gas and +1000 HU corresponds to bone (64). Since the lung tissue is a mixture of water (the same as tissue: 0 HU) and gas, lung weight can be estimated by multiplying density by voxel volume, and arbitrary thresholds can be defined to distinguish hyper-aerated, normally aerated, poorly aerated and non-aerated (atelectatic) lung tissue (64).

Standard lung CT scans allow high-resolution imaging. However, they are usually performed as a single-phase examination, providing good anatomical information, but little functional information. Nowadays, modern CT scanners have very fast scan apertures, allowing dynamic imaging during ongoing ventilation. Through continuous scanning, dynamic CT gives information about aeration changes over time (65–67).
Rationale and aims of the studies

Given the gap in knowledge needed to enable fully protective ventilatory strategies, we wanted to investigate regional lung mechanics during mechanical ventilation. For this purpose, four experimental studies were conducted. Lung CT imaging was combined with respiratory variables and indices of diaphragmatic function. In parallel, a new methodological approach to enable a simultaneous breath-by-breath analysis at high temporal and spatial resolution was developed. The present doctoral thesis is composed of four studies described in brief below.

In **Study I**, the main purpose was to test a new method for assessing regional mechanics and gravitational distribution of compliance under mechanically ventilated conditions. The hypothesis studied was that lung injury and PEEP influence the effects of the gravitational field on volume distribution. Therefore, we assessed the distribution of regional volume (V\text{REG}) and transpulmonary pressure (P\text{TP,REG}) along the gravitational axis in healthy lungs (HL) and experimental acute lung injury (eALI) at different PEEPs and inflation volumes.

In **Study II**, the main purpose was to investigate the micromechanics of intraparenchymal gas redistribution during the inspiratory phase. We evaluated the effects of PEEPs and external resistances (xRaw) on gas redistribution at the acinar level in heterogeneously injured lungs, both during the flow-independent phase of inspiration (classical pendelluft) and during ongoing inspiration (gas mingling) in SB and MV.

In **Study III**, the main purpose was to investigate whether expiratory diaphragmatic contraction occurs under ventilatory conditions that jeopardises lung patency. The occurrence of expiratory diaphragmatic contraction could be finalised at stabilising peripheral airways, preventing or reducing cyclic expiratory lung collapse.

We investigated:

a. whether there is an electromechanical coupling between electrical activity of the diaphragm (EAdi) and transdiaphragmatic pressure (Pdi) during expiration at different lung volumes, and

b. the influence of an active diaphragm on atelectasis formation and content of gas, by comparing SB with MV.
In *Study IV*, the main purpose was to investigate whether the regional distribution of ventilation is affected by expiratory resistances (ExpR) in lungs prone to collapse. The role of the diaphragmatic brake was also investigated by comparing SB and MV under the same ventilatory conditions.

We assessed whether ExpR would:

a. affect eccentric diaphragmatic contraction (EDC) during SB,

b. reduce expiratory flow and make lung compartments more homogeneous, and

c. reduce tidal atelectasis, simultaneously avoiding hyperinflation.
Materials and Methods

All studies have been approved by the Regional Animal Ethics committee of Uppsala. They were performed at the Hedenstierna Laboratory (Uppsala University, Sweden) and conducted in accordance with the European Union Directive 2010/63/EU on the protection of animals used for scientific purposes and the National Institutes of Health Guidelines for the care and use of laboratory animals (68). All studies included in the current doctoral thesis are experimental studies conducted on ARDS models. In all these studies, regional respiratory mechanics has been investigated through a combination of spirometrical data and lung CT imaging.

Animal preparation

In **Study I**, after premedication, five tracheotomised pigs underwent general anaesthesia and muscle relaxation. An arterial catheter, a central venous catheter and a pulmonary artery (PA) catheter were inserted. A baseline mechanical ventilation was then initiated using a volume-controlled ventilation with a tidal volume of 9 ml/kg, a respiratory rate (RR) of 20 bpm, a PEEP of 5, a inspiratory-to-expiratory (I:E) ratio of 1:2 and a fraction of inspired oxygen (FIO2) equal to 0.5. After preparation, the animals were mechanically ventilated for 60 minutes before lung injury was induced.

In **Studies II, III and IV**, after premedication, six (for study II) and ten (for Studies III and IV) tracheotomised pigs underwent general anaesthesia, ensuring a continuous spontaneous respiratory activity. Muscle relaxation was achieved only during lung lavage and MV. An arterial catheter and a central venous catheter were placed in the femoral artery and femoral vein, respectively. A PA catheter was then introduced through the central venous catheter. An EAdi catheter was placed in the oesophagus to record the EAdi signal at the diaphragmatic dome. A baseline ventilation was applied with pressure support (PSV) and PEEP of 5 cmH2O, an inspiratory pressure above PEEP (Pinsp) of 10 cmH2O and a Fio2 of 0.5.

In **all studies**, oxyhaemoglobin saturation (SpO2) was continuously assessed, and haemodynamics and body temperature were continuously monitored.
through arterial and PA catheters. The urinary output was measured via a suprapubic urinary catheter. Two balloon catheters were positioned in the distal third of the oesophagus and in the stomach to monitor oesophageal pressure (Pes) \(^{(69)}\) and gastric pressure (Pga), respectively. Pressure (Paw) and flow (V') were continuously measured at the airway opening. Volume (V) was computed by V' integration. All respiratory signals were acquired via an analogue-to-digital converter card (DAQ-card AI-16XE50, National Instruments Corp, Austin, USA) controlled using the Biobench Software (ver. 1.0, National Instruments Corp., Austin, USA).

The ARDS model

In Study I, lung injury was induced by repeated injection of oleic acid (OA) (Apoteksbolaget, Göteborg, Sweden) boluses of 0.5 ml through the central venous catheter, to reach a maximal dose of 0.1 ml/kg and/or a SpO2 value equal or less than 80% with a FIO2 of 0.5. During OA injection, haemodynamic instability was counteracted by repeated adrenalin boluses of 0.01 mg. This condition was referred to in the manuscript as eALI (experimental acute lung injury).

In Studies II, III and IV, a model for mild ARDS and lung collapse was induced by repeated lung lavages using 30 ml/kg of warmed (37 °C) isotonic saline until a stable partial pressure of arterial oxygen to inspired oxygen fraction ratio (PaO2/FIO2) equal to 250 mmHg at PEEP of 5 cmH2O was established. This condition was referred to in the manuscripts as IL (injured lung).

Lung computed tomography

In all studies, the CT voxel dimensions were 5 x 0.5 x 0.5 [mm]. For each voxel, the HU density was converted into gas volume expressed in ml by applying the equation below \((70)\):

\[
V_{\text{gas}} = V_{\text{vox}} \times \frac{-\text{HU}}{1000}
\]

where \(V_{\text{vox}}\) was the volume of the voxel, and HU was the density, measured as Hounsfield units. Equally, tissue volume was obtained by applying the equation \((70)\):

\[
V_{\text{tissue}} = V_{\text{vox}} \times (1 - \frac{-\text{HU}}{1000})
\]
where \( V_{\text{tissue}} \) was the volume of tissue contained in a voxel.

**Image registration**

Image registration (IR) is a method widely used in processing of medical images (71–73). It aims at enabling comparisons between images with different dimensions. Anatomical and structural details in image sets are used as references to generate a three-dimensional map of the lung comparing two different states, as two different inflation volumes.

In **Study I**, IR allowed comparison between pairs of lung images selected from the same anatomical region but at different levels of lung inflation. Each pair of images was defined by a reference image and a moving image. The reference images, with which the other (moving) images were compared, were always arbitrarily chosen at half of the inspiratory capacity (IC). “Correlation points” in each pair of images were selected manually. The “piece-wise linear algorithm” (74) was chosen for registration. This algorithm assumes that the morphological changes in lung tissue are locally linear. IR allowed the subtraction of subsequent images and the computation of regional and transitory delta volumes throughout the inspiration. A validation test ascertained that the sum of regional volume changes after IR was comparable to the entire lung volume changes.

In **Study II**, a non-rigid IR algorithm called “Damon’s method” (75) was chosen. Unlike in Study I, the IR algorithm was applied to consecutive pairs of images acquired under dynamic conditions and only 0.05 seconds apart. In practice, in a sequence of \( i \) CT images (CTim) along the inspiratory phase, CTim1, CTim2, CTim3 … CTimi, IR was performed for each pair of consecutive CT images (e.g., between CTim1 and CTim2, between CTim2 and CTim3, etc.). For each examined pair of images, the second in temporal order was chosen as the reference image, while the first was transformed (moving image) in accordance with the IR process. “Damon’s method” is a non-rigid IR algorithm. It detects anatomical, unchangeable structures shared by the two paired images, estimates displacement and applies a geometric transformation to adapt the chosen image to the reference image. Thereafter, all pairs of images were completely comparable and superimposable.

**Magnitude of gas redistribution and quadtree decomposition**

To assess structural homogeneity, quadtree decomposition (QtD) (76) was applied. The QtD is an iterative algorithm that divides images, or parts of them, into four equal-sized squares and then tests if each square satisfies the criterion
of homogeneity. If the criterion of homogeneity is not satisfied, the square is further divided into four, until the criterion is met.

In **Study II**, the QtD algorithm was applied to the ΔVol images. The criterion of homogeneity was defined as a flow variation equal to or lower than 10% between contiguous areas in the same square. As the regional flow computed per voxel was in the range of \([-1\times10^{-4}, +1\times10^{-4}\) \) mL/min, a difference in flow equal to or lower than \(2\times10^{-5}\) was considered homogeneous. The numerosity of the squares was referred to as NumSq, while the corresponding area was called AreaSq. In Study II, the larger the AreaSq, the larger the gas redistribution phenomena.

**Protocol and data analysis**

**Study I**

Two PEEP levels (5 and 10 cmH\(_2\)O) were tested. After a recruitment manoeuvre (RM) at 40 cm H\(_2\)O for 40 s, the IC of each animal was calculated by measuring the inspired volume when a constant pressure of 40 cmH\(_2\)O was applied for 20 s (see Figure 1). The IC was then divided into 12 isovolumetric steps and, for each step, a series of static CT images and respiratory tracings was obtained, under static conditions, during inspiratory hold manoeuvres (IHM). To restore a steady-state condition, the IHMs were separated by 2–3 min of tidal breathing. Data were collected in both HL and eALI.

*Figure 1.* Thoracic CT scans were collected during IHMs at 12 increasing volumes covering the entire IC. FRC: functional residual capacity.
On the assumption that the lungs behave as a fluid (77), the superimposed hydrostatic pressure was added to the regional Pes (78), for every layer of the lung along the gravitational plane, each composed of a layer of voxels.

With the aim to obtain the regional distribution of transpulmonary pressure ($P_{TP}$) for each layer, the following equation was applied (79):

$$
\Delta P_{TP} = (P_{aw,plat} - P_{aw,EE}) - (P_{es,plat} - P_{es,EE})
$$

Where $P_{aw,plat}$ and $P_{es,plat}$ were Paw and Pes, respectively, during IHMs, and $P_{aw,EE}$ and $P_{es,EE}$ were Paw and Pes at the end of expiration. In this way, maps of transpulmonary pressure ($\Delta P_{TP,MAP}$) were obtained.

CTs were acquired at five transverse planes, 25 mm apart, along the longitudinal axis. The slice thickness was 5 mm. As previously described (see the section Image registration, Study I), IR enabled comparison between consecutive regional volumes ($V_{REG}$) generating delta volume maps ($\Delta V_{map}$). Compliance maps were computed by dividing $\Delta V_{map}$ by $\Delta P_{TP,MAP}$ (see Figure 2).

![Figure 2. Computation of regional compliance. V: voxel regional volume; P: estimated voxel transpulmonary pressure; C: voxel compliance.](image)

To enable analysis of the gravitational course of elasticity, $V_{REG}$ vs $P_{TP,REG}$ curves were computed into eleven isogravitational planes (see Figure 3) and analysed by applying polynomial regressions.
The isogravitational alignment of CT scans. CT images were acquired at five levels along the cranio-caudal axis.

ΔVol vs ΔPTP relationships were fitted to a polynomial model with the following equation:

$$ΔPTP = (a * ΔV^3) + (b * ΔV^2) + (c * ΔV) + d$$

A regression curve was obtained for all studied lung conditions and tested for statistical significance using the F-test ($α = 0.05$). The inflection points of each regression curve were computed by calculating the corresponding second derivative.

The tested null hypothesis was that corresponding isogravitational planes showed equal courses between healthy and injured lungs and between PEEP levels. If the null hypothesis was rejected, additional factors, beyond gravitational forces, affected the distribution of regional compliance.

**Study II**

Six PEEP levels ranging from 15 to 0 cmH₂O, in steps of 3 cmH₂O, and two external resistance (xRaw) were combined, during both SB and MV. SB and MV corresponded to CPAP and pressure controlled ventilation (PCV) respectively. Pinsp during PCV was select to ensure tidal volumes comparable to CPAP ventilation. SB was tested at both high (SB-HighR) and low resistance
(SB-LowR), while MV was performed at only low xRaw. CT scans were acquired at two cranio-caudal levels: at 1 (L1) and 4 (L4) cm cranially to the diaphragmatic dome. At each PEEP level, respiratory mechanics and dynamic CT scans were simultaneously recorded (see Figure 4).

Figure 4. After preparations and lung injury, the animals underwent six decremental PEEP steps from 15 to 0 cm H₂O. The protocol was applied during both SB and MV and at two xRaws.

CT images were acquired with a time frame of 0.05 seconds and processed using IR to obtain delta volume images (ΔVol). For each inspiration, the first three ΔVol, at 0.05, 0.1 and 0.15 seconds (ΔVol 0.05, ΔVol 0.1 and ΔVol 0.15), respectively, were used for the pendelluft analysis; the following ΔVol sequence was used for the analysis of gas redistribution during ongoing inspiration (see Figure 5, left panel).
Figure 5. Left panel: Definition of ΔVol images obtained by the subtraction of two consecutively registered images. Right panel: The two kinds of gas redistribution analyses conducted in Study II, isovolumetric phase (pendelluft) analysis highlighted in yellow and flow-dependent inspiration (gas mingling) analysis highlighted in grey.

For the *pendelluft analyses*, each ΔVol image was divided into four gravitationally oriented regions of interest (from ROI1 to ROI4) of equal height, with ROI1 being the most non-dependent region (see Figure 6). The ROI analysis provided the computation of positive delta volume (PosΔV) [mL], negative delta volume (NegΔV) [mL] and the total effect derived from them (TotΔV = PosΔV – NegΔV) [mL]. Since the ROIs had differing extensions depending on their gravitational location, and were changeable – with different ventilatory modes, PEEP levels and distances from the diaphragm – the TotΔV values calculated for each ROI were normalised based on the corresponding ROI volume [mm$^3$]. Accordingly, the normalised TotΔV was expressed as [mL/mm$^3$]: TotΔV/mm$^3$. 
Figure 6. Partition of lung parenchyma in gravitationally oriented ROIs used in the pendelluft analyses.

To reveal the pattern of gas redistribution during ongoing inspiratory flow, the QtD algorithm (see previous section, Magnitude of gas redistribution and quadtree decomposition) was applied to the flow-related ΔVol images (see Figure 7). QtD enabled the calculation of the mean areas of the squares (AreaSq). For a mean AreaSq equal to or lower than 2 cm², the pattern was called gas-scattering; for an AreaSq higher than 2 cm², the pattern was called gas-displacing.
For each ventilatory condition, the neuro-ventilatory efficiency (tidal volume/unfiltered EAdi peak) was calculated.

**Study III**

As in Study II, six PEEP levels (15, 12, 9, 6, 3 and 0 cmH₂O, respectively) were applied during both SB and MV. SB and MV corresponded to CPAP and PCV respectively. Pinsp during PCV was select to ensure tidal volumes comparable to CPAP ventilation. CT scans were acquired at two cranio-caudal levels: 1 (L1) and 4 (L4) cm cranially from the diaphragmatic dome. At each PEEP level, respiratory mechanics, electrical activity of the diaphragm (EAdi) and dynamic CT scans were recorded simultaneously (see Figure 8).
Figure 8. After preparations and lung injury, the animals underwent six decremental PEEP steps from 15 to 0 cm H₂O. The protocol was applied during both SB and MV.

For each recorded breath, CT images acquired at both half- and end expiration were selected and further analysed. Both the non-aerated compartment, corresponding to atelectasis (voxel population from −100 to +100 HU), and the total content of gas (voxel population from −1,000 to +100 HU) were computed.

The expiratory electrical activity of the diaphragm (EAdi_exp) was defined as the signal during ongoing expiration. EAdi_exp and the corresponding expiratory Pdi (Pdi_exp) over time were divided into equally sized quartiles. The mean EAdi_exp of each quartile was expressed as the percentage of EAdi at the peak of that breath (Q1EAdi_exp, Q2EAdi_exp, Q3EAdi_exp, Q4EAdi_exp). The minimum electrical diaphragmatic activity (EAdi_min) was defined as the mean value of the EAdi signal during the apnoea between the end of the expiratory flow and the beginning of the following neurological breath.
Figure 9. Recording and analysis of EAdi. EAdi during ongoing expiration (EAdi_{exp}) was divided into four portions (Q1EAdi_{exp}, Q2EAdi_{exp}, Q3EAdi_{exp}, Q4EAdi_{exp}). EAdi min: minimum electrical diaphragmatic activity.

An analogous analysis was performed for the Pdi signal (Q1Pdi_{exp}, Q2Pdi_{exp}, Q3Pdi_{exp}, Q4Pdi_{exp}). Because of the potential errors deriving from a noise-removing low pass digital filter included in the NAVA software (Getinge, Sweden), an “unfiltering” process of the EAdi signal was applied.

Study IV

The animals were studied during dynamic CT with a sampling rate of 20 images per second and at one cm from the diaphragmatic dome. Three PEEP levels and four ExpRs were tested during both SB and MV. In this study, CPAP was chosen as SB ventilation mode, whereas volume controlled ventilation was selected as MV mode. In the latter, V and RR were set depending
on V and RR developed during CPAP ventilation at corresponding PEEP levels. The PEEP applied was decreased in a stepwise manner from 12 to 0, in steps of 6 cmH₂O. The ExpR tested were: no resistance added to the expiratory circuit (R0) or addition of constant, time-invariant expiratory resistances (ExpR) to the expiratory limb of the ventilator.

The tested ExpR were defined as follow (see Figure 9):
R0. no resistance added to the expiratory circuit, thus keeping a measured total expiratory resistance of 14.5 cmH₂O/L/s at a reference flow of 0.8 L/s;
R1. addition to R0 of an external resistance to reach measured total ExpR of 31.4 cmH₂O/L/s at a reference flow of 0.8 L/s;
R2. addition to R0 of an external resistance to reach measured total ExpR of the ExpR of 53.9 cmH₂O/L/s at a reference flow of 0.8 L/s;
R3. addition to R0 of an external resistance to reach measured total ExpR of the ExpR of 76.5 cmH₂O/L/s at a reference flow of 0.8 L/s.

![Figure 10](image)

Figure 10. The Paw/V’ curves characterising each ExpR applied.

To ensure a steady state before a new ventilatory condition was tested, a baseline ventilation at R0 and PEEP of 12 was delivered for at least two minutes between the ventilation with ExpR. In case of MV, a recruitment manoeuvre was also performed.
Figure 11. Protocol. At each grey arrow, simultaneous acquisition of CT images and spirometrical data occurred.
To perform spirometrical and CT scan-related analyses, the expiratory phase was divided in quartiles. In this way, five different points were selected throughout the expiratory phase: end inspiration (End Insp), one quarter (1/4 Exp), two quarters (2/4 Exp), three quarters (3/4 Exp) and four quarters (4/4 Exp) of expiration.

We investigated:

a. Effects of ExpR on expiratory diaphragmatic contraction. Changes in EAdi_{exp} and Pdi_{exp} following changes in ExpR and PEEP were analysed. As in Study III, an “unfiltering” process of the EAdi signal was necessary to avoid errors deriving from a noise-removing low pass digital filter included in the NAVA software (Getinge, Sweden).

b. Expiratory flow limitation and changes in T_{exp} through the expiratory part of volume-flow curves. Changes in T_{exp} for rapid and slow lung compartments were computed. T_{short} represented the T_{exp} of the rapid lung compartment and T_{long} represented the T_{exp} of the slow lung compartment. T_{exp} at a given time during the expiration was calculated as the angular coefficient at that time on the expiratory volume-flow curve.

c. Differences in expiratory lung collapse and gas distribution. A subdivision of the lung in four compartments (atelectasis, poorly aerated, well-aerated or hyper-aerated) was made for data from throughout the expiration. With atelectasis defined between –100 and +100 HU, poorly aerated between –500 and –100 HU, well-aerated between –800 and –500 HU and hyper-aerated between –1000 and –800 HU.

Statistics

*Study I*

The F-test was chosen for testing statistical significance of regression curves obtained by applying a polynomial model to (superimposed tissue weight) vs (plane position). For the remaining statistical questions, a paired-samples Student’s t-test (α = 0.05) was used to detect statistically significant differences.
**Study II**

A paired-samples Student’s t-test ($\alpha = 0.05$) was used to detect statistically significant differences. Descriptive statistics were reported using means and standard errors.

**Study III**

Normal distribution was tested using a one-sample Kolmogorov-Smirnov test ($\alpha = 0.05$; $p < 0.05$). Statistically significant differences between the two expiratory time points (half- and end expiration), the two ventilatory conditions (CPAP and MV), and the two layers were tested using a paired-samples Student’s t-test ($\alpha = 0.05$).

For each studied CPAP level, the linear correlation between $\text{Pdi}_{\text{exp}}$ and $\text{EAdi}_{\text{exp}}$ through all expiration was tested and its statistical significance was estimated by applying the F-test ($\alpha = 0.05$). Descriptive statistics were reported using means and standard errors.

**Study IV**

Studied variables were tested for normal distribution using one-sample Kolmogorov-Smirnov test ($\alpha = 0.05$). The analysis of variance was used to test statistical differences characterising expiratory mechanics, EAdi and lung compartments. A two-sample Student's t-test ($\alpha = 0.05$) was used for paired comparisons. Bonferroni’s correction for multiple comparisons was applied when needed. Descriptive statistics were reported using means and standard errors.
Results

Study I

Following a polynomial regression, the superimposed hydrostatic pressure was higher in more dependent lung regions when compared with non-dependent ones. Lung injury caused an increase of the weight of superimposed tissue (see Figure 12) as well as of the differences in regional lung inflation. The subpopulation of non-aerated lung voxels presented a significantly higher average volumetric mass under healthy conditions ($1.023 \pm 0.187$ gr/cm$^3$) if compared with injured ones ($1.013 \pm 0.136$ gr/cm$^3$). However, injured lungs presented a larger extension of the non-aerated lung compartment.

Figure 12. Weight of superimposed tissue for each gravitational plane and differences between healthy and injured lungs. *: for significant differences (F-test applied to polynomial regression curves).

Higher PEEPs significantly reduced regional differences in lung inflation, under both healthy and injured conditions (see Figure 13).
Figure 13. Compliance maps of the lung for a representative pig.

$V_{REG}$ vs $P_{TP,REG}$ curves derived from different isogravitational anatomical planes, exposed to different PEEP levels or different lung status were statistically different from each other with only two exceptions, involving adjacent planes (see Figure 14).

A double curvature, reflecting an initially low compliance that suddenly changed to higher compliance, characterised the more dependent $V_{REG}$ vs $P_{TP,REG}$ curves under injured conditions (eALI).
Figure 14. Regional volume (y-axis) vs regional transpulmonary pressure (x-axis) curves derived from different isogravitational anatomical planes. All $V_{REG} \text{ vs } P_{TP,REG}$ curves are presented as starting from end-expiratory lung volume (EELV) in order to facilitate comparisons. Panel E includes the legend for the graphs above. eALI: lung injury; EELV: end expiratory lung volume.

At similar $\Delta P_{TP}$, the most dependent regions (white in Figure 14) of the lung received more gas than non-dependent ones (red-brown in Figure 14). The most dependent regions in injured lungs (eALI) showed volume/pressure curves characterised by a double curvature: an initially low compliance (at low $\Delta P_{TP}$) that gradually changed to higher compliance, with a new pattern in line with the other more non-dependent $V_{REG} \text{ vs } P_{TP,REG}$ curves. The mean inflection points characterising $V_{REG} \text{ vs } P_{TP,REG}$ curves were significantly different when comparing healthy vs injured conditions. Changes in PEEP determined significant differences in the mean inflection points in healthy lungs only.

At higher inspiratory volume, the superimposed pressure tended to decrease, albeit not significantly. This was more evident in more dependent planes (see Figure 15, red triangles).
Figure 15. Relationship between transpulmonary pressure (left y-axis, blue circles, cmH₂O) and superimposed pressure (right y-axis, red triangles, cmH₂O) vs volume curves (x-axis, ml). Planes 1, 6 and 11 are included, with plane 1 being the most non-dependent and plane 11 the most dependent one.

Study II
Large pendelluft at the beginning of the inspiratory effort in absence of flow at the airway opening characterised only SB; it developed along the cranio-to-caudal and nondependent-to-dependent directions and was reduced/prevented by high PEEP. For SB at PEEP equal to or higher than 9 cmH₂O, a small but significant amount of gas inflation in the caudal region (ROI3 and ROI4) at 1 cm from the diaphragm (L1) could be detected in the later portions of the isovolumetric inspiratory phase (ΔVol 0.1 and ΔVol 0.15). For SB at PEEP values lower than 9 cmH₂O, a significant, non-dependent (ROI1 and ROI2) deflation at L4 (during ΔV0.05 and ΔV0.1) was quasi-simultaneous with a significant dependent (ROI3 and ROI4) inflation at L1 (during ΔV0.1 and ΔV0.15). The same events were demonstrated in SB conditions during both high and low external resistances. The latter showing more evident pendelluft. No significant pendelluft events were detected during MV, regardless of PEEP level, ROI and distance from the diaphragm (see Figure 16).
Figure 16. Pendelluft analysis. Gas redistribution during the isovolumetric phase of inspiration, corresponding to the first 0.15 seconds (from ΔVol 0.05 to ΔVol 0.15). A. Spontaneous breathing at low external resistance. B. Spontaneous breathing at high external resistance. C. Mechanical ventilation during muscle paralysis and low external resistance. For each analysed ventilatory condition, the total amount of gas redistribution (Tot ΔVol) normalised for the corresponding ROI volume [mL/mm³; mean ± SE] (y-axis) was calculated at six different PEEP levels (x-axis). The grey line indicates a distance of 1 cm (L1), and the black line indicates 4 cm from the diaphragmatic dome (L4).

The QtD analysis allowed the definition and identification of two patterns of gas redistribution (gas mingling) during ongoing inspiration: 1) few large areas were referred to as gas-displacing, and 2) several small areas were referred to as gas-scattering (see Figure 17 and Table 1).

Figure 17. Visual differences in gas redistribution during ongoing inspiratory flow. The representative ΔVol images shown in the figure were all selected at end inspiration. The figure allows for a comparison between PEEP 15 (the highest PEEP – upper panel) and PEEP 0 (the lowest PEEP – lower panel). Macro gas redistribution events (gas displacement) characterised low PEEP, MV and high external resistance (SB-HighR). SB-HighR: high external resistance, SB-LowR: low external resistance.
Table 1. Definitions of different patterns of gas redistribution during ongoing inspiration.

<table>
<thead>
<tr>
<th>Label</th>
<th>Ventilation phase</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pendelluft</td>
<td>no gas flow at airway opening</td>
<td>Pre-inspiratory or during end-inspiratory pause. Gas already present in the lungs moves from one mechanical compartment to another.</td>
</tr>
<tr>
<td>Gas mingling</td>
<td>during ongoing inspiratory flow</td>
<td>During and throughout the inspiration. Gas already present in the lungs and fresh gas arriving from airway opening moves between mechanical compartments.</td>
</tr>
</tbody>
</table>

**Air redistribution**

**Gas-scattering**
- Numerous, small, intermingled areas, typical of spontaneous breathing

**Gas-displacing**
- Fewer, larger, patchy, redistribution areas, typical of mechanical ventilation
Gas scattering (small and numerous areas of gas redistribution) mainly characterised SB-LowR, both at high PEEP levels (vs low PEEP) and at 1 cm (vs 4 cm) from the diaphragmatic dome. Gas scattering came closer to the arbitrary limit of 2 cm² during SB-HighR (central panels in Figure 17 and Figure 18) if compared with SB-LowR. Gas displacement (large and few areas of gas redistribution) mainly characterised low PEEP during MV (right panels in Figure 17 and Figure 18). This was true especially in regions closer to the diaphragm (see Figure 18).

Figure 18. QtD for the analysis of gas redistribution during ongoing inspiration. A. Mean area of square at different ventilatory conditions (the larger the area of the square, the larger the local phenomena of gas redistribution). B. Iterative divisions in squares of representative images. The number of iterative divisions of squares was visibly higher for PEEP 15 than for PEEP 0.

When PEEP was decreased from 12 to 0 cmH₂O during SB, the neuro-ventilatory efficiency also decreased gradually. The highest tested PEEP (15 cmH₂O), despite a low ΔPes and high tidal volume, showed a lower neuro-ventilatory efficiency index compared with a PEEP of 12 cmH₂O.
Study III

When reducing PEEP from 15 to 0 cmH₂O, the decrease of expiratory EAdi throughout the expiration was slowed down. Expiratory EAdi was significantly different throughout the expiration for PEEP levels between 15 and 6 cmH₂O, but remained unchanged when PEEP was lower than 6 cmH₂O. The visible increase in minimum EAdi by decreasing PEEP did not reach statistical significance (see Figure 19).

The Pdiexp analysis showed similar results as the EAdiexp analysis: A significant increase in the Pdi peak and higher expiratory Pdi for Q1Pdiexp, Q2Pdiexp, and Q3Pdiexp, were shown to follow decreasing PEEP (see Figure 20).
Figure 20. Expiratory transdiaphragmatic pressure (Pdi) and expiration (mean of 10 pigs). X-axis: End inspiration and quartiles (Q1–Q4). Y-axis: Pdi [cmH2O].

In SB animals, a linear correlation between EAdi_{exp} and Pdi_{exp} was demonstrated for all analysed breaths. The Pdi_{exp}/EAdi_{exp} ratio increased with decreasing end-expiratory lung volume, which indicated that, for a given electric activity, the diaphragm exerted a higher force at lower lung volumes (see Figure 21).

Figure 21. Expiratory electromechanical coupling of the diaphragm during spontaneous breathing.
When PEEP decreased, the total amount of end-expiratory gas significantly decreased, and the amount of end-expiratory atelectasis increased (see Figure 22).

Figure 22. Lung aeration, lung collapse, and relations with diaphragmatic electric activity (EAdi).

The comparison between end-expiratory CT images collected during SB and MV showed a higher amount of atelectasis and a lower content of gas under mechanically ventilated conditions compared with spontaneous breathing (see Figure 23).

Figure 23. Representative examples of end-expiratory CT images collected during SB and MV, respectively. CT images collected at end expiration and CPAP of 3 cmH₂O.
Atelectasis increased with decreasing PEEP, always more during MV than SB. During SB, the lung area near the diaphragmatic dome (L1) was less atelectatic than the area further away from it (L4). At half-expiration, there was already more atelectasis during MV than during SB (see Figure 24).

![Figure 24. Lung atelectasis. An active versus a passive diaphragm.](image)

**Study IV**

As a consequence of additional ExpR and mainly in lungs prone to collapse (at low PEEP):

1. The eccentric diaphragmatic contraction was modulated

As a consequence of additional expiratory resistances, both expiratory EAdi and expiratory Pdi were kept lower throughout the expiration (see Figure 25 and Figure 26).
Figure 25. EAdi_{exp} during SB. EAdi peak: EAdi at the beginning of the expiration. EAdi_{exp} was divided into quartiles 1/4 Exp (at 1/4 of the expiration), 2/4 Exp (at 2/4 of the expiration), 3/4 Exp (at 3/4 of the expiration) and 4/4 Exp (at 4/4 of the expiration) and each value was expressed as a percentage of EAdi peak. * indicates statistical differences between PEEP 12 and 0 cmH$_2$O.
Figure 26. Pdi_{exp} during SB. Pdi peak: Pdi at the beginning of the expiration. Pdi_{exp} was divided into quartiles: 1/4 Exp (at 1/4 of the expiration), 2/4 Exp (at 2/4 of the expiration), 3/4 Exp (at 3/4 of the expiration) and 4/4 Exp (at 4/4 of the expiration), and each value was expressed as a percentage of Pdi peak. * indicates statistical differences between PEEP 12 and 0 cmH₂O.
2. **Both the expiratory flow and the tidal EFL were reduced**

No differences in expiratory flow were detected when changing PEEP during MV (Figure 26, R0). Additional ExpR significantly reduced the expiratory flow during both SB and MV. During SB, the higher the ExpR, the lower the expiratory flow. Comparing the same ventilatory conditions, the early phase of the expiratory flow (quartiles 1/4 Exp and 2/4 Exp) was significantly lower during SB than during MV. Additional ExpR induced a significant decrease in RR combined with a progressive reduction in I:E ratio and a prolongation of the expiratory phase (see Figure 27).
Figure 27. Expiratory flow during SB and MV. End Insp: Expiratory flow at the beginning of the expiration. Expiratory flow was divided into quartiles $\frac{1}{4}$ Exp (at $\frac{1}{4}$ of the expiration), $\frac{2}{4}$ Exp (at $\frac{2}{4}$ of the expiration), $\frac{3}{4}$ Exp (at $\frac{3}{4}$ of the expiration) and $\frac{4}{4}$ Exp (at $\frac{4}{4}$ of the expiration), and each value was expressed as a percentage of End Insp flow. * indicates statistical differences between PEEP 12 and 0 cmH$_2$O.
The slow compartment showed a significantly shorter expiratory time constant ($T_{\text{exp}}$) during SB as compared with during MV. During both SB and MV, the addition of an ExpR significantly reduced the $T_{\text{exp}}$ characterising the slow lung compartment ($T_{\text{long}}$) and made it similar to the $T_{\text{exp}}$ corresponding to the rapid lung compartment ($T_{\text{short}}$). Lowering PEEP during R0 tended to make $T_{\text{exp}}$ less homogeneous throughout the expiration, especially during MV (see Figure 28).

![Figure 28](image_url)

*Figure 28.* Volume-flow curves and expiratory time constants ($T_{\text{exp}}$). Representative volume-flow curves for four ventilatory conditions: SB and MV (R0, PEEP 0 and R3, PEEP 12). During R0, $T_{\text{long}}$ was significantly longer than $T_{\text{short}}$ in both SB and MV. The slow compartment showed a significantly shorter $T_{\text{exp}}$ during SB, compared with during MV.

3. **The expiratory onset of atelectasis was reduced, without increasing hyperinflation**
   
   A significant risk of hyperinflation resulted from high PEEP but not ExpR. In case of low PEEP, an additional ExpR simultaneously expanded the normally aerated compartment and reduced the atelectasis. This was true for both SB and MV. Comparing SB with MV, differences in atelectasis were found only without ExpR (R0), where SB was characterised by a lower amount of atelectasis than MV. Additional ExpR decreased atelectasis during both SB and MV and made the atelectasis amounts during SB and MV similar (see Figure 29).
B. Mechanical Ventilation

### PEEP 12

- **R0**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R1**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R2**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R3**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

### PEEP 6

- **R0**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R1**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R2**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R3**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

### PEEP 0

- **R0**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R1**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R2**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

- **R3**:  
  - End
  - Insp
  - 1/4
  - 2/4
  - 3/4
  - 4/4

[mm^3]

- Hyper
- Normally
- Poorly
- Not
Figure 29. Extension of CT image compartments [mm³]. A. During SB. B. During MV. End Insp: Analysis corresponding to CT images acquired at end inspiration; the expiratory phase was divided into quartiles 1/4 Exp, 2/4 Exp, 3/4 Exp and 4/4 Exp. Inflation was defined based on voxel radiodensity, and four lung compartments were classified (atelectasis (defined as non-aerated), poorly aerated, normally aerated and hyper-aerated) and reported as percentages of the total extension of lung parenchyma in the same slice [% mm³]. Both during SB and MV, additional ExpR (R1–R3) significantly reduced the amount of atelectasis and increased normally aerated areas at PEEP 0 and 6 cmH₂O. ExpR did not alter the hyper-aerated compartment.
Discussion

VILI and VIDD are common complications characterising invasive mechanical ventilation. This research project had as one major aim to provide a better understanding of regional pathophysiological mechanisms so as to create the basis for a more protective mechanical ventilation. This purpose was achieved through a combined methodological approach characterised by high spatial and temporal resolution.

Study I

In Study I, we tested a new methodological approach that estimated pressures and volume distributions at a regional level. Previous attempts to estimate regional pressure were based on the computation of superimposed pressures (78). In this study, we computed transpulmonary pressure, combining superimposed pressures with oesophageal and airway pressures. Confirming classical observations on gas distribution (36), dependent lung regions showed higher compliance (higher volume-to-pressure ratios) than non-dependent ones. The double curvature characterising $V_{\text{REG}}$ vs $P_{\text{TP,REG}}$ curves, found in the more dependent regions of injured lungs, was explained by tidal airway closure. In these lung regions, low EELV and low compliance (lower volume-to-pressure ratios) at the beginning of the inspiratory phase were followed by a sudden increase in both lung compliance and fraction of inhaled volume once the inspiratory critical opening pressure was reached. The shift towards higher $P_{\text{TP,REG}}$ values induced by lung injury indicated a reduction in lung compliance. On the other hand, the increase in PEEP caused a shift towards higher $P_{\text{TP,REG}}$ values only under healthy conditions, indicating that the effects of PEEP in injured lungs modified mechanical behaviour only at a regional level. The effects of PEEP on the lung parenchyma as a whole remained undetectable.

Gravitational forces cannot be considered to be the exclusive mechanism causing an organised distribution of regional compliance alongside the gravitational axis. Regional differences in elastic proprieties and increased permeability also affect the mechanical load on the elastic structures (80). Increased lung permeability under injured conditions has been confirmed in our study, where the non-aerated compartment in injured lungs showed a HU density
typical of fluid exudation. Moreover, our approach was based on the assumption that the lungs act as a fluid-like structure (81–83), disregarding unpredictable heterogeneous forces deriving from attractors.

Study II

Pendelluft is usually defined as the redistribution of gas within the lungs while keeping the inspiratory flow at the airway opening equal to zero. Large pendelluft happening at the beginning of the inspiratory effort in case of inappropriately strong respiratory drive can be harmful to injured lungs (39).

We demonstrated that large pendelluft was characteristic for suboptimal SB and was more likely to happen at low PEEP levels. Pendelluft was not a unique event, as collapsible lungs showed continuous, multi-fold, local and transient redistributions of gas (gas mingling) throughout inspiration. Gas mingling occurred during both SB and MV.

Diffuse, small and highly intermingled gas redistribution areas (gas-scattering) characterised SB, whereas less numerous but larger areas of gas redistribution (gas-displacing) characterised MV.

PEEP level, external airway resistance and distance from the diaphragm also affected these patterns. The optimisation of ventilatory settings reduced the size of the gas redistribution phenomena, passing from gas-displacing to gas-scattering. The presence of gas-scattering during SB and high PEEP reflected more stable lung conditions and might be associated with less local stress and a lower risk for inflammatory response. This can be interpreted as lung-stabilising and considered related to alveolar interdependency. MV was more prone to unstable patterns of gas redistribution (gas displacement).

Study III

In Study III, we showed that the diaphragm has a central role in the maintenance of lung patency during expiration. For the first time, we demonstrated a braking effect of diaphragmatic contraction during expiration, likely serving to preserve EELV when conditions endanger the state of lung patency.

By showing a linear correlation between expiratory EAdi and expiratory Pdi, an electromechanical coupling has been demonstrated. Variation in the slope of the expiratory Pdi/EAdi ratio at different PEEPs, with significantly higher ratios at low PEEP levels, indicated an improved efficiency of the expiratory brake at lower PEEP. These results should be interpreted in light of the force-length properties of the diaphragmatic muscle.

For the first time, we demonstrated that the expiratory contraction of the diaphragm can significantly reduce lung collapse and atelectasis appearance
already at half-expiration. Thus, during the post-inspiratory phase, diaphragmatic expiratory contraction slowed down the onset of atelectasis compared with when the diaphragm was paralysed. During muscle paralysis, when the diaphragm was completely relaxed, end-expiratory lung collapse could not be avoided, impeding ventilation efficiency.

Despite the positive effects deriving from a braking of the expiratory flow, an expiratory diaphragmatic contraction could enhance VIDD (30). Moreover, during MV, the diaphragmatic contraction is completely blocked. In view of this, we hypothesised that external expiratory resistances could still have an expiratory brake effect retaining the positive effects on lung parenchyma but avoiding diaphragmatic contraction during expiration, hence reducing the risk of VIDD. These were the hypotheses upon which Study IV was based.

**Study IV**

In this study, we demonstrated that additional expiratory resistances can prevent or limit tidal EFL and consequently reduce lung collapse and optimise lung mechanics. This was confirmed during both SB and MV. During SB, in the presence of ExpR, the diaphragm relaxed early during expiration. ExpR preserved distal airway patency and kept the $T_{\text{exp}}$ more homogeneous throughout the expiration. Thus, the onset of expiratory atelectasis was reduced and the normally aerated lung compartment was kept more extended throughout the expiration. Despite the additional ExpR, the hyper-aerated compartment did not significantly increase. Conversely to ExpR, high PEEP levels significantly increased the risk of lung hyperinflation. Positive effects of ExpR were demonstrated during both SB and MV.
Conclusions

Study I
Lung parenchyma exhibits different elastic behaviours depending on the gravitational position and the density of superimposed tissue, which increases during lung injury. Changes in PEEP or induction of injury do not have unambiguous effects on lung elasticity. Dependent regions in injured lungs have sudden, volume-dependent changes in compliance, which can be interpreted as collapsed regions undergoing inspiratory reopening when reaching critical opening pressures.

Study II
Collapsible lungs showed multi-fold, local and transient redistributions of gas throughout inspiration. Although pendelluft is specific for SB, both SB and MV are characterised by gas redistribution during ongoing inspiration. SB, high PEEP and low external resistance are characterised by small phenomena of gas redistribution (gas-scattering). In this situation, continuous and multiple interactions between temporarily inflating and deflating micro-areas create a macroscopic stability of the entire lung parenchyma. This has been demonstrated in asthma models previously (4, 37). MV is more prone to unstable patterns of gas redistribution (gas displacement).

Study III
The diaphragm is an important regulator of expiration during SB. Its expiratory activity seems to preserve lung volume and protect against lung collapse. The loss of diaphragmatic expiratory contraction during mechanical ventilation and muscle paralysis may be a factor contributing to unsuccessful respiratory support. The possibility of assisting the diaphragm during expiration may be of importance in the management of injured lungs.
Study IV

The expiratory brake deriving from the application of ExpR improves lung inflation under conditions promoting lung collapse (low PEEP) and is not associated with hyperinflation. The application of an ExpR preserves the positive effects of the expiratory brake while minimising EDC, thus potentially reducing VIDD and P-SILI. If confirmed in patients, the application of external expiratory brakes might gain clinical relevance in ventilated lungs prone to collapse (e.g. in cases of laparoscopic procedures, thorax surgery, paediatric ventilation, prolonged weaning and critical illness).
We find ourselves in a time in which we, as medical doctors and researchers in the field of intensive care, are desperately looking for strong evidence and a consensus that can guide us in the difficult process of therapeutic decision-making for critically ill patients.

Several multi-centre randomised trials are unfortunately failing in demonstrating differences in outcomes of and mortality in a number of key treatments in intensive care (84, 85). On the other hand, we are becoming more and more aware of the importance of individualising medicine. Medicine based on large numbers can probably guide us on a large scale, but will unfortunately be unable to describe the individual patients we meet in our intensive care.

A better understanding of pathophysiological mechanisms will be fundamental to improving therapeutic strategies and patient outcomes. Trials should instead aim at a second-phase corroboration of physiological evidence.

The key to fully protective mechanical ventilation of lung-injured critically ill patients is a deeper investigation of respiratory physiology. We still lack a full monitoring and understanding of potentially injurious regional events. The studies on which this thesis is based were aimed at a deeper investigation of the complex regional behaviours regulating unstable airways and lung units. The first challenge to face, after this doctoral research project, will be the clinical proving of the results obtained in these experimental studies, to ensure significant improvements of individualised respiratory care.
Varje år drabbas tusentals patienter i Sverige av en allvarlig akut lungsjukdom, ARDS (acute respiratory distress syndrome), som kräver avancerad andnings-hjälp på intensivvårdsavdelning. ARDS är ett akut inflammatoriskt tillstånd som omfattar respiratorisk svikt, nytillkomna bilateral förtätningar på lungröntgen och är förenat med syrebrist (hypoxi). Andningen hos patienter med ARDS behöver ofta stödjas med ventilator (respirator).


Även om ventilatorbehandling är nödvändig och många gånger räddar liv kan den också skada lungorna, eftersom den bläser in luft med relativt högt tryck i lungorna. Detta kallas för ventilator-inducerad lungskada, med den engelska akronymen VILI. VILI, som är känt sedan flera år tillbaka, är en allvarlig komplikation av ventilatorbehandling. Många studier har gjorts i syfte att finna metoder som kan minimera VILI. Detta har lett till att ventilatorbehandlingen har förbättrats och gjorts mycket säkrare sedan den användes på patienter för första gången år 1952. Numeras finns mycket avancerad övervakningsutrustning och dessutom har kunskapsnivån hos användarna ökat kraftigt under de sista åren.

Nyligen har man funnit att patienternas egen andningsaktivitet under assisterad ventilation kan skada lungorna. I en del fall kan patienterna inte anpassa andningskraften, andningsfrekvensen och andetagsdjupet på ett bra sätt, vilket kan leda till att skadliga tryck och volymer uppstår i lungorna. Den här typen av VILI kallas för patient-/självinducerad lungskada, med den engelska akronymen P-SILI. I dessa fall är det svårt att ställa in ventilat orn på ett säkert sätt, eftersom övervakningsutrustning under assisterad ventilation inte alltid visar farliga ventilationsmönster.

En ytterligare komplikation som nyligen upptäckts är ventilator-inducerad diafragmaskada, med den engelska akronymen VIDD. Diafragman är den

Vid ventilatorbehandling av en patient är det viktigt att veta hur svårt skadade lungorna är. Det kan också noteras att skadorna i lungorna aldrig är jämnt fördelade, vilket leder att olika lungdelar beter sig på olika sätt under ventilatorbehandlingen. En konsekvens av detta är att ventilatorbehandlingen blir mer komplicerad.

Som påpekats ovan kan ventilatorbehandling vara skadlig. Det är därför nödvändigt att nya studier görs för att vidare undersöka lungornas fysiologi. Syftet med sådana studier är att utveckla en helt ofarlig ventilatorbehandling.

Som bidrag till detta gjordes i denna avhandling fyra experimentella djurstudier med avancerade radiologiska och lungfysiologiska mättekniker för att kunna utreda hur en säker ventilatorbehandling ska utföras. Vi begränsade våra studier till djurförsök eftersom vissa av mätningarna av etiska skäl inte kan utföras på svårt sjuka, ventilatorbehandlade patienter (fr. a. de upprepade datortomografiundersökningarna, på grund av stråldoserorna).


I den första studien visade vi att luftfördelning i lungorna, under kontrollerad ventilation, påverkas av både respektive lungas tyngd och den regionala elasticitet i lungan. Trycket i lungan ökade uppifrån och ned, d.v.s. längs gravitationsaxeln. Effekterna av gravitationen var olika i friska och sjuka lungor. Lungskadan i sig gav en ojämn fördelning av luft i lungorna. I denna studie testade vi även våra egenutvecklade nya mätmetoder för första gången.

I den andra studien fokuserade vi på assisterad ventilation, dvs. när patienten andas delvis själv och delvis med hjälp av ventilator. En nyligen publicerad studie har visat att lufttrycket i lungorna under assisterad ventilation i vissa fall blir så högt att stora mängder luft förskjuts mellan olika delar av lungorna, vilket kan öka risken för P-SILL. Den luft som förflytts mellan två olika lungområden utan att komma ut genom luftstrupen kallas för pendelluft. Studien ledde till att vissa experter avråde från att använda assisterad ventilation vid ARDS. Vår studie visade dock att risken för pendelluft och således...
för lungskador bara ökar vid felaktiga ventilatorinställningar. Dessutom visade vi att små mängder luft, oberoende av vilken ventilationsform man väljer, alltid förskjuts mellan olika lungområden. Denna pendelluft är troligtvis viktig för att lungblåsorna (alveolerna) ska förbli stabila och inte falla samman, och är ofarlig, då den alltid finns, överallt i våra lungor. Om ventilatorbehandling är optimal orsakar pendelluft således inte några skador, utan är troligtvis positiv.

I den tredje studien visades att när lungorna är sjuka och lätt faller ihop under utandningen, som vid ARDS, kontraheras diafragman även under utandningen. Denna kontraktion bromsar utandningen och förhindrar att luftvägar stängs. Detta i sin tur gör att luft inte stängs inne. Dessutom leder bromsningen till att lungorna inte faller ihop i slutet av utandningen. Datortomografiundersökningen visade att detta gör att luftfördelningen i lungorna blir jämnare.

Emellertid kan diafragmans aktivitet under utandningen leda till att den skadar sig själv (VIDD). Därför testades i den fjärde studien om andningsmotstånd som bromsar utandningen kan minska risken för VIDD, men samtidigt bibehålla de positiva effekterna av en bromsad utandning. Andningsmotståndet inducerades genom att minska lumen i utandningstuben till ventilatorn. Vi fann att ökat andningsmotstånd gav en utandningsbromsning som bevarade de positiva effekterna på luftfördelningen och förhindrade att lungorna kollapsade i slutet av utandningen. Samtidigt kontraherede sig diafragman mindre kraftigt under utandningen, vilket borde minska risken för VIDD.
Ogni anno molti pazienti vengono ricoverati in terapia intensiva per problemi respiratori. Le malattie respiratorie più gravi portano ad una condizione definita sindrome da distress respiratorio acuta, il cui acronimo inglese è ARDS. L’ARDS è uno stato infiammatorio acuto caratterizzato da insufficienza respiratoria, infiltrati polmonari bilaterali e ipossia. I pazienti con ARDS hanno spesso bisogno dell’aiuto di una macchina, il ventilatore meccanico, che li aiuti a respirare.

Il ventilatore meccanico può farsi carico completamente del lavoro respiratorio. In questi casi si parla di ventilazione meccanica controllata e il paziente, per adeguarsi a questo trattamento, ha bisogno di essere profondamente sedato e nei casi più gravi anche farmacologicamente paralizzato. In alcuni altri casi il ventilatore meccanico assiste solo parzialmente il respiro, permettendo al paziente, che gradualmente recupera le capacità respiratorie, di contribuire in parte al lavoro respiratorio. Quest’ultimo tipo di ventilazione si chiama ventilazione assistita.

Per quanto fondamentale per la sopravvivenza di molti pazienti ricoverati in terapia intensiva, la ventilazione meccanica può a sua volta, se non accuratamente monitorata e impostata, peggiorare il danno polmonare inducendo uno stato chiamato danni polmonare da ventilazione meccanica, il cui acronimo inglese è VILI. Il VILI è una grave complicazione della ventilazione meccanica nota ormai da molti anni. Molti studi sono stati eseguiti allo scopo di minimizzare questo danno e si sono sicuramente fatti grandi passi avanti rispetto a 70 anni fa quando la ventilazione meccanica è stata inventata. Oggi si hanno a disposizione dei sistemi di monitoraggio più avanzati e si hanno delle conoscenze più approfondite.

Recentemente si è inoltre visto che, nel caso della ventilazione assistita il VILI può essere dovuto in parte al paziente che non essendo in grado di graduare la propria forza, frequenza e profondità del respiro, sviluppa delle pressioni e dei volumi polmonari dannosi. Questo particolare tipo di VILI viene chiamato danno polmonare indotto dal paziente il cui acronimo inglese è P-SILI. In questo caso è più difficile ventilare in maniera atraumatica perché attualmente non disponiamo di sistemi di monitoraggio in grado di indicare con certezza che il paziente respira in maniera non appropriata.

Una ulteriore complicazione recentemente scoperta è il danno diaframmatico indotto da ventilazione meccanica anche chiamato VIDD. Il diaframma è
un grande muscolo a forma di cupola che si trova tra il torace e l’addome, proprio al di sotto dei polmoni e del cuore. Il diaframma è il muscolo principale della respirazione. Ogni volta che inspiriamo il diaframma si contrae e la sua cupola si abbassa verso l’addome facendo espandere i polmoni. Quando poi espiriamo il diaframma torna alla posizione iniziale e i polmoni si svuotano. Durante la ventilazione meccanica il diaframma può diventare atrofico o contrarsi in maniera inappropriata e per questo danneggiarsi.

Va anche ricordato che i polmoni danneggiati, per esempio da una grave polmonite, non sono omogenei in quanto il danno si distribuisce in maniera diffusa e variabile nei tessuti dell’organo. Questo rende la ventilazione meccanica ancora più difficoltosa e il rischio di danno più elevato rispetto alla ventilazione meccanica di polmoni sani.

Tanti studi sono stati fatti su questo argomento e, come detto prima, sicuramente un grande miglioramento è stato raggiunto. Tuttavia ancora adesso non si conosce tutto sul danno da ventilazione meccanica. In molti pensano che studi di fisiologia polmonare, come gli studi raccolti in questa tesi di dottorato, possano aiutare a comprendere in maniera più approfondita cosa accade a livello regionale nei polmoni. Lo scopo di questi studi è quello di raggiungere delle conoscenze più approfondite per rendere la ventilazione meccanica, e soprattutto quella assistita, il meno dannosa possibile.

A tal scopo abbiamo condotto quattro studi sperimentali (su modello suino) in parte utilizzando tecniche di monitoraggio avanzato che frequentemente si usano nei pazienti di terapia intensiva ed in parte utilizzando tecniche parecchio invasive, tra queste la tomografia assiale computerizzata (TAC) ad alta frequenza di acquisizione, che non sarebbe etico applicare direttamente sui pazienti.

Tutti e quattro gli studi hanno previsto innanzitutto la preparazione degli animali che sono stati sedati appena arrivati in laboratorio e poi sottoposti a ventilazione meccanica attraverso un tubo posizionato in trachea. Durante tutto l’esperimento ci si è costantemente assicurati che gli animali non avessero dolore grazie alla infusione continua di potenti analgesici. Per poter simulare un polmone malato è stato indotto un danno iatrogeno nel polmone. Diverse impostazioni del ventilatore sono state testate sia durante ventilazione meccanica controllata che durante ventilazione meccanica assistita. Per ognuna di queste modalità ventilatorie sono stati raccolti i dati che poi sono stati in seguito analizzati. I dati comprendono diverse pressioni, i flussi e i volumi registrati dall’apparato respiratorio, l’attività elettrica del diaframma e simultaneamente le immagini TAC acquisite ad alta frequenza.

Nel primo studio abbiamo dimostrato che durante la ventilazione meccanica controllata il campo gravitazionale ha un effetto importante sulla distribuzione della ventilazione nei polmoni. Le pressioni polmonari si distribuiscono seguendo l’asse gravitazionale. Questo effetto è differente tra polmone sano e polmone danneggiato. Il danno polmonare rende la distribuzione
dell’aria più eterogenea. Lo studio I è anche stato l’occasione per testare per la prima volta il nostro innovativo metodo d’analisi.

Nel secondo studio abbiamo valutato la ventilazione meccanica assistita, quando il paziente può respirare in parte da solo. Prima di noi altri ricercatori hanno dimostrato che in alcuni casi, quando il paziente respira in parte da solo, si sviluppano pressioni così alte che una grande quantità di aria si sposta da un’area all’altra dei polmoni rischiando il P-SILI. Lo spostamento di aria tra due parti del polmone viene chiamato pendelluft che in tedesco significa pendolo d’aria. In seguito a questo studio, numerosi esperti in questo campo hanno sconsigliato l’utilizzo della ventilazione assistita nei pazienti con ARDS. In questo studio noi abbiamo dimostrato che in realtà questo spostamento di grandi quantità d’aria dipende dalle impostazioni ventilatorie scelte. Se si è accurati nella scelta di queste impostazioni il pendelluft di grandi quantità d’aria non avviene. Inoltre in questo studio abbiamo dimostrato che sempre, sia durante la ventilazione assistita che in quella controllata, c’è uno spostamento di piccole quantità di aria tra diverse regioni del polmone. Piccoli pendelluft avvengono continuamente nei nostri polmoni e si pensa che questo fenomeno sia importante per stabilizzare i polmoni. Se la ventilazione meccanica è ben impostata la quantità d’aria che si sposta resta esigua pertanto non produce danno.

Nel terzo studio abbiamo dimostrato che in realtà, per evitare che i polmoni danneggiati collassino su se stessi durante l’espirazione, il diaframma resta contratto anche durante l’espirazione. Questo meccanismo di freno dell’espirazione può essere vantaggiose perché mantiene le vie aeree aperte durante l’espirazione e impedisce l’intrappolamento d’aria. Le immagini TAC hanno confermato che grazie a questo freno espiratorio esercitato dal diaframma durante la ventilazione assistita, la distribuzione dell’aria nei polmoni migliora. Per quanto positivo, il meccanismo di freno espiratorio da parte del diaframma dimostrato nello studio III, può essere causa di danno diaframmatico (il VIDD definito prima). Pertanto, nel quarto studio abbiamo testato se un freno esterno, indotto da una resistenza espiratoria, potesse sostituire il diaframma e portare gli stessi vantaggi contrastando il collasso dei polmoni durante l’espirazione, evitando allo stesso tempo la contrazione espiratoria del diaframma e altre complicazioni polmonari. Per creare una resistenza esterna abbiamo aggiunto dei tubi di diametro ridotto al circuito espiratorio del ventilatore meccanico e abbiamo analizzato le conseguenze su polmoni e diaframma. Abbiamo così potuto dimostrare che una resistenza espiratoria esterna porta gli stessi benefici del freno espiratorio diaframmatico e allo stesso tempo permette al diaframma di rilassarsi durante l’espirazione, riducendo in tal modo il rischio di VIDD.
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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)