# MONITORING ALVEOLAR RECRUITMENT IN THE CRITICALLY ILL –

## Patient studies using Electric Impedance Tomography and Volume-Dependent Compliance

Karin Löwhagen

Department of Anaesthesiology and Intensive Care Medicine
The Sahlgrenska Academy, Institute of Clinical Sciences
University of Gothenburg
Sweden
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*Till mamma och till minne av pappa*

# MONITORING ALVEOLAR RECRUITMENT IN THE CRITICALLY ILL –

## Patient studies using electric impedance tomography and volume-dependent compliance

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# ABSTRACT

**Background:** Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are associated with a high mortality rate and poor long term outcome in terms of quality of life, for those who survive. Similarly, patients with morbid obesity are at risk for respiratory complications when subjected to anaesthesia and surgery. To improve treatment and subsequently outcome for these patient groups, new treatment strategies and bedside monitoring techniques are needed.

**Methods:** 31 patients were studied, of whom 15 were morbidly obese patients undergoing laparoscopic gastric by-pass surgery, and 16 ALI/ARDS patients mechanically ventilated in the early phase of the disease. Electric impedance tomography (EIT) was used to follow changes in end-expiratory lung volume (EELV), to titrate positive end-expiratory pressure (PEEP) and to monitor regional distribution of ventilation, as well as intratidal gas distribution of the inspiratory phase of the respiratory cycle. Tracheal pressure was measured and combined with volume measures to obtain tracheal pressure/volume (P/V) loops, from which were obtained alveolar P/V curves and volume dependent compliance (VDC). Cardiac output was measured using oesophageal Doppler technique.

**Results:** When EIT was used to titrate PEEP in patients with morbid obesity during laparoscopic surgery, a high PEEP of 13-17 $cmH_2O$ was needed to maintain EELV. A prolonged moderate pressure recruitment manoeuvre resulted in a slightly larger EELV increase in ALI/ARDS patients compared to a vital capacity manoeuvre, both when measured at PEEP 16 $cmH_2O$ after the recruitment manoeuvre (RM). The prolonged manoeuvre also led to a lower optimal PEEP and plateau pressure when assessed during a decremental PEEP trial post RM. The vital capacity manoeuvre caused a marked decrease in cardiac output, which was not seen with the prolonged lower pressure RM. Volume-dependent compliance appeared more sensitive for detection of lung recruitment than conventional two-point compliance. Potential lung recruitability was assessed using an extrapolation method in combination with EIT for open lung volume determination. Potentially recruitable lung volume varied widely among the ALI/ARDS patients, where patients with high recruitability seemed to benefit from higher PEEP levels than those with low recruitability. The increase in EELV following a RM was mainly distributed to the non-dependent lung areas, whereas the tidal volume gas distribution was shifted towards more dependent areas. Intratidal gas was gradually redistributed dorsally during inspiration when pressure increased.

**Conclusion:** Electric impedance tomography has many potential clinical applications, including monitoring of alveolar recruitment, assessment of lung recruitability when combined with volume-dependent compliance, and determining regional and intratidal distribution of ventilation. This will help to improve individualized ventilatory treatment, with the potential to decrease the incidence of ventilator induced lung injury (VILI).

**Key Words:** ALI, ARDS, compliance, end-expiratory lung volume, EELV, EIT, electric impedance tomography, lung recruitment, morbid obesity, PEEP, recruitment manoeuvre, regional ventilation, volume dependent compliance

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# CONTENTS

# ABBREVIATIONS

ΔEELV = change in end-expiratory lung volume
ΔZ = impedance change
ΔZGLOB = global impedance change
ΔZROI = impedance change for a region of interest
ALI = acute lung injury
ANOVA = analysis of variance
ARDS = acute respiratory distress syndrome
BL = baseline
BMI = body mass index
BW = body weight
Cconv = conventional 2-point compliance
Cfin = compliance for the upper part of a tidal volume
Cini = compliance for the lower part of a tidal volume
Cmid = compliance for the middle part of a tidal volume
COPD = chronic obstructive pulmonary disease
C.O. = cardiac output
$CO_2$ = carbon dioxide
CPAP = continuous positive airway pressure
CT = computed tomography
EELV = end-expiratory lung volume
EIT = electric impedance tomography
$FiO_2$ = inspiratory fraction of oxygen
FRC = functional residual capacity
HU = Hounsfield unit
I:E = inspiratory to expiratory ratio
ICU = intensive care unit
ITV = intratidal ventilation distribution
$N_2$ = nitrogen
$O_2$ = oxygen
OR = operating room
P = pressure
Palv = alveolar pressure
$P(A\text{-}a)O_2$ = alveolar-arterial oxygen partial pressure difference
$PaCO_2$ = arterial carbon dioxide tension
$PaO_2/FiO_2$ = fraction of arterial oxygen to inspired oxygen
PEEP = positive end-expiratory pressure
PET = positron emission tomography
Pinsp = inspiratory pressure
Pexp = expiratory pressure
PRLV = potentially recruitable lung volume

P/V = pressure/volume
Rexp = expiratory resistance
Rinsp = inspiratory resistance
RM = recruitment manoeuvre
ROI = region of interest
SD = standard deviation
$SF_6$ = sulphur hexafluoride
SLRM = slow lower pressure recruitment manoeuvre
SPECT = single photon emission computed tomography
V = volume
Vexp = expiraotory volume
Vinsp = inspiratory volume
$\dot{V}$ = flow
$\dot{V}$exp = expiratory flow
$\dot{V}$insp = inspiratory flow
VCV = volume control ventilation
VDC = volume-dependent compliance
VICM = vital capacity manoeuvre
VILI = ventilator induced lung injury
Vt = tidal volume
VtROI = tidal volume for a region of interest
ZEEP = zero end-expiratory pressure

# LIST OF PUBLICATIONS

The thesis is based on the following studies I-IV:

I. **Positive end-expiratory pressure optimization using electric impedance tomography in morbidly obese patients during laparoscopic gastric bypass surgery.** Erlandsson K, Odenstedt H, Lundin S, Stenqvist O. *Acta Anaesthesiol Scand 2006; 50: 833-839*

II. **A prolonged moderate pressure recruitment manoeuvre results in lower optimal PEEP and plateau pressure.** Lowhagen K, Lindgren S, Odenstedt H, Stenqvist O, Lundin S. *Accepted for publication in Acta Anaesthesiol Scand*

III. **A new non-radiological method to assess potential lung recruitability – a pilot study in ALI patients.** Lowhagen K, Lindgren S, Odenstedt H, Stenqvist O, Lundin S. *Acta Anaesthesiol Scand 2010; October 29 [Epub ahead of print]*

IV. **Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome - assessed by electric impedance tomography.** Lowhagen K, Lundin S, Stenqvist O. *Accepted for publication in Minerva Anestesiol*

# INTRODUCTION

## Acute Respiratory failure

### *Acute Lung Injury and Acute Respiratory Distress Syndrome*

Acute respiratory distress syndrome (ARDS) was first described in 1967 by Ashbaugh [1] and is a serious complication that can arise from a number of primary disorders where the lungs were not necessarily involved initially. The syndrome has since been divided into two forms: acute lung injury (ALI) and ARDS. These diseases have a major influence on mortality and morbidity in intensive care unit (ICU) patients worldwide. In a systematic review by Phua et al [2], 89 studies with a total of 18900 enrolled patients were assessed with respect to mortality and morbidity. It was found that since 1994, when the currently used definition of ARDS was introduced [3], mortality has been unchanged. The mortality rate differs depending on the type of study, with 44% for observational studies and 36% for randomized controlled interventional studies.

Moreover, to emphasize the magnitude of the problem which ARDS constitutes to public health, one needs to look not only at the high 30 day-mortality, but also at the long-term prognosis for those patients who survive the ICU stay. In a prospective cohort study, 1-year outcome of patients who had received mechanical ventilation for an extended period of time was investigated. At one year, 56% of patients were alive, but only 9% without significant functional dependency [4]. When assessing quality of life for the survivors, only 27% had a good quality of life at one year follow-up.

Although heavily debated [5], the definitions of the syndromes from 1994 [3] are still widely accepted. These definitions consist of three criteria involving radiological evidence, oxygenation score and the exclusion of cardiogenic causes: 1) bilateral infiltrates on a chest radiograph, 2) pulmonary artery wedge pressure of less than 19 mmHg or the clinical absence of left atrial hypertension and 3) a $PaO_2/FiO_2$ ratio of less than 300 mmHg (40 kPa) for ALI, while for the more hypoxemic form, ARDS, a $PaO_2/FiO_2$ of less than 200 mmHg (27 kPa) is present. In addition to the three criteria, diagnostic criteria for both syndromes require acute onset. One weakness of this definition of the syndromes is that it is not specified at which $FiO_2$ to measure and consequently, depending on which fraction of oxygen is given, the results may differ [6], and the patient may thus either meet the criteria or not. Similarly the definitions lack any specification on at which end-expiratory pressure the criteria should be met, also this conferring risk of misclassification [7].

The ARDS syndrome has a wide range of different origins, and the definition does not take into account if the etiology is pulmonary or extra-pulmonary. Pulmonary ARDS is caused by a primary pulmonary disease such as pneumonia or aspiration, while extra-pulmonary ARDS is most often due to abdominal sepsis, for example developing from pancreatitis with raised intra-abdominal pressure. Since 1998 when this subdivision was first proposed [8], many studies have supported the idea that the pulmonary and extra-pulmonary ARDS should even be regarded as two different syndromes, and that perhaps these should be treated with different ventilatory management [9,10].

### *Perioperative respiratory management in the morbidly obese*

During the last several decades the increasing prevalence of morbid obesity has become a major epidemiological phenomenon and a serious threat to public health. Although not suffering from primary lung disease, 'healthy' morbidly obese patients constitute a clinical challenge with respect to lung function [11]. During general anaesthesia, especially in the supine position where in the obese patients the abdominal contents displace the diaphragm into the chest, a reduced functional residual capacity (FRC) is typically present [12-15] together with increased atelectasis formation [16]. These patients can in fact be compared to extra-pulmonary ARDS patients, from a lung-mechanical point of view. Their respiratory function is further negatively affected by a reduction in lung compliance [11]. This reduction is believed to be caused by the lowered FRC since the lung parenchyma's intrinsic mechanics appear to be unchanged compared to normal weight subjects. In addition, the morbidly obese have high oxygen consumption and a ventilation-perfusion mismatch [17-19] during general anaesthesia. Not only do these issues constitute a medical challenge during general anaesthesia, but they also lead to increased risk for postoperative complications, such as prolonged presence of atelectasis [16,20] which predisposes for impaired gas exchange [21]. To minimize the negative effects on gas exchange, both peri- and postoperatively, positive end-expiratory pressure (PEEP) may be effective [15,22-24]. Two recent studies suggest that PEEP needs to be preceded by a recruitment manoeuvre in order to attain the greatest improvement in respiratory function [25,26]. To reduce the negative effects of the increased abdominal pressure seen in the obese [15,21], the recommended position during surgery is the reverse Trendelenburg [27,28] although one study showed that body position might not be so important [29].

## Ventilatory management

Considering the major impact of ALI/ARDS on intensive care medicine, it is not surprising that a tremendous amount of research has been done in an attempt to better understand the syndromes and to improve outcome. Despite this, only a few studies have shown interventions with improvement in outcome. The most important single study is the ARDSnet study from 2000, in which large tidal volumes (Vt) were compared to small, and a reduction in mortality was found for the group ventilated with lower (6 ml/kg BW) Vt [30]. This lower tidal volume regimen has since been widely implemented into the ventilatory treatment programs for this patient group.

Except for to the low tidal volume regimen, it has been difficult to prove advantages of specific ventilatory strategies with respect to outcome – at least until this year, when a systematic review [31] was published which indicated that ARDS patients with severe hypoxemia appear to benefit from being placed in the prone position, with a higher survival rate compared to patients who are managed solely in the supine position. This subgroup of ARDS patients with the most pronounced hypoxemia is the group at highest risk for 'stress and strain' injuries of the alveoli [32], which might be an explanation for why they benefit from the prone position. Without causing hyperinflation [33] or increasing airway pressure [34], this position recruits atelectatic lung [33,35]. That means that the given airway pressure is spread over a larger area of the lung, with a decreased risk for injuring alveoli with hyperinflation. For those ARDS patients who are not severely hypoxemic, and who are not as sensitive to alveolar strain forces, the prone position has not proved beneficial with respect to survival. Instead, the risk of complications related to lifting and turning prone critically ill patients must be taken into account. These include obstruction of the endotracheal tube, accidental extubation, displacement/malfunction of catheters (urinary and vascular) and thoracic drains, pressure ulcers, conjunctival hemorrhage and edema [34].

Although necessary and life-saving for patients with ALI/ARDS, ventilator treatment is not itself completely harmless, and ventilator induced lung injury (VILI) is a well known phenomenon [36,37]. Incorrect ventilator settings can cause baro-[38], volu- [39], atelect- [40] and biotrauma [41,42]. To minimize these negative effects which can be seen with mechanical ventilation, different approaches have been proposed.

Currently, there is much focus on airway pressures. In the ARDSnet study [30] where a tidal volume of 6 ml/kg BW proved superior with respect to survival, the protective ventilatory strategy included an upper plateau pressure limit of 30 $cmH_2O$. This pressure limit has since been investigated specifically, and Terragni and co-workers have shown that there can be tidal hyperinflation of the small, normally aerated lung despite this limit for plateau pressure, and that values of lower plateau pressure ($<28$ $cmH_2O$) were associated with less hyperinflation [43]. In addition, in a randomized controlled study from 2006 [44], better outcome was associated with lower plateau pressures. Also, Hager et al performed a secondary analysis of the patient data from the ARDSnet study [30], and found decreasing mortality with decreasing plateau pressures [45]. This suggests that maybe a tidal volume even lower than 6 ml/kg BW could be clinically advantageous in order to further reduce plateau pressure. However, risk for respiratory acidosis will then increase, and this has lead to the renewed evaluation of alternative non-pulmonary means of carbon dioxide elimination. Some extracorporeal methods were tested in patients with severe ARDS in the mid 1980's [46] and proved efficient, but have not been used much because of high risk of complications. Now, with the goal of lower Vt to achieve plateau pressures as low as possible, veno-venous bypass for removal of carbon dioxide has been performed in ARDS patients with promising results [47].

Other strategies have been assessed to minimize the shear and strain caused by opening and closing of alveoli and over-distension respectively and, not to forget, to improve oxygenation. The most important of these strategies are lung recruitment and the attempts to titrate optimal PEEP.

## *Lung recruitment*

Atelectasis, the condition for alveoli when they are collapsed and not air-containing, is present in ALI/ARDS to a greater or lesser extent. In addition to impairing gas exchange, atelectasis formation also leads to unfavourable and high shear forces when open alveoli are adjacent to closed ones, as proposed 40 years ago by Mead [48]. Furthermore, it seems that the repeated closure and reopening of atelectases during the respiratory cycle, which can lead to alveolar damage and is called atelectrauma, is worse than atelectasis per se [49].

A treatment strategy is to open up – or recruit – closed alveoli and keep them open [50], and recruitment manoeuvres have successfully been used to open up dependent areas in anesthetized healthy patients [51]. However, the composition of inhaled gas affects the time to atelectasis recurrence, where re-expanded lung remains open for more than 40 minutes at low oxygen concentrations [52] while with 100% oxygen, lung collapse reappears within a few minutes [53].

Recruitment manoeuvres can be performed in a number of ways, and there is no consensus on the optimal performance of such manoeuvres. The most common form seems to be the sustained inflation, also called the 'vital capacity manoeuvre', where a constant airway pressure in the range 30-45 $cmH_2O$ is applied typically for 20-40 seconds [54-59], though it has recently been suggested that most of the recruitable lung is open already after two seconds [60]. In a study by Borges et al [61], a considerably higher pressure was used, 60 $cmH_2O$, and application of even higher pressure has been described as lifesaving in a case report with the most severely hypoxemic form of ARDS [62].

Positive pressure ventilation was already in 1948 described as influencing cardiac output in humans [63], and although well tolerated by many patients, there have been several studies reporting unwanted effects on circulation [53,56,58,59,64-67] related to sustained lung inflation for recruitment. Other serious complications have also been reported, such as pneumothorax and severe arrhythmia, although these are not common [58,66,68]. Moreover, a recent study showed that a single recruitment manoeuvre in ventilated critically ill children can lead to release of pulmonary cytokines into the circulation [69], whereas in adults conflicting data exist with one study [41] reporting an increase in inflammatory mediators, secondary to mechanical ventilation (not lung protective), while another study finds no change in cytokine release after a RM [70].

Maybe even more importantly, the usefulness of lung recruitment has been questioned. In a randomized controlled study [71], only immediate and brief effects were observed, and no additional sustained improvement was seen from a RM performed after a PEEP trial. Similar findings were presented in other studies [56,57,70], and the Cochrane systematic review on the subject from 2009 [72] concludes that there is not enough evidence to determine whether recruitment manoeuvres has an effect on outcome.

One of the reasons for the ambiguous results on RMs may be that the ARDS patient group is very heterogeneous. Gattinoni reported in 2006 that there is a wide variability with respect to amount of potentially recruitable lung in patients with ALI/ARDS [73]. When determined by CT, the recruitability of the lung varied from -9% to 59% in different patients. This suggests that there is a need for a method to find the appropriate patients, the ones who could most benefit from a RM.

The best method for achieving recruitment is yet not clear. As mentioned above, there have been negative side effects reported with sustained lung inflation. Other methods for recruitment have been proposed, such as sighs [74], incremental positive end-expiratory pressure [75] and variable ventilation methods, the later where the tidal volume size is varied [76]. Odenstedt et al showed in 2005, in a porcine ARDS model, that a slower and moderate pressure recruitment manoeuvre resulted in greater improvement in $PaO_2/FiO_2$ and compliance compared to sustained inflations, and this lower pressure RM also resulted in less hemodynamic side effects [77].

The efficacy of RMs also depends on ARDS category (pulmonary vs. extra-pulmonary) [10,78,79], although some studies found that lung injury etiology did not affect the result of a RM [80]. Other factors affecting the efficacy of RMs include stage of the syndrome [56] and PEEP level after RM, which will be discussed below.

## *Optimal PEEP*

PEEP relates to the expiratory part of the respiratory cycle, and aims at preventing already open lung units or regions from collapsing particularly when lung volumes are lowest, but also throughout the respiratory cycle. The importance of PEEP has been recognized for decades [1,81], and it has been shown that without a subsequent increase in PEEP, the effect of recruitment manoeuvres is only transient [75,82,83]. Also, the stability of the alveoli has been shown to be dependent on sufficient PEEP after a recruitment manoeuvre in a surfactant deficient porcine lung model [84]. However, it has been difficult to prove the benefit of PEEP on outcome or survival in acute respiratory failure. Recently, two large studies found that there was no difference in mortality between ARDS patients ventilated with higher PEEP compared to lower PEEP levels [85,86]. This most likely does not indicate that PEEP does not matter, but rather this is likely an indication of the heterogeneity of this patient group [73], and supports the idea that there is a need for individualized PEEP setting [87,88]. High PEEP is likely to be important in patients with substantial lung edema and atelectasis formation [89] whereas patients who have only little collapse in dependent lung areas should probably not expect to benefit from high PEEP levels.

Since the 1970's, attempts have been made to determine optimal PEEP levels [90]. Methods using lung mechanics have been proposed, including the stress index method [91] where the airway pressure-time curve is analyzed, or setting PEEP above the lower inflection point [54,92] of the static respiratory P/V curve, or by monitoring dynamic compliance [93]. Defining optimal PEEP based on oxygenation [61,94] or carbon dioxide decrease [95] has been investigated. Caramez and co-workers compared a number of methods for identifying optimal PEEP [95] in an ARDS experimental model and found no difference when using dynamic compliance, maximum oxygenation, minimum shunt, lower inflection point or maximum inspiratory compliance increase. They found, however, that setting PEEP based on minimum carbon dioxide value resulted in lower optimal PEEP compared to the other methods. Another group has suggested setting PEEP high enough to keep a positive transpulmonary pressure [79,96]. In some studies [91,93], the investigated method was compared to computed tomography findings. Computed tomography is widely considered to be a reliable reference method for determining optimal PEEP and successful recruitment [87] (see below). Lichtwarck-Aschoff et al compared static and volume-dependent compliance (VDC) as two different means to set optimal PEEP, and found that the VDC (SLICE, see below) method suggested a lower optimal PEEP with subsequent lower plateau pressure [97], compared to when using the lower inflection point of the static pressure/volume curve.

Not only in the ICU, but also for patients undergoing surgery and subjected to general anaesthesia, optimal PEEP is important, since atelectasis formation will occur also in this patient group [53]. Especially in morbidly obese patients, this atelectasis formation is very pronounced [12], with the subsequent problem of hypoxemia [11] which can be severe without PEEP application [18].

## Respiratory Assessment and Monitoring

In order to optimize ventilation, assessment and monitoring are essential. The question is what to measure, how to measure, when to measure, and how often.

Increase in $PaO_2$ has been traditionally used to evaluate the effect of a recruitment manoeuvre [55,75,78]. However, changes in oxygenation are only indirect measures and do not necessarily reflect successful recruitment. Oxygenation changes can also be due to changes in cardiac output or redistribution of pulmonary blood flow, as discussed already in 1972 by Falke and co-workers [81].

Similarly, decrease in $PaCO_2$ has been suggested to define lung recruitment [98] although this approach is not thought to be fully reliable as an indicator of recruitment [99].

## *Lung volume measurements*

Lung recruitment aims at increasing the lung volume involved in gas exchange, i.e. to decrease alveolar dead space and venous admixture. Measuring lung volume can be performed in a number of ways, including computed tomography (see below), body plethysmography [100] and by gas dilution methods which employ gases such as sulphur hexafluoride ($SF_6$) [101], helium [102] or nitrogen [103]. A modified version of the nitrogen washout technique [104] has recently become available for clinical use.

## *Compliance*

Compliance is defined as the lung volume change achieved per unit of airway pressure change. Although simple in its definition, there are numerous ways of determining compliance, depending on at what conditions the measurements take place. An increase in compliance should reveal successful lung recruitment [99,105].

One should distinguish between static and dynamic compliance. S*tatic compliance* is calculated during stable airway conditions where there is no air flow. To reach not only 'no flow' conditions but also a state of equilibrated visco-elastic forces of the lung at the end of inspiration, a pause as long as 5 seconds is needed [106]. This makes continuous calculation of true static compliance not feasible for clinical purposes. In contrast, *dynamic compliance* is determined during ongoing gas inflow into the lungs. In this thesis, *dynamic compliance* denotes *'quasi-static'* compliance, that is, compliance measured at 'no flow' or very low flow conditions, but not with full visco-elastic equilibration. Dynamic compliance is here obtained during ongoing ventilation in volume control mode (VCV) [107], in which a very short end-inspiratory pause is incorporated. This pause leads to no or very low flow, and an immediate pressure drop to plateau pressure is seen at the end of inspiratory flow from the ventilator. The resistance to flow is eliminated but the visco-elastic forces are not at equilibration. *Volume-dependent compliance*, or compliance at different levels of the tidal volume, is compliance during ongoing ventilation and can, regardless of ventilatory mode, be obtained by one of two methods. These methods, the SLICE method [108,109] and the Dynostatic algorithm [110] provide alveolar P/V curves during ongoing ventilation where the effects of airway resistance on measurements are eliminated. Since the P/V curves are obtained during ongoing therapeutic ventilation these methods have been called *functional lung mechanics* [111].

## P/V curves

P/V curves can be obtained from the respiratory tract during static conditions or during ongoing ventilation. The former case, with static conditions calls for 'no flow', or a short end-inspiratory pause where very low flow conditions are reached (see previous paragraph). One technique is the super-syringe method where a stepwise inflation and subsequent deflation of the lungs are performed, each step 50-100 ml and with a pause of at least 3 seconds before next step [112]. For each step, pressure is recorded. This technique has the obvious disadvantage of disconnecting the patient from the ventilator in order to connect the super-syringe. Another method, which is based on recordings from one single breath [113], is the slow inflation technique. The ventilator is then used to deliver a constant flow breath with a markedly prolonged time for inspiration [113,114]. The flow is then so low that the pressure drop between the airways and the alveoli can be disregarded. Only inspiration can be analyzed since expiration is not controlled. Koefoed-Nielsen and co-workers proposed for this method to be used to predict alveolar recruitment [115]. However, these methods cannot be employed without changing from therapeutic ventilator settings, which clearly limits their use.

In contrast, volume-dependent dynamic methods are now available in the clinical setting, with measurements performed during ongoing unchanged ventilation. The SLICE method [108,109] and its refined follow-up, the gliding-SLICE method [116], use the ventilator pressure and flow together with an algorithm for tube resistance to calculate tracheal pressure. The obtained tracheal P/V loop is divided into six equal volume slices, and volume-dependent compliance for each breath can be estimated. Another dynamic method is the dynostatic algorithm [110,117,118] in which tracheal pressure is actually measured to obtain the tracheal P/V loop. Based on the assumption that airway resistance is the same for inspiration as for expiration at the same volume, at least 20 iso-volume planes of the tracheal P/V loop are used to calculate the alveolar (dynostatic) pressure and create the alveolar P/V curve for each breath, rendering dynamic volume-dependent compliance. Both methods measure compliance during ongoing, therapeutic ventilation and are thus giving information on functional lung mechanics.

## Computed Tomography

Computed tomography (CT) is widely accepted as a reference method for determining lung volume and detecting lung recruitment. Since its introduction into this field during general anaesthesia in the mid 1980's [119,120] and simultaneous diagnostic use in ARDS patients [121], CT has been widely employed to study acute respiratory failure patients, and is the only technique which can determine degree of aeration while in addition offering a high spatial resolution with respect to morphology. For CT, Hounsfield units (HU) are used to describe the x-ray attenuation, so called radiodensity, caused by different tissues. This attenuation is linearly correlated to tissue density [122] and the radiodensity of water at standard temperature and pressure is defined as zero HU while that of air is -1000 HU. Alveolar recruitment can be detected by quantifying the decrease in non-aerated lung parenchyma characterized by radiodensity between -100 and +100 HU in a single juxtadiaphragmatic CT section [123,124]. This approach was challenged by Malbouisson and co-workers [125] who included also tissues with CT attenuations ranging between -500 and -100 HU in order to also detect recruitment occurring in poorly but already aerated areas; they also analyzed the whole lung instead of only one CT section. The technique has further been developed to include monitoring during dynamic conditions [126,127], and CT is clearly valuable to describe regional distribution of ventilation [124,128-130]. Although popular and useful for research studies, CT is not an ideal method for repeated or continuous measurements in the clinical setting, since it depends on radiation and also in most cases CT machines are not located within the ICU, thereby requiring transportation and care outside the ICU for sometimes very ill patients [131].

## *Electric Impedance Tomography*

Electric impedance tomography (EIT) was first developed for medical monitoring in the early 1980's by Brown and Barber [132,133] who suggested its suitability for imaging of the lungs and ventilation. EIT is similar to CT in the sense that it is a non-invasive imaging tool, and just like CT it provides cross-sectional images of the thorax. However, unlike CT, EIT is a bedside, radiation-free tool suitable for continuous monitoring of changes in lung volume, although with poor morphological resolution [133,134].

EIT is based on the principle that different tissues have different electrical properties in terms of conductivity, where lung tissue is characterized by very low conductivity (high resistivity), since the presence of air makes the alveoli behave like insulators, enclosing the lung tissue and blood, where the applied current can pass. EIT can detect small changes in air content [135], as such changes will stretch or relax the lung tissue and increase and decrease the resistance like a strain gauge. The periodic increase and decrease in the volume of air with every breath makes the technique well suited to follow ventilation induced impedance changes. By stepwise inflating and deflating the lungs, a close correlation between impedance changes and lung volume changes has been established [135-137]. Also, the tidal amplitude of the impedance change co-varies with the size of the tidal volume [138,139].

The impedance changes, reflecting the changes in lung volume, are gathered as a result of surface voltage measurements. EIT involves placement of electrodes circumferentially around the thorax. These electrodes are used for application of small alternating electrical currents in a fast rotating manner. The voltage differences generated between the passive adjacent electrode pairs are measured, recorded and analyzed (Fig.1) [133].

Most commonly, one set of electrodes is used, that is, measurements are performed in one cross-sectional plane, while there are studies where three cross-sectional planes are studied by use of multiple sets of electrodes [138]. Also, the number of electrodes in one plane might affect the quality of the image, mainly in the periphery [140]. EIT has been validated for the detection of changes in global end-expiratory lung volume (EELV) [139,141] as well as regional EELV [142]. Moreover, when comparing EIT with the pneumotachograph, EIT estimation of changes in lung volume has been found reliable regardless of body position or body habitus, such that the correlation between methods is excellent irrespective of the patient's body position or if the patient is normal weight or heavily overweight [141]. During the last decade several studies have shown how EIT can be used to assess regional lung ventilation [88,142-148], and the possible clinical applications are numerous. EIT has been used to detect lung recruitment [146,147,149,150], regional overdistension [149,151,152], regional lung injury [153], pneumothorax [154], one-lung ventilation [155] and has been proposed to help in optimizing PEEP in the individual patient [88,146,156]. EIT has also been used to better understand regional lung mechanics [157].

# AIMS

The overall aim of this thesis was to study lung function and ventilator treatment of patients with ALI/ARDS or morbid obesity and in this work further develop EIT-based methods for bedside monitoring of lung volume. Specific aims included the following:

- To optimally assess lung recruitment and titrate optimal PEEP

- To test and compare selected alternatives for recruiting lung volume

- To identify the balance between regional recruitment and overdistension

- To assess the effect of lung recruitment and PEEP on regional ventilation and lung volume

# PATIENTS AND METHODS

## Patients

The studies were approved by the Human Ethics Committee of the University of Gothenburg, Sweden. A total of 31 patients were included after informed written consent was obtained from the patients (Study I) or patients' next of kin (Studies II, III, and IV).

### *Study I*

Fifteen consecutive patients scheduled for laparoscopic gastric by-pass surgery were included. The patients were morbidly obese with an average body mass index (BMI) of 49±8 $kg/m^2$.

### *Studies II, III and IV*

Sixteen patients with ALI or ARDS due to various causes were recruited from a university hospital mixed adult intensive care unit. Patients were included if their $PaO_2/FiO_2$ ratio was < 300 mmHg when PEEP > 5 $cmH_2O$. Patients with severe COPD or heart failure were not included.

## Methods

### *Anaesthesia (Study I)*

Anaesthesia was induced using propofol 2 mg/kg BW and fentanyl 1,5 µg/kg BW. Drug dosage was based on body weight corresponding to a BMI of 30 $kg/m^2$. Muscle relaxation before intubation was achieved using succinylcholine 100-200 mg. Relaxation was then maintained using rocuronium. Total intravenous anaesthesia was used during measurements, and these measurements were conducted before and after completion of the surgical procedure.

### *Analgesia and sedation (Studies II, III and IV)*

Patients were sedated with propofol and fentanyl, and infusion rates were increased before start of measurements, to avoid spontaneous breathing efforts during study procedure. No muscle relaxants were used.

## Lung mechanics

Ventilatory pressures, volumes and flow were measured proximal to the tube, at the y-piece, using sidestream spirometry (D-lite, GE Healthcare, Helsinki, Finland).
Tracheal pressure was measured continuously using an air-filled pressure measurement tubing with an outer diameter of 2 mm. This tubing was inserted through the endotracheal tube, and the distal tip was positioned at the distal end of the endotracheal tube. At its proximal end, the pressure line was connected to a standard clinical blood pressure transducer, the same system as used for intravascular pressure monitoring [110].
Two-point compliance, was calculated as Vt divided by the difference between end-inspiratory pause pressure and end-expiratory pause pressure. Whether called dynamic or quasi-static - when reported in this thesis, two-point compliance is always referring to compliance measured during on-going ventilation in volume control mode, but with 'no flow' guaranteed by the short end-inspiratory pause. However, viscoelastic forces are not fully equilibrated.

## EELV measurements

A modified nitrogen wash-out/wash-in technique was used to measure EELV by increasing the fraction of inspired oxygen ($FiO_2$) in one step by 0.1-0.2, and then decreasing it back again, to achieve nitrogen wash-out and wash-in [104].

## Electric Impedance Tomography

Changes in lung volume, caused by ventilation (spontaneous or controlled), can be followed as changes in impedance, using EIT. The method is non-invasive, radiation-free and can be used bedside on awake or anesthetised subjects/patients. It allows high frequency sampling which enables real time monitoring.

In Study I, 16 standard electrocardiographic electrodes were placed circumferentially around the thorax in one plane, approximately at the level of the fifth intercostal space, and were all connected to the EIT monitor (Dräger/GoeMFII, Lübeck, Germany). Measurements were started before start of anaesthesia. By the time we were performing the measurements for Studies II, III and IV, the method had been refined, and the electrodes had been incorporated into an elastic band (Fig. 1), which was placed around the thorax, and this provided the signals for the EIT device.

Impedance data were generated by application of electrical currents of 5 mA and 50 kHz, enabling measurements of the voltage differences between neighbouring electrode pairs in a sequential rotating process. A scan, displaying the ventilation-induced impedance changes ($\Delta Z$), was obtained every 50 to 77 ms (13 - 20 Hz). The scan represents a 15-20 cm thick slice of the thorax. The absolute level of the end-expiratory signal of the EIT at baseline PEEP was calibrated using the modified nitrogen wash-out/wash-in measurement of EELV [104]. Tidal impedance changes were calibrated against known lung volume changes by increasing the Vt in steps of 200 (Study I) or 100 (Studies II, III and IV) ml (Fig. 1). The changes in end-expiratory lung volume above the baseline level (baseline EELV level measured by $N_2$ wash-in/wash-out method) were followed as changes in end-expiratory impedance.

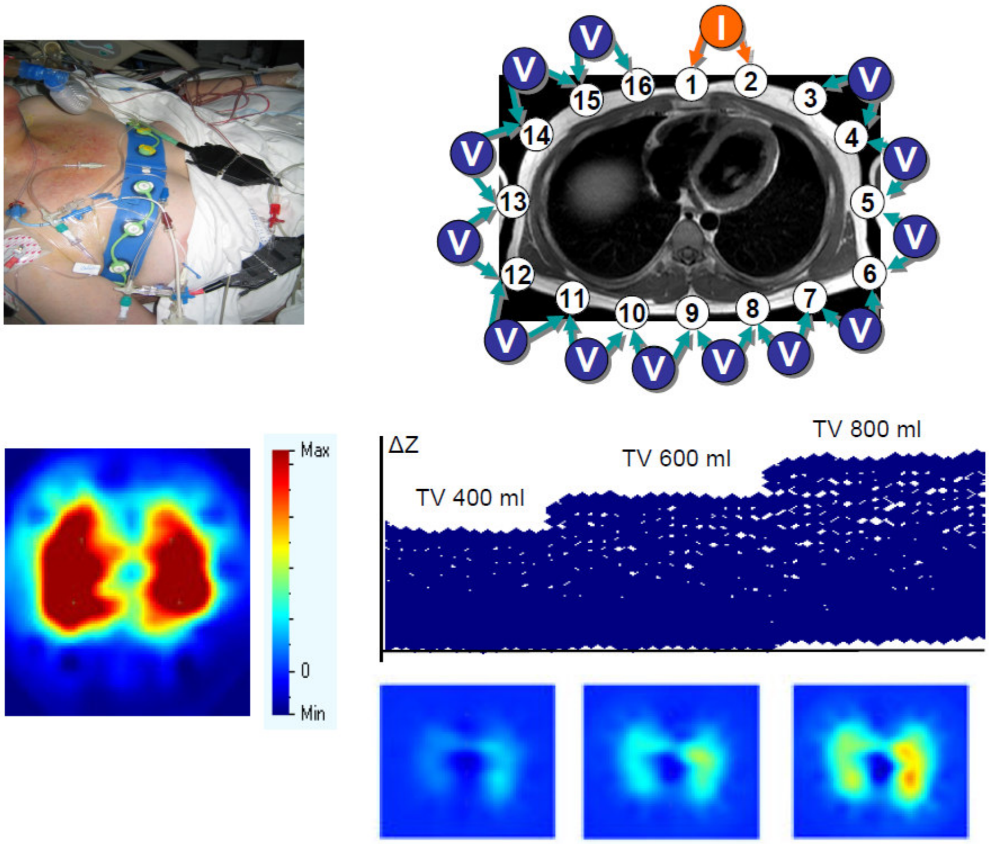

**Figure 1.** Electric impedance tomography. Upper left: EIT elastic band containing 16 electrodes, placed at the level of the 5th intercostal space. Upper right: schematic figure explaining the application of electrical current (I) in a rotating manner, and the subsequent measurements of the created voltage (V) differences. Lower left: example of image, here at maximal inspiration where maximal impedance changes (ΔZ) take place in the red zones. Lower right: calibration of the EIT, with tidal volume (TV) increases in steps of 200 ml, with the corresponding image displayed below the global EIT signal.

The EIT software (Dräger Medical, Lübeck, Germany) analyzes both global and regional aeration-related impedance variations. Four regions of interest (ROI) of the cross-sectional plane were chosen: ventral, mid-ventral, mid-dorsal, and dorsal (Fig. 2). The fractional impedance changes (ΔZROI) during tidal breathing were continuously analyzed and presented. For Study IV, regional Vt values (VtROI) were calculated as: VtROI= (ΔZROI/ΔZGLOB) ×Vt, ΔZROI being the regional impedance change for a ROI, and ΔZGLOB being the sum of all impedance changes in the ROIs (=global tidal impedance changes).

Regional intra-tidal gas distribution was analyzed in Study IV by dividing the inspiration into eight parts with equal volume (Fig. 2). Consequently, impedance changes of the inspiratory part of the four ROIs were divided into eight parts with equal volume, (ITV1-8). Analyzes were based on data from three consecutive breaths at each PEEP level. The fractional regional ITV1-8 (rITV1-8) of the ΔZROI is (ITV1-8ΔZROI/ ITV1-8ΔZGLOB).

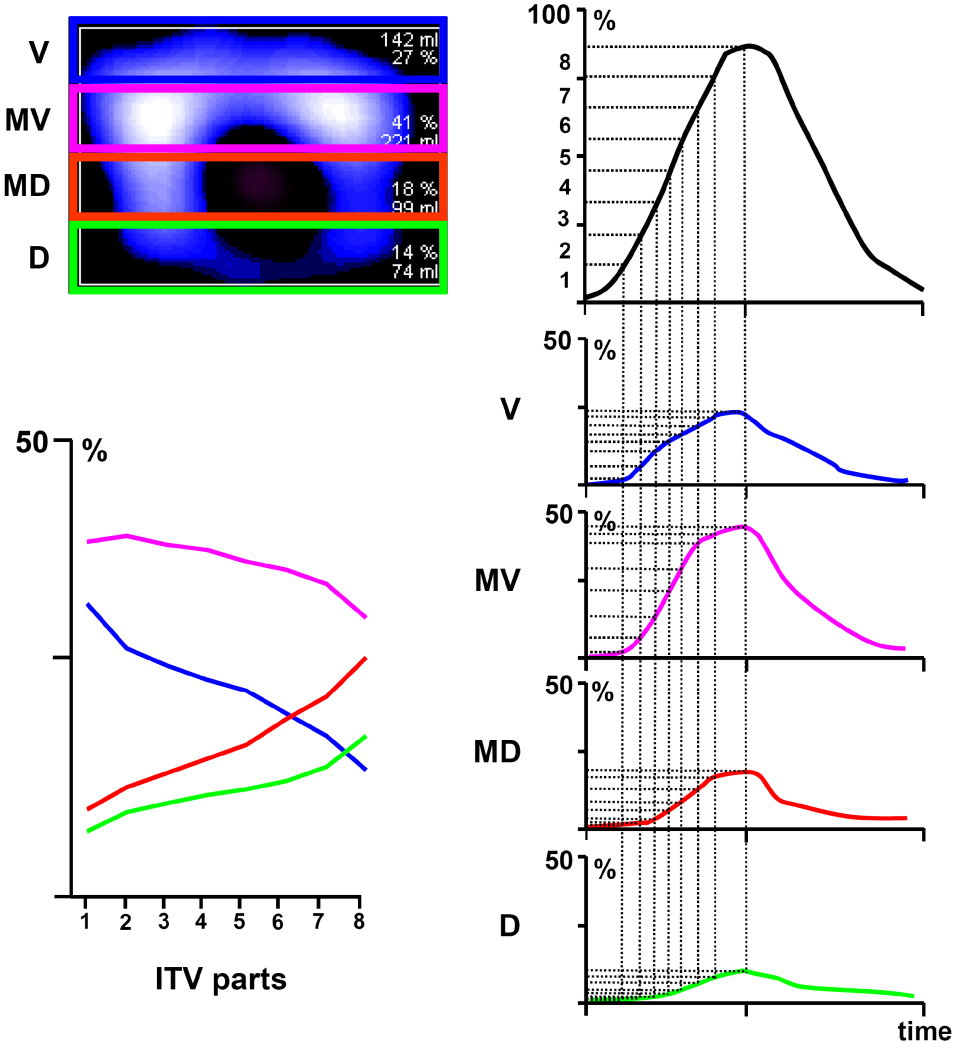

**Figure 2.** Upper left: regional areas of interest (ROI) of EIT image; Ventral (V), Mid-ventral (MV), Mid-dorsal (MD) and Dorsal (D). Upper right: global inspiratory tidal impedance curve (black) divided into 8 iso-volume parts. Lower left: fractional regional gas distribution during inspiration (sequential ITV 1-8). Lower right: regional tidal impedance curves. Vertical dashed lines transfer iso-volume time points to from the above global curve to the regional curves, which enable calculation of regional fractional volume distribution for each of the 8 iso-volume parts.

## *Volume-Dependent Compliance*

The tracheal pressure measurements enable the formation of a complete tracheal dynamic P/V-loop, with flow ($\dot{V}$), pressure (P) and volume (V) registered at each data sampling point. For each point on the inspiratory limb ($\dot{V}$insp, Pinsp, Vinsp), a corresponding point on the expiratory limb ($\dot{V}$exp, Pexp, Vexp) at the same volume (iso-volume level) was identified, creating a pair (Fig. 3).

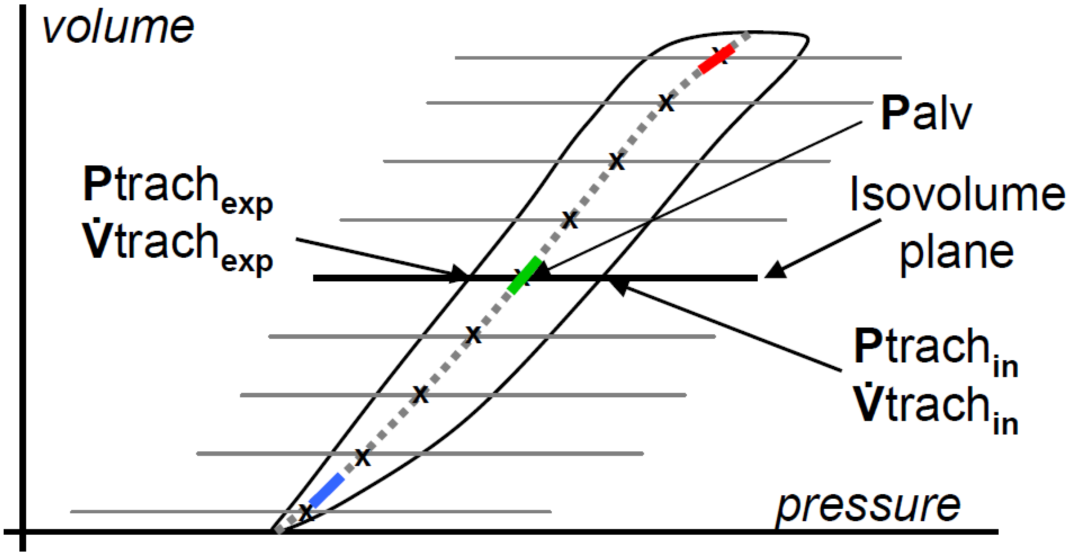

**Figure 3.** Schematic graph of the technique for calculation of ”dynostatic” alveolar pressure/volume curve (hatched line) from the measured tracheal pressure/volume loop during ongoing ventilation. At each iso-volume plane (horizontal lines) the inspiratory and expiratory tracheal pressure (Ptrachin, Ptrachexp) and flow (Vin, Vexp) are registered and used for calculation of the alveolar pressure (Palv) at that iso-volume plane, using the equation Palv = (Pin x Vexp – Pexp x Vin)/(Vexp-Vin).

The blue, green and red marks on the P/V curve indicate the level where initial, mid and final volume-dependent compliance (Cini, Cmid and Cfin) are calculated. The Cini represents the compliance below a possible lower inflection point and the Cfin represents the compliance above a possible upper inflection point.

Based on the assumption that inspiratory resistance (Rinsp) is equal to expiratory resistance (Rexp) at iso-volume levels [158], the following equations were used to calculate the alveolar pressure, which equals dynostatic pressure (Pdynostatic) for each data pair :

$$R_{insp} = \left(P_{insp} - P_{dyn}\right) / \dot{V}_{insp}$$
$$R_{\exp} = \left(P_{\exp} - P_{dyn}\right) / \dot{V}_{\exp}$$
$$R_{insp} = R_{\exp}$$
$$P_{dynostatic} = \left(P_{insp} \times \dot{V}_{\exp} - P_{\exp} \times \dot{V}_{insp}\right) / \left(\dot{V}_{\exp} - \dot{V}_{insp}\right)$$

Note that the flow is negative during expiration. The alveolar P/V-curve can thus be formed. Subsequently, compliance for the different parts of this alveolar P/V-curve can be determined; volume-dependent initial, middle and final compliance of the total respiratory system are calculated by analysis of the pressure and volume differences at 5-15% (Cini), 45-55% (Cmid) and 85-95% (Cfin) of the Vt.

## *Cardiac Output*

Cardiac output was measured using an oesophageal Doppler technique (Cardio-Q, Deltex Medical Ltd., Chichester, West Sussex, UK). A probe is inserted into the oesophagus, and measures the velocity of blood flow in the descending aorta. The device has an algorithm for estimation of the aortic diameter based on patient age, height and weight. Using this estimation and measured velocities of aortic blood flow, stroke volume can be calculated, which along with observed heart rate provides cardiac output. In Study I, the weight corresponding to a BMI of 30 kg/m$^2$ was used. If the Doppler technique was not suitable, for example due to surgery on the oesophagus, thermodilution and pulse contour analysis (PICCO, Pulsion Medical System AG, Munich, Germany) was used instead.

## *Gas Exchange*

Breath-by-breath oxygen and carbon dioxide concentrations were measured with paramagnetic and infrared absorption methods respectively (COVX-module, S/5, GE Healthcare, Helsinki, Finland). Oxygen consumption and carbon dioxide production were measured continuously by indirect calorimetry by the module. Mixed venous oxygen content was calculated by Fick's equation using blood gas measurements to obtain arterial oxygen content. Indirect calorimetry was used to measure oxygen consumption, and cardiac output was derived from oesophageal Doppler/ pulse contour measurements.

Pulmonary shunt fraction or venous admixture was determined using a standard formula.

## *Study procedures*

In Study I, the patients were assessed with EIT from the period before induction until after extubation. With the patients in a 20 degree head-up tilted position, CPAP 10 cm$H_2O$ was applied during pre-oxygenation and induction. Immediately after intubation, PEEP was set to 10 cm$H_2O$ in VCV with Vt 8ml/kg BW corresponding to BMI of 30, and $FiO_2$ of 0.3. An EELV measurement was performed. After calibration of the EIT (see above under the EIT section), PEEP was changed from 10 to 0, 10, 15 and

20 $cmH_2O$ while the slopes of the end-expiratory impedance tracings were monitored. For each patient, PEEP was then set to the level where the tracing was horizontal (Fig. 4), with the goal to maintain end-expiratory lung volume. EELV was measured at this optimized PEEP.

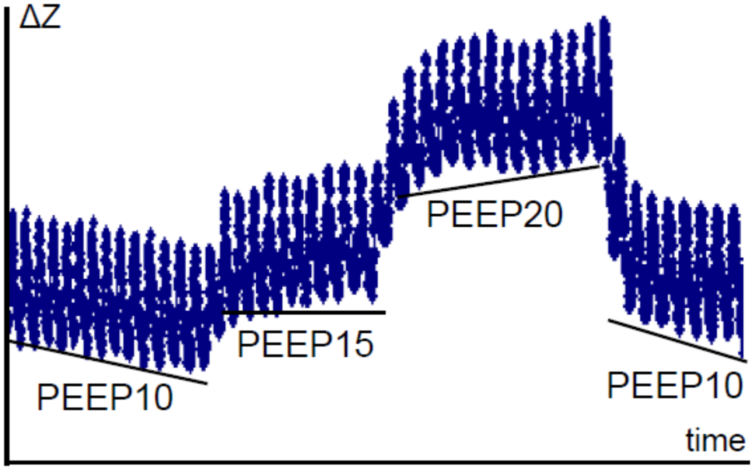

**Figure 4.** Global EIT signal during changes in positive end-expiratory pressure. The slope of the end-expiratory impedance changes was monitored and PEEP was set in an attempt to maintain a horizontal end-expiratory signal corresponding to a maintained end-expiratory lung volume. A decrease in slope indicates derecruitment, while an increase indicates recruitment.

Measurements were discontinued during surgery, because of interference from electrocautery with the EIT signal, but were resumed immediately after, and EELV was again measured at the optimized PEEP level, followed by a new calibration series. Finally, a recruitment manoeuvre was performed when PEEP was increased by 5 cm $H_2O$ and Vt by 50% during 2 minutes.

In the 16 ICU patients that were included for Studies II, III and IV, EELV measurements and EIT calibration were performed at baseline ventilatory settings, which were set to VCV with Vt 6 ml/kg BW, I:E of 1:2, end-inspiratory pause of 10 seconds and PEEP 6 $cmH_2O$. Two recruitment manoeuvres (RMs) were performed in random order in each patient. The RMs were followed by a decrease of PEEP, from 16 back to baseline 6 $cmH_2O$ in steps of 2$cmH_2O$, each step kept for 2 minutes. The RMs were separated in time by 30 minutes of baseline ventilation, and EELV measurement prior to the second RM affirmed the same baseline level as prior to the first RM. The RMs performed were:

1) a vital capacity manoeuvre (VICM) with a pressure of 40 $cmH_2O$ kept for 20 seconds performed twice, with a 40 second intermission of VCV 6 ml/kg BW at PEEP 16 $H_2O$ for 40 seconds in between,

2) a slower, more moderate pressure RM (SLRM) where PEEP was increased to 16 $cmH_2O$ for 30 minutes and prolonged (7 seconds) end-inspiratory pauses were performed twice a minute.

In Study II, the two RMs are compared with respect to both lung mechanical and gas exchange parameters.

Study III contains only the VICM where it is used to determine the fully recruited open lung volume at 40 $cmH_2O$ (OLV40). This volume is in turn used for the calculation of potentially recruitable lung volume (PRLV) (Fig. 5) in such way that the non-recruited open lung volume at the same pressure (NRLV40) is determined and subtracted from the OLV40, giving the PRLV. The NRLV40 is attained by adding three volumes: the EELV, the Vt and the XVOL40. The XVOL40 is a volume generated by extrapolation of the alveolar P/V-curve, above the tidal volume, to a pressure of 40 $cmH_2O$. The extrapolation was performed graphically and was later confirmed mathematically.

In Study IV, only the SLRM is used, when studying regional distribution of ventilation and the intratidal distribution of gas, the later which can be determined by dividing the inspiration into 8 parts with equal volume.

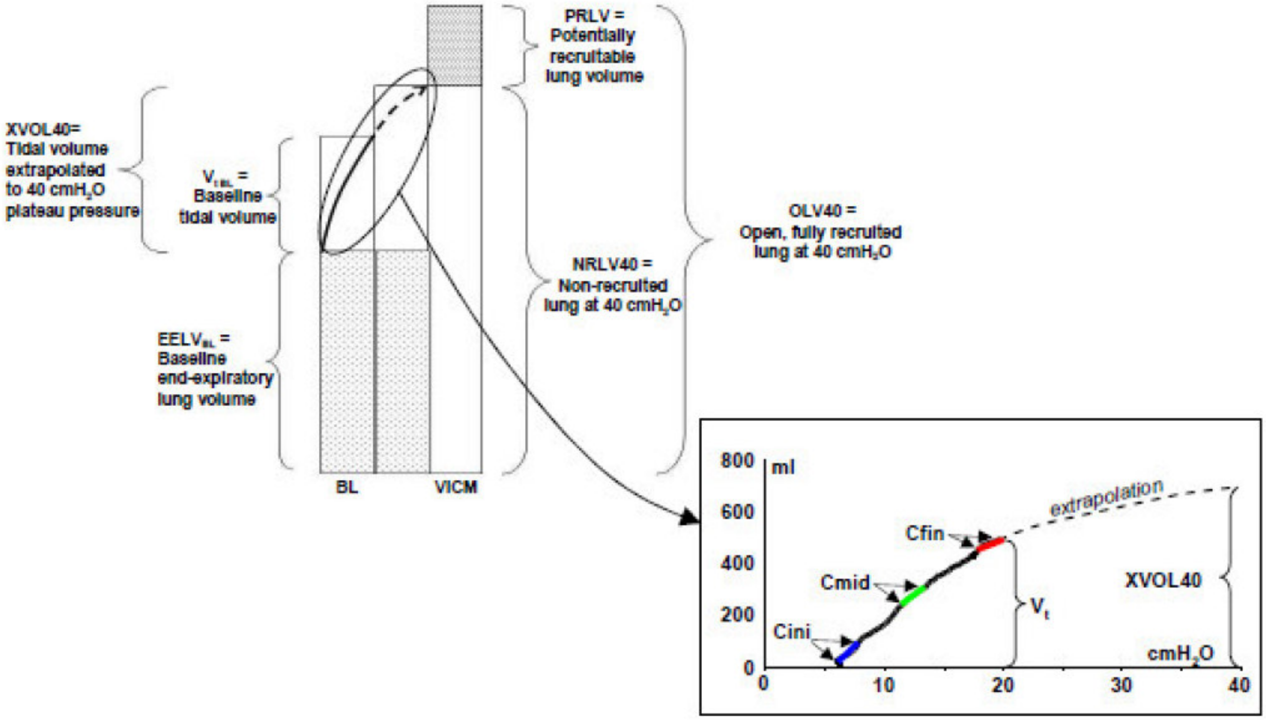

**Figure 5.** Schematic graph of the graphical extrapolation method, to obtain potentially recruitable lung volume (PRLV). The fully recruited open lung volume (OLV40) was defined as lung volume at the end of the second vital capacity manoeuvre, at 40$cmH_2O$. The open non-recruited lung volume (NRLV40 ) at the same pressure was defined as the end-expiratory lung volume at baseline, plus a volume (XVOL40). This volume XVOL40 consists of the baseline tidal volume ($Vt_{BL}$) plus a volume determined by graphical extrapolation, of the upper part of the alveolar P/V-curve of a tidal breath, to the pressure of 40 $cmH_2O$. The PRLV was defined as OLV40 minus NRLV40. Three alveolar P/V-curves at baseline were used for the extrapolation.

# Statistics

In all four papers results are presented as mean values ± standard deviation. A *P* value of <0.05 is considered statistically significant.

## *Study I*

Comparisons between values pre- and post-surgery, and pre- and post-recruitment, were performed using a paired Student's t-test. Correlation between impedance changes and lung volume changes was assessed using linear regression analysis.

## *Study II*

A positive response to a RM was defined as an increase (or for shunt; decrease) in a parameter of ≥ 25%. Two-way analysis of variance (ANOVA) and a paired Student's t-test were used for comparison between RMs and to evaluate changes between baseline and maximum (for shunt; minimum) values during the decremental PEEP trial. Bonferroni's correction for multiple comparisons was performed.

## *Study III*

Coefficient of variation for the calculation of non-recruited lung volume at 40 $cmH_2O$ was calculated. Correlation between graphical and mathematical extrapolation to determine non-recruited lung volume was assessed using linear regression analysis. In a post hoc analysis, patients were divided into a low and a high PRLV group, and differences between the groups were assessed using unpaired Student's t-test.

## *Study IV*

Two-way analysis of variance (ANOVA) and a paired Student's t-test were used for comparison between the response in different regions to the SLRM and to evaluate changes between baseline values and values after the SLRM during the decremental PEEP trial. Bonferroni's correction for multiple comparisons was performed.

# RESULTS

## Study I

There was a satisfactory global impedance signal throughout measurements (fig. 6), and a good correlation between impedance changes and tidal volume changes. For each individual patient, this correlation was the same before and after surgery.

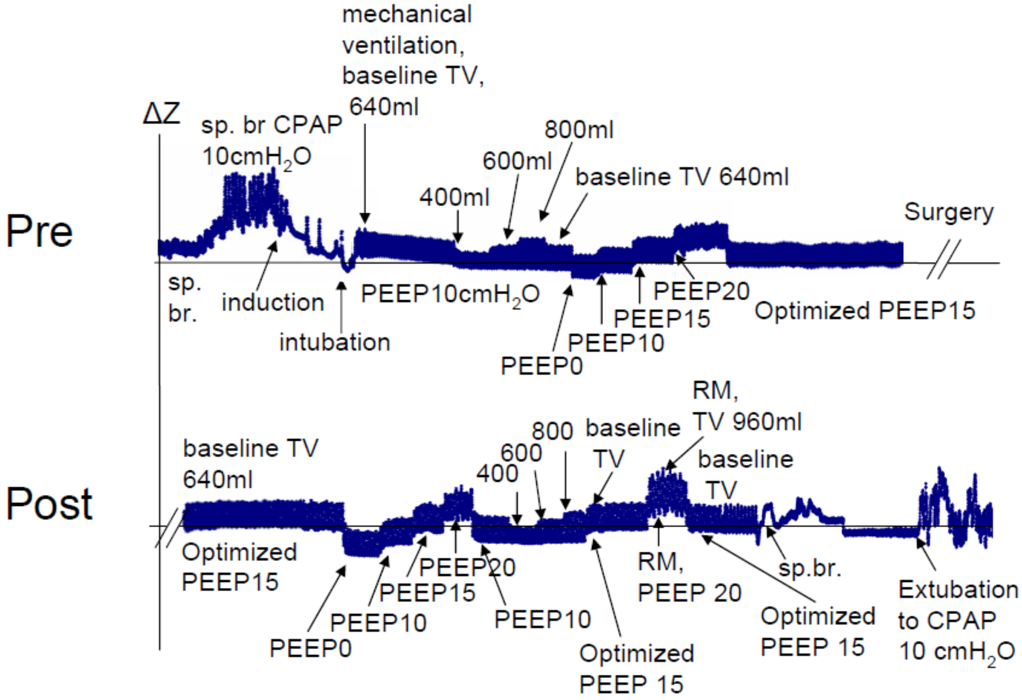

**Figure 6.** Recording of global EIT signal from one of the patients during the perioperative period. Changes in impedance (ΔZ), corresponding to changes in lung volume, are presented on the y axis. Note the increase in end-expiratory lung volume prior to induction, due to CPAP in the awake patient. This EELV increase results in a "volume buffer" which attenuates the result of the decrease in EELV seen during induction and intubation. *CPAP* continuous positive airway pressure, *PEEP* positive end-expiratory pressure, *RM* recruitment manoeuvre, *sp.br* spontaneous breathing, *TV* tidal volume

When PEEP was titrated before surgery in order to maintain a stable end-expiratory lung volume, a PEEP of 15 ± 1 cm$H_2O$ was found.

When using this optimized PEEP level throughout the entire anaesthetic period, EELV could be maintained and was actually found to increase from 1706 ± 447 ml before to 2210 ± 540 ml after surgery. Compliance (65 ± 14 before surgery vs. 66 ± 14 ml/cm$H_2O$ after), plateau pressure (27 ± 2 cm$H_2O$ before and after), total dead space fraction (0.46 ± 0.06 before and after) and shunt fraction (0.14 ± 0.05 before vs. 0.12 ± 0.04 after surgery) were unchanged, while a significant increase was seen in cardiac output (6.4 ± 1.1 before vs. 7.5 ± 2.0 l/min after) and a significant decrease in alveolar dead space fraction (0.12 ± 0.05 before vs. 0.07 ± 0.03 after surgery).

The recruitment manoeuvre at the end of the post surgical period caused an increase in $PaO_2/FiO_2$ and compliance, while a decrease was seen in cardiac index, shunt, alveolar dead space, plateau pressure and $PaCO_2$.

## Study II

### *Pre vs. post RM*

When comparing baseline values with values after recruitment manoeuvres, there was an increase in end-expiratory lung volume, maximal at PEEP 16 $cmH_2O$ for all of the patients, from 1074±354 and 1067±402 ml before, to 1926±501 ml and 1983±562 after the VICM and the SLRM respectively. $PaO_2/FiO_2$ increased from 177±71 mmHg to maximum 230±86 mmHg ($p<0.01$) at a PEEP of 13.6±3.5 $cmH_2O$ (VICM), and from 179±69 at baseline to 209±72 mmHg ($p<0.01$) at a PEEP level of 10.9±3.3 (SLRM).
There was a marked decrease in cardiac output during the VICM to 2.8±1.2 l/min, with a lowest value of 0.5 l /min in one patient (in whom RM was interrupted prematurely). Cardiac output was still significantly lower after the VICM at PEEP 16. This is in contrast to the SLRM, during and after which cardiac output was unchanged (Fig. 7).

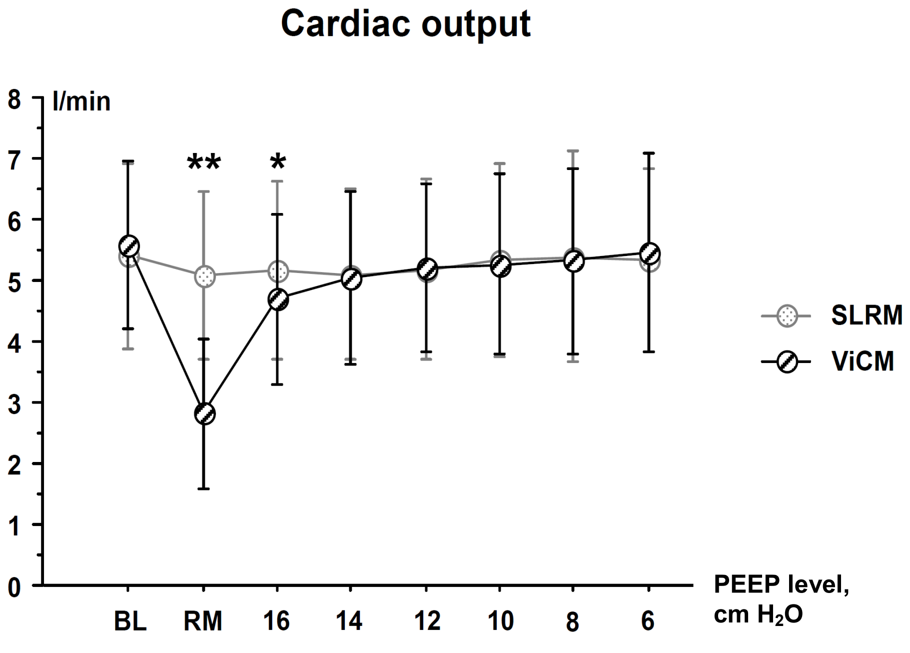

**Figure 7.** Cardiac output at PEEP 6 $cmH_2O$ baseline (BL), during recruitment manoeuvre (RM) and during decremental PEEP trial from PEEP 16 down to PEEP 6 $cmH_2O$, for the vital capacity manoeuvre (ViCM) and the prolonged lower pressure manoeuvre (SLRM). * $p < 0.05$, ** $p < 0.01$, when comparing the RMs.

Shunt fraction decreased after the VICM from 0.24±0.10 at baseline to a lowest value of 0.17±0.08 ($p<0.001$) at a PEEP of 14.3±2.5 $cmH_2O$, and after the SLRM from 0.23±0.08 at baseline to 0.19±0.07 ($p<0.01$) at a PEEP of 10.9±3.3 $cmH_2O$.

As for compliance, both volume-dependent initial compliance and conventional static two-point compliance increased significantly after recruitment. The increase in Cini was more pronounced, from 47±18 to 82±48 at PEEP 13.5±3.0 $cmH_2O$ (VICM) and from 46±17 to 76±38 at PEEP 11.4±3.2 $cmH_2O$ (SLRM), compared to Cconv which increased from 34±9 to 42±10 at PEEP 10.0±2.8 $cmH_2O$ (VICM) and from 35±9.0 to 46±12 at PEEP 9.0±2.1 $cmH_2O$ (SLRM). Though clearly increasing for the patient group as a whole, there were individual patients who did not respond to recruitment. Some of the non-responders actually experienced a decrease in volume-dependent compliance (Fig. 8).

## *VICM vs. SLRM*

The PEEP levels at which maximum values for the different parameters were reached, here called optimal PEEP, were not the same after the two RMs. Optimal PEEP was significantly lower after the SLRM than after the VICM, irrespective of which parameter was studied, that is, for $PaO_2/FiO_2$, shunt, Cconv, Cini and Cfin, with exception of EELV for which max was reached at PEEP 16 $cmH_2O$. Correspondingly, these optimal PEEP levels were associated with significantly lower plateau pressures after the SLRM than after the VICM for the mentioned parameters.

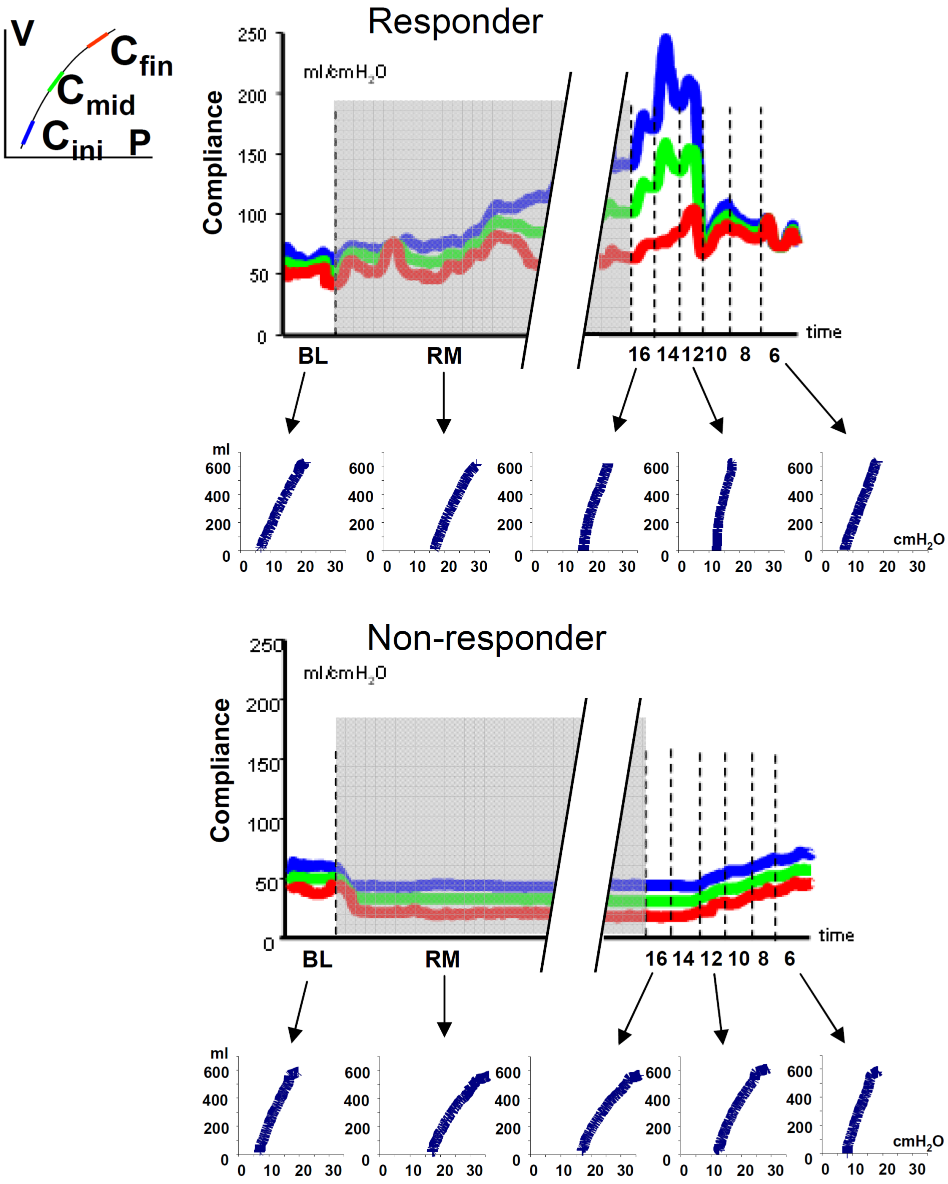

**Figure 8.** Recordings from two different patients - one responder and one non-responder. Volume-dependent compliance (Cini, Cmid and Cfin) as well as corresponding alveolar pressure/volume curves before, during and after a recruitment manoeuvre (RM) are shown. The RM is the slow, lower pressure recruitment manoeuvre (SLRM), shaded grey in the figure. The Cini represents the compliance below a possible lower inflection point and may be sensitive to recruitment or collapse of dorsal lung regions.
The Cfin represents the compliance above a possible upper inflection point and should be sensitive to overinflation, which will cause a decrease in Cfin.
In the responder, during the end of the SLRM, there is a marked increase in particularly Cini, indicating recruitment. This increase is accentuated during the early part of the decremental PEEP trial. Note the abrupt decrease in Cini when PEEP is further decreased, indicating derecruitment.
In the non-responder, volume-dependent compliance actually decreases during the RM, which indicates increased stress/strain.

# Study III

Potentially recruitable lung volume (PRLV) was determined by graphical extrapolation and then verified by mathematical extrapolation. PRLV for the 16 patients was 786±556 ml (range 226-2530 ml). Correspondingly, PRLV%, which was defined as PRLV expressed in percentage of open lung volume, was 26±11% (range 11-47%).
The patients were divided using the median value into two groups – a high PRLV and a low PRLV group. In the high PRLV group, PRLV% was 35±7% and in the low PRLV group 17±6%. At baseline ventilation, PEEP 6cm$H_2O$, compliance (Cconv as well as Cini) was significantly lower in the high PRLV group than in the low PRLV group. For conventional two-point compliance, baseline values in the high PRLV group were 29±9 ml/cm$H_2O$ compared to 40±6 ml/cm$H_2O$ in the low PRLV group. In the same way, volume-dependent initial compliance in the high PRLV was 37±11 ml/cm$H_2O$, significantly lower than 58±18 ml/cm$H_2O$ in the low PRLV group.

While the OLV40 at the end of the second vital capacity manoeuvre was similar in the two groups, there was a tendency towards lower end-expiratory lung volume at baseline in the high PRLV group. Accordingly, the fraction of EELV at baseline in relation to OLV40 was significantly lower in the high PRLV group compared to the low PRLV group. The number of hours of mechanical ventilation prior to the study differed between the high PRLV group, 52±20 hours, and the low PRLV group, 30±16 hours ($p<0.05$).

Patients in the high PRLV group had a significantly higher maximal increase in EELV (+99±31 vs. +68±19%, $p<0.05$) as well as higher maximal increase in conventional compliance (+40±19 vs. +12±16%, $p<0.01$) during the decremental PEEP trial after the vital capacity manoeuvre, compared to patients in the low PRLV group. Similar trends were observed in $PaO_2/FiO_2$ ratio, shunt and volume-dependent initial compliance. Optimal PEEP was significantly higher in the high PRLV group than in the low PRLV group, whether defined based on compliance (PEEP 12±3 vs 8±2 cm$H_2O$, $p<0.02$) or based on PRLV (PEEP 14±3 vs. 9±2 cm$H_2O$, $p<0.002$) (Fig. 9).

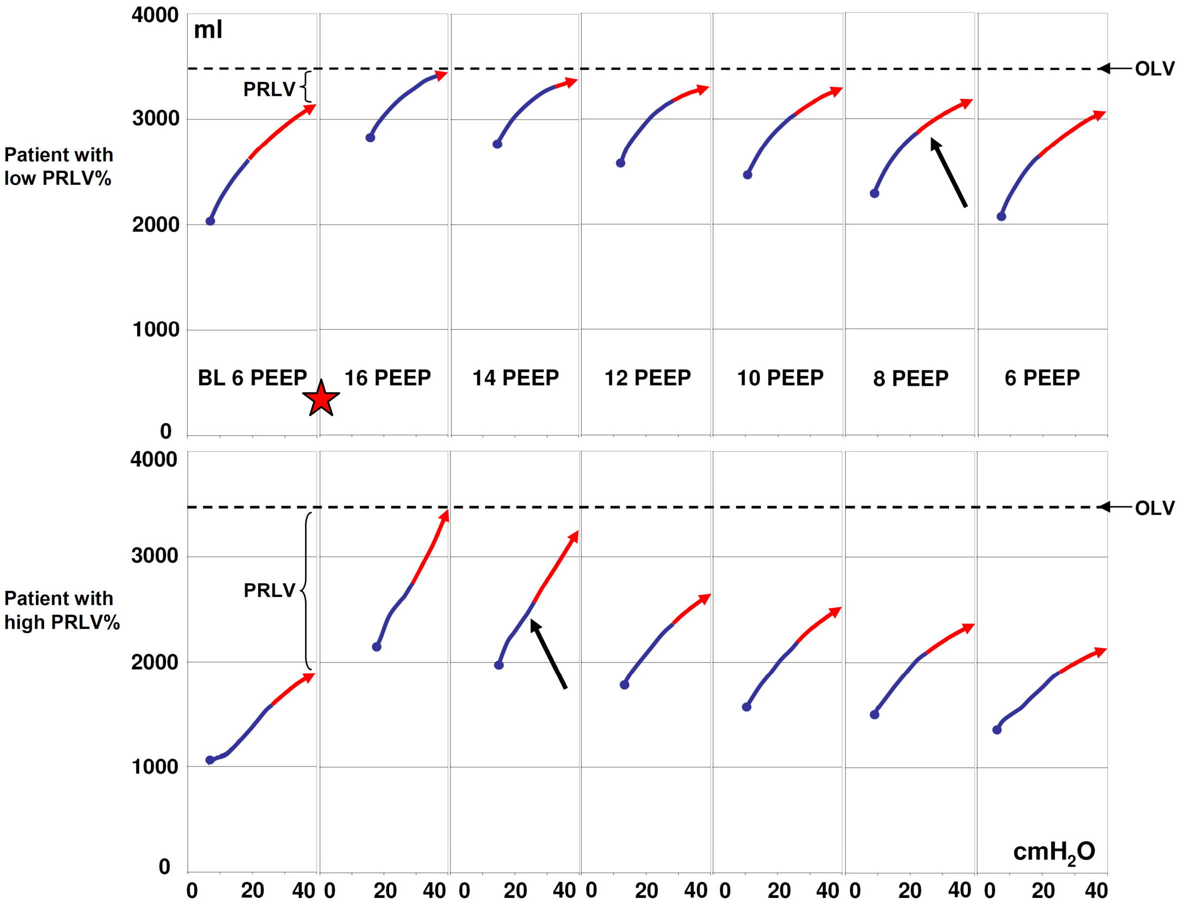

**Figure 9.** Typical examples of alveolar P/V curves from one patient with low potentially recruitable lung volume (PRLV) (upper panel) and one patient with high PRLV (lower panel). Both panels display P/V curves at baseline (BL) and after the vital capacity manoeuvre (VICM, indicated by red star) at each PEEP level during the decremental PEEP trial. Each P/V curve consists of a blue and a red part, the blue being the actual curve measured, and the red the extrapolated part of the curve. The hatched line indicates the "open lung volume" (OLV40).

In the patient with low PRLV%, graphic extrapolation at PEEP 6 $cmH_2O$ (before the VICM) reaches a point fairly close to the OLV40 indicating a PRLV% of around only 10%. At PEEP 16, following the VICM, the extrapolated P/V-curve nearly reaches the OLV40. Note how the curve is depressed at high PEEP, indicating a fall in compliance. During decremental PEEP trial PRLV increases only slightly and optimal PEEP (arrow) occurred at $8cmH_2O$. In contrast, in the patient with high PRLV% there is a marked decrease in PRLV following the vital capacity manoeuvre and an increase in compliance can be seen at high PEEP. This is followed by rapid derecruitment and a large increase in PRLV during the decremental PEEP trial already at fairly high PEEP levels, with optimal PEEP defined as 14 $cmH_2O$. It could also be noted that there seems to be a lower inflection point (LIP) at baseline in the high PRLV patient. This LIP disappears after the VICM but then possibly reappears again at PEEP $6cmH_2O$.

# Study IV

EELV at baseline (PEEP 6 $cmH_2O$) was 1067±402 ml and increased by 916±312 ml (=ΔEELV) after the SLRM, at 16 $cmH_2O$ (Table 1). This EELV increase was mainly seen in the mid-ventral region (46±15%), followed by the ventral (29±11%), mid-dorsal (19±16%) and dorsal (6±11%) regions (Fig. 10).

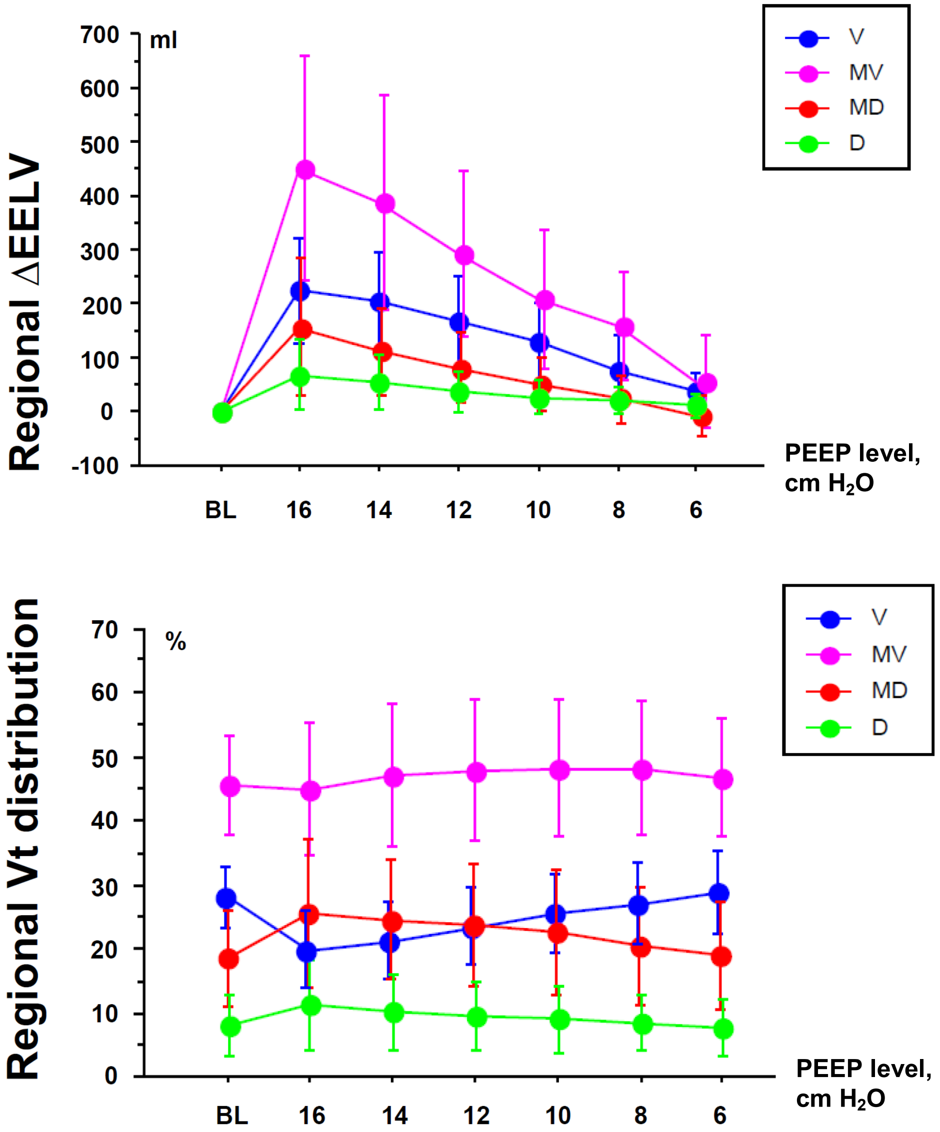

**Figure 10.** The upper panel shows the increase in end-expiratory lung volume (EELV) from baseline (BL, PEEP 6) values, and the regional distribution of the EELV increase, during the decremental PEEP trial at PEEP 16, 14, 12, 10, 8 and 6 $cmH_2O$. At all PEEP levels, the increase is compared to BL value and is expressed in ml.
Lower panel displays regional distribution of tidal volume (Vt), expressed in percent of whole tidal volume, at BL before the recruitment manoeuvre and at PEEP 16, 14, 12, 10, 8 and 6 $cmH_2O$.
Ventral (V), Mid-ventral (MV), Mid-dorsal (MD) and Dorsal (D) regions. Mean values ± SD.

Irrespective of PEEP level, the tidal volume was mainly distributed to the mid-ventral region. There was however a clear redistribution of gas from ventral to dorsal regions when increasing PEEP, where the changes in the ventral and mid-dorsal regions were reciprocal ($p<0.001$) (Fig. 10). The regional compliance distribution was in accordance with regional tidal volume distribution.

The fractional regional increase in EELV between 6 and 16 cmH$_2$O was correlated to the fractional regional conventional compliance at baseline, $R^2=0.91$.
Regional distribution of the volume-dependent compliance (Cini, Cmid and Cfin) at baseline, PEEP 16 and at PEEP 12 (where Cini, mid and fin were highest), is shown in Table 1.

**Table 1**

| | | Global | Ventral | Mid-ventral | Mid-dorsal | Dorsal |
|---|---|---|---|---|---|---|
| Δ EELV (ml) BL -> PEEP 16 | | 916±312 | 223±97 | 451±209 | 155±127 | 68±65 |
| Distrib. Δ EELV (%) BL -> PEEP 16 | | | 29±11 | 46±15 | 19±16 | 6±11 |
| Vt distribution (%) | BL | | 28±5 | 45±8 | 18±8 | 8±5 |
| | PEEP 16 | | 20±6 | 45±10 | 26±12 | 11±7 |
| Cini (ml/cmH$_2$O) | BL | 46±17 | 13±6 | 17±8 | 10±5 | 5±3 |
| | PEEP 16 | 64±34 | 16±11 | 25±15 | 15±7 | 8±5 |
| | PEEP 12 | 69±34 | 18±11 | 28±16 | 15±7 | 8±4 |
| Cmid (ml/cmH$_2$O) | BL | 43±14 | 12±5 | 17±7 | 9±5 | 6±3 |
| | PEEP 16 | 51±25 | 11±7 | 19±12 | 13±6 | 8±3 |
| | PEEP 12 | 58±28 | 14±8 | 23±14 | 14±8 | 7±3 |
| Cfin (ml/cmH$_2$O) | BL | 37±13 | 10±4 | 14±5 | 8±5 | 5±3 |
| | PEEP 16 | 37±16 | 8±4 | 13±8 | 10±5 | 6±2 |
| | PEEP 12 | 44±20 | 10±7 | 16±10 | 11±7 | 6±2 |
| Cconv (ml/cmH$_2$O) | BL | 35±9 | 10±3 | 16±5 | 6±3 | 3±12 |
| | PEEP 16 | 37±10 | 7±2 | 17±6 | 9±6 | 4±2 |
| | PEEP 10 | 44±12 | 11±3 | 22±8 | 10±6 | 4±2 |

End-expiratory lung volume increase from baseline to PEEP 16 cmH$_2$O, presented as absolute values and regional percentage distribution. Regional tidal volume distribution at baseline and at PEEP 16. Volume-dependent compliance and conventional two-point compliance presented as absolute values at baseline, 16cmH$_2$O and at PEEP level where peak value was seen.

Δ EELV = end-expiratory lung volume change, BL = baseline, Vt = tidal volume, Cini = volume-dependent compliance at 5-15% of tidal volume, Cmid = volume-dependent compliance at 45-55% of tidal volume, Cfin = volume-dependent compliance at 85-95% of tidal volume, Cconv = two-point quasi-static compliance.

There was a significant regional intratidal gas redistribution during the course of inspiration, when performing the SLRM and increasing PEEP to 16 cm$H_2O$. This redistribution was from the two ventral to the two dorsal regions. When lowering PEEP, this redistribution was diminished, and back at PEEP 6 cm$H_2O$, the regional distribution of intratidal gas had returned to baseline appearance (Fig. 11)

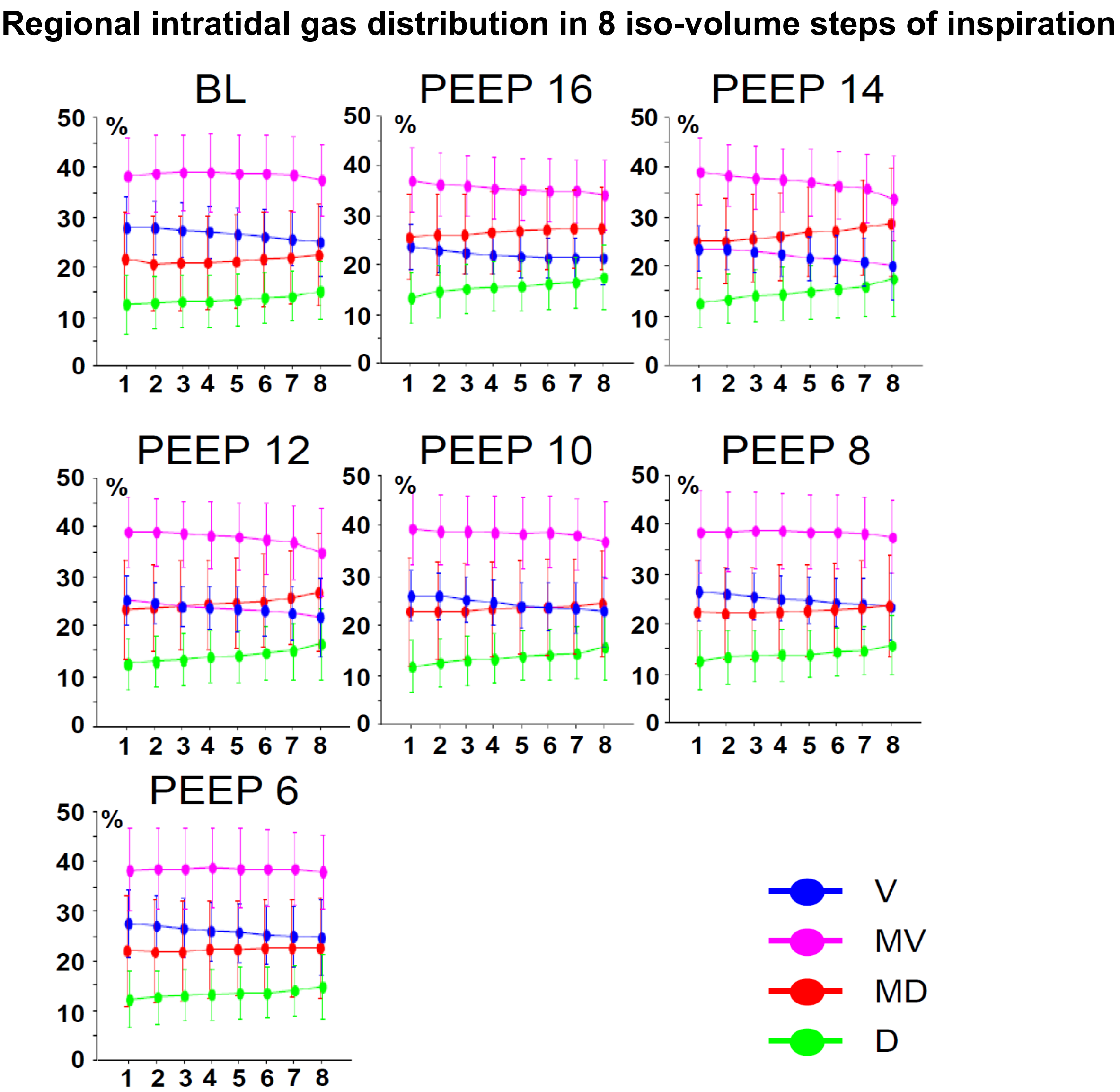

**Figure 11.** Regional intratidal gas distribution at baseline (BL) and during the decremental PEEP trial The inspiration is divided into eight iso-volume steps (x-axis). The main part of the gas is distributed mid-ventrally throughout the entire inspiration, and least dorsally. Note how the ventral and mid-dorsal regions have reciprocal courses and intersect at different time-points during the inspiration, depending on PEEP level.
Ventral (V), Mid-ventral (MV), Mid-dorsal (MD) and Dorsal (D) regions.

Three different intratidal gas distribution patterns were identified. In some patients, ventral and mid-ventral intratidal gas distribution decreased and mid-dorsal and dorsal increased throughout inspiration at all PEEP levels. In other patients, regional distribution only changed marginally irrespective of PEEP level. A third pattern was seen, where ventral distribution increased substantially and mid-dorsal decreased substantially at low PEEP levels and moderately at high PEEP levels. These patterns are illustrated by examples from patients number 4, 6 and 10 (Fig. 12 and 13).

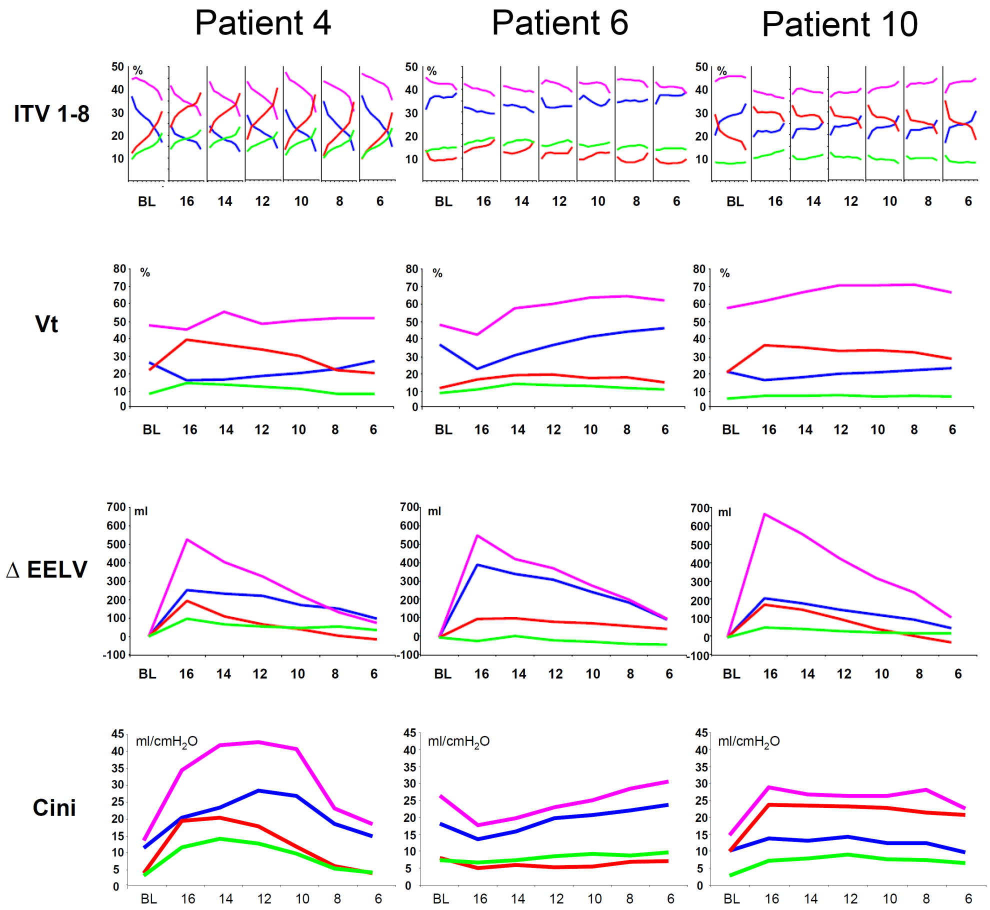

**Figure 12.** Regional intratidal gas (ITV) distribution of eight isovolume parts of inspiration (upper panel), regional tidal volume (Vt) distribution (upper mid panel), regional distribution of the increase in EELV from baseline (BL) (lower mid panel) and regional volume-dependent compliance at lower part of the breath (Cini) (lower panel) for patients number 4, 6 and 10. Upper: in patient 4, ventral and mid-ventral intratidal gas distribution decreased and mid-dorsal and dorsal increased throughout inspiration at all PEEP levels. In patient 6, regional distribution only changed marginally irrespective of PEEP level. In patient 10, ventral distribution increased substantially and mid-dorsal decreased substantially at low PEEP levels and moderately at high PEEP levels. Upper mid: Irrespective of ITV gas distribution pattern, ventral tidal volume decreased when increasing PEEP level. Mid-dorsal tidal volume showed a clear increase in pat 4, a marginal increase in patient 6 and a moderate increase in patient 10. Lower mid: Baseline EELV was 719, 2228 and 928 mL in patient 4, 6 and 10 respectively. When PEEP was increased, ΔEELV was distributed preferentially mid-ventrally, in all three patients. In patient 6, also the ventral portion of ΔEELV increased substantially, whereas in patient 4 and 10 the increase was moderate. In patient 6, the dorsal portion of ΔEELV decreased. Lower: Regional Cini in patient 4, increased in all regions, with peak values occurring around a PEEP level of 12 cm $H_2O$. The increase was most pronounced in the mid-ventral region. The same pattern was seen in patient 10, but the response was less marked than in patient 4. In contrast, patient 6 showed decreasing ventral and mid-ventral Cini, in response to increased PEEP.

Ventral (V, blue), Mid-ventral (MV, purple), Mid-dorsal (MD, red) and Dorsal (D, green) regions.

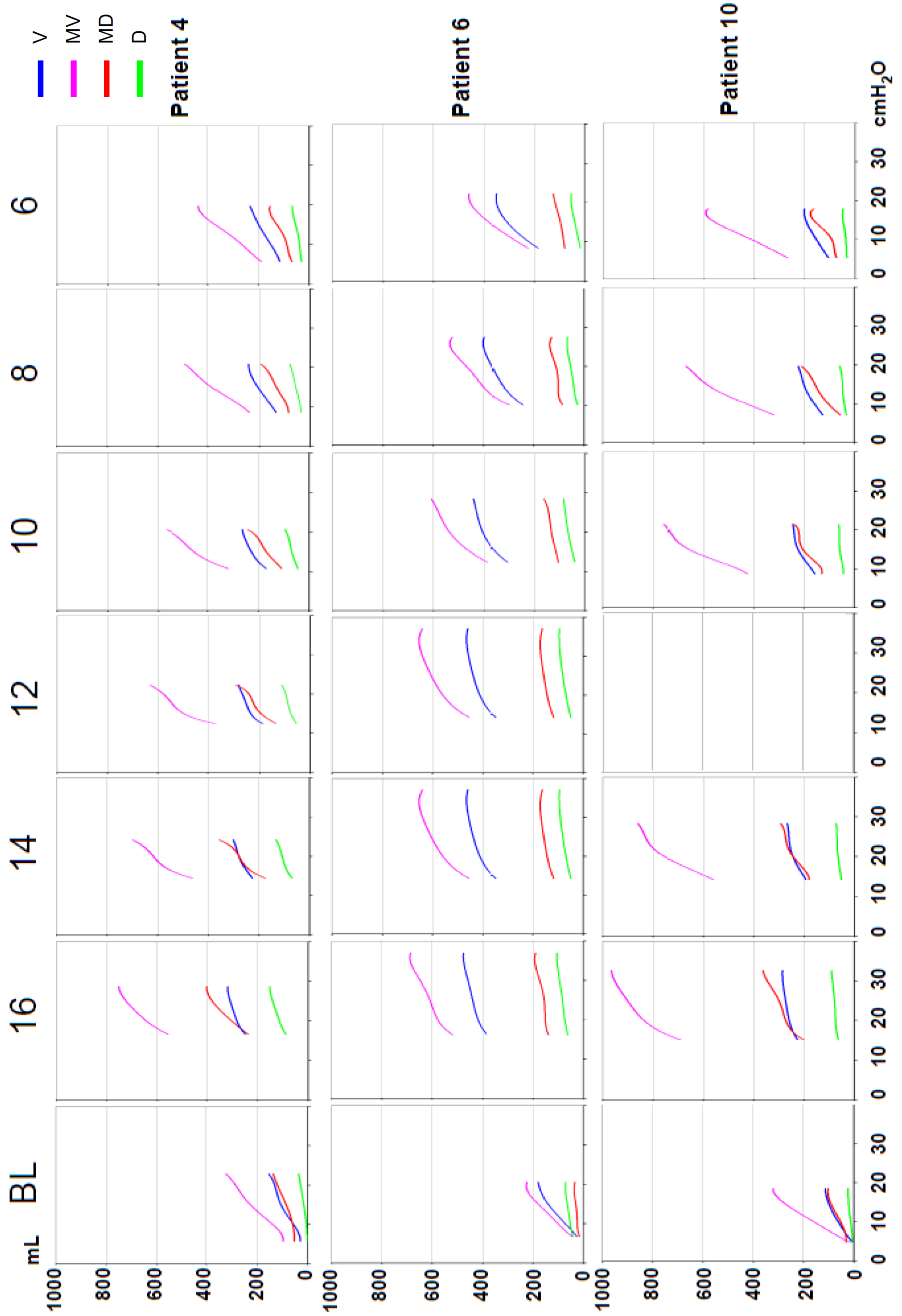
V
MV
MD
D
Patient 4
Patient 6
Patient 10
BL
16
14
12
10
8
6
mL
1000
800
600
400
200
0
cmH$_2$O
0
10
20
30

**Figure 13** Regional tidal pressure/volume curves, displayed starting at corresponding regional ΔEELV. The presence of lower inflection points is seen in all regions at baseline (BL, PEEP 6 $cmH_2O$) in patient 4. At 16 $cmH_2O$ there is an upper inflection point in the ventral region, which disappears at a PEEP 14 $cmH_2O$. At a PEEP 8 $cmH_2O$, the lower inflection points reappear in the mid-dorsal and dorsal region. In patient 10, mainly the same pattern is seen, but the re-appearance of a lower inflection point in the mid-dorsal region occurs already when PEEP is lowered to 14 $cmH_2O$. Also, in patient 10, there is an upper inflection point ventrally and mid-ventrally at all PEEP levels, possibly with the exception for PEEP 16 $cmH_2O$.Registrations from patient 10 at PEEP 12 $cmH_2O$ are missing. Ventral (V), Mid-ventral (MV), Mid-dorsal (MD) and Dorsal (D).

# DISCUSSION

The main findings of this thesis are the following:

- EIT can be used to successfully monitor rapid lung volume changes and titrate PEEP in patients with ALI/ARDS in the ICU as well as in patients with morbid obesity undergoing surgery in general anaesthesia

- A prolonged moderate pressure recruitment manoeuvre resulted in a slightly higher EELV increase in ALI patients compared to a vital capacity manoeuvre, with EELV measured at PEEP 16 $cmH_2O$ after recruitment manoeuvre

- Optimal PEEP and corresponding plateau pressure were significantly lower after a prolonged moderate pressure recruitment manoeuvre than after a vital capacity manoeuvre, when assessed during a decremental PEEP trial, indicating more effective recruitment

- Volume-dependent compliance, and its initial/lower part (Cini) in particular, seems to be more sensitive for detection of lung recruitment in ALI/ARDS patients than conventional two-point compliance

- Potential lung recruitability can be assessed using a radiation-free extrapolation method in combination with electric impedance tomography for open lung volume determination

- There was a large variability in potentially recruitable lung volume among the ALI/ARDS patients, where patients with high recruitability seemed to benefit from higher PEEP levels compared to those with low recruitability

- After a recruitment manoeuvre followed by PEEP in ALI/ARDS patients, the increase seen in end-expiratory lung volume was mainly distributed to the non-dependent lung areas, whereas the tidal volume gas distribution was shifted towards more dependent areas

- Intratidal gas distribution followed a similar pattern, where gas was gradually redistributed dorsally during inspiration when pressure increased. This redistribution was mainly found in responders to recruitment

# Methodological considerations

## *Electric Impedance Tomography*

In this thesis, electric impedance tomography was used to assess changes in global and regional lung volume. PEEP titration in Study I was based on the slope of the end-expiratory EIT signal, where a horizontal end-expiratory tracing was interpreted as a PEEP level high enough to preserve EELV, where a decrease in slope was seen as de-recruitment and an increase as possible recruitment. In Study I we used the term "optimal PEEP" for the PEEP chosen for each patient. A more appropriate term could have been "end-expiratory lung volume-preserving PEEP" since that is another expression for what it was that we aimed at and meant by "optimal".

We have calibrated the EIT lung volumes against absolute EELV, which was measured at baseline using a modified nitrogen wash-out/wash-in method, and also against different known tidal volumes. We have chosen to convert all impedance changes ($\Delta Z$), global and regional, to volume values (ml). This conversion is thus based on a calibration to the $\Delta Z$ signal from at least three different tidal volumes, where we found a very good linearity in the relationship between $\Delta Z$ and ml. The EIT has then been used to determine EELV at different PEEP levels. This procedure is supported by the findings by Hinz and co-workers, who compared EIT to nitrogen wash-out EELV measurements at different PEEP levels, and found that EIT reliably monitors lung volume changes induced by for example PEEP changes [139]. In contrast, Bikker et al found only a fairly weak, although significant, linear relationship between EELV changes ($\Delta$EELV) and end-expiratory impedance changes ($\Delta$EELI) [159], wherefore they questioned the use of EIT to assess EELV changes. However, Bikker has just recently published a study [88] in which he concludes that during a decremental PEEP trial in ICU patients, EIT clearly visualizes improvement and loss of ventilation in the individual patient. Also, in a recent study [142], Richard et al performed comparisons between EIT and positron emission tomography (PET) where both methods were used simultaneously. They concluded that ventilation and volume were accurately measured at a wide range of PEEP and tidal volumes, which supports the methods used in this thesis. Thus, EIT has repeatedly been shown to accurately assess rapid lung volume changes [135,145,160], and the combination with the modified nitrogen wash-out method for calibration appears solid. Yet, it may be wise to recalibrate the EIT at higher PEEP levels.

In this thesis, EIT with measurements in one cross-sectional plane was used. It can be debated whether or not the observed single EIT scan/signal is representative for the whole lungs. In Study I, the thickness of the cross-sectional image was stated to be 5-10 cm, a number which we have since then changed to be 15-20 cm [135,161]. This is a scan which thus includes the major part of the thorax. In agreement with this, a study [147] comparing CT scans of the whole lungs with the EIT system used in this thesis, found a close correlation between the lung volume changes detected by EIT and CT.

Nevertheless, an EIT study in which three electrode belts were used simultaneously at different levels of the thorax, showed that gas distribution changes occurred also in cranio-caudal direction [138]. However, in studies where regional EIT signal has been compared to computed tomography [145] and SPECT scanning [144], correlations with $r^2 = 0.92$ for the different regions have been obtained. Also, during a slow inflation of gas to high pressures, new regions of the lung are likely to be recruited and filled with gas. If these recruited regions were outside the cross-sectional field which is registered by EIT, a lower ΔZ/ml ratio at high pressure/volumes would be expected as gas escapes the measurement field of the EIT, and this does not seem to be the case [139,162]. This might be explained by the inhomogeneity of the lung being mainly in ventral-dorsal direction and to a lesser extent in cranio-caudal direction. Apparently, the measurement field of the EIT is fairly representative for inhomogeneities in the ventro-dorsal direction of the whole lung.

To avoid baseline drift, calibration against known changes in tidal volume was performed both before and after surgery (Study I) and before and after RM and decremental PEEP trial (Studies II, III and IV). And although a considerable variation between the patients was seen, there was a close and unchanged linear relationship between tidal volume changes and impedance changes for each patient before and after surgery/RM. As for the EIT image, it could sometimes be distorted in the morbidly obese patients, but there was always a good global EIT signal quality, which agrees with results from a recent study showing that lung volume measurements by EIT are unaffected by body composition [141].

The global EIT field was divided into four regions of interest (ROI) in the ventro-dorsal direction, with each ROI having the same height/size. This was done to ascertain equal superimposed pressure within each ROI. However, the spatial resolution of EIT is low, and the true height/size of the ROIs may not be exactly equal. From a geometrical point of view, the volumes of the ROIs are about 20, 30, 30 and 20% of the total volume for the ventral, mid-ventral, mid-dorsal and dorsal ROI respectively. From looking at the image one can be mislead to believe that when the dorsal lung part constitutes such a small part of its ROI, it would “drown” in the non-lung area. This however is not the case since EIT only detects changes in impedance, and these only occur in the lung part of each ROI.

## *Cardiac output and shunt determination*

For this thesis, both in the OR and in the ICU, cardiac output was measured using an oesophageal Doppler technique, which is a validated non-invasive method [163]. This technique measures the descending aortic blood flow and uses an algorithm for estimating the aortic diameter based on patient age, height and body weight [164-166], and then the aortic diameter is used to calculate the stroke volume. The algorithm for this device includes weights of up to 150 kg. During pilot measurements before Study I, we had several patients who exceeded the maximum weight, and consequently we had some concern about the cardiac output measurements. After the pilot measurements, attempts were made to gather facts on what happens with the aortic diameter and with cardiac output as a patient gains weight and becomes heavily overweight. Already in 1962, Alexander et al described obesity to be associated with elevated blood volume, enlarged vascular tree and increased cardiac output [167]. The increase in cardiac output is explained mainly by an increase in stroke volume [168]. However cardiac output seems to be correlated more to fat-free body mass than adipose tissue [169], and although there is a positive relationship between BMI and both cardiac output and stroke volume, it has been shown that with increasing BMI, the higher the BMI the less pronounced is the increase in cardiac output [170]. To challenge the algorithm of the oesophageal Doppler prior to the study, we used several probes in the same patients during steady state conditions, and entered weights corresponding to BMI values of 33-50 kg/m$^2$. This did not affect the C.O. values obtained with this algorithm. We therefore decided to enter weights corresponding to BMI 30 kg/m$^2$ for all patients in the study. We could most certainly have chosen to enter the total weight of the patient, and for the patients exceeding 150 kg we could have entered 150 kg and possibly ended up with the same results. A recent study [170] of this issue showed that body habitus has little clinical relevance in hemodynamic monitoring, where the difference in stroke volume between a normal weight and an obese patient was only 8 ml. In addition the diameter of the aorta does not increase in proportion to body weight [171], but correlates well with height and age.

In this thesis, we have used the term shunt, which is often used in this context. However, strictly speaking, measuring shunt requires a $FiO_2$ of 1.0, which was not the case in our studies. More accurate would instead have been to, like in Study II, use the term venous admixture. Venous admixture denotes the degree of admixture of mixed venous blood with pulmonary end-capillary blood, which would be needed to produce a measured $P(A\text{-}a)O_2$ difference. It is thus a calculated, not necessarily completely in agreement with the actual, venous admixture which is presented here.

## *Extrapolation method for determination of lung recruitability*

In Study III, a combination of tracheal pressure measurements and EIT was used to obtain alveolar P/V curves and estimates of open lung volume defined as the volume at the end of an ongoing RM at pressure 40 $cmH_2O$. In addition, for the same pressure, non-recruited but open lung volume at the end of a normal breath was assessed. To reach the pressure of 40 $cmH_2O$ for a normal breath, the upper part of the P/V curve of the breath was extrapolated up to that pressure (Fig. 5). The extrapolations were made graphically for all patients and were repeated for three breaths at each PEEP level. There was very good agreement between the three values obtained at each level. However, the graphical extrapolation is impractical and not possible to automatize, and this is why we later re-performed the extrapolations mathematically, using a logarithmic method. When we did this, we found a close correlation between results obtained by the two methods.

Therefore, in the future, the extrapolation should probably be performed online using appropriate software, providing the potentially recruitable lung volume at the bedside.
EELV at baseline was determined using a nitrogen wash-out method [104] and EIT was used to monitor changes in lung volume. Our extrapolation method for determination of potential lung recruitability is however not dependent on EIT - other methods could have been used as well for volume determination, such as spirometry or respiratory inductive plethysmography.

Moreover, a fundamental assumption for this method is that a volume delivered at the speed of a normal respiratory rate will not recruit the lung but just lead to further expansion of already open alveoli. This assumption is based on the findings from Katz and colleagues, who described that when increasing PEEP, the resulting volume increase takes time, and the volume increase during the first breath is due only to expansion of already open alveoli, since this increase is directly proportional to the elasticity of the already open lung [172]. The issue of time constant and slowly distensible lung compartments has been studied further by Fretschner et al [173], and future studies are needed to confirm that assumption (of only further expansion of open alveoli) before the extrapolation method can be widely introduced into use.
The open lung pressure of 40 $cmH_2O$ was chosen based on concern for patient safety since there is a known risk of barotrauma such as pneumothorax associated with high pressures [61,66,68]. Similarly, other proposed methods for determination of lung recruitability have used the pressure of 40-45 $cmH_2O$ [73,115,174]. Nevertheless, the method is not limited to the pressure of 40 $cmH_2O$, and can be used for higher pressures as well.

## Determining lung recruitability

The ability of the alveoli to become and remain open can be called lung recruitability, and to date the value in terms of outcome of lung recruitment has yet to be proved [72]. Since there is increasing evidence that lung recruitability in ALI/ARDS patients varies markedly between patients [73] (supported by findings in this thesis), it follows that there is a need for a method which can easily distinguish between patients who will benefit, based on intermediate endpoints, from a RM as well as patients for whom RMs might even be harmful. A CT method for determination of lung recruitability has been described by Gattinoni et al [73], but is not useful in everyday clinical work or at the bedside, instead rather as a standard or reference method for research purposes. In other studies in ARDS patients where a slow inflation-deflation P/V loop method was performed, the shape of the inflation limb of the P/V curve has been found to correlate with degree of recruitability [175,176]. A lower inflection point together with a steep slope of this curve seemed to denote high recruitability, although there is concern regarding the information from the inspiratory limb [177] as well as uncertainties on how to perform the measurements [178]. The technique was modified by Koefoed-Nielsen and co-workers, who measured the volume differences between the inspiratory and expiratory limbs of a P/V loop (hysteresis) [115] and found a correlation between amount of hysteresis and lung recruitability in an experimental porcine model. Similarly and just recently, Demory and colleagues described that the hysteresis of a quasi-static P/V curve could be used to assess lung recruitability [174] in ARDS patients. These methods all include ventilation periods at zero PEEP (ZEEP) to obtain the necessary P/V curves. ZEEP is since long known to cause lung collapse and subsequent hypoxia [179], wherefore these methods might not be suitable in all patients.

The method described in Study III for determination of potentially recruitable lung volume includes a recruitment manoeuvre up to a pressure of 40 cm$H_2O$. This pressure was also used in the methods just described using hysteresis, but in the CT method described by Gattinoni, 45 cm$H_2O$ was used. Our method however does not in any way interrupt ongoing ventilation, which can be maintained at settings relevant to the ventilatory therapy.

Previous studies [73], and also our study, have assessed recruitability in an unselected group of ALI/ARDS patients. However, recent studies suggest that there may be large differences in lung and chest wall compliance between patients. Talmor and co-workers showed [79], that in patients with high chest wall elastance, a higher PEEP was needed to avoid lung collapse at end-expiration. It would be interesting in the future to study lung recruitability using our method, or CT, together with measurements of lung and chest wall elastance, to determine a possible connection between the cause of ALI/ARDS and recruitability.

## Optimal PEEP

The Gattinoni study [73], in which CT was used, showed the importance of knowing the lung recruitability in a patient, in order to individually set PEEP at the appropriate level. Similar results were found in our study, where patients with high recruitability were found to benefit from significantly higher PEEP levels, compared to patients with low potentially recruitable lung volume. With this in mind, one cannot help but suspect that the results of the two large randomized controlled studies on PEEP [85,86] would have been different if PEEP had been set on the basis of recruitability for each patient rather than just using the same values (high vs. low) for everyone. One can speculate that they might then have shown a positive correlation between outcome and PEEP for those patients who had a high recruitability and a need for higher PEEP, according to our method as well as Gattinoni´s.

In this thesis, we have used two different methods for assessing the best individual PEEP level. In Study I, as discussed in the above section on methodology, we used EIT to set PEEP in morbidly obese patients at the beginning of general anaesthesia, aiming at maintaining EELV throughout the whole perioperative period. The EIT-based individual PEEP was kept unchanged during the entire anaesthesia and resulted in a slight increase in EELV. Others have used EIT for determination of optimal PEEP; Zhao and co-workers used EIT to define and set PEEP according to ventilation homogeneity [180] and they found that optimal PEEP was similar as when using dynamic (quasi-static, same as in this thesis) compliance or the volume-dependent compliance curve obtained by the SLICE method.

In the ALI/ARDS patients of this thesis, a decremental PEEP trial was performed post RM, starting from 16 $cmH_2O$ with decreasing PEEP in steps of 2 $cmH_2O$ down to baseline PEEP of 6 $cmH_2O$. A very similar decremental PEEP trial was performed by Girgis et al., also with the attempt to determine optimal PEEP based on oxygenation [94] where optimal PEEP was identified 2 $cmH_2O$ above the level where arterial saturation decreased below 90%. In Study II for this thesis, we analyzed several different parameters for optimal PEEP setting, including $PaO_2/FiO_2$, shunt, EELV increase, conventional two-point compliance and dynamic volume-dependent compliance. In Study III, we also assessed optimal PEEP based on lung recruitability, such that when there was an increase in potentially recruitable lung volume to more than 10%, the PEEP level before this increase was defined as optimal.

When analyzing our results from Study II, we found that if PEEP had been set based on maximum EELV increase, all patients would have needed PEEP 16 $cmH_2O$, which however does not seem reasonable. This indicates that that maximum EELV increase is not an appropriate parameter in setting PEEP. When comparing the other parameters, these parameters estimated optimal PEEP to fairly the same values, except for conventional two-point compliance which gave lower values for optimal PEEP. Interestingly, we found that optimal PEEP after the slow moderate pressure recruitment manoeuvre was significantly lower than optimal PEEP after the vital capacity manoeuvre, regardless of which parameter optimal PEEP was based on (except for EELV increase). The difference was around 2 $cmH_2O$ which may be of clinical importance, promoting the use of a long duration lower pressure manoeuvre. The advantages from using a slow moderate pressure recruitment manoeuvre have previously been proposed by Odenstedt et al [77] and Rzezinski et al [181]. Odenstedt et al showed in an experimental ALI model in pig, that a prolonged moderate pressure RM resulted in more pronounced improvement in oxygenation, shunt and compliance compared to a vital capacity manoeuvre, and with less circulatory depression. Rzezinski et al used a rat ALI model and interestingly showed not only better results on gas exchange and lung mechanics with their prolonged recruitment procedure, but also a reduced activation of inflammatory mediators, favourable mRNA expression and less apoptosis of lung epithelial cells when using a prolonged recruitment manoeuvre. When they studied the effects on distal organs, no differences were seen between RMs, but there was only one hour follow-up, so possible later effects might have gone unobserved. What are the implications of these findings together with the findings in this thesis? In the next phase, a study should be designed where conventional vital capacity manoeuvre is compared to our prolonged moderate pressure method, with respect to inflammatory mediators, not in an experimental model, but in ALI/ARDS patients. The prolonged lower pressure method for recruitment is truly lung protective, and this could be part of the explanation for its better clinical results.

Respiratory mechanics are considered a better surrogate for assessment of lung recruitment compared to gas exchange variations [87]. In Study II we showed that the end-expiratory pressure needed for stabilization of the lung after a recruitment manoeuvre was lower based on lung mechanic parameters than on gas exchange parameters. Since the patients in our study all had arterial oxygen saturation above 90% and thus were not hypoxemic, it seems natural that the aim, when performing the RM, should be to improve lung mechanics.

## Should we monitor regional ventilation?

Regional ventilation is determined by pleural hydrostatic gradients, regional compliances and the geometry of the airways, and should be matched to regional lung perfusion to result in acceptable gas exchange. In ALI/ARDS, regional ventilation is altered [123,182] and an increased ventilation-perfusion mismatch is seen [183].

Knowledge concerning regional distribution of ventilation has increased during the last decade. Studies using CT [59,130,184-186] and positron emission tomography (PET) [142] have undoubtedly contributed to the understanding of regional lung function. These methods, however, are not useful in everyday practice, which is why a lot of attention has been drawn to EIT, as a promising technique. EIT is the only method which can provide non-invasive assessment of regional lung volumes in real time at the bedside, and it has been validated against CT [145-147]and PET [142] for regional measurements. Recent and ongoing studies also indicate that in the future it may be possible to assess regional lung perfusion [187] and subsequently to optimise the relationship between regional circulation and ventilation [188,189].

In this thesis, EIT was used to obtain information on regional ventilation (Study IV). We found that the increase in end-expiratory lung volume, when increasing PEEP from 6 to 16 $cmH_2O$, was distributed mainly to ventral and mid-ventral areas, which is in accordance with previous findings where CT [184] and EIT [190] were used. Regional conventional static two-point compliance at baseline correlated well with the regional distribution of the increase in end-expiratory lung volume seen with increased PEEP, similar to previous CT based findings [191]. Moreover, when analysing regional tidal volume distribution, we found a redistribution of gas from ventral to dorsal regions when increasing PEEP, which is in line with recent experimental studies [146,192] and a previous study in ARDS patients [184].

Regional alveolar P/V curves were obtained, combining regional EIT volume distribution with global alveolar P/V curves. By doing so, identification of regional lower inflection points (typically in dependent areas) and regional upper inflection points (in non-dependent areas) was possible, which indicate areas of potential regional recruitment and overdistension respectively, similar to findings in animal ALI models [152,193] and ALI patients [194]. We observed how increasing PEEP was sometimes accompanied by an upper inflection point in the ventral areas, indicating that the lung tissue had been stretched to the extent that the gas was then redistributed to the more dorsal regions. Regional overdistension was also studied by Terragni et al who used CT and found regional hyperinflation in a number of patients despite protective ventilatory strategies [43].

We have implemented a new analysis tool for regional intra-tidal gas distribution; ITV. This technique analyzes the inspiratory part of the tidal volume with respect to regional tidal volume distribution during ongoing normal tidal ventilation. Inspiration is divided into 8 iso-volume parts, and for each part the fractional regional volume is calculated from start of inspiration, ITV 1, to end of inspiration, ITV8. In the 16 ALI patients of this study, PEEP elevation was associated with an increase in dependent and decrease in non-dependent distribution throughout the inspiration, as inspiratory pressure increased (Fig. 11). During the decremental PEEP trial, this redistribution returned to baseline conditions. A probable explanation for this distribution pattern is that as airway pressure increases during the course of inspiration, ventral lung regions get increasingly filled until compliance starts to fall below the compliance of more dependent lung parts, resulting in a more dorsal distribution during the inspiration. This general pattern is not unexpected, since the same is seen in the regional tidal volume distribution in response to increased PEEP (Fig. 10).

Although the above reported regional findings were reliable as mean values for the whole group, when analyzing the different patients individually a striking heterogeneity was found, which was not surprising in the light of the recruitability study by Gattinoni et al [73] and our own findings (Studies II and III) showing substantial heterogeneity in this patient group. However, when studying the regional intra-tidal gas distribution at baseline and during the decremental PEEP trial, the patients seemed to belong to either one of three groups with completely different patterns, here exemplified by patients number 4, 6 and 10. Patients with different intra-tidal gas distribution patterns had different patterns in regional tidal volume distribution, regional EELV increase, regional distribution of volume-dependent compliance and regional tidal PV curves as well. In two patients with low baseline EELV, ~ 700 and ~900 ml (Pat 4 and 10, Fig. 12), there was a similar ventral and mid-ventral distribution of ΔEELV and redistribution of the tidal volume to dorsal lung regions. With increasing PEEP, a marked increase in Cini in non-dependent lung regions was seen in patient 4, and also in patient 10 but to a much lesser extent. In contrast, the intra-tidal gas distribution pattern (ITV) pattern was completely different between these two patients. In patient 4, a decrease in non-dependent and an increase in dependent gas distribution were seen during inspiration. In patient 10 the distribution was quite the opposite. We speculate that this may be explained by patient 10 having much more consolidated dorsal atelectasis, requiring higher recruitment pressure than patient 4, in whom the applied recruitment pressure, around 32 $cmH_2O$ during the end-inspiratory pauses, were high enough to open the lung. This is also supported by the fact that the lower inflection point seen in the mid-dorsal region in patient 10, is only absent at the highest PEEP level. In patient 4, the lower inflection points disappear when increasing PEEP to 16 $cmH_2O$ and upper inflection points appear in ventral, mid-ventral and mid-dorsal regions. When PEEP is lowered stepwise, the upper inflection points in mid-ventral and ventral regions disappear and the lower inflection point in the mid-dorsal region does not appear until PEEP is 8 $cmH_2O$. In patient 6, who had high baseline EELV, the distribution pattern is quite different with very small changes in intra-tidal gas distribution in the different regions and volume-dependent compliance of the non-dependent lung regions decreasing when PEEP is increased. In the regional pressure volume curves no lower inflection points are seen at baseline and the curves remain depressed until PEEP is 8 $cmH_2O$ (Fig 13). Probably this patient has no need for high PEEP.

The difference in gas distribution patterns in our study, indicates that it is unlikely that a single parameter value can give information enough to discriminate between patients with low or high potential for recruitability or need for high or low PEEP, as the ALI/ARDS syndrome includes patients with a wide variety of lung mechanical conditions. Furthermore, we lack information on balance between lung and chest wall compliance [195,196], since oesophageal pressure was not measured in our study. The difference in effect of PEEP changes in pulmonary and extra-pulmonary ARDS [184] can thus be an important reason for the varying intra- and intertidal gas distribution seen in this study.

Our findings of different individual regional gas distribution patterns during inspiration, which co-varied with regional tidal volume distribution, suggest that a lot of information might be gained by addition of measurement of regional intra-tidal gas distribution to our bedside patient assessment tools. More research needs to be done in this field.

## The morbidly obese patient – a perioperative challenge

In Study I, we found that end-expiratory lung volume could be preserved in the morbidly obese when using high PEEP levels, 15 (13-17) $cmH_2O$, during anaesthesia for laparoscopic surgery. This is in contrast to other studies where a marked reduction in EELV/FRC has been observed. However, in those studies, PEEP was not used [12,197], or PEEP was set at a lower level [15]. In two studies [18,22], equally high PEEP as the one we used was applied and positive effects were seen on venous admixture and regional gas distribution, also when comparing to PEEP 10 $cmH_2O$ [18]. Unfortunately, EELV measures were not presented. Strategies other than PEEP have been tried, to optimize ventilation in this patient group, such as large Vt [198] (no positive effect), prone position [197](increased FRC) and recruitment manoeuvre [26](improved $PaO_2$ and compliance, most improved if recruitment manoeuvre was combined with PEEP and repeated every 10 minutes). Large Vt led to tidal recruitment but did not markedly improve oxygenation, which was not completely surprising since a low PEEP was used, and was not increased. This low PEEP will lead to cyclic opening and closing of collapsed alveoli [84] . The prone position was shown to be advantageous, but is for most surgical procedures not applicable. The fact that RMs had to be repeated every 10 minutes [26] to achieve good compliance and $PaO_2$, may very well be an indication that the chosen PEEP level of 10 $cmH_2O$ was too low to keep the alveoli open, supported by our findings of PEEP 15 $cmH_2O$ necessary for maintaining EELV.

An additional explanation to why we succeeded in maintaining EELV might have been that CPAP was used during the pre-oxygenation and induction phases, so the time for EELV loss (here only during intubation) was minimized (Fig. 6). For the morbidly obese, the benefit from CPAP 10 $cmH_2O$ during induction has previously been shown [23,24] whereas CPAP 7.5 $cmH_2O$ showed no beneficial effect [199].

Pneumoperitoneum, the abdominal insufflation of carbon dioxide during laparoscopy, is an additional strain on respiratory mechanics, since it has per se been shown to increase atelectasis formation by 66% in normal weight subjects, such that when measured by CT, volume of atelectasis increased from 49 to 70 $cm^3$ [200]. CT showed that when insufflating the abdomen with $CO_2$ in normal weight patients, the diaphragm was cranially displaced by 2 cm, and FRC decreased by 16% [200]. In morbidly obese patients, pneumoperitoneum has been shown to lower compliance and result in worsened gas exchange [26,201,202]. However, in Study I, we did not find, somewhat surprisingly, any noticeable changes in end-expiratory lung volume or compliance due to carbon dioxide insufflation. Possibly, the negative effects of pneumoperitoenum were counteracted by the higher PEEP levels used in our study.

## Future ventilatory strategies

We can now summarize the results from this thesis, merge them with what is known from other studies and suggest some recommendations for how to manage critically ill ventilator patients with respect to ventilatory strategies. This means improving conditions for an acceptable gas exchange while minimizing the risk for VILI [36,37]. It seems justified to ventilate our ICU patients with low tidal volumes of 6 ml/kg BW [30], and plateau pressures preferably not exceeding 30 $cmH_2O$, and the lower the plateau pressure the better [43-45]. To avoid atelectasis formation or tidal opening and closing of alveoli, a sufficient PEEP is needed. The optimal PEEP level needs to be titrated for each patient, since some patients, mostly those with high degree of lung recruitability, are in need of high PEEP levels, while PEEP can be harmful to others, typically patients with low or no lung recruitability [73]. RMs should be used in patients who have high lung recruitability, but not in those who do not have any lung volume to recruit. In such cases, RMs are likely to cause nothing but negative side-effects. When performing RMs, one should probably use a prolonged method [77,181] with limited pressure, and make sure to set optimal PEEP following the RM, since otherwise the recruiting effect will be lost [75,82,83]. Since ALI/ARDS are dynamic syndromes, one has to frequently re-evaluate the ventilatory settings and strategies. To enable re-evaluation on at least a daily basis, bedside methods for ventilatory monitoring are needed. EIT seems to be suitable since it is radiation-free, non-invasive and bedside, and enables continuous monitoring of global as well as regional lung volume changes.

For the extreme cases, for patients in whom hypoxia is the major problem and above ventilatory strategy is not enough to secure an acceptable oxygenation even with $FiO_2$ of 1.0, other rescue strategies can be tried. Prone position should be applied in this patient category [31]. In the case where the patient has high recruitability, pressures substantially higher than those normally recommended for a RM can be tried [62], and PEEP can be set to levels above those usually seen. EIT can be of guidance in this case, to ensure that dependent lung areas are actually ventilated again after such a high pressure RM.

## New perspectives

The introduction of CT and EIT for regional and more dynamic evaluation, denotes the beginning of a new era in ventilatory assessment of the critically ill patients. EIT enables continuous bedside monitoring. Already today, we find that ALI/ARDS patients are very complex and heterogeneous regarding their lung function. Thus, there is a need for individualized treatment with frequent follow-ups to tailor ventilatory treatment. Maybe in this way, we can reduce VILI and help the patient to an earlier recovery. In the long run, this will hopefully improve outcome and decrease the substantial burden on health care, constituted by ALI/ARDS today.

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# POPULÄRVETENSKAPLIG SAMMANFATTNING

Akut lungsvikt är ett allvarligt syndrom som kan orsakas av sjukdomar i lungan, men också av sjukdomar som inte primärt omfattar lungan. Respiratorkrävande akut lungsvikt har en mycket hög dödlighet, ca 40 %. Detta är en siffra som står sig oförändrad sedan flera decennier – trots att intensiv forskning gjorts för att bättre förstå och kunna behandla syndromet. Utöver hög dödlighet på kort sikt, är långtidsresultaten för dem som överlever sjukhusvistelsen dåliga. Efter ett år lever fortfarande 56 % av patienterna, men bara 9 % är utan behov av någon form av funktionshjälp. Av dem som överlever, har bara 27 % en bra livskvalitet vid ett-års-uppföljning.

Ett annat, ökande, hälsoproblem idag är sjuklig övervikt, som är ett av västvärldens största hot mot hälsan. Patienter med sjuklig övervikt, har i samband med operation en ökad risk för lungkomplikationer, bland annat för att de har kraftigt sänkt volym i lungorna vid avslutad utandning, något som i förlängningen leder till försämrad syresättning.

Det finns många sätt att ställa in respiratorn, och man har funnit att det spelar roll hur man väljer att göra. Lungskada kan uppkomma som en följd av respiratorbehandlingen i sig. Att välja små andetag (tidalvolymer) framför stora, har visats skydda lungan. Likaså är det viktigt att luftvägarna inte utsätts för tryck som är för höga; platåtryck, dvs. trycket vid avslutad inandning, bör inte överstiga 30 $cmH_2O$, och helst vara ännu lägre. Man har också visat att de patienter som har mest uttalade syresättnings-problem, har glädje av att ligga på magen under pågående respiratorbehandling.

Mycket vanligt förekommande hos patienter med akut lungsvikt, och också hos patienter med sjuklig övervikt i samband med narkos, är så kallade atelektaser, dvs delar av lungvävnad som är sammanfallna och därför inte kan delta i gasutbytet, dvs. inte kan ta upp syrgas och inte kan avge koldioxid till respektive från blodbanan. Man har förordat att öppna dessa atelektaser med hjälp av så kallad lungrekrytering, när man ökar luftvägstrycket under en kort tid, varvid sammanfallna lungblåsor öppnas. Man har visat att för att inte bara ha en övergående kortvarig effekt, bör man efter avslutad rekrytering ställa in ett så kallat PEEP (positivt end-expiratoriskt tryck) under utandningen, vilket minskar risken för förnyad lungkollaps, samt kan förhindra att ömtåliga lungdelar öppnas och stängs under varje andetag. Flera studier har gjorts för att påvisa en vinst med PEEP, men har inte kunnat visa någon sådan. Detta beror sannolikt på att PEEP-nivån måste individualiseras för den enskilda individen och ställas in från dag till dag. För att kunna individualisera behandlingen krävs förbättrade övervakningsmetoder för att vid sängkanten omedelbart kunna följa effekten av åtgärder. Vi har fått vara med under utvecklingen av en ny metod för övervakning av lungvolymsförändringar. Denna metod, Elektrisk Impedans-tomografi (EIT), är en strålningsfri metod som möjliggör att vid sängkanten kontinuerligt kunna övervaka förändringar i lungvolym.

I Arbete I studerades patienter med sjuklig övervikt, som genomgick titthålskirurgi för att förbikoppla magsäcken, så kallad gastric bypass, i syfte att åstadkomma viktreduktion för patienten. Med hjälp av EIT kunde vi se att man behöver ställa in ett högt mottryck, PEEP, för att på denna patientgrupp kunna bibehålla lungvolymen vid slutet av ett andetag. Denna lungvolym, som upprepat har rapporterats vara kraftigt sänkt för den här patientgruppen, sågs faktiskt till och med öka något under operationen.

Arbete II studerar patienter med akut lungsvikt, och jämför två olika rekryteringsmanövrar, dels en klassisk så kallad vitalkapacitetsmanöver där man utsätter lungorna för högt tryck under en kort tid, 2 x 20 sekunder, dels en förlängd, skonsammare manöver med endast måttligt tryck under en halvtimmes tid. Det visar sig att den förlängda manövern åstadkommer samma ökning i lungvolym som den klassiska högtrycksmanövern, men utan den negativa inverkan på blodcirkulationen som ses med högtrycksmanövern. Dessutom verkar lungan stabiliserats på ett annorlunda sätt med den förlängda manövern, då denna behöver efterföljas av lägre PEEP, för samma effekt, vilket är skonsammare för lungorna.

Arbete III presenterar en metod för att bestämma vilka patienter som kan ha nytta av lungrekryteringsmanövrar och högt PEEP, och vilka som istället riskerar att skadas av detta. Nyligen har visats att detta kan bestämmas med hjälp av datortomografi, en metod som dock innebär att patienten utsätts för röntgenstrålning och oftast måste transporteras till röntgenavdelningen. Lungrekryterbarhet, bedömd med datortomografi, skulle möjligen komma att bestämmas en gång i början av vårdtillfället, vilket vore mindre lyckat då sjukdomsförloppet är mycket dynamiskt och rekryterbarheten kan variera från en stund till en annan. Vår metod bygger på EIT, som patienten kan vara kopplad till under lång tid, vilket möjliggör upprepade mätningar för att följa sjukdomens utveckling. Vi fann att patienter med akut lungsvikt är en mycket heterogen patientgrupp, där lungrekryterbarheten varierade mellan 11 och 47 %. Patienter med hög rekryterbarhet, vilka verkade vara sjukare från start, hade nytta av högt PEEP, medan det motsatta gällde för patienter med låg rekryterbarhet.

Arbete IV är en vidareutveckling av EIT på patienter med akut lungsvikt. Vi har studerat lungans olika delar och följt till vilka regioner luften tar vägen. Vi fann att den ökning i lungvolym som sker när man gör en rekryteringsmanöver och ökar PEEP, sker i främre delar av lungan, medan det sker en omfördelning i hur andetaget är fördelat mellan de olika delarna av lungan. Högre tryck fördelar större del av andetaget till bakre delar av lungan. På liknande sätt kommer luften under inandningen, vid höga PEEP framför allt, att flyttas till mer bakre belägna lungdelar, ju mer av inandningen som gjorts.

Sammantaget beskriver avhandlingen nya metoder för att följa och behandla akut lungsvikt hos kritiskt sjuka patienter på intensivvårdsavdelningar och operation. Vår förhoppning är att detta i förlängningen skall kunna leda till snabbare tillfrisknad och förbättrad överlevnad i denna grupp av mycket allvarligt sjuka patienter.

# ORIGINAL STUDIES (I-IV)