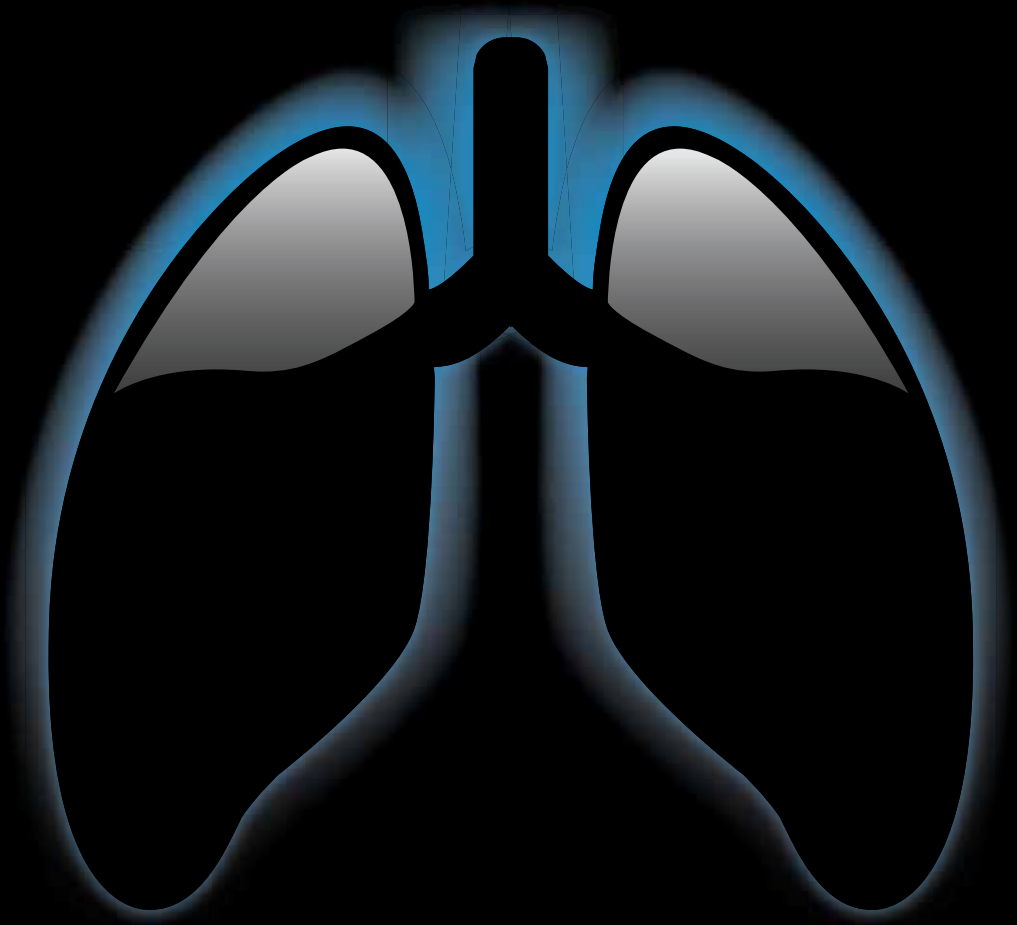
Bedside Lung Monitoring in Order to Optimize Ventilator Settings in ICU Patients



Paul Blankman

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Bedside Lung Monitoring in Order to Optimize Ventilator Settings in ICU Patients

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CHAPTER 1

General introduction

The ARDSnetwork trial

The Acute Respiratory Distress Syndrome (ARDS) was described for the first time in 1967 by Ashbaugh *et al.*[1]. Twelve adult patients, suffering from respiratory failure identified by severe dyspnea, tachypnea, hypoxemia, reduced lung compliance and infiltrates seen on a chest X-ray, did not respond to conventional respiratory therapy. They showed great similarities to infants with the infant respiratory distress syndrome. Therefore, the disease was referred to as adult respiratory distress syndrome and later on as acute respiratory distress syndrome.

In ARDS patients the gas exchange is impaired due to atelectasis of, in particular, the dependent lung region. Multiple strategies were applied in the treatment of ARDS, but only the application of Positive End-Expiratory Pressure (PEEP) improved patient outcome by recruiting alveoli[1] and preventing alveolar collapse during expiration. Due to the use of PEEP, arterial carbon dioxide tension (P_aCO_2) increased, and therefore ventilation with tidal volumes of 12-15 ml/kg became standard of care in order to achieve normocapnia.

In Rotterdam professor Lachmann[2] developed the Open Lung Concept (OLC). The OLC uses Recruitment Maneuvers (RM) to open up atelectatic lung tissue, after which an adequate PEEP level should be applied in order to keep the recruited alveoli open. However, the OLC resulted in ventilation with high PEEP levels. The high PEEP levels had as disadvantage overdistention of alveoli in particular the non-dependent lung region. Overdistention of lung tissue induces an inflammatory reaction leading to lung injury. Lung damage due to mechanical ventilation is better known as Ventilator Induced Lung Injury (VILI).

In 2000 the hallmark paper of the ARDSnetwork[3] was published in which they demonstrated that mechanical ventilation with smaller tidal volume (6 vs 12ml/kg) and a plateau pressure ≤ 30 cm H_2O improved survival of mechanically ventilated ARDS patients. Between 2004 and 2008 multiple studies have been performed in which higher amounts of PEEP were applied as compared to the ARDSnetwork trial[4-7]. However, these studies showed the same mortality rate indicating that higher PEEP was not better. Two meta-analyses, however, showed that higher PEEP levels are beneficial to the more severe ARDS patients, whereas the less severe ARDS patients, the so-called Acute Lung Injury (ALI), were better off with lower PEEP levels[8;9].

From the literature it can be concluded that a standard ventilation protocol is not recommended, but a personalized ventilation strategy should be preferred. Therefore, bedside monitoring tools are needed to assess and optimize ventilatory settings for the individual patient. Through the years different bedside monitoring techniques have been developed, in order to assess and optimize ventilatory settings. The two main techniques in this thesis are Electrical Impedance Tomography (EIT) and Functional Residual Capacity (FRC) measurements. These two techniques are described in detail in **Chapter 2**.

Lung monitoring systems

The first technique we used to detect best PEEP is the measurement of lung volume. In the past measurements of FRC were difficult due to bulky and expensive equipment and the use of tracer gasses[10]. Stenqvist *et al.*[11] developed the Nitrogen Multiple Breath Washout (NMBW) technique to measure FRC non-invasively and without interruption of mechanical ventilation. For the NMBW a step change in fraction of inspired oxygen (FiO_2) is required, and this tool is now integrated in ICU mechanical ventilators. However, FRC is influenced by the amount of PEEP applied during mechanical ventilation and therefor it is better to speak of End-Expiratory Lung Volume (EELV). It is known that FRC is reduced by 25% in healthy volunteers due to changing from sitting to supine position[10]. Hedenstierna *et al.*[12] found a FRC reduction of 0.8-1.0L by changing from sitting to supine position, whereas the use of sedative reduced the FRC with another 0.4-0.5L. Recently we found that FRC at a PEEP level of 5 cm H_2O is reduced with 34% in normal lungs, whereas in patients with pneumonia this was 58%[13]. After increasing the PEEP to 10 cm H_2O the FRC values increased with 7 and 12% respectively. Thus PEEP is able to improve EELV, and therefore, in **Chapter 3** we investigated an EELV driven PEEP protocol to restore the patients' ideal lung volume. We performed a randomized controlled trial in which EELV was used to titrate PEEP, after which during 48 ours the PEEP was titrated to maintain the patients' ideal lung volume. This was compared to the PEEP titration based on the FiO_2/PEEP table as used in the ARDSnetwork trial.

Lung stress and strain are two definitions, which are introduced to describe forces acting on lung tissue during mechanical ventilation[14]. Lung stress describes the distribution of forces due to PEEP and tidal volume, whereas strain describes the resulting change in lung volume. Mead et al. [15] demonstrated in a mathematical model that inhomogeneous ventilated lungs are exposed to increased forces acting on lung parenchyma. They calculated that if a transpulmonary pressure of 30 cm H_2O is acting on lung parenchyma, this would be increased with a factor 4.5 in inhomogeneous lungs, resulting in a force of 140 cm H_2O. Recently, Protti *et al.*[16;17] calculated lung stress and strain during an experimental study using different amounts of tidal volume and PEEP. They demonstrated that a lung strain of 2.5 was harmful and resulted in lung edema[16]. However, in the second study they ventilated the pigs with a total strain of 2.5 but with different amounts of PEEP (static strain) and tidal volume (dynamic strain). They found that if strain mainly exists from dynamic strain the lungs got damaged and lung edema developed, whereas ventilation with mainly static strain protected the lungs. This indicates that PEEP is protective tot the lungs. In ARDS lungs alveoli show cyclic collapse and high forces are needed to open these alveoli up. Therefore, the alveolar walls are exposed to high stress during each breath. Due to the high forces the alveolar walls are stretched and inflammatory mediators are released causing lung damage, but might also induce systemic inflammation leading to multi-organ failure and death. To calculate lung stress and strain based on non-invasive lung volume measurements, specific elastance or transpulmonary pressure. However, transpulmonary pressure measurements are difficult to perform reliable. Therefore, Stenqvist *et al.*[18;19] developed a method to calculate specific elastance from EELV measurements without the need for transpulmonary pressure measurements. This method has been shown to correlate well with esophageal pressure measurements (r^2=0.96). In **Chapter 4** we calculated lung stress and strain from non-invasive FRC measurements using the Multiple Breath Nitrogen Washout (NMBW) technique. We calculated lung stress and strain in ARDS, ALI and normal lungs without performing esophageal pressure measurements.

In **Chapter 5** we used different global and regional monitoring systems in an experimental study to find best PEEP, including EELV and EIT measurements. EIT is a non-invasive bedside monitoring tool to assess ventilation distribution in a 5-10 cm thick lung slice[20;21]. Therefore, a silicon belt with 16 electrodes is placed around the thoracic cage of the patient. A small electric current (5mA, 50kHz) is sent between two electrodes, while the remaining electrode pairs measure the remaining electrical signal[22]. The electric impedance is translated in a ventilation map of 32x32 pixels. For the analysis of EIT data multiple parameters have been developed.

Therefore, in **Chapter 6,** 7 different EIT parameters are compared to investigate their capability to detect optimal PEEP. From Chapter 4 we learned that EIT is able to detect homogeneous ventilation, during the inspiration, by means of the intratidal gas distribution (ITV). This parameter returns frequently in this thesis. One of the main parameters during mechanical ventilation is capnography, which is the visualization of the expired carbon dioxide. Capnography during ventilation with a fixed tidal volume is called volumetric-capnography, and is able to measure which amounts of expired air are originated from the alveoli or airways. In **Chapter 7** we compared EIT and volumetric-capnography in order to study which technique should be preferred for bedside PEEP optimization.

Reducing sedatives

After 2008 the focus of research shifted towards reduction of sedatives. Levine *et al.*[23] found that controlled mechanical ventilation results in atrophy of the diaphragm within 18 hours of mechanical ventilation which causes a delayed weaning[24]. However, a randomized multicenter study in 340 mechanically ventilated ARDS patients found that the use of neuromuscular blocking agent just for the first two days during volume-controlled ventilation increased survival and ventilator free-days within the first month without increasing muscle weakness compared to a control group without muscle relaxation[25]. In the group that received muscle relaxation there was less number of pneumothoraxes and barotrauma, suggesting better patient-ventilator synchrony. In addition, Strøm and colleagues[26] have shown that omitting sedation in critically ill patients receiving mechanical ventilation resulted in four days reduction of ventilation and 23 days shorter stay in the hospital compared with standardized daily interruption of sedation. This result is exceptional and suggests that optimal patient-ventilator synchrony is of particular importance[27;28]. Due to these results more patients are ventilated using partial assist modes like Pressure Support Ventilation (PSV) or Neurally Assisted Ventilatory Assist (NAVA). In **Chapter 8** we studied the effect of PSV and Pressure Control Ventilation (PCV) on the distribution of tidal volume using EIT. To assess ventilation distribution we used the ITV developed by Löwhagen *et al.*[29]. The ITV divides the inspiratory impedance curve into eight equal volume sections after which the contribution of the dependent and non-dependent lung region to the inspiration can be calculated. In **Chapter 9** we also analyzed the ventilation distribution, based on ITV, but now at different levels of assist during PSV and NAVA. During NAVA the diaphragm activity is measured using a gastric feeding-tube containing seven electrodes. The electric signal of the diaphragm is multiplied by a certain amount of assist per μV, which results in a certain amount of pressure assist. The diaphragm of the patient will increase when lower assist levels are applied and therefore the patient is able to control the amount of tidal volume that is delivered by the ventilator, whereas during PSV the patients receives a pressure assist which is defined by the attending physician.

Aim of the thesis

Mechanical ventilation set according to standard protocols or tables is not sufficient for the individual patient. Therefore, we should aim to personalized mechanical ventilation strategies and personalized physiology. The aim of this thesis is to optimize PEEP and the level of ventilatory assist in the individual patient at the bedside, in order to minimize VILI.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE: Acute respiratory distress in adults. Lancet 1967; 2: 319-23
2. Lachmann B: Open up the lung and keep the lung open. Intensive Care Med. 1992; 18: 319-21
3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N.Engl.J.Med. 2000; 342: 1301-8
4. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N.Engl.J.Med. 2004; 351: 327-36
5. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 637-45
6. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 646-55
7. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH: Mechanical ventilation guided by esophageal pressure in acute lung injury. N.Engl.J.Med. 2008; 359: 2095-104
8. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010; 303: 865-73
9. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P: Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann. Intern.Med. 2009; 151: 566-76
10. Ibanez J, Raurich JM: Normal values of functional residual capacity in the sitting and supine positions. Intensive Care Med. 1982; 8: 173-7
11. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O: Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth. Analg. 2005; 101: 206-12, table

12. Hedenstierna G, Edmark L: The effects of anesthesia and muscle paralysis on the respiratory system. Intensive Care Med. 2005; 31: 1327-35
13. Bikker IG, van Bommel J, Reis MD, Bakker J, Gommers D: End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. Crit Care 2008; 12: R145
14. Wilson TA: Solid mechanics. American Physiological Society., Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Baltimore, MD Waverly, 1986, pp 35-9
15. Mead J, Takishima T, Leith D: Stress distribution in lungs: a model of pulmonary elasticity. J.Appl.Physiol 1970; 28: 596-608
16. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: any safe threshold? Am.J.Respir.Crit Care Med. 2011; 183: 1354-62
17. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L: Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?. Crit Care Med. 2013; 41: 1046-55
18. Lundin S, Grivans C, Stenqvist O: Transpulmonary pressure and lung elastance can be estimated by a PEEP-step manoeuvre. Acta Anaesthesiol.Scand. 2015; 59: 185-96
19. Stenqvist O, Grivans C, Andersson B, Lundin S: Lung elastance and transpulmonary pressure can be determined without using oesophageal pressure measurements. Acta Anaesthesiol.Scand. 2012; 56: 738-47
20. Hedenstierna G: Using electric impedance tomography to assess regional ventilation at the bedside. Am.J.Respir.Crit Care Med. 2004; 169: 777-8
21. Putensen C, Wrigge H, Zinserling J: Electrical impedance tomography guided ventilation therapy. Curr.Opin.Crit Care 2007; 13: 344-50
22. Bikker IG, Leonhardt S, Bakker J, Gommers D: Lung volume calculated from electrical impedance tomography in ICU patients at different PEEP levels. Intensive Care Med. 2009; 35: 1362-7
23. Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, Rubinstein NA, Powers SK, Shrager JB: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N.Engl.J.Med. 2008; 358: 1327-35
24. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G: Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 2010; 14: R127
25. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guerin C, Prat G, Morange S, Roch A: Neuromuscular blockers in early acute respiratory distress syndrome. N.Engl.J.Med. 2010; 363: 1107-16
26. Strom T, Martinussen T, Toft P: A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010; 375: 475-80

27. Petrof BJ, Jaber S, Matecki S: Ventilator-induced diaphragmatic dysfunction. Curr.Opin.Crit Care 2010; 16: 19-25
28. Powers SK, Kavazis AN, Levine S: Prolonged mechanical ventilation alters diaphragmatic structure and function. Crit Care Med. 2009; 37: S347-S353
29. Löwhagen K, Lundin S, Stenqvist O: Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol. 2010; 76: 1024-35

CHAPTER 2

Lung monitoring at the bedside in mechanically ventilated patients

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Curr Opin Crit Care 2012; 18(3): 261-266

Abstract

Purpose of review

It has become clear that mechanical ventilation itself can cause damage to the lung in critically ill patients, also known as ventilator-induced lung injury (VILI). Insight into the mechanisms of VILI has learned that a compromise must be found between positive end-expiratory pressure (PEEP) induced alveolar recruitment and prevention of hyperinflation. Therefore, there is a need for clinicians to optimize the PEEP settings for the individual patient at the bedside. In this review, we will discuss several lung-monitoring techniques to improve patient ventilator settings.

Recent findings

Recently, new monitoring tools like electrical impedance tomography (EIT), vibration response imaging, respiratory inductive plethysmography and functional residual capacity (FRC) have been (re-)introduced in our ICU. Nowadays, FRC can be measured without the use of tracer gases and without disconnection from the ventilator. EIT is another noninvasive bedside monitoring tool that provides regional ventilation distribution images and can be used for qualitative and quantitative assessment of regional change in ventilation after a ventilator change. These new noninvasive techniques are discussed and seem promising to help clinicians to improve their ventilator settings in the individual patient at the bedside.

Summary

In conclusion, both FRC and EIT are promising clinical monitoring systems but clinical studies are needed to prove whether these monitors help the clinician toward effective and better ventilator management.

Introduction

In patients with the acute respiratory distress syndrome (ARDS), parts of the lungs are atelectatic or consolidated, particularly in dependent regions, so that they cannot participate in gas exchange. During mechanical ventilation, the less affected lung regions must therefore accommodate most of the tidal volume, with the risk of tidal hyperinflation. The ARDS network trial established the importance of hyperinflation by demonstrating that ventilation using lower tidal volumes (6 versus 12 ml/kg) and maintaining a plateau pressure of not more than 30 cm H_2O, improves survival[1;2]. Atelectotrauma (cyclic atelectasis) has been shown to be another important contributor to ventilator-induced lung injury (VILI). Atelectotrauma may be mitigated by recruitment maneuvers to open up collapsed alveoli followed by application of higher levels of positive end-expiratory pressure (PEEP) to prevent further collapse. Because application of higher PEEP levels may increase the risk of hyperinflation, a compromise must be found between PEEP-induced alveolar recruitment and prevention of hyperinflation. Recently, two meta-analyses have shown that high PEEP levels were associated with improved survival among the subgroup of patients with ARDS, who were sicker[3;4]. This indicates that PEEP levels should be titrated for the individual patient depending on their lung injury. Thus, "optimal" PEEP can only be achieved by using individual settings that differ from patient-to-patient but also from time-to-time when lung function is changing. In this article, we described the recent available bedside lung monitors and their applications in order to optimize ventilator settings.

Functional residual capacity measurements

Blood gases are frequently used to monitor the patient's lung function during mechanical ventilation. One should note that determining lung collapse by PaO_2/FiO_2 ratio assumes a minimal extrapulmonary shunt. Cressoni *et al*.[5] have shown that variation in gas exchange cannot be used with sufficient confidence to assess anatomical lung recruitment in patients with acute lung injury (ALI) or ARDS. Therefore, it seems reasonable to monitor lung volume changes due to alveolar recruitment or alveolar collapse by repeated measurements of functional residual capacity (FRC) instead of arterial oxygenation. FRC is defined as the relaxed equilibrium volume of the lungs when there is no muscle activity and no pressure difference between alveoli and the atmosphere and is regularly determined at pulmonary function laboratories. FRC is normally measured in sitting or standing position and is sex, length and age dependent. It has been shown that FRC is decreased by 25% in healthy volunteers after changing from sitting to supine position during spontaneous breathing[6]. This is confirmed by Hedenstierna and Edmark [7] who observed that changing from sitting to supine position resulted in FRC decrease of 0.8-1L. If the patient is also sedated FRC further decreased with another 0.4-0.5 L. In critically ill patients receiving mechanical ventilation, the level of PEEP determines FRC, and therefore it would be better to use end-expiratory lung volume (EELV).

Measurements of EELV at the ICU have always been limited by the use of expensive and bulky equipment and the use of tracer gases[8;9]. Stenqvist's group[10] have introduced a novel method to measure EELV without interrupting mechanical ventilation, based on a simplified and modified nitrogen multiple breath washout technique (NMBW), which is integrated in the Engström ventilator (GE Healthcare, Madison, WI, USA). This method requires a stepwise change in the inspired oxygen fraction (FiO_2) without the need for supplementary tracer gases or specific additional monitoring equipment. This system is successfully used in children[11;12] and adults[10;13;14]. Chiumello *et al.*[15] studied EELV measurements using the NMBW technique, helium dilution and computed tomography (CT). The latter is regarded as the golden standard. In 30 ICU patients, they found a very good relation ($R^2 = 0.89$; $p \leq 0.01$) between NMBW technique and CT. Bikker *et al.*[13] performed EELV measurements during a PEEP-trial in 45 ICU patients with healthy and diseased lungs. At a PEEP level of 5 cm H_2O, EELV was 34% lower compared with FRC based on length, sex and age in patients without respiratory failure. For patients with pneumonia, EELV was 58% lower of the predicted sitting FRC at a PEEP level of 5 cm H_2O and increased with 7 and 12% after increasing PEEP to 10 and 15 cm H_2O, respectively. Maisch *et al.*[16] performed EELV measurements at different PEEP levels before and after a recruitment maneuver in patients undergoing plastic surgery. EELV increased by adding more PEEP and was higher after recruitment at the same level of PEEP. After the lung recruitment, compliance had a maximum and dead space had a minimum value at a PEEP level of 10 cmH_2O. This indicates that EELV should be combined with compliance or dead space measurements to differentiate between recruitment or further dilation of already open alveoli and airways in order to find the 'best' PEEP. Dellamonica *et al.*[17] created a bedside monitoring tool to calculate the alveolar recruitability by using EELV measurements. The baseline FRC was defined at zero PEEP, and thereafter they increased PEEP to 5 and 15 cm H_2O, respectively. By calculating the ΔEELV/FRC ratio, they defined low recruiters and high recruiters at a cut-off point of 73%.

Electrical impedance tomography

Electrical impedance tomography (EIT) is a non-invasive and radiation-free bedside-imaging device that provides images of ventilation by measuring changes in electrical impedance. The technique is based on the injection of small currents and voltage (5 mA, 50 kHz) using electrodes on the skin surface[18]. The measured impedance changes will be translated in a cross-sectional picture of 32x32 pixels (Fig. 1). The EIT visualizes the ventilation distribution and increase or decrease in the amount of air in a 5 cm thick slice of the thorax[19-21].

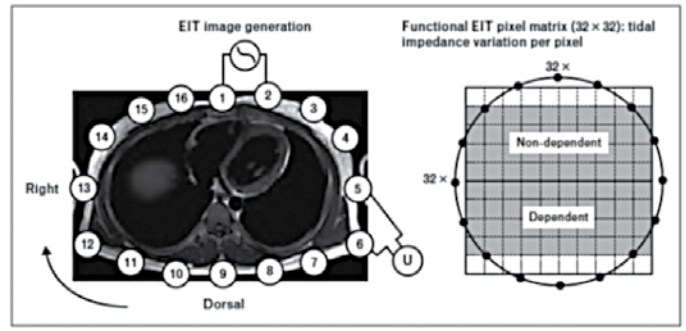

Fig. 1: Impression of the electrical impedance tomography measurement. Electrical impedance tomography (EIT) will provide pictures by measuring impedance between 16 electrodes. A cross-sectional picture of 32x32 pixels will be created.

All clinical available EIT systems use relative changes instead of absolute impedance values due to its higher quality of the images[22]. The difference between relative and absolute impedance is explained by a case report[23]. During an experimental study, a pneumothorax developed accidentally in the right lung. A prominent increase of impedance was found in the ventral part of the right lung followed by a gradual decrease in ventilation-related impedance changes in the same region. Thereafter, the ventilation-related impedance changes of the right lung almost disappeared from the image because the thoracic cage was filled with air and tidal ventilation was impossible. If an EIT image was made using absolute impedance at that time, the right side of the image should have shown high impedance values because of the high air content. In two patients with pneumonia, Costa *et al.*[24] measured the tidal impedance change during pressure-controlled ventilation expressed as the regional compliance. This regional compliance was calculated for a small area in both the dependent and non-dependent lung region during a decremental PEEP trial, from 25 to 5 cm H_2O. It was shown that both areas had their own optimum in compliance. PEEP levels above this optimum represent hyperdistention and below this optimum alveolar collapse. Meier *et al.*[25] introduced the subtraction of EIT images when altering the PEEP level. This enables a qualitative and quantitative assessment of regional change in ventilation after a PEEP change. In an experimental model, it was shown that ventilation appeared and disappeared in certain lung regions when altering the PEEP level. This was confirmed by our group[26] in mechanically ventilated ICU patients with and without respiratory failure in whom a PEEP trial (15, 10, 5 and 0 cm H_2O) was performed. It was shown that ventilation increased in the non-dependent area but decreased in the dependent lung regions after the first PEEP reduction in patients without respiratory failure. During the next PEEP steps, ventilation decreased in both regions. In patients with respiratory failure, ventilation decreased after each decremental PEEP step indicating alveolar collapse at lower PEEP levels.

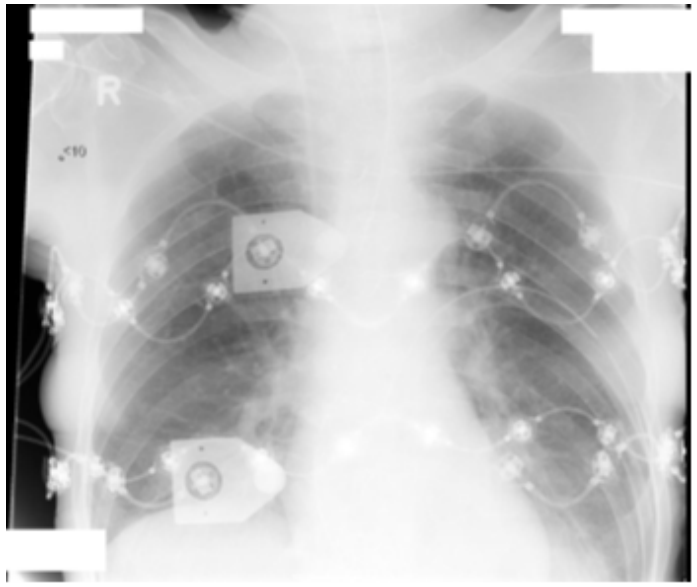

Fig. 2: Electrical impedance tomography belt locations on the thoracic cage. Chest radiograph of two electrical impedance tomography belts on the thoracic cage of a patient. Cranial belt (upper) and a caudal belt (lower).

We[27] also performed EIT measurements at two thoracic levels in ICU patients undergoing the same PEEP trial (Fig. 2). EIT measurements were performed just above the diaphragm and at the level of the armpits. During the decremental PEEP trial, ventilation decreased at the dependent part and increased at the non-dependent part at the caudal level (just above diaphragm). In addition, ventilation decreased at the caudal level and increased at the cranial level during this PEEP trial. Thus, the ventilation distribution is moving from dorsal to ventral and from caudal to cranial when lowering the PEEP. Löwhagen *et al.*[28] utilized the high temporal resolution of EIT to assess intratidal gas distribution in mechanically ventilated patients with ALI/ARDS. Intratidal regional gas distribution was analyzed by dividing the regional tidal impedance signal into eight iso-volume parts (Fig. 3). Also, in this study, a shift in tidal gas distribution from dependent regions to non-dependent regions was noticed after decreasing PEEP. Further, the intratidal gas distribution varied widely among patients and it was shown that this offers additional bedside information on recruitability and optimal PEEP for the individual patient.
In a recent study by Maisch *et al.*[29] it is shown that EIT can also be used to monitor heart-lung interaction. In mechanically ventilated pigs, EIT is able to measure impedance changes because of better conductance after injection of 20 ml of iced iso-tonic saline. By creating functional EIT images, it is possible to visualize regional perfusion. In addition, they observed a good correlation between stroke volume variation measured by EIT and pulse contour analysis.

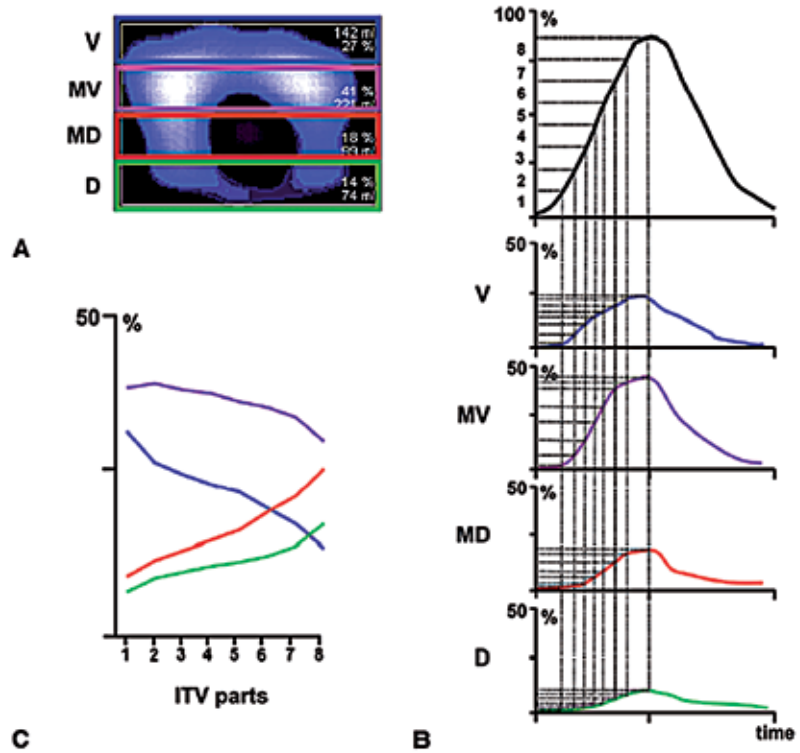

Fig. 3: Iso-volume curves of electrical impedance tomography data. (A) Shows how the intratidal gas distribution in an electrical impedance tomography image is divided in four equal regions of interest. (B) Shows how the global tidal impedance curve is divided in eight iso-volume parts. The vertical dashes transfer the iso-volume time points from the global to the regional curves. (C) Shows the fractional regional gas distribution during inspiration. D: dorsal; ITV: intratidal volume; MD: mid-dorsal; MV: mid-ventral; V: ventral. (Image: K. Löwhagen et al. Minerva Anestesiol. 2010; 76(12):1024-35)

Vibration response imaging

Vibration response imaging (VRI) is another non-invasive technique that uses 36 electronic stethoscopes placed on the back of the patient which record the distribution and intensity of lung sounds[30]. Every time the patient breathes, the stethoscopes will detect the sound vibrations and translates this into to electrical signals. The VRI device reconstructs the electrical signals to a black-gray image. The vibration intensity is significant higher in mechanical-ventilated patient compared to spontaneous breathing patients. Lev *et al.*[31] used VRI to differentiate between several chest radiographic densities and observed increased vibration intensity for consolidations and congestion, but not for atelectasis, pleural effusion or normal radiographs. Dellinger *et al.*[30] compared volume control ventilation with pressure control and pressure support ventilation using VRI. Each patient was his own control and received the three ventilation types with the same tidal volume. Using VRI, it was shown that PS leads to higher vibration intensity in the lower, basal lung parts compared with volume control and pressure control ventilation. VRI could also be used to measure vibration intensity at different PEEP levels.

Respiratory inductive plethysmography

Respiratory inductive plethysmography (RIP) uses two coils of wire in elastic bands around the thorax and the abdomen. Due to the respiratory motion, the self-inductance of the bands change and an electrical signal will be sent to the device and translated in to a volume. This technique cannot be used to measure FRC but only the change in volume due to a change in ventilator settings[32]. RIP can be used for detecting obstructive apnea[33] and measuring respiratory rate and tidal volume changes.

Valta *et al.*[34] evaluated RIP in six postoperative open-heart surgery patients, eight healthy spontaneous breathing individuals and six spontaneous breathing chronic obstructive pulmonary disease patients. They found that in controlled ventilated patients, the RIP measurements adequately reflected changes in EELV. The accuracy of tidal volume measurements by RIP was reliable and comparable between mechanical ventilated and spontaneous breathing patients. In spontaneous breathing patients, tidal volumes were measured with RIP and compared with spirometry; an error below 5% was found.

Conclusion

There is a need for easy to use bedside monitor systems in order to optimize patient ventilator settings. It has been shown that FRC measurements based on the NMBW method are easy to perform with stable and reliable measurements. However, PEEP induced changes in FRC are not only recruitment but can also be the result of hyperinflation of already ventilated lung regions. Therefore, FRC alone is not the 'magic' bullet but should be combined with other parameters, such as compliance in order to optimize PEEP levels. Another strategy for individual titration of PEEP is electrical impedance tomography (EIT). After extended research, EIT has proven to be safe and can be used to monitor lung volume changes in ICU patients. In contrast to global lung parameters such as FRC, EIT can differentiate between dependent and non-dependent regions. The VRI and RIP are infrequently used in optimizing ventilator settings and more elegant studies are needed to prove their effectiveness. In conclusion, both FRC and EIT are promising clinical monitoring systems but clinical studies are needed to prove whether these monitors help the clinician toward effective and better ventilator management.

References

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N.Engl.J.Med.* 2000, 342:1301-1308.
2. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N.Engl.J.Med.* 2004, 351:327-336.
3. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P: Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann. Intern.Med.* 2009, 151:566-576.

4. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010, 303:865-873.
5. Cressoni M, Caironi P, Polli F, Carlesso E, Chiumello D, Cadringher P, Quintel M, Ranieri VM, Bugedo G, Gattinoni L: Anatomical and functional intrapulmonary shunt in acute respiratory distress syndrome. *Crit Care Med.* 2008, 36:669-675.
6. Ibanez J, Raurich JM: Normal values of functional residual capacity in the sitting and supine positions. *Intensive Care Med.* 1982, 8:173-177.
7. Hedenstierna G, Edmark L: The effects of anesthesia and muscle paralysis on the respiratory system. *Intensive Care Med.* 2005, 31:1327-1335.
8. Hewlett AM, Hulands GH, Nunn JF, Minty KB: Functional residual capacity during anaesthesia. I: Methodology. *Br.J.Anaesth.* 1974, 46:479-485.
9. Ibanez J, Raurich JM, Moris SG: A simple method for measuring the effect of PEEP on functional residual capacity during mechanical ventilation. *Crit Care Med.* 1982, 10:332-334.
10. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O: Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. *Anesth. Analg.* 2005, 101:206-12, table.
11. Olegard C, Sondergaard S, Palsson J, Lundin S, Stenqvist O: Validation and clinical feasibility of nitrogen washin/washout functional residual capacity measurements in children. *Acta Anaesthesiol.Scand.* 2010, 54:370-376.
12. Bikker IG, Scohy TV, Ad JJCB, Bakker J, Gommers D: Measurement of end-expiratory lung volume in intubated children without interruption of mechanical ventilation. *Intensive Care Med.* 2009, 35:1749-1753.
13. Bikker IG, van Bommel J, Reis MD, Bakker J, Gommers D: End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. *Crit Care* 2008, 12:R145.
14. Erlandsson K, Odenstedt H, Lundin S, Stenqvist O: Positive end-expiratory pressure optimization using electric impedance tomography in morbidly obese patients during laparoscopic gastric bypass surgery. *Acta Anaesthesiol.Scand.* 2006, 50:833-839.
15. Chiumello D, Cressoni M, Chierichetti M, Tallarini F, Botticelli M, Berto V, Mietto C, Gattinoni L: Nitrogen washout/washin, helium dilution and computed tomography in the assessment of end expiratory lung volume. *Crit Care* 2008, 12:R150.
16. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, Bohm SH: Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. *Anesth.Analg.* 2008, 106:175-81, table.
17. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard JC, Diehl JL, Mancebo J, Rouby JJ, Lu Q, Bernardin G, Brochard L: PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. *Intensive Care Med.* 2011, 37:1595-1604.

18. Bikker IG, Leonhardt S, Bakker J, Gommers D: Lung volume calculated from electrical impedance tomography in ICU patients at different PEEP levels. *Intensive Care Med.* 2009, 35:1362-1367.
19. Brunow dC, Fonseca MC, Johnston C: Electric impedance tomography, the final frontier is close: the bedside reality. *Crit Care Med.* 2007, 35:1996-1997.
20. Hedenstierna G: Using electric impedance tomography to assess regional ventilation at the bedside. *Am.J.Respir.Crit Care Med.* 2004, 169:777-778.
21. Putensen C, Wrigge H, Zinserling J: Electrical impedance tomography guided ventilation therapy. *Curr.Opin.Crit Care* 2007, 13:344-350.
22. Costa EL, Lima RG, Amato MB: Electrical impedance tomography. *Curr.Opin.Crit Care* 2009, 15:18-24.
23. Preis C, Luepschen H, Leonhardt S, Gommers D: Experimental case report: development of a pneumothorax monitored by electrical impedance tomography. *Clin.Physiol Funct.Imaging* 2009, 29:159-162.
24. Costa EL, Borges JB, Melo A, Suarez-Sipmann F, Toufen C, Jr., Bohm SH, Amato MB: Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. *Intensive Care Med.* 2009, 35:1132-1137.
25. Meier T, Luepschen H, Karsten J, Leibecke T, Grossherr M, Gehring H, Leonhardt S: Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. *Intensive Care Med.* 2008, 34:543-550.
26. Bikker IG, Leonhardt S, Reis MD, Bakker J, Gommers D: Bedside measurement of changes in lung impedance to monitor alveolar ventilation in dependent and non-dependent parts by electrical impedance tomography during a positive end-expiratory pressure trial in mechanically ventilated intensive care unit patients. *Crit Care* 2010, 14:R100.
27. Bikker IG, Preis C, Egal M, Bakker J, Gommers D: Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. *Crit Care* 2011, 15:R193.
28. Löwhagen K, Lundin S, Stenqvist O: Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. *Minerva Anestesiol.* 2010, 76:1024-1035.
29. Maisch S, Bohm SH, Sola J, Goepfert MS, Kubitz JC, Richter HP, Ridder J, Goetz AE, Reuter DA: Heart-lung interactions measured by electrical impedance tomography. *Crit Care Med.* 2011, 39:2173-2176.
30. Dellinger RP, Jean S, Cinel I, Tay C, Rajanala S, Glickman YA, Parrillo JE: Regional distribution of acoustic-based lung vibration as a function of mechanical ventilation mode. *Crit Care* 2007, 11:R26.
31. Lev S, Glickman YA, Kagan I, Shapiro M, Moreh-Rahav O, Dahan D, Cohen J, Grinev M, Singer P: Computerized lung acoustic monitoring can help to differentiate between various chest radiographic densities in critically ill patients. *Respiration* 2010, 80:509-516.
32. Valta P, Takala J, Foster R, Weissman C, Kinney JM: Evaluation of respiratory inductive plethysmography in the measurement of breathing pattern and PEEP-induced changes in lung volume. *Chest* 1992, 102:234-238.

33. Yang GG, Yang MC, Chung CY, Chen YT, Chang ET: Respiratory-inductive-plethysmography-derived flow can be a useful clinical tool to detect patients with obstructive sleep apnea syndrome. *J.Formos.Med.Assoc.* 2011, 110:642-645.
34. Valta P, Takala J, Foster R, Weissman C, Kinney JM: Evaluation of respiratory inductive plethysmography in the measurement of breathing pattern and PEEP-induced changes in lung volume. *Chest* 1992, 102:234-238.

CHAPTER 3

End-expiratory lung volume-guided positive end-expiratory pressure setting in moderate acute respiratory distress syndrome: a randomized controlled trial

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Submitted

Abstract

Background
Although ventilatory strategies to reduce tidal volumes have improved mortality in acute respiratory failure, the optimal setting of positive end-expiratory pressure (PEEP) remains uncertain. This study aimed at restoring end-expiratory lung volume (EELV) to predicted levels, for supine position.

Methods
Critically ill, mechanical ventilated patients (n=37) with a PaO_2/FiO_2 ratio ≤300 mmHg were randomized to either the PEEP setting by EELV measurement (intervention group) or to the ARDSnet $PEEP/FiO_2$ table (controls). After a baseline EELV measurement, hemodynamic and respiratory measurements were collected immediately after a recruitment maneuver, at 24 and 48h.

Results
Baseline EELV was significantly lower in the intervention group compared to controls (64 vs. 85% of predicted supine EELV). To reach the predicted EELV the PEEP had to be increased from 11±2 to 16±2 cm H_2O intervention group, whereas in the controls, a PEEP of 10±3 cm H_2O had to be applied and was reduced to 8±2 cm H_2O at 48h. The EELV-driven protocol significantly increased the PaO_2/FiO_2 ratio in the intervention group whereas remained unchanged in controls, and airway pressures were significantly higher in the intervention group (20±6 vs. 26±6 cm H_2O p=0.024). In addition, patients with a baseline EELV ≤1.5L responded well by the EELV-driven protocol and the EELV was 0.5L higher compared to controls but at a PEEP difference of almost 10 cm H_2O. Dynamic strain was below 0.27 after 24h in control patients with a baseline EELV >1.5L. Patients with an EELV ≤1.5L in both protocols had a dynamic strain above 0.27.

Conclusions
An EELV-guided PEEP strategy is recommended to optimize ventilatory settings in patients with moderate ARDS, but with a reduced EELV and therefore EELV measurement should be performed in advance.

Introduction
Mechanical ventilation is essential in the treatment of patients with acute respiratory distress syndrome (ARDS), but mortality remains high[1]. Ventilatory strategies with reduction of tidal volumes have shown to improve mortality in ARDS patients[2]. In these studies the level of positive end-expiratory pressure (PEEP) is based on the amount of FiO_2 used to achieve a peripheral saturation of 88-93%. Large clinical trials comparing high vs. low PEEP with fixed low tidal volume were unable to demonstrate a benefit of higher PEEP levels on mortality[3;4]. A meta-analysis of 3500 patients showed a significant difference between the severe ARDS (PaO_2/FiO_2 <100 mmHg) and mild ARDS (PaO_2/FiO_2 200-300 mmHg) patients, in favor of higher PEEP protocols in the severe ARDS patients and lower PEEP levels in mild ARDS patients[5]. Therefore, it is recommended to use higher PEEP levels tailored to the individual patient, with adequate monitoring to minimize the risk of overstretching of the 'healthy' alveoli[6].
Despite decades of extensive research, a method to reliably obtain optimal PEEP levels for the individual patient remains elusive. Ideally, PEEP should be set to maintain an end-expiratory lung volume (EELV) to prevent alveolar collapse in the dependent lung and, simultaneously, overdistention in the non-dependent lung[7].The rationale behind EELV measurements to titrate PEEP is that PEEP prevents re-collapse of recruited alveoli resulting in improved V/Q ratios, but also diminishes shear stress. Measurements of EELV have been shown to be useful in estimation of lung recruitability[8] as well as for the estimation of forces applied to lung tissue by means of lung stress and strain[9;10]. Bedside methods to monitor EELV without interruption of mechanical ventilation and without additional tracer gases are now available[11]. Our group has shown that these EELV measurements can be employed in critically ill patients and that markedly reduced lung volumes are found in combination with gas exchange abnormalities[12;13]. In addition, Protti *et al.*[9;10] recently demonstrated that strain induced by tidal volume is harmful to the lungs whereas PEEP protects the lungs. If a ventilatory strategy is able to reverse these reduced lung volumes, this will improve arterial oxygenation and diminishes lung strain, which may be beneficial for critically ill patients.
In the present single-site randomized controlled trial (RCT) we studied a ventilatory protocol aiming at normalizing EELV by changing the PEEP levels after lung recruitment. This strategy was compared to the ARDSnet protocol[2]. The main hypothesis was that an EELV driven PEEP protocol, based on gender, height, age and body position, will result in higher PEEP levels and improved oxygenation and less lung strain as compared to the ARDSnet FiO_2/PEEP table.

Methods
Study population
The "Medical Ethical Committee Rotterdam" approved the study protocol (permit no. NL28396.078.09) and written informed consent was obtained from each patient's legal representative.
The present pilot study was designed as a randomized controlled trial. As this is a pilot study we were unable to perform a sample size calculation. Therefore we decided to study a total of 37 patients with a PaO_2/FiO_2 ratio <300mmHg, during mechanical ventilation. The inclusion criteria were: age ≥ 18 years, written informed consent, inclusion within 48 hours after intubation, and respiratory failure according to the New Berlin ARDS criteria (mild ARDS: PaO_2/FiO_2 200-300 mmHg; moderate ARDS: PaO_2/FiO_2 100-200 mmHg; severe ARDS: PaO_2/FiO_2 <100

mmHg)[14]. The exclusion criteria were: thoracic deformity, severe hemodynamic instability, inability to reliably measure EELV (e.g. due to air leak, pneumothorax, and emphysema), and severe airflow obstruction due to chronic obstructive pulmonary disease (COPD). COPD was defined as forced expiratory volume in one second or vital capacity below the predicted value minus two standard deviations (SD).

Study protocol and measurements

Patients were randomized to the control group or intervention group using the closed envelope method. In the control group, patients were ventilated following the PEEP/FiO_2 table according to the ARDS network trial[2]. In the intervention group PEEP was set to restore the predicted EELV with a range of 10%. In a previous publication we showed that EELV was reduced with 34% at 5 cm H_2O PEEP as compared to predicted sitting FRC values in normal lungs [12]. In the primary lung disorder group EELV was reduced to 35% of predicted EELV, but could be restored to 55% of predicted sitting FRC at 15 cm H_2O PEEP. If this 55% should be corrected for supine position, these patients should reach an EELV of 85-90% as compared to healthy patients. Therefore, we aimed to restore EELV with at least 90% of predicted EELV in supine position. The predicted EELV was calculated as follows[15]: "for Men: (2.34 x height [m] + 0.009 x age – 1.09) x 0.70" and "for Women: (2.24 x height [m] + 0.001 x age – 1.00) x 0.70". In this formula the EELV is already corrected for a 30% reduction due to the supine position[12;16;17]. According to the ARDS-network trial, the peak pressures were kept at ≤30 cm H_2O to avoid alveolar overdistention. PEEP was adjusted during the entire 48-hour study period. Inspiratory pressures were set to deliver a tidal volume of 6±2 ml/kg predicted body weight during pressure-controlled ventilation. This was also attempted during support ventilatory modes; however, the support level was reduced to a minimal value of 7 cm H_2O according to the resistance of the tube [18] and larger tidal volumes were then accepted. FiO_2 was set to keep PaO_2 between 8 and 11 kPa. If oxygenation was not adequate using 100% FiO_2 and lung recruitment maneuvers (RM), rescue therapy was allowed and the protocol was stopped.

All patients were ventilated with the Engström Carestation (GE Healthcare, Madison, WI, USA). The Engström Carestation has an integrated COVX module (GE Healthcare, Helsinki, Finland), which allows measurement of EELV[12]. EELV was measured using the simplified and modified nitrogen multiple-breath washout technique, devised by Olegard *et al.*[11]. In both groups, after a baseline EELV measurement, a recruitment maneuver was performed with a peak inspiratory pressure (PIP) of 50 cm H_2O and 20 cm H_2O PEEP. Thereafter, the protocol was set according to study allocation. Measurements of EELV, arterial blood gas analysis, and hemodynamic and respiratory variables were collected immediately after the RM, 24 and 48 h. In order to perform reliable EELV measurement the maximal PEEP level used was 20 cm H_2O. EELV measurements were performed after the volume of exhaled carbon dioxide (VCO_2) remained stable for at least 15 minutes.

For analysis purposes both groups were divided in a baseline EELV ≤1.5L and >1.5 L. This threshold is based on two previous studies[12;19], which showed that EELV in lung disorder patients was around 1.5 L and around 2.5 L in normal lungs.

Stress and strain is a concept to describe forces acting on lung tissue during mechanical ventilation[20]. Global strain describes the forces induced by tidal volume and application of PEEP[21] and can be divided in a static (PEEP volume) and dynamic (tidal volume) component[10]. Strain

can be calculated by dividing static or dynamic components by EELV or by FRC. However, in the present study we did not measure EELV at zero PEEP and thus FRC is unknown. Therefore we calculated dynamic strain based on EELV according to Gonzalez Lopez *et al.*[22] (formula 1).

$$\textit{Dynamic strain} = \frac{\textit{tidal volume}}{\textit{EELV}} \quad (1)$$

Statistical analysis

Statistical analyses were performed using SPSS 21 (IBM, Chicago, IL, USA). Unless otherwise specified all values are presented as mean ± SD. Differences in EELV, PaO_2/FiO_2 and PEEP between the groups were analyzed using the Mann Whitney *U*-test. Differences in EELV, PaO_2/FiO_2, PEEP and FiO_2 within each group were calculated using a mixed linear model. Main endpoints were the change in EELV and PaO_2/FiO_2 ratio at 24 h. All differences were considered statistically significant if $p < 0.05$.

Results

Baseline characteristics of the study group are presented in Table 1. Time between intubation and inclusion to the study was 23±12 and 28±21 hours (p=0.599) in the control and intervention group respectively. The control group contained 8 primary ARDS and 11 secondary ARDS patients, whereas in the intervention group this was 11 and 7 patients (p=0.375). All 37 patients were ventilated according to the protocol for at least 24 h and 29 completed the 48-h observation period. Reasons for dropout were: death (2 control patients and 1 intervention patient), nitric-oxide ventilation (2 control patients), extubation (2 control patients), and need of extracorporeal membrane oxygenation treatment (1 intervention patient). Despite randomization, at baseline EELV was significantly lower in the intervention group compared with controls (Table 1).

Characteristics of the study population

		Control group	Intervention group
N		19	18
Gender (M/F)		17/2	10/8
Age (years)		64±10	59±13
Height (cm)		176±7	173±10
Weight (kg)		83±15	89±27
PBW (kg)		71±7	68±10
Body mass index		27±5	30±7
Heart rate (BPM)		94±27	93±16
MAP (mmHg)		76±15	79±14
PaO_2/FiO_2 ratio (mmHg)		181±52	180±67
PEEP (cmH_2O)		11±4	11±2
Ppeak (cmH_2O)		22±6	24±6
Tve/PBW (mL/kg)		11±5	9±3
EELV (L)		2.1±0.7	1.5±0.4*
Predicted EELV (L)		2.5±0.2	2.3±0.4
PSV/PCV		14/5	14/4
Lung injury score		2.2±0.7	2.3±0.6
Time between intubation and inclusion (Hours)		23±12	28±21
ARDS origin	Primary	8	11
	Secondary	11	7
ARDS category (N)	Mild	6	6
	Moderate	12	9
	Sever	1	3

Table 1: Data are shown as mean ± SD. Number of patients (N); Predicted Body Weight (PBW); Beats per minute (BPM); Mean Arterial Pressure (MAP); End-Expiratory Lung Volume (EELV); Positive End-Expiratory Pressure (PEEP); Expiratory Tidal Volume (Tve); Pressure Support Ventilation (PSV); Pressure Controlled Ventilation (PCV); ARDS category: Mild= PaO_2/FiO_2: 200-300 mmHg; Moderate= PaO_2/FiO_2: 100-200 mmHg; Severe= PaO_2/FiO_2: <100 mmHg. * p <0.05

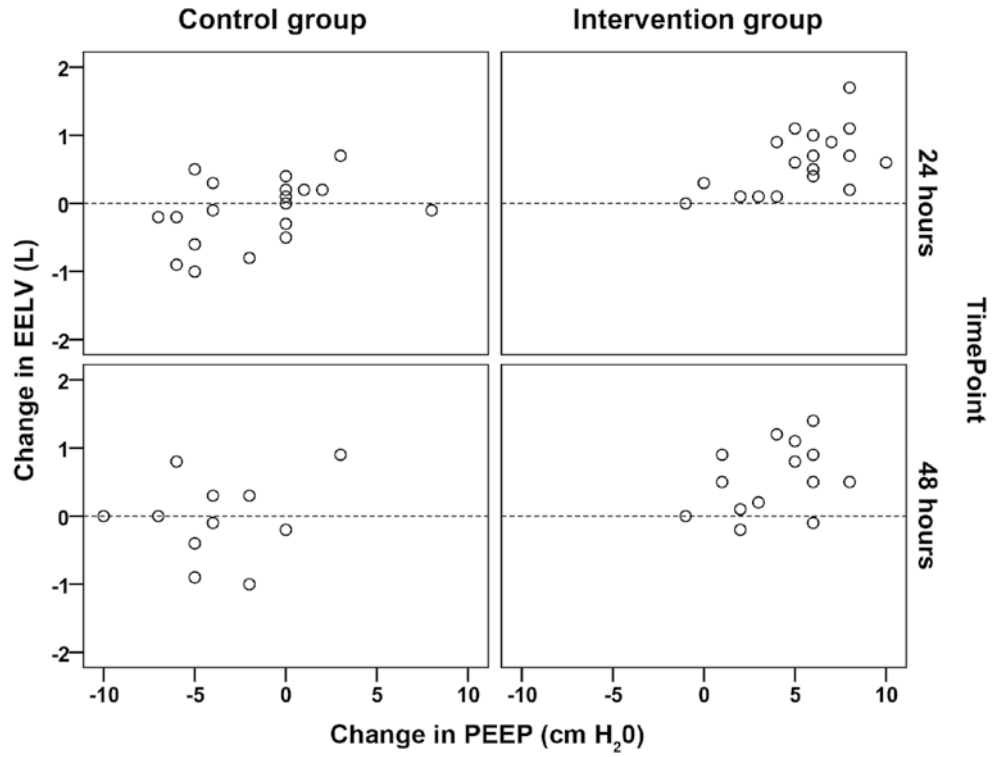

Fig. 1: Changes in End-Expiratory Lung Volume and Positive End-Expiratory Pressure for each group. Changes in EELV and PEEP are shown as compared to baseline. Data are shown as mean. End-Expiratory Lung Volume (EELV), Positive End-Expiratory Pressure (PEEP).

In the intervention group, PEEP had to be increased from 11±2 to 16±2 cm H_2O (p= <0.001) to achieve the predicted supine EELV (Table 2) and was 15±2 cm H_2O at 48 h. However, in 7 of the 18 patients we were unable to reach ≥90 % of the predicted supine EELV (Table 2). In controls, a PEEP of 10±3 cm H_2O had to be applied according to the PEEP/FiO_2 table and was reduced to 8±2 cm H_2O at the 48-h observation period. In the control group, at baseline, 8 of the 19 patients already had an EELV ≥ 90% of the predicted EELV (Table 2). The PaO_2/FiO_2 ratio remained unchanged in the control group but showed a significant increase in the intervention group (Table 2). Dynamic strain was significantly reduced after 24 and 48 hours in both study groups, but remained above a threshold of 0.27 during the entire study period (Table 2). Figure 1 shows the effect of PEEP change on EELV for each group at 24h and 48h. In the intervention group PEEP was increased in almost all patients resulting in an increase in EELV, whereas in the control group PEEP was decreased during the study period but EELV was stable.

Data on ventilatory parameters

		Baseline	RM	24 h	48 h
Number of patients	Control	19	19	19	13
	Intervention	18	18	18	16
PaO_2/FiO_2 (mmHg)	Control	181±52	185±69	176±77	191±82
	Intervention	180±67	189±55	272±114*	255±82*
EELV (L)	Control	85±28% (2.1±0.7)	81±23% (2.0±0.6)	81±23% (2.0±0.6)	90±24% (2.3±0.6)
	Intervention	64±20% (1.5±0.4)	72±17%* (1.6±0.4)	90±18%* (2.1±0.5)	91±16%* (2.1±0.4)
Number of patients reaching ≥90% of predicted supine EELV (N)	Control	8/19	8/19	6/19	7/13
	Intervention	4/18	3/18	11/18	11/16
PEEP (cm H_2O)	Control	11±4	10±3*	10±3*	8±2*
	Intervention	11±2	14±3*	16±2*	15±2*
FiO_2 (%)	Control	54±13	58±14	57±17	52±12
	Intervention	55±14	53±13	51±14	44±12*
Ppeak (cm H_2O)	Control	22±6	19±5*	20±6	17±5*
	Intervention	24±6	25±7	26±6	24±6
Tve/PBW (mL/kg)	Control	11±4	10±4	8±2*	8±2*
	Intervention	9±2	9±2	9±3	8±2
Dynamic strain	Control	0.41±0.24	0.38±0.20	0.30±0.10*	0.28±0.11*
	Intervention	0.47±0.18	0.38±0.15	0.30±0.90*	0.28±0.06*

Table 2: Data are shown as mean ± SD. Recruitment maneuver (RM); End-Expiratory Lung Volume (EELV); Positive End-Expiratory Pressure (PEEP); Fraction of inspired oxygen (FiO_2); Expiratory Tidal Volume (Tve); Predicted Body Weight (PBW). EELV is expressed as percentage of predicted values in supine position; *significant difference compared to baseline (p <0.05).

Figure 2 shows the change in VCO_2 and PEEP, as compared to baseline, after 24 hours of ventilation according to the study protocol for each group. In the intervention group the VCO_2 decreased although PEEP was increased. The control group showed an increase in VCO_2 despite PEEP was decreased in that group. However, the changes in VCO_2 were not statistically significant in any of the groups.

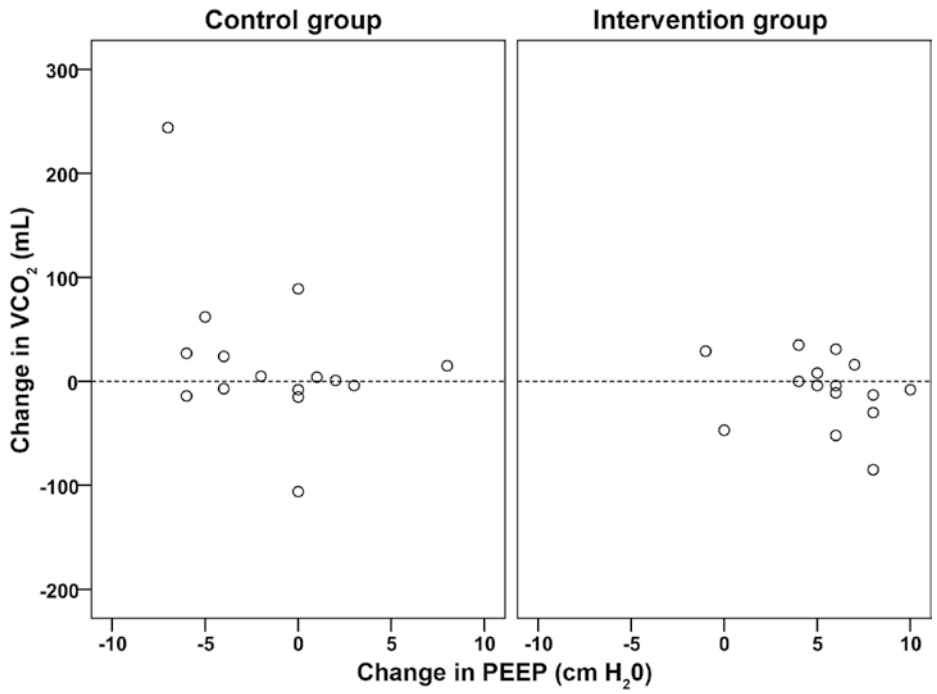

Fig. 2: Changes in volume of exhaled carbon dioxide and Positive End-Expiratory Pressure for each group after 24 hours. Changes in VCO_2 and PEEP are shown as compared to baseline. Data are shown as mean. Volume of exhaled carbon dioxide (VCO_2), Positive End-Expiratory Pressure (PEEP).

Afterwards, patients of both groups were divided into patients with a low baseline EELV (≤1.5 L) or higher baseline EELV (>1.5 L). In the low baseline EELV patients, the difference in EELV between the EELV driven protocol and the ARDS net table was 0.5 L at both time points (Table 3). However, the difference in PEEP between both groups was almost 10 cm H_2O at 48 h (Table 3). The difference in EELV increase was also 0.5L between the low and high baseline EELV patients in both groups at 48 h (Table 3). In controls, EELV decreased during the 2 days observation period in the EELV >1.5 L group whereas increased by 0.5±0.64 L in the EELV ≤1.5 L group, despite a decrease in PEEP (Table 3). Dynamic strain was significantly higher in the control group with a baseline EELV ≤1.5 L at baseline and after 24 hours (0.67±0.25 vs. 0.30±0.12 and 0.39±0.11 vs. 0.26±0.06) (Table 3). Dynamic strain only differed between intervention patients with a baseline EELV ≤1.5 L or >1.5 L at baseline. However, in patients with a baseline EELV >1.5L, dynamic strain was below 0.27 in the control group after 24 and 48h, whereas the intervention group reached this threshold only after 48h.

Changes in respiratory parameters related to baseline EELV

		Baseline	24 hours	48 Hours
Baseline EELV ≤1.5L				
Number of patients	**Control group**	6	6	4
	Intervention group	11	11	10
Delta EELV (L)	**Control group**	-	0.2±0.4$	0.5±0.6$
	Intervention group	-	0.7±0. 5#$	0.9±0.5$
Delta PEEP (cm H_2O)	**Control group**	-	1±5	-4±9
	Intervention group	-	6±2#$	5±2$
Dynamic strain	**Control group**	0.67±0.25	0.39±0.11$	0.43±0.12
	Intervention group	0.54±0.19	0.29±0.09$	0.28±0.06$
Baseline EELV >1.5L				
Number of patients	**Control group**	13	13	11
	Intervention group	7	7	6
Delta EELV (L)	**Control group**	-	-0.3±0.5	-0.2±0.5
	Intervention group	-	0.4±0.4#$	0.3±0.3*
Delta PEEP (cm H_2O)	**Control group**	-	-3±3*$	-3±3$
	Intervention group	-	4±3#$	3±3#$
Dynamic strain	**Control group**	0.30±0.12*	0.26±0.06*	0.26±0.10
	Intervention group	0.35±0.07*	0.30±0.10	0.27±0.07

Table 3: Data are shown as mean ± SD. Changes in Positive End-Expiratory Pressure (PEEP), End-Expiratory Lung Volume (EELV), and dynamic strain as compared to baseline are shown for both the control and intervention group. Both groups are divided into patients with a baseline EELV >1.5L or baseline EELV ≤1.5L. * Indicates significant differences according to patients from the same protocol, but with a baseline EELV ≤1.5L. Significant difference between the intervention group and control group, within the same baseline EELV group are indicated by #. Significant differences as compared to baseline are indicated by $. p <0.05 was considered to be statistically significant.

Discussion

In the present study, an EELV-guided PEEP protocol was able to restore EELV to predicted supine values and resulted in a significant increase of arterial oxygenation during the 48-h observation period. In controls, PEEP levels applied according the FiO_2-PEEP ARDSnetwork table could be lowered whereas EELV kept stable during the observation period.

A possible method to identify optimal PEEP is the measurement of functional residual capacity (FRC). FRC is the lung volume at the end of expiration during spontaneous breathing; therefore, it is more appropriate to speak of EELV during mechanical ventilation. FRC is normally measured in the sitting or standing position and is gender, height and age dependent. Ibanez *et al.*[17] showed in healthy volunteers that FRC decreased by 25% after changing their position from sitting to supine during spontaneous breathing. If one assumes that ventilation of a 'healthy' lung at a PEEP of 5 cm H_2O occurs approximately at the FRC level, we found a reduction of 34% of the predicted values in patients mechanically ventilated but without lung disorders[12]. This extra reduction of EELV (34% vs. 25%) is probably due to loss of muscle tension attributed to the use of sedation in patients in the intensive care unit. Therefore, in the present study, we used a 30% correction for predicted EELV in supine position. Thus, in controls, at baseline the EELV measurement of 85% of the predicted supine position means 55% of the predicted sitting position (Table 2).

Chiumello *et al.*[23] measured FRC (without PEEP) in patients with and without lung injury and found a FRC of 83±37% of expected supine FRC in surgical patients and 42±21% in ARDS patients. Dellamonica *et al.*[8] measured a FRC of 31±11% of predicted supine position in patients with ARDS, and only 5 of the 30 patients reached the predicted supine EELV after a recruitment and a PEEP of 15 cm H_2O. In an earlier study we measured EELV at three PEEP levels (5, 10 and 15 cm H_2O) in patients with and without lung disorders and found that EELV was only 34% and 65% of predicted sitting values in patients with moderate ARDS at a PEEP level of 5 and 10 cm H_2O, respectively[12]. In the present study, EELV was 34% of the predicted sitting value in the intervention group, but already 55% in controls at baseline, both ventilated at a PEEP level of around 11 cm H_2O.

Maisch *et al.*[24] performed an incremental and decremental PEEP trial values ranging from 0-15 PEEP, in 20 patients undergoing faciomaxillary surgery. EELV increased with each PEEP step and EELV was maximal at the highest PEEP level used. Therefore, it was concluded that EELV cannot be used as a parameter to describe the optimal PEEP, but could be used in combination with dynamic compliance or dead space. Thus, EELV should be measured to establish if the lung is atelectatic and, thereafter, a recruitment maneuver in combination with an increase in PEEP could be performed, followed by another EELV measurement. The improvement in EELV should be more than the volume of the product of the initial compliance times the PEEP increase in cm H_2O by recruitment, otherwise there is only dilatation of already extended airways and open alveoli. However, because most patients in the present study were ventilated by means of pressure support, compliance could not be adequately calculated due to the additional effort of the diaphragm. Therefore, we analyzed VCO_2 (Fig. 2) and found a decrease in VCO_2 in the intervention group and this suggests alveolar hyperinflation due to the high PEEP levels applied. Too high PEEP levels leads to a V/Q mismatch and thus lower amounts of exhaled CO_2. In the control group VCO_2 increased while lower PEEP levels were applied after 24 hours of ventilation according to the protocol (Fig. 2).

Protti *et al.*[9] recently showed that animals ventilated with a strain of 2.5 due to high tidal volumes increased mortality, whereas ventilation at 2.5 strain but mainly due to applied PEEP in combination with low tidal ventilation did not result in edema and the animals survived. This indicates that applying high PEEP is not necessarily harmful but EELV measurements should be performed regularly in order to identify recruiters from non-recruiters in avoiding hyperventilation. Gonzales Lopez *et al.*[22] calculated lung strain, due to tidal volume, based on EELV (=dynamic strain) in 22 patients (6 controls and 16 ALI) during volume-controlled ventilation, and found that a dynamic strain >0.27 significantly increased inflammatory cytokines as measured in bronchoalveolar lavaged fluid. In the present study, dynamic strain could be improved only in the EELV-guided PEEP protocol in patients with low lung volumes (EELV ≤1.5 L) whereas not in controls (Table 3).

This study has some limitations. Firstly, the maximum PEEP level that could be applied during the study was 20 cm H_2O, as the COVX-module has an upper pressure limit of 20 cm H_2O to reliably measure EELV[11]. Secondly, this study was designed to assess the feasibility of an EELV-guided PEEP protocol but, despite randomization, differences were present between the groups at baseline; the intervention group had more patients with severe ARDS and the lung injury score was slightly higher. However, because the present study was not designed to examine outcome measures, larger RCTs are required for this purpose and to decrease the probability of imbalances between the groups.

Conclusion

In this single-center RCT an EELV-guided PEEP strategy was able to restore EELV to predicted values in patients with moderate ARDS and resulted in significantly increased arterial oxygenation but at an expense of high PEEP levels. In patients with a reduced EELV, the EELV-guided PEEP protocol reduced dynamic strain significantly. An EELV driven protocol is recommended to optimize ventilatory settings in patients with moderate ARDS, but with a reduced EELV and therefore EELV measurement should be performed in advance.

References

1. Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Penuelas O, Abraira V, Raymondos K, Rios F, Nin N, Apezteguia C, Violi DA, Thille AW, Brochard L, Gonzalez M, Villagomez AJ, Hurtado J, Davies AR, Du B, Maggiore SM, Pelosi P, Soto L, Tomicic V, D'Empaire G, Matamis D, Abroug F, Moreno RP, Soares MA, Arabi Y, Sandi F, Jibaja M, Amin P, Koh Y, Kuiper MA, Bulow HH, Zeggwagh AA, Anzueto A: Evolution of mortality over time in patients receiving mechanical ventilation. Am.J Respir.Crit Care Med. 2013; 188: 220-30
2. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N.Engl.J.Med. 2000; 342: 1301-8
3. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 646-55

4. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 637-45
5. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P: Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann. Intern.Med. 2009; 151: 566-76
6. Blankman P, Gommers D: Lung monitoring at the bedside in mechanically ventilated patients. Curr.Opin.Crit Care 2012; 18: 261-6
7. Slutsky AS, Tremblay LN: Multiple system organ failure. Is mechanical ventilation a contributing factor? Am.J.Respir.Crit Care Med. 1998; 157: 1721-5
8. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard JC, Diehl JL, Mancebo J, Rouby JJ, Lu Q, Bernardin G, Brochard L: PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intensive Care Med. 2011; 37: 1595-604
9. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: any safe threshold? Am.J.Respir.Crit Care Med. 2011; 183: 1354-62
10. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L: Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?. Crit Care Med. 2013; 41: 1046-55
11. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O: Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth. Analg. 2005; 101: 206-12, table
12. Bikker IG, van Bommel J, Reis MD, Bakker J, Gommers D: End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. Crit Care 2008; 12: R145
13. Bikker IG, Leonhardt S, Bakker J, Gommers D: Lung volume calculated from electrical impedance tomography in ICU patients at different PEEP levels. Intensive Care Med. 2009; 35: 1362-7
14. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS: Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307: 2526-33
15. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur.Respir.J.Suppl 1993; 16: 5-40
16. Hedenstierna G, Edmark L: The effects of anesthesia and muscle paralysis on the respiratory system. Intensive Care Med. 2005; 31: 1327-35

17. Ibanez J, Raurich JM: Normal values of functional residual capacity in the sitting and supine positions. Intensive Care Med. 1982; 8: 173-7
18. Brochard L, Rauss A, Benito S, Conti G, Mancebo J, Rekik N, Gasparetto A, Lemaire F: Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. Am.J.Respir.Crit Care Med. 1994; 150: 896-903
19. Neumann P, Zinserling J, Haase C, Sydow M, Burchardi H: Evaluation of respiratory inductive plethysmography in controlled ventilation: measurement of tidal volume and PEEP-induced changes of end-expiratory lung volume. Chest 1998; 113: 443-51
20. Wilson TA: Solid mechanics. American Physiological Society., Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Baltimore, MD Waverly, 1986, pp 35-9
21. Gattinoni L, Carlesso E, Caironi P: Stress and strain within the lung. Curr.Opin.Crit Care 2012; 18: 42-7
22. Gonzalez-Lopez A, Garcia-Prieto E, Batalla-Solis E, Amado-Rodriguez L, Avello N, Blanch L, Albaiceta GM: Lung strain and biological response in mechanically ventilated patients. Intensive Care Med. 2012; 38: 240-7
23. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am.J.Respir.Crit Care Med. 2008; 178: 346-55
24. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, Bohm SH: Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth.Analg. 2008; 106: 175-8

CHAPTER 4

Lung stress and strain calculations in mechanically-ventilated patients in the intensive care unit

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Abstract

Background

Stress and strain are parameters to describe respiratory mechanics during mechanical ventilation. Calculations of stress requires invasive and difficult to perform esophageal pressure measurements. We hypothesized: can lung stress be reliably calculated based on non-invasive lung volume measurements, during a decremental PEEP trial in mechanically-ventilated patients with different diseases?

Methods

Data of 26 pressure-controlled ventilated patients admitted to the ICU with different lung conditions, were retrospectively analyzed: 11 Coronary-Artery Bypass Graft (CABG); 9 neurology; 6 lung disorders. During a decremental PEEP trial (from 15 to 0 cmH_2O in 3 steps) End-Expiratory Lung Volume (EELV) measurements were performed at each PEEP step, without interruption of mechanical ventilation. Strain, specific elastance and stress were calculated for each PEEP level. Elastance was calculated as delta PEEP divided by delta PEEP volume, whereas, specific elastance is elastance times FRC. Stress was calculated as specific elastance times strain. Global strain was divided in dynamic (tidal volume) and static (PEEP) strain.

Results

Strain calculations based on FRC showed mainly changes in static component, whereas calculations based on EELV showed changes in both the static and dynamic component of strain. Stress calculated from EELV measurements was 24.0±2.7 and 13.1±3.8 cm H_2O in the lung disorder group at 15 and 5 cm H_2O PEEP. For the normal lungs, the stress values were 19.2±3.2 and 10.9±3.3 cm H_2O, respectively. These values are comparable to earlier publications. Specific elastance calculations were comparable in patients with neurologic and lung disorders and lower in the CABG group due to recruitment in this latter group.

Conclusion

Stress and strain can reliably be calculated at the bedside based on non-invasive EELV measurements during a decremental PEEP trial in patients with different diseases.

Introduction

In the field of engineering, stress and strain are frequently used terms to describe the effect of external force acting on a subject. Stress is defined as the internal distribution of forces per unit of area of a specific material by an external force. The resulting change in shape of the material by the stress applied is called strain. In the 1960s, the terms stress and strain were introduced by pulmonary physiologists to describe respiratory mechanics[1]. Lung stress describes the distribution of forces due to PEEP and tidal volume, whereas strain describes the resulting change in lung volume.

Calculations of strain require measurements of functional residual capacity (FRC). Traditional FRC measurements needed tracer gases, and expensive and bulky equipment[2;3].Olegard *et al.*[4] devised the nitrogen multiple breath wash-out (NMBW) technique to measure FRC at the bedside without interruption of mechanical ventilation and additional tracer gases. The NMBW method is integrated in a standard ICU-ventilator and uses a step change in fraction of inspired oxygen (FiO_2) to calculate FRC. However, lung volume is influenced by the use of PEEP and therefore it is better to speak of EELV[5].

For the calculation of stress, the specific elastance should be known or transpulmonary pressures measurements are required. Stenqvist et al. [6] recently developed a technique to calculate elastance without the use of transpulmonary pressure measurements by using EELV measurements. They showed[6] that calculating elastance from EELV measurements correlates very well with elastance calculated from esophageal pressure measurements (r^2=0.96) in patients with moderate or severe respiratory failure. For patients with pulmonary and extrapulmonary acute respiratory distress syndrome (ARDS), this comparison resulted in a r^2=0.99. With this knowledge, the elastance can be calculated by dividing the change in PEEP by the change in PEEP volume. However, specific elastance is the elastance normalized for FRC.

The hypothesis of the present study was: Can lung stress be reliably calculated based on non-invasive lung volume measurements, during a decremental PEEP trial in mechanically ventilated patients with different diseases? Therefore, FRC (EELV at ZEEP) and EELV were measured during a decremental PEEP trial, in patients with different lung conditions, and stress and strain were calculated at each PEEP step.

Materials and methods

Study population

Retrospective lung volume data were collected from 26 pressure-controlled mechanically-ventilated patients admitted to the intensive care unit (ICU). The data of the included patients have been used earlier and the results are described in two earlier publications[5;7]. Patients were considered eligible for inclusion in this study if lung volume data at zero PEEP (ZEEP) were present, and if they were mechanically-ventilated for <48h at inclusion to the original study. The local Medical Ethics committee (Medical Ethical Committee Rotterdam. Dr. Molewaterplein 50, 3015 GE Rotterdam, The Netherlands.) approved the study protocol (02 July 2009; permit nr. MEC-2009-222) and informed consent was obtained from the patient or a legal representative. The exclusion criteria were severe hemodynamic instability (arterial pressure below 60 mmHg, active bleeding, or adrenergic agents other than dobutamin required to maintain blood pressure or output), pneumothorax, thoracic deformations, and severe airflow obstruction due to chronic obstructive pulmonary disease (COPD). COPD was defined as forced expiratory volume in 1 s or vital capacity below predicted value minus two standard deviations.

Study protocol and measurements

All patients received pressure-controlled ventilation (PCV) (Engström Carestation, GE Healthcare, Madison, WI, USA) as this is the standard of care in our hospital. The inspiratory pressure above PEEP (Pinsp) was tailored to reach a tidal volume of 8±2 ml/kg predicted body weight, and remained unchanged during the entire PEEP trial. In addition, FiO_2 was set to achieve a PaO_2 of 8-12 kPa. First baseline measurements were performed, after which a recruitment maneuver (RM) was performed using a peak inspiratory pressure (PIP) of 40 cm H_2O with 20 cm H_2O PEEP for 30-40 seconds, during which the respiratory cycle continued, in order to continue gas exchange. A PEEP of 15 cm H_2O was applied for 15 minutes to achieve a steady-state situation, by means of a stable carbon-dioxide volume (VCO_2) signal for at least 10 min. Steady-state was based on VCO_2 as this is the main parameter in the formula to calculate EELV[4], which is integrated in the Engström Care station. The first PEEP level was set to 15 cm H_2O in order to avoid peak inspiratory pressures above 30 cm H_2O. Thereafter, a decremental PEEP-trial was performed from 15 to 0 cm H_2O PEEP in steps of 5 cm H_2O. Each PEEP level was applied for 10-20 min, dependent on the hemodynamics and respiratory stability of patient.

Calculation of EELV, FRC, PEEP volume, strain, specific elastance, and stress

We measured EELV using the NMBW technique devised by Olegard et al.[4] The Engström Carestation ventilator is equipped with an integrated COVX-module, which delivers data required to calculate EELV. EELV measurements require a step change in FiO_2. EELV is automatically measured twice (wash-out and wash-in) within one procedure, using a FiO_2 step change of 0.2. At each PEEP level, the EELV measurements were repeated. We considered the EELV measurement at ZEEP as FRC of the lungs.

Strain describes the relation between end-inspiratory volume (i.e. tidal volume + PEEP volume) and FRC, and is calculated using formula [1][8]:

$$Strain_{global} = \frac{V_T + V_{PEEP}}{FRC} \quad [1]$$

(V_T = tidal volume; VPEEP= difference between EELV and FRC; FRC= EELV measured at ZEEP)

Protti *et al.*[9], introduced the terms static strain and dynamic strain. Lung tissue deformation due to application of PEEP is called static strain, as the energy is only once applied to the lungs. Tidal ventilation is a dynamic process, as the energy is cyclically applied to the lungs. Therefore, lung deformation due to tidal volume is called dynamic strain[9]. Static strain and dynamic strain are calculated according to the following formulas [2 and 3][9]:

$$Strain_{static} = \frac{V_{PEEP}}{FRC} \quad [2]$$

$$Strain_{dynamic} = \frac{V_T}{FRC} \quad [3]$$

(VPEEP= difference between EELV and FRC; VT= tidal volume; FRC= EELV measured at ZEEP)

Stress is calculated using the following formula [10]:

$$Stress = Specific\ elastance \times Strain \quad [4]$$

Elastance was calculated by the formula as proposed by Stenqvist et al.[6]:

$$Elastance = \frac{\Delta PEEP}{\Delta VPEEP} \quad [5]$$

$$Specific\ elastance = elastance \times FRC \quad [6]$$

(V_{PEEP} = *VPEEP= difference between EELV and FRC*)

For stress calculations, both the strain and specific elastance at a particular PEEP level were used. For example, to calculate stress at a PEEP level of 15 cm H_2O the strain and specific elastance at that PEEP level were used.

Statistics

Statistical analyses were carried out using SPSS 21 (IBM, Chicago, IL, USA). Unless specified otherwise, the values are stated as mean ± SD. We screened the distribution of our data using the Kolmogorov-Smirnov-test for normal distribution and the Brown-Forsythe-test for homoscedasticity. If the data appeared to be distributed normally, we applied ANOVA. Otherwise, the analysis was carried out using the independent samples Kruskal-Wallis test. A linear regression model was performed to compare the stress measured by Chiumello et al. [10] with our stress calculations (Graphpad Prism version 5.0, Graphpad Software Inc., San Diego, USA). For all comparisons $p < 0.05$ was considered to be significant.

Results

The included patients are divided into three groups based on the diseases (Table 1): coronary-artery bypass graft (CABG), neurology patients, and lung disorder patients.

Disease characterization of the patient groups

	CABG	Neurology	Lung disorders
CABG	11		
SAH		7	
Neuro-trauma		2	
Pneumonia			5
Abdominal sepsis			1
N	11	9	6

Table 1: Coronary artery bypass graft (CABG); sub-arachnoidal haemorrhage (SAH); number of patients (N).

Patient characteristics are shown in Table 2. The patients were ventilated with a constant pressure amplitude or driving pressure (CABG: 10±2 cm H_2O; neurology: 13±4 cm H_2O; lung disorders: 15±5 cm H_2O) during the entire PEEP trial. The PaO_2/FiO_2 ratio was significantly lower in the lung disorder group compared to both other groups, whereas EELV measured at 5 cm H_2O of PEEP were comparable between the groups. At ZEEP, the FiO_2 was increased in three CABG patients to maintain a PaO_2 between 8 and 12 kPa. The measured baseline EELV was presented as a percentage of predicted supine FRC to estimate the amount of collapsed lung tissue (Table 2), and no significant differences were found between the groups (Table 2). Changes in respiratory parameters during the decremental PEEP trial for each group are shown in Table 3. There were no significant differences in tidal volume during the PEEP trial for each group, except at ZEEP in the CABG and lung disorders group. At 5 and 0 cm H_2O of PEEP, EELV significantly decreased in each group (Table 3). Only in the CABG group, a significant decrease in PaO_2/FiO_2 was seen at 5 and 0 cm H_2O PEEP (Table 3).
Figure 1 represents the global, static, and dynamic strain for each PEEP level based on FRC. The global strain was above 2 only in the CABG group at a PEEP of 15 cm H_2O (Fig. 1). At the three PEEP levels (15, 10, and 5 cm H_2O), global strain in the lung disorder group was significantly higher compared to neurology group (Fig. 1), but global strain in the CABG group was significantly higher compared to the lung disorder group (Fig. 1). Dynamic strain did not change significantly in any of the groups during the decremental PEEP trial, except at ZEEP in the CABG group due to collapse (Fig. 1).

Baseline demographics

	CABG	Neurology	Lung disorders
N	11	9	6
Age (years)	70 ± 10	54 ± 18[a]	63 ± 11
Male : Female (n)	7 : 4	6 : 3	5 : 1
Heart rate (BPM)	75 ± 15	78 ± 10	84 ± 32
Weight (kg)	78 ± 13	75 ± 10	77 ± 17
PBW (kg)	66 ± 9	71 ± 10	71 ± 8
Height (cm)	172 ± 9	177 ± 9	176 ± 7
BMI	27 ± 4	24 ± 3	25 ± 5
Respiratory rate (BPM)	15 ± 1	16 ± 4	16 ± 2
PEEP (cmH_2O)	5	5	5
PIP (cmH_2O)	15 ± 2	18 ± 4	20 ± 5[b]
V_{Te} (mL)	559 ± 89	518 ± 46	728 ± 158[b,c]
V_T/PBW (mL/kg)	8.5 ± 1.1	7.2 ± 1.2[a]	10.3 ± 1.8[c]
EELV (L)	2.49 ± 0.80	2.29 ± 0.49	2.12 ± 0.64
EELV of predicted supine FRC (%)	69.1 ± 28.3	79.4 ± 28.5	64.7 ± 22.6
LIS	1.4 ± 0.4	1.2 ± 1.0	1.8 ± 0.8
PaO_2/FiO_2 ratio (kPa)	40 ± 17	49 ± 4	28 ± 5[b,c]
FiO_2 (%)	41 ± 2	37 ± 5[a]	52 ± 13[bc]

Table 2: Coronary Artery Bypass Graft (CAB); Predicted body weight (PBW); Body Mass Index (BMI); Positive End-Expiratory Pressure (PEEP); Peak Inspiratory Pressure (PIP); expiratory tidal volume (V_{Te}); End-Expiratory Lung Volume (EELV); Functional Residual Capacity (FRC); Lung Injury Score (LIS); Positive End-Expiratory Pressure (PEEP). Fraction of inspired oxygen (FiO_2). The results are shown as mean ± SD unless otherwise specified. Significant differences are marked as: a)= CABG vs. neurology; b)= CABG vs. Lung disorders; c)= neurology vs. Lung disorders. Differences are considered to be significant if $p < 0.05$.

Specific elastance was calculated for each PEEP level and is shown in figure 2. The lung disorder group and neurology group had comparable specific elastance values, whereas specific elastance was significantly lower in the CABG group at all PEEP levels (Fig. 2).
The stress is shown in figure 3. At PEEP of 15 cm H_2O, the global stress decreased with each PEEP step in all groups (Fig. 3). Global stress was significantly lower in the CABG group as compared to the neurology and lung disorders groups at all PEEP levels.
In addition, we divided the CABG group in patients with and without collapse-prone lungs based on PaO_2/FiO_2 ratio <40 or >40 kPa (Fig. 4). In patients with a PaO_2/FiO_2 ratio <40 kPa (collapse-prone lungs), global strain was significantly higher in CABG patients with a PaO_2/FiO_2 ratio <40 kPa as compared to CABG patients with P/F ratio >40 kPa (Fig. 4).
In addition, we calculated the global, static, and dynamic strain for each PEEP level based on EELV to diminish the effect of recruitment (Fig. 5). In contrast to strain calculations based on FRC (Fig. 1), the dynamic strain based on EELV increased at lower PEEP levels (Fig. 5). Dynamic strain was significantly higher in the lung disorder group compared to both other groups at the used PEEP levels (Fig. 5)

Respiratory parameter during the decremental PEEP trial

PEEP (cm H_2O)	15	10	5	0
Peak inspiratory pressure (cm H_2O)				
CABG	25±2	20±2*	15±2*	10±2*
Neurology	28±4	22±4*	18±4*	14±5*
Lung disorders	32±4	25±5*	20±5*	15±5*
Delta inspiratory pressure (cm H_2O)				
CABG	10±2	10±2	10±2	10±2
Neurology	13±4	12±4	13±4	14±5
Lung disorders	17±4	15±5	15±5	16±4
Expiratory Tidal volume (ml)				
CABG	587±117	613±102	559±89	397±91*
Neurology	509±50	511±53	518±46	509±60
Lung disorders	674±120	701±158	728±158	579±79*
Respiratory elastance (cm H_2O/L)				
CABG	17.5±2.6	16.7±2.2	18.2±2.6	26.2±5.1*
Neurology	26.3±6.9	24.5±7.4	24.8±8.0	27.7±9.1
Lung disorders	26.1±9.5	21.3±8.3	21.0±9.7	26.5±11.5
EELV (L)				
CABG	3.97±0.70	3.35±0.86	2.49±0.80	1.58±0.63*
Neurology	2.91±0.49	2.68±0.47	2.29±0.49	1.83±0.53*
Lung disorders	2.72±0.89	2.52±0.79	2.12±0.64	1.57±0.48*
PEEP-volume (L)				
CABG	2.39±0.42	1.77±0.45*	0.91±0.25*	-
Neurology	1.08±0.49	0.84±0.32	0.46±0.22*	-
Lung disorders	1.20±0.37	0.95±0.43	0.55±0.30*	-
PaO_2/FiO_2 (kPa)				
CABG	63±14	61±14	45±14*	27±10*
Neurology	55±10	55±11	54±12	49±13
Lung disorders	37±15	34±11	29±4	24±3
FiO_2 (%)				
CABG	41±2	41±2	41±2	45±8*
Neurology	37±5	37±5	37±5	36±4
Lung disorders	52±13	52±13	52±13	50±6*

Table 3: Respiratory elastance was calculated as the ratio of delta inspiratory pressure and expiratory tidal volume. End-Expiratory Lung Volume (EELV) at 0 cm H_2O PEEP was considered as functional residual capacity. Fraction of inspired oxygen (FiO_2). Significant differences as compared to 15 cm H_2O PEEP are indicated by *. p <0.05 was considered to be statistically significant.

Discussion

Specific elastance and strain can easily be calculated at the bedside using the non-invasive FRC measurements technique without interruption of mechanical ventilation, and from these results stress can be calculated without the measurement of esophagus pressure. Calculations of stress and strain based on non-invasive lung volume measurements can be reliably performed during a decremental PEEP trial. Strain has low values in low collapse-prone lungs, whereas high values in high collapse-prone lungs after increasing PEEP. This indicates that recruitability of lung tissue influences strain more compared to collapse of lung tissue.

Strain calculated during the decremental PEEP trial based on FRC.

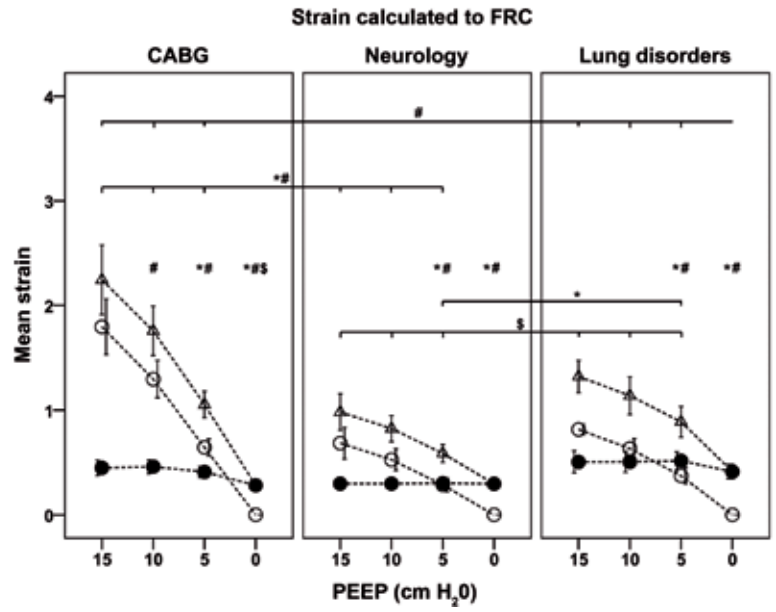

Figure 1: Calculated strain during the decremental PEEP trial. Data are shown as mean ± SE. Open triangles: global strain; open circles: static strain (PEEP); closed circles: dynamic strain (tidal volume); dashed lines: interpolation lines. Differences are considered to be significant if p <0.05. * indicates significant changes in global strain; # indicates significant changes in static strain; *$* indicates significant changes in dynamic strain.

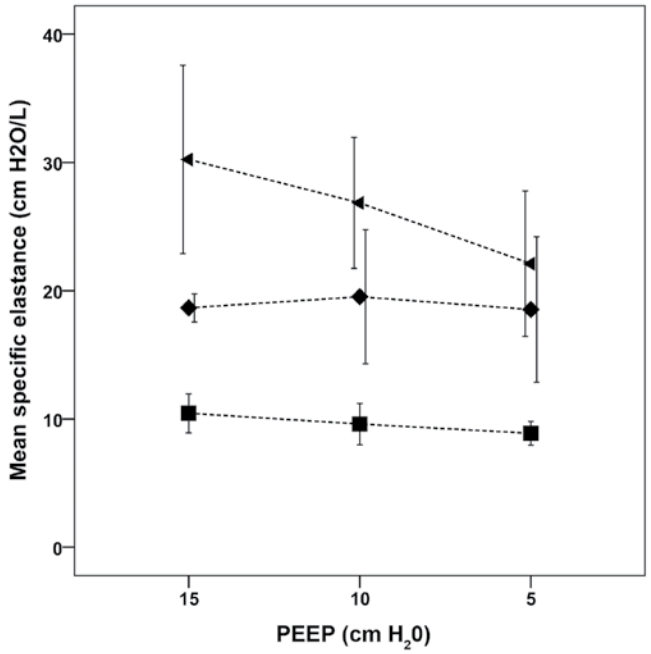

Figure 2: Data are shown as mean ± SE. Solid squares: CABG group; Solid arrow: neurology group; Solid diamond: lung disorders group.

During mechanical ventilation, external energy is applied to the lung due to tidal ventilation and application of PEEP. This energy is applied to the lung parenchyma creating lung tissue damage, known as ventilator-induced lung injury (VILI). To describe the stress raisers on lung parenchyma, the parameters stress, specific elastance, and strain are introduced (stress = specific elastance x strain). Chiumello *et al.*[10] calculated lung stress and strain in 80 volume-controlled ventilated patients with and without lung disorders, at four different tidal volumes (6, 8, 10, and 12 mL/kg) and during two different PEEP levels (5 and 15 cm H_2O). EELV was measured using a balloon with helium, and mechanical ventilation was interrupted during each measurement. Stress was calculated based on esophageal pressure measurements. From both results, specific elastance was calculated and was around 13.5 cm H_2O/l for all patients with and without lung disorders and did not change with tidal volume and PEEP. Our results of specific elastance values were comparable for both the lung disorder and neurology group, whereas not for the CABG group in which specific elastance was around 50% due to recruitability (Fig. 2). Dellamonica *et al.*[11] calculated lung strain in 30 volume-controlled ventilated patients and found that the static strain was higher in patients with high collapse prone lungs compared to low recruiters between high and low PEEP. This was also seen in the present study in which global strain was the highest in the CABG patients with a P/F ratio <40 kPa (Fig. 4).

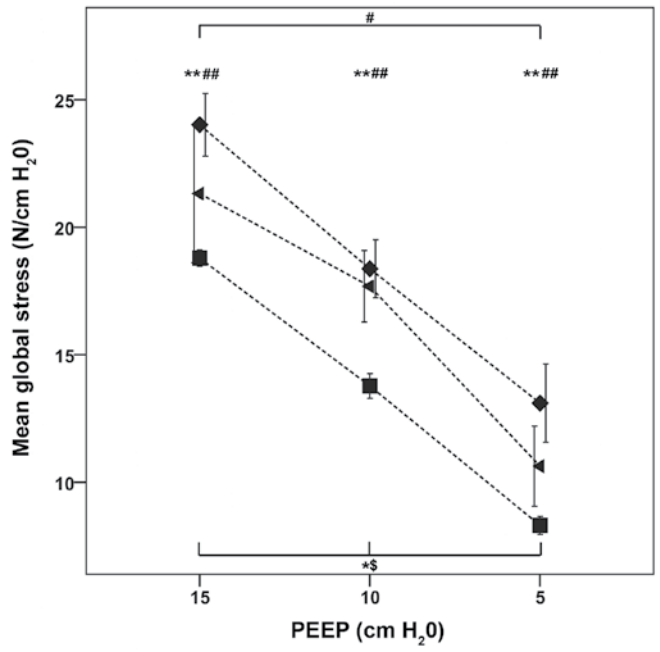

Figure 3: Calculated stress for three groups of patients with different lung conditions. Data are shown as mean ± SE. In both the CABG and lung disorders groups, global stress significantly decreased with each PEEP step, as indicated by * and $ respectively. In the neurology group global stress only significantly decreased at 5 cm H_2O PEEP as compared to 15 cm H_2O PEEP, as indicated by #. At all PEEP levels the global stress was significantly lower in the CABG group as compared to the neurology and lung disorders groups (indicated by ** and ## respectively). Solid squares: CABG group; Solid arrow: neurology group; Solid diamond: lung disorders group. Data was considered to be significantly different if $p < 0.05$.

Gonzalez-Lopez *et al.*[12] calculated lung strain during volume-controlled mechanical ventilation in 22 patients (16 ALI, 6 controls), without changing ventilator settings. They used EELV instead of FRC and then dynamic strain is only calculated. It was shown that in patients with ALI and a strain > 0.27 resulted in significantly more inflammatory cytokines, measured in bronchoalveolar lavage fluid (BALF). In the present study, patients with lung disorders had a dynamic strain of > 0.27 at all used PEEP levels, but in the CABG, and neurology group dynamic strain was > 0.27 only at ZEEP (Fig. 5). This means that tidal volume is harmful at ZEEP due to the risk of hyperinflation in an atelectatic lung.

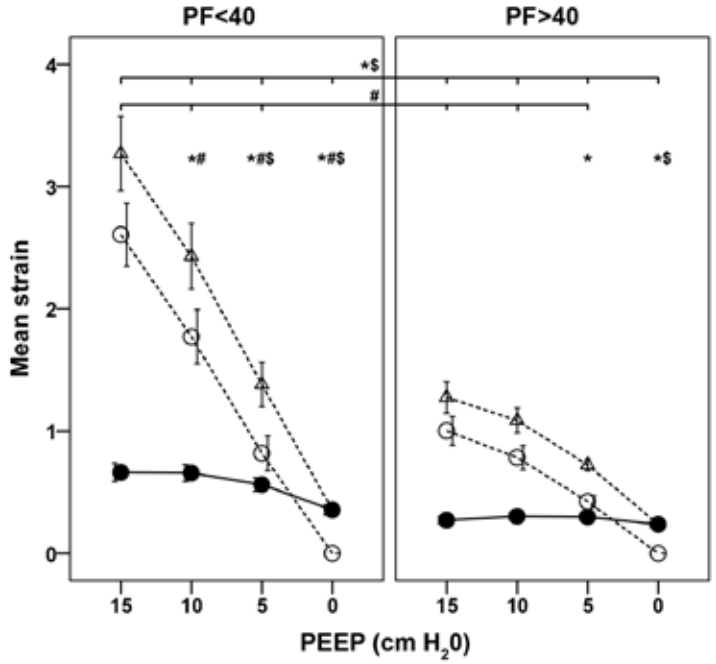

Figure 4: Data are shown as mean ± SE. strain is calculated for Coronary Artery Bypass Graft (CABG) patients with a PaO_2/FiO_2 ratio smaller or larger than 40 kPa. Open triangles: global stress or strain; open circles: static stress or strain (PEEP); closed circles: dynamic stress or strain (tidal volume); dashed lines: interpolation lines. All differences are considered to be significant if $p < 0.05$. *) Indicates significant differences in global strain; #) indicates significant differences in static strain; $) indicates significant differences in dynamic strain.

Transpulmonary pressure is considered as the main factor of ventilator-induced lung injury. However, measurements of transpulmonary pressure using an esophageal pressure balloon are challenging and therefore a less used technique in daily practice. Therefore, there is a need for an easy to use method to calculate transpulmonary pressure. Recently, Stenqvist *et al.*[6] proposed a method to calculate transpulmonary pressures based on non-invasive EELV measurements, during an incremental PEEP trial. They showed in 13 ex-vivo pigs that the change in lung volume could be predicted from the change in PEEP divided by lung elastance calculated from esophageal pressure measurements. Therefore, specific elastance could be calculated by multiplying elastance by FRC, in which elastance is calculated as delta PEEP divided by delta EELV. Recently Lundin *et al.*[13] confirmed this method in 12 ARDS patients. They calculated elastance from esophageal pressure measurements and the Stenqvist method, and found a close correlation (r^2=0.80).

In the study of Chiumello *et al.*[10], it was shown that stress values, based on esophagus pressure measurements, were 21.8±5.4 and 13.3±3.7 cm H_2O at respectively 15 and 5 cm H_2O of PEEP and tidal volume of 10 ml. In the present study, we found 24.0±2.7 and 13.1±3.8 cm H_2O in the

lung disorder group at the same PEEP and tidal volume. In addition, Chiumello *et al.*[10] showed that for patients with normal lungs, the stress values were 19.2±3.2 and 10.9±3.3 cm H_2O at respectively 15 and 5 cm H_2O of PEEP and tidal volume of 8 ml, whereas we found similar values: 21.3±8.1 and 10.6±4.7 cm H_2O at the same PEEP and tidal volume. It is shown that the validity of esophageal pressure measurements as a surrogate for transpulmonary pressure measurements is limited[14-16]. Recently, Chiumello *et al.*[17] compared two different methods to define transpulmonary pressures: directly measured via absolute esophagus pressure and indirectly measured via the ratio of lung elastance and respiratory system elastance. They found that the directly measured esophageal pressure by an esophageal balloon were highly variable between patients and was not related to lung weight, chest wall elastance, and amount of lung collapse. It was concluded that the elastance derived method to calculate esophageal pressure should be preferred because no disconnection from the ventilator is required and thereby avoiding PEEP loss and derecruitment.

Strain calculated during the decremental PEEP trial based on EELV.

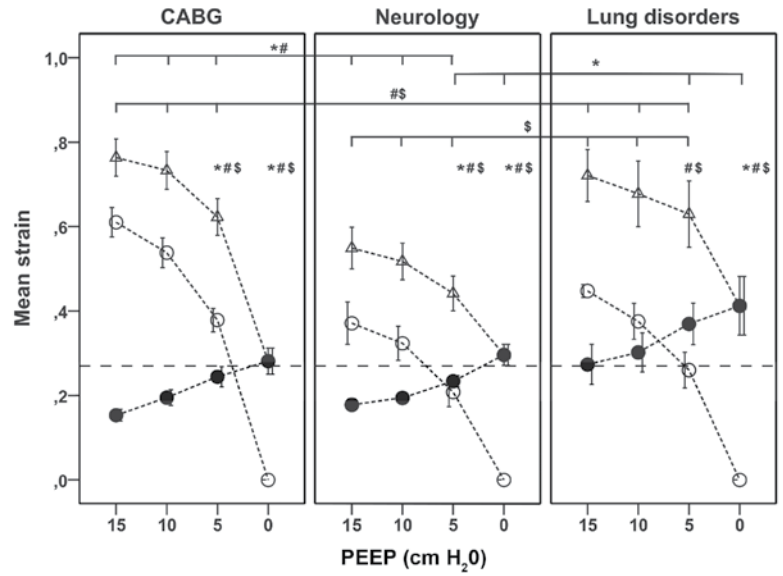

Figure 5: Calculated strain, based on EELV, during the decremental PEEP trial. Data are shown as mean ± SE. The horizontal wide-dashed line represents a threshold strain of 0.27 according the suggestion of Gonzalez-Lopez et al. 12. Open triangles: global strain; open circles: static strain (PEEP); closed circles: dynamic strain (tidal volume); dashed lines: interpolation lines. Differences are considered to be significant if $p < 0.05$. *) Indicates significant changes in global strain; #) indicates significant changes in static strain; $) indicates significant changes in dynamic strain.

Do the stress and strain calculations have additional information at the bedside for the clinicians to guide ventilation strategies? Stress increases linearly with the PEEP and the highest values were around 20-25 cmH_2O in the present study. It has been demonstrated that transpulmonary pressures of above 25 cmH_2O are injurious but this is different[18]. Transpulmonary pressure increases during spontaneous breathing due to negative pleural pressure whereas decreases in patients with stiff chest wall or low lung compliance as seen in patients with ARDS. Therefore, stress calculations do not have additional information compared to transpulmonary pressure. However, the strain calculations based on EELV might be a useful parameter at the bedside to assess ventilator settings. The studies of Protti *et al.*[9;19] clearly demonstrated that tidal volume is harmful to the lungs, whereas PEEP worked protective. In the present study, we found that dynamic strain (Vt/EELV) calculated on EELV corrects the strain for alveolar recruitment but resulted also in higher values at lower PEEP levels although the inspiratory pressure were the same. The highest values were seen during ZEEP and this is of special interest. During ZEEP, the lung could be collapsed and less alveoli are available to receive tidal ventilation, whereas after recruitment in combination with higher levels of PEEP, higher tidal volume can be applied without damaging the lung. Therefore, we believe that dynamic strain calculations based on EELV could be useful at the bedside but outcome studies are needed to investigate the roll of a strain-guided ventilation protocol.

As we analyzed data of lung volume measurements from earlier studies with a different research question, the study design has some limitations: Firstly, we did not measure esophagus pressures in the present study and compared our data with previous published data[6;13]. Secondly, Stenqvist et al. calculated specific elastance [6] during an incremental PEEP trial, whereas we performed a decremental PEEP trial. In a recent experimental study[20], we performed an incremental and decremental PEEP trial in healthy and ARDS lungs. EELV at ZEEP did not significantly differ between both PEEP trials for both healthy and ARDS lungs. Therefore, in our opinion specific elastance, stress and strain can be calculated reliably during a decremental PEEP trial. Thirdly, the lung injury group is a relative small group of patients in this study. Finally, we did not use CT or EIT to assess ventilation homogeneity. However, we believe that all techniques used to gather all the information are reliable and suitable for the research goal of the present study.

In conclusion, calculations of specific lung elastance, stress and strain based on non-invasive lung volume measurements can be reliably done and also during a decremental PEEP trial, in mechanically ventilated patients with different lung conditions. In addition, stress and strain calculations based on EELV should be preferred to correct for lung volume recruitment.

References

1. Wilson TA: Solid mechanics. Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Baltimore, MD Waverly: American Physiological Society 1986: 35-9
2. Hewlett AM, Hulands GH, Nunn JF, Minty KB: Functional residual capacity during anaesthesia. I: Methodology Br J Anaesth 1974; 46: 479-85

3. Ibanez J, Raurich JM, Moris SG: A simple method for measuring the effect of PEEP on functional residual capacity during mechanical ventilation. Crit Care Med 1982; 10: 332-4
4. Olegard C, Sondergaard S, Houltz E, Lundin S, Stenqvist O: Estimation of functional residual capacity at the bedside using standard monitoring equipment: a modified nitrogen washout/washin technique requiring a small change of the inspired oxygen fraction. Anesth Analg 2005; 101: 206-12, table
5. Bikker IG, van Bommel J, Reis MD, Bakker J, Gommers D: End-expiratory lung volume during mechanical ventilation: a comparison with reference values and the effect of positive end-expiratory pressure in intensive care unit patients with different lung conditions. Crit Care 2008; 12: R145
6. Stenqvist O, Grivans C, Andersson B, Lundin S: Lung elastance and transpulmonary pressure can be determined without using oesophageal pressure measurements. Acta Anaesthesiol Scand 2012; 56: 738-47
7. Bikker IG, Preis C, Egal M, Bakker J, Gommers D: Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. Crit Care 2011; 15: R193
8. Gattinoni L, Carlesso E, Caironi P: Stress and strain within the lung. Curr Opin Crit Care 2012; 18: 42-7
9. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L: Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?. Crit Care Med 2013; 41: 1046-55
10. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 2008; 178: 346-5
11. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard JC, Diehl JL, Mancebo J, Rouby JJ, Lu Q, Bernardin G, Brochard L: PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intensive Care Med 2011; 37: 1595-604
12. Gonzalez-Lopez A, Garcia-Prieto E, Batalla-Solis E, Amado-Rodriguez L, Avello N, Blanch L, Albaiceta GM: Lung strain and biological response in mechanically ventilated patients. Intensive Care Med 2012; 38: 240-7
13. Lundin S, Grivans C, Stenqvist O: Transpulmonary pressure and lung elastance can be estimated by a PEEP-step manoeuvre. Acta Anaesthesiol Scand 2015; 59: 185-96
14. Keller SP, Fessler HE: Monitoring of oesophageal pressure. Curr Opin Crit Care 2014; 20: 340-6
15. Higgs BD, Behrakis PK, Bevan DR, Milic-Emili J: Measurement of pleural pressure with esophageal balloon in anesthetized humans. Anesthesiology 1983; 59: 340-3
16. Mead J, Gaensler EA: Esophageal and pleural pressures in man, upright and supine. J Appl Physiol 1959; 14: 81-3
17. Chiumello D, Cressoni M, Colombo A, Babini G, Brioni M, Crimella F, Lundin S, Stenqvist O, Gattinoni L: The assessment of transpulmonary pressure in mechanically ventilated ARDS patients. Intensive Care Med 2014; 40: 1670-8

18. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH: Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008; 359: 2095-104
19. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: any safe threshold? Am J Respir Crit Care Med 2011; 183: 1354-62
20. Bikker IG, Blankman P, Specht P, Bakker J, Gommers D: Global and regional parameters to visualize the 'best' PEEP during a PEEP trial in a porcine model with and without acute lung injury. Minerva Anestesiol 2013; 79: 983-92

CHAPTER 5

Global and regional parameters to visualize the 'best' PEEP during a PEEP trial in a porcine model with and without acute lung injury

Bikker I.G, Blankman P, Specht P, Bakker J, Gommers D
Minerva Anestesiol 2013; 79(9): 983-992

Abstract

Background
Setting the optimal level of positive end-expiratory pressure (PEEP) in critically ill patients remains a matter of debate. 'Best' PEEP is regarded as minimal lung collapse and overdistention to prevent lung injury. In this study, global and regional variables were evaluated in a porcine model to identify which variables should be used to visualize 'best' PEEP.

Methods
Eight pigs (28-31 kg) were studied during an incremental and decremental PEEP trial before and after the induction of acute lung injury (ALI) with oleic acid. Arterial oxygenation, compliance, lung volume, dead space, esophageal pressure and electrical impedance tomography (EIT) were recorded at the end of each PEEP step.

Results
After ALI, 'best' PEEP was comparable at 15 cm H_2O between regional compliance of the dorsal lung region by EIT and the global indicators: dynamic compliance, arterial oxygenation, alveolar dead space and venous admixture. After ALI, the intratidal gas distribution was able to detect regional overdistention at 15 cm H_2O PEEP. 'Best' PEEP based on transpulmonary pressure was lower and no optimal level could be found based on lung volume measurements alone. In addition, the recruitment phase significantly improved end-expiratory lung volume, PaO_2, venous admixture and regional and global compliance, both in ALI and the 'healthy' lung.

Conclusion
Most of the evaluated parameters indicate comparable 'best' PEEP levels. However, a combination of these parameters, and especially EIT-derived intratidal gas distribution, might provide additional information. The application of lung recruitment was beneficial in both ALI and the 'healthy' lung.

Introduction
Although mechanical ventilation is essential for the survival of most patients with respiratory failure admitted to the intensive care unit (ICU), it can exacerbate lung damage and may even be the primary factor in acute lung injury (ALI)[1]. Protective ventilatory strategies have been introduced to attenuate ventilator-induced lung injury, including reduction of tidal volume and prevention or minimization of lung collapse and overdistention by optimal setting of the positive end-expiratory pressure (PEEP)[2-4]. However, large clinical trials comparing high vs. low PEEP with fixed low tidal volume were unable to demonstrate differences in mortality. Even a meta-analysis could only demonstrate a significant difference in the subgroup with ARDS patients, in favor of higher PEEP protocols[5]. Therefore, endpoints other than mortality are needed to guide PEEP settings in individual patients.

Currently, PEEP setting is often guided by global lung parameters such as arterial oxygenation, global compliance and dead space ventilation[3;6;7]. PEEP is generally only increased after increased oxygen requirements following the ARDSnet protocol; however, this may also lead to overdistention in some of these patients[3;8]. The highest dynamic compliance obtained from a decremental PEEP titration has been proposed as a tool to find an optimal balance between the mechanical forces acting on the lung and set 'best' PEEP[6;7;9]. However, global indicators are not specific for regional lung collapse or overdistention and, especially in patients with respiratory failure, the lung may be atelectatic or consolidated in the dependent regions[10]. Talmor *et al.* [11] used transpulmonary pressures measured with an esophageal balloon to set the 'best' PEEP, aiming at preventing alveolar collapse by counterbalancing the gravitational force of the dependent lung with an equal or higher PEEP level than the measured intra-thoracic pressure. In addition, electrical impedance tomography (EIT), a real-time imaging method, provides a cross-sectional image of the ventilated lung and is able to monitor regional ventilation distribution[12-14]. Using this method, our group has shown the possibility to differentiate between collapse and overdistention during a PEEP trial in mechanically ventilated patients[15;16]. In addition, Löwhagen *et al.* [14] introduced the EIT parameter 'intratidal gas distribution' to monitor the effect of PEEP on gas distribution to optimize PEEP in ARDS patients.

Therefore, in a porcine model before and after the induction of ALI, this study evaluates global and regional variables to identify which parameters should be used to describe 'best' PEEP. Another aim is to establish whether EIT parameters have additional value over the existing parameters in order to describe the 'best' PEEP.

Materials and Methods

Ethics Statement

The study was approved by the Erasmus MC Animal Experimental Committee (Permit nr. 142-08-01) and conducted in accordance with the National Guidelines for Animal Care and Handling. The entire experiment was performed under midazolam and fentanyl anesthesia. After completion of the experiment, animals were sacrificed with pentobarbital overdose. All efforts were made to minimize suffering.

Animal preparation and data acquisition

(A more extensive description is available as an online supplement) In eight Yorkshire/Landrace pigs (28-31 kg) anesthesia was induced and venous access established. Cervical tracheotomy was performed and the pigs were connected to the EVITA XL ventilator (Dräger Medical, Lübeck, Germany). Both an arterial and pulmonary artery thermodilution catheter were placed. Respiratory variables were monitored with the NICO (Novametrix, Wallingford, CT, USA), the LUFU system for end-expiratory lung volume (EELV) measurements (Dräger Medical, Lübeck, Germany), the Bicore 2 for esophageal pressures (Cardinal Health, Palm Springs, CA) and with EIT (EIT evaluation kit 2, Dräger, Lübeck, Germany). The EIT data were analyzed offline, using special software (EITdiag, Dräger Medical, Lübeck, Germany), EIT images were subdivided into two symmetrical non-overlapping ventral to dorsal oriented layers defined as regions of interest (ROI).

Acute lung injury model

Oleic acid (OA) administration is a well-studied model of induction of ALI[17]. The mechanism is probably mainly due to a direct toxic effect on the endothelial wall. Grotjohan *et al.* [18] described a titrated approach (mean dose 0.12 ml/kg) which resulted in a stable, reproducible model of ALI, with increased shunt fraction, decreased compliance, increased lung weight and alveolar edema in all lung lobes on chest X-ray. Hemodynamically, they observed decreased blood pressure and increased pulmonary artery pressure, mainly caused by vasoconstriction of pulmonary muscular arteries. The authors recommended a stabilization period of at least 30 min after the last OA injection[18], whereas we applied a 90-min period.

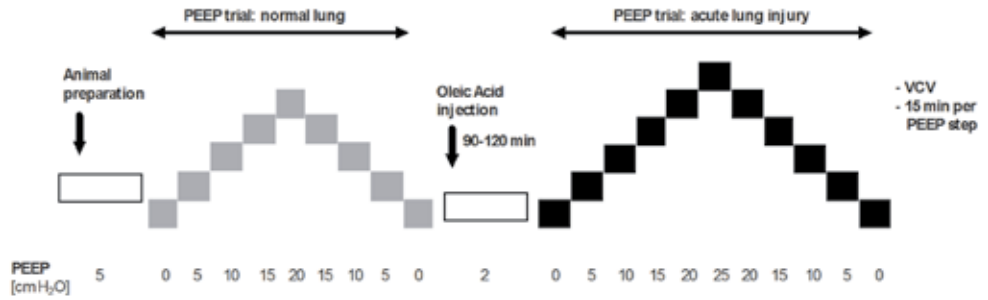

Figure 1: Schematic drawing of the ventilatory procedures throughout the experiment. Increases and decreases of positive end-expiratory pressure (PEEP). The highest applied PEEP step was considered as the recruitment maneuver, 20 cm H_2O before and 25 cm H_2O after the induction of acute lung injury with oleic acid. VCV; volume controlled ventilation.

Experimental protocol

Ventilatory procedures throughout the experiment are shown in Figure 1. The animals were ventilated in volume-controlled mode. Tidal volume was set at 8 ml/kg, respiratory rate adjusted to a $PaCO_2$ of 4.5-6.0 kPa and the inspiratory to expiratory ratio was 1:2. The FiO_2 was set at 0.8 to obtain adequate levels of blood gases even after induction of ALI and to minimize the development of resorption atelectasis. These settings were kept constant throughout the experiment. Ventilation was started at a PEEP of 5 cm H_2O.

After completion of the surgical protocol and the set-up of all necessary equipment, a stabilization period of at least 30 min followed. Baseline values were recorded and the PEEP was stepwise increased by 5 cm H_2O from 0 to 20 and then decreased in the same manner to 0. Each step lasted for about 15 min. Severe ALI was induced by OA injection (OA $C18H34O_2$ Boom BV, Meppel, the Netherlands) (0.14±0.03 ml/kg) into the right atrium with the PEEP set at 2 cm H_2O. Each animal received a bolus of 0.1 ml/kg injected over 20 min to obtain a PaO_2 below 10 kPa, if necessary additional injections were given to reach this target. During OA injection a continuous infusion (0.02-0.28 mcg/kg/min) of norepinephrine (100 mcg/ml, Centrafarm Services BV, Etten-Leur, The Netherlands) through the ear vein was given to maintain a stable mean arterial pressure. After a steady state of at least 1.5 h after the induction of ALI, measurements were repeated during a PEEP trial from 0 to 25 cm H_2O PEEP and again decremental steps to 0 cm H_2O PEEP, in the same manner as before ALI. The highest PEEP level during each trial was considered as the recruitment phase. During the PEEP trials, norepinephrine was administered to maintain a stable perfusion pressure; no additional fluid boluses were used to avoid fluid overload during the decremental PEEP steps.

At baseline and at the end of each step during the PEEP trials the following variables were obtained: airway and esophageal pressures during an inspiratory and expiratory hold of 5 s, arterial and mixed venous blood gases, volumetric capnography and EIT recordings; also, EELV was measured by changing the FiO_2 from 0.8 to 0.6 and from 0.6 to 0.8. In addition, hemodynamic and ventilatory data were obtained.

In the present study, 'best' PEEP was defined for each individual parameter, aiming at the lowest amount of lung collapse and, if possible, an optimum between lung collapse and lung overdistention. Therefore, maximum EELV, (regional) compliance and PaO_2, the lowest venous admixture and dead space just before a significant increased value, and transpulmonary pressures equal to or exceeding zero during end expiration were defined as 'best' PEEP.

Hemodynamic variables during the PEEP trials, before and after induction of acute lung injury (ALI)

PEEP (cm H_2O)	0	5	10	15	20	25	20	15	10	5	0
Before ALI											
CO (L/min)	4.4	4.6	4.2	3.9	3.3			3.4	3.7	4.1	4.7
	(2.0)	(2.3)	(1.7)	(1.9)	(1.7)			(1.4)	(1.3)	(0.9)	(1.0)
HR (bpm)	85	86	91	90	107			110	99	87	91
	(27)	(39)	(33)	(56)	(69)			(64)	(52)	(34)	(24)
MAP (mmHg)	92	87	94	85	88			83	90	97	105
	(21)	(29)	(24)	(28)	(6)			(29)	(20)	(25)	(19)
CVP (mmHg)	4	5	7	9	10			9	8	7	6
	(8)	(8)	(8)	(4)	(8)			(9)	(7)	(8)	(9)
PAP (mmHg)	16	16	19	20	23			22	20	19 (	20
	(10)	(6)	(8)	(8)	(9)			(9)	(9)	(10)	(8)
Lactate (mmol/L)	0.7	0.6	0.7	0.6	0.6			0.7	0.7	0.6	0.6
	(1.1)	(0.8)	(0.7)	(1.0)	(1.0)			(1.0)	(0.7)	(0.5)	(0.5)
Norepinephrine (mcg/kg/min)	0.00	0.00	0.00	0.02	0.10			0.05	0.00	0.00	0.00
	(0.00)	(0.00)	(0.00)	(0.12)	(0.25)			(0.15)	(0.05)	(0.00)	(0.00)
After ALI											
CO (L/min)	4.2	4.3	4.1	3.9	3.3	2.8	2.6	3.0	3.5	3.9	5.2
	(1.1)	(3.0)	(2.7)	(1.5)	(0.9)	(0.9)	(0.6)	(1.8)	(1.9)	(1.6)	(1.5)
HR (bpm)	128	129	127	131	151	169	163	167	151	152	163
	(53)	(86)	(45)	(30)	(55)	(75)	(75)	(67)	(45)	(46)	(25)
MAP (mmHg)	86	91	97	100	81	79	81	84	91	89	78
	(28)	(25)	(24)	(22)	(25)	(27)	(25)	(43)	(28)	(31)	(36)
CVP (mmHg)	4	7	8	8	10	10	9	7	6	6	6
	(6)	(7)	(7)	(7)	(7)	(7)	(7)	(7)	(8)	(8)	(7)
PAP (mmHg)	48	40	42	38	36	37	35	31	41	41	45
	(13)	(9)	(10)	(12)	(13)	(14)	(10)	(9)	(13)	(11)	(12)
Lactate (mmol/L)	0.8	0.8	0.9	0.9	1.0	1.1	0.9	0.9	1.0	0.9	1.4
	(0.7)	(0.6)	(0.5)	(0.4)	(0.5)	(0.6)	(0.6)	(0.7)	(0.7)	(0.7)	(1.1)
Norepinephrine (mcg/kg/min)	0.12	0,08	0.07	0.08	1.12	0.32	0.25	0.12	0.12	0.12	0.12
	(0.23)	(0.10)	(0.07)	(0.08)	(0.37)	(0.55)	(0.57)	(0.37)	(0.35)	(0.22)	(0.53)

Table 1: Data are presented as mean (SD); CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; PAP, pulmonary artery pressure.

Statistical analysis

Statistical analysis was performed with Graphpad software package (Graphpad software Inc. San Diego, USA). Results are expressed as mean ± SD for normal distributed data and median + interquartile range (IQR) for not normally distributed data. The Shapiro-Wilk normality test was used to evaluate the distribution of all data. Changes of EELV, PaO_2, venous admixture, dead space and regional and global compliance were evaluated by the Wilcoxon test. Correlation between dynamic and static compliance was evaluated using Pearson's correlation. *P*-values < 0.05 were considered statistically significant.

Results

Hemodynamic data during the PEEP trial are given in Table1. The effect of PEEP on the global lung parameters is shown in Figure 2. The induction of ALI led to a significant decrease in EELV, dynamic compliance and arterial oxygenation, and to a significant increase in both dead space and venous admixture at the corresponding PEEP level. Dynamic compliance was highly correlated with the static compliance of the respiratory system (p <0.001, r=0.97, R^2=0.94).

Best PEEP values are presented in Table 2. Before and after ALI, EELV had its maximum at the highest PEEP level directly after a recruitment maneuver (Fig. 2). Between identical PEEP levels before and after recruitment, EELV was significantly higher at PEEP 15, 10 and 5 cm H_2O before ALI and at PEEP 20, 15 and 10 cm H_2O after ALI (Fig. 2). Dynamic compliance was maximal at PEEP level of 10 cm H_2O before ALI and at 15 cm H_2O after ALI (Fig. 2). After ALI, alveolar dead space showed a significant increase after decreasing PEEP from 10 to 5 cm H_2O (Fig. 2). Before and after ALI, PaO_2 was maximum at the highest PEEP level (Fig. 2). Between identical PEEP levels before and after recruitment, PaO_2 was significantly higher at PEEP 15, 10 and 5 cm H_2O before ALI, and at PEEP 20 and 15 cm H_2O after ALI (Fig. 2). Venous admixture was minimum at the highest PEEP level and showed a significant increase after decreasing the PEEP level from 15 to 10 cm H_2O, and during the subsequent PEEP steps before and after ALI.

Best PEEP values for the different parameters, before and after induction of acute lung injury (ALI)

	Definition	Before ALI	After ALI
End-expiratory lung volume	Highest	20	25
PaO_2	Highest	5	15
Venous admixture	Lowest	15	15
Alveolar dead space fraction	Lowest	5	15
Compliance (global)	Highest	10	15
EIT regional compliance			
- ventral	Highest	5	0
- dorsal	Highest	10	15
EIT intratidal gas distribution		5	10
Transpulmonary pressure	End expiratory ≥ 0	5	10

Table 2: All values are expressed in cm H_2O PEEP; PaO_2, arterial oxygen tension; EIT, electrical impedance tomography

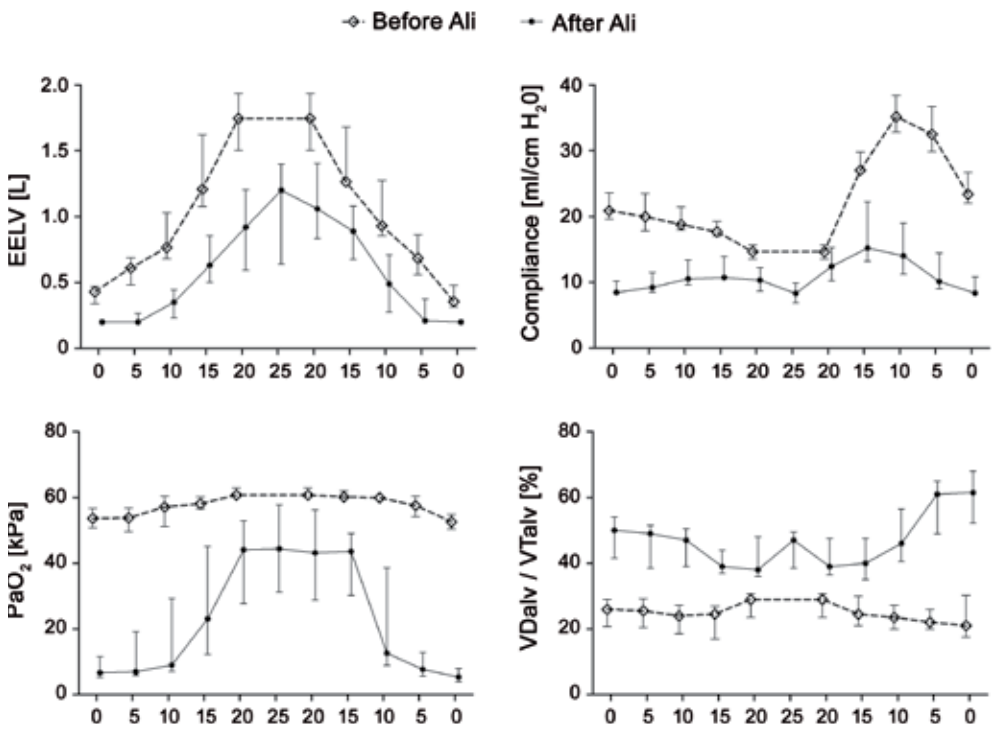

Figure 2: End-expiratory lung volume (EELV), dynamic compliance, the ratio between alveolar dead space to alveolar tidal volume (VDalv/VTalv) and PaO_2 are shown at each positive end-expiratory pressure (PEEP) step. The highest applied PEEP step was considered as the recruitment maneuver, 20 cm H_2O before and 25 cm H_2O after the induction of acute lung injury (ALI) with oleic acid. Data are presented as median with interquartile range.

Transpulmonary pressures during an inspiration and expiration hold at the studied PEEP levels are shown in Figure 3. During expiration, transpulmonary pressure was zero at 5 cm H_2O PEEP before ALI and at 10 cm H_2O PEEP after ALI (Fig. 3). During decremental PEEP steps, lower inspiratory transpulmonary pressures were required to maintain constant tidal volumes at the decremental PEEP steps, as compared to the equal incremental PEEP steps. This was not present in the expiratory curves (Fig. 3).

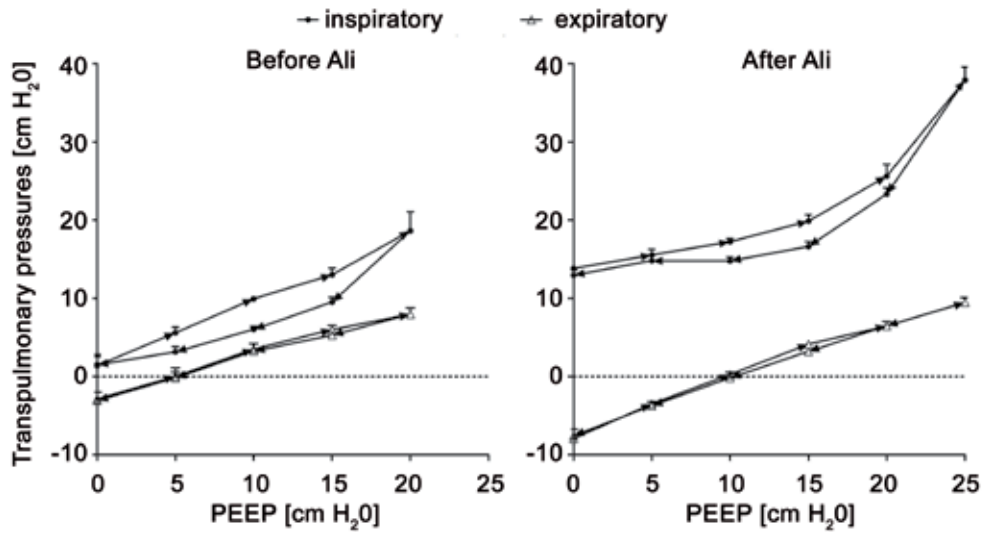

Figure 3: Transpulmonary pressures during inspiration and expiration holds at the applied PEEP levels, before (left panel) and after (right panel) the induction of acute lung injury (ALI) with oleic acid. Transpulmonary pressure was calculated by subtracting the esophageal pressure from the airway pressure. Solid dots represent inspiratory values and open triangles represent expiratory values. Data are presented as mean + standard error of the mean.

Regional compliance calculated from the EIT in the dorsal to ventral orientated ROIs is shown in Figure 4. Higher regional compliance, caused by decreased inspiratory pressures while maintaining equal tidal volumes, was found with decreasing PEEP. This was observed especially before ALI, and was more pronounced for the dorsal region (Fig.4). The maximal regional compliance for the dorsal region during the decremental PEEP trial after the recruitment maneuver was 10 cm H_2O before ALI, and 15 cm H_2O after ALI (Fig. 4). The contribution of the dependent lung regions to the inspiration increased at higher PEEP levels.

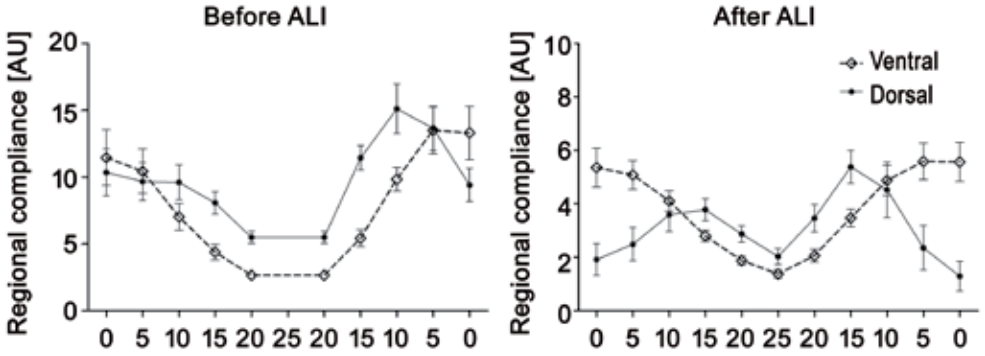

Figure 4: Regional compliance in the ventral and dorsal regions of interest at the applied PEEP levels, before and after the induction of lung injury (ALI) with oleic acid. Regional compliance was calculated by dividing tidal impedance variation by the applied driving pressure. Data are presented as mean ± SE.

Intratidal gas distribution (Fig. 5) shows a significantly different contribution of the dependent and non-dependent regions to the inspiration for each PEEP step after ALI. Also, before ALI, the intratidal gas distribution showed a significant difference between both regions at each PEEP level, except during 5 cm H_2O. At this latter PEEP level, there was a cross-section between the dependent and non-dependent lung region before induction of ALI (Fig. 5). This cross-section indicates the moment at which the non-dependent lung region becomes overdistended, which occurred between 15 and 10 cm H_2O after induction of ALI.

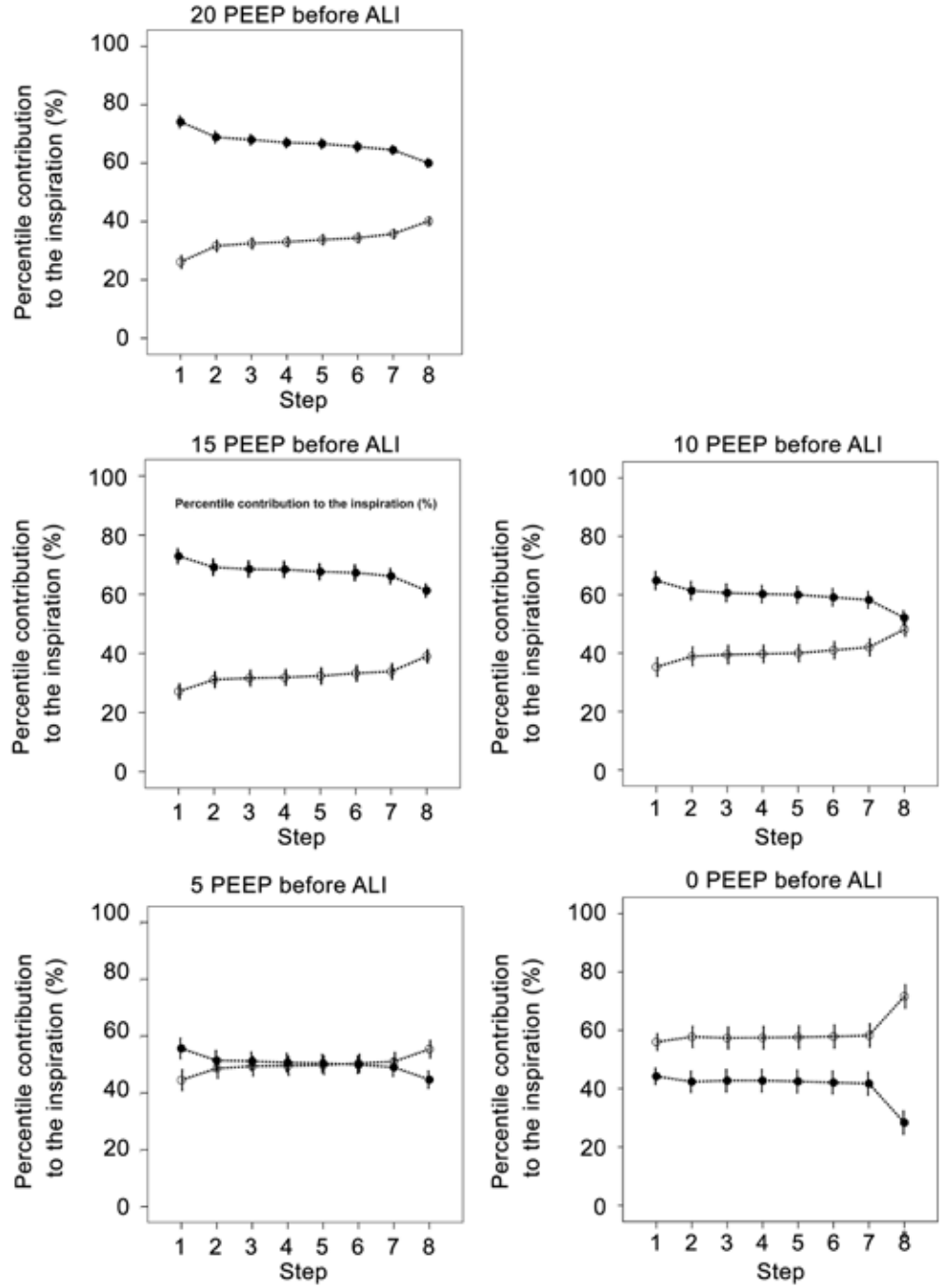

Figure 5a: Data are shown as mean ± SE. Intratidal gas distribution before acute lung injury (ALI). *Open circles* = non-dependent lung region; *solid circles* = dependent lung region

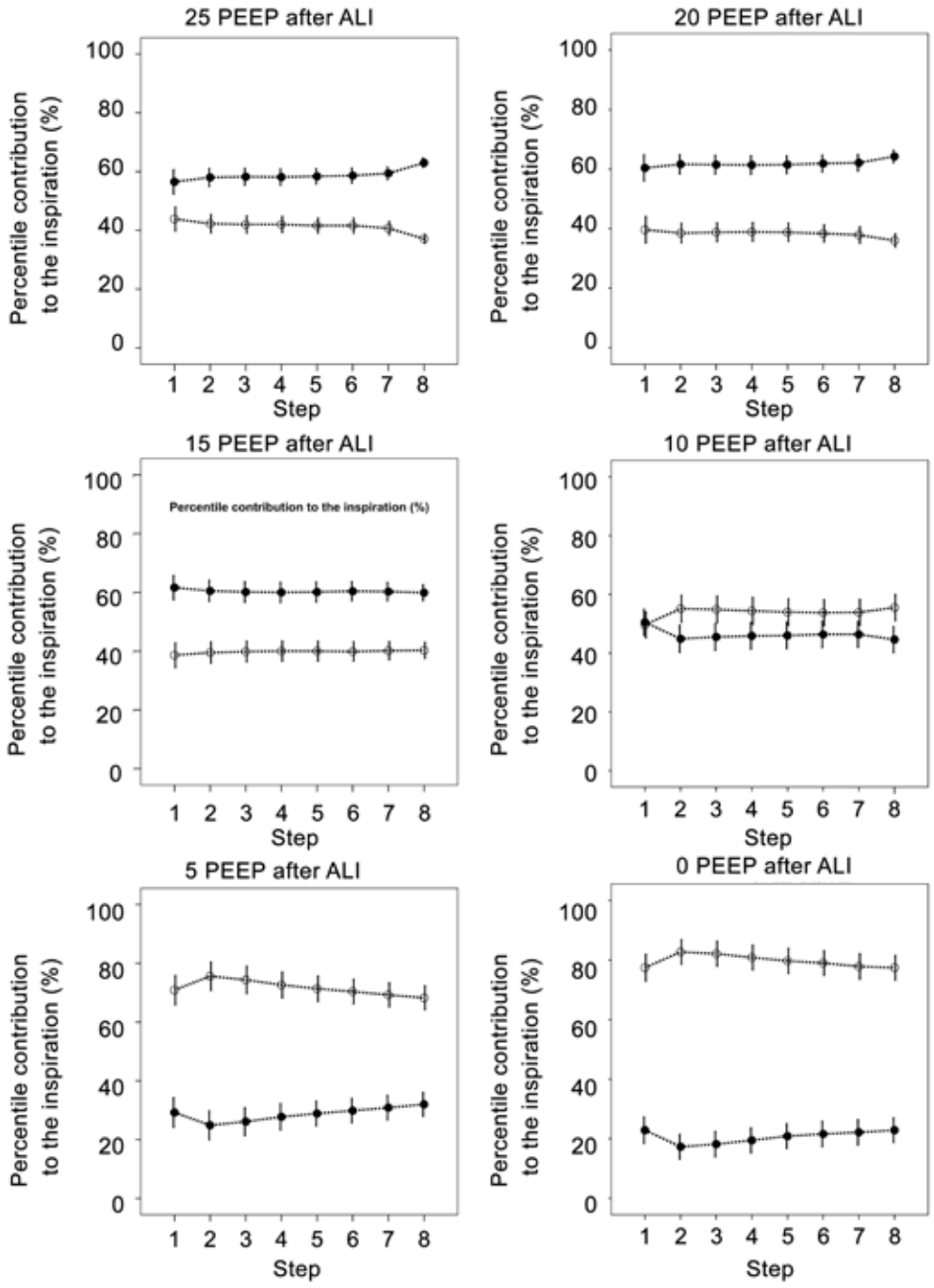

Figure 5b: Data are shown as mean ± SE. Intratidal gas distribution after acute lung injury (ALI). *Open circles* = non-dependent lung region; *solid circles* = dependent lung region.

Discussion

In an experimental model of ALI, 'best' PEEP was comparable between regional compliance of the dependent lung region by EIT and the global indicators: dynamic compliance, arterial oxygenation, alveolar dead space and venous admixture. The 'best' PEEP based on transpulmonary pressure was lower in this experimental setting of ALI. The EIT derived intratidal gas distribution was able to identify the onset of overdistention.

In 2000 it was already known that mechanical ventilation with low tidal volume (6 ml/kg) was superior to high tidal volume (12 ml/kg) in patients with ALI or ARDS[1]. High tidal volume ventilation in the presence of atelectasis, as seen in patients with ALI/ARDS, leads to overdistention of the 'healthy' aerated lung regions causing barotrauma and volutrauma, and this provokes biotrauma due to lung inflammation with the release of cytokines and mediators. This inflammatory response is called ventilator-induced lung injury and leads to a higher mortality rate[1-3]. Studies applying higher PEEP levels showed improved oxygenation and compliance but were unable to further reduce the mortality rate[2;7]. Two meta-analysis studies (including ≥ 3500 patients with ALI or ARDS) reported that a moderate level of PEEP (around 9 cm H_2O) is superior in patients with ALI, whereas high PEEP levels (around 15 cm H_2O) are superior in patients with ARDS[9;10]. Higher PEEP may increase the risk of hyperinflation and a compromise must be found between PEEP-induced alveolar recruitment and prevention of hyperinflation. Also, Gattinoni *et al.* [19] found extremely variable amounts of potential recruitable lung tissue on CT scanning and this was strongly associated with the response to PEEP. Therefore, one should not use a universal level of PEEP but rather the 'best' PEEP level that the individual patient needs at a specific time. This implies constant re-evaluation of the individual ventilator settings, and the need for an optimal parameter to apply the 'best' PEEP.

Several studies investigated the 'best' PEEP setting during standardized PEEP steps in various forms of lung conditions in both experimental and human subjects[6;7;20;21]. Maisch et al. studied 20 anesthetized patients with healthy lungs during incremental and decremental steps of 5 cm H_2O PEEP and compared EELV, arterial oxygenation, compliance and a modified dead space calculation[6]. The authors concluded that, in these patients without lung disorders, compliance and dead space were able to detect lung collapse and overdistention and therefore are suitable to guide 'best' PEEP settings[6]. In the present study, the lung condition before ALI is comparable to the study of Maisch *et al.*[6] and the results are similar, except for dead space. In the present study, dead space increased from 15 to 20 cm H_2O, whereas no significant changes occurred thereafter (Fig. 2). This may be due to the influence of shunt with increased $PaCO_2$ in the dead space calculations. Suarez-Sipmann *et al.*[7] and Carvalho *et al.*[20], who studied, respectively, lung lavage induced ALI and OA-induced ALI during decremental PEEP steps, showed that compliance was a good parameter to guide 'best' PEEP. Also in the present study, dynamic compliance increased significantly during the decremental PEEP trial after the recruitment phase.

In this study we also evaluated the relation between regional and global parameters and whether they provide additional information. Costa *et al.*[22] and Meier *et al.*[23] demonstrated that EIT can be used to monitor regional compliance. In our study, we calculated the regional compliance for each pixel in the EIT matrix and divided them into ventral and dorsal ROIs. As the studied pigs were ventilated in volume-controlled mode with constant tidal volume, a change in regional impedance was caused by a change in the driving pressure and a spatial change in tidal volume distribution between PEEP steps. Others also described the change in

tidal volume distribution with EIT and CT scanning in a ventral to dorsal manner during PEEP change[10;15;24]. In our study, regional compliance decreased as a result of the increased driving pressure after ALI. The optimal value differed not only before and after the induction of lung injury, but also between the dorsal to ventral ROIs. In the dependent lung parts the optimum value increased from 10 to 15 cm H_2O PEEP after the induction of lung injury. A study by Löwhagen *et al.*[14] showed that the relatively new parameter 'intratidal gas distribution' (which divides regional tidal impedance into eight iso-volume parts) was able to identify intratidal regional recruitment and overdistention. These authors showed that the contribution of the dependent lung regions to the inspiration increases at higher PEEP levels. This is also seen in the present study for both lung conditions. In the present study we could identify the onset of overdistention, but this was only for one slice of the lung. EIT might be a practical new tool for optimal PEEP setting, especially as an adjunct to existing parameters.

Esophageal pressures were recorded during inspiration and expiration holds to calculate the transpulmonary pressure. Pelosi et al. studied the relation between esophageal pressure and the actual pleural pressure at three ventral to dorsal thoracic levels, in six supine dogs with OA respiratory failure[25]; esophageal pressure underestimated the dorsal pleural pressure by about 4 cm H_2O and overestimated the ventral pleural pressure by about 6 cm H_2O. This was confirmed in the present study in which the 'best' PEEP based on transpulmonary pressure was 5 cm H_2O lower compared to the other parameters.

An important finding of the present study is that a recruitment maneuver in combination with PEEP, both before and after the induction of ALI, significantly improved EELV, PaO_2, venous admixture and regional and global compliance (Figs. 2 and 3). This means that not only patients with respiratory failure, but also patients with 'healthy' lungs benefit from a recruitment maneuver in conjunction with an adequate PEEP level. This is in agreement with the study of Maisch *et al.*[6] in which a recruitment maneuver during PEEP titration, combined with a PEEP of 10 cm H_2O improved EELV, PaO_2, compliance and dead space in anesthetized, intubated patients just before surgery. Although the stable animal model used in the present study showed a high potential for lung recruitability (as evidenced by changes in shunt fraction), the extent of lung recruitability may differ from that in ARDS patients[19]. Potential limitations of this study are the use of relatively large PEEP steps of 5 cm H_2O. Although this enabled measurement in both normal and injured lungs, a PEEP trial with smaller steps is more suitable to identify the 'best' PEEP in an individual patient. We did not use a formal recruitment maneuver, but used phases of recruitment and regarded the highest used PEEP as the recruitment maneuver; these levels resulted in high inspiratory and transpulmonary pressures exceeding most conventional recruitment maneuvers. Also, we did not use CT scanning to identify hyperinflation and alveolar collapse; however, the application of the highest and lowest PEEP levels in the present study has clearly been shown on CT scanning to induce lung overdistention and lung collapse, respectively[7;20].

Conclusion

In this experimental model of ALI, parameters that describe only lung volume, such as EELV, are inappropriate to indicate 'best' PEEP level. The EIT derived parameter, intratidal gas distribution, was able to indicate at which PEEP level overdistention of the non-dependent lung started; however, this was only for one slice of the lung. Therefore, we believe that the combination of parameters might provide important additional information. Best PEEP should prevent lung collapse and also overdistention; therefore, a combination of parameters should resemble both of these physiological principles. Finally, this study indicates that the application of a recruitment maneuver might be of benefit not only in ALI, but also in a healthy lung.

Methods supplement

Animal preparation

In eight healthy female crossbred Yorkshire/Landrace pigs (28-31 kg) anesthesia was induced with an intramuscular injection of 2.5 mg/kg azaperon (Stresnil 40 mg/ml, Janssen Pharmaceutical, Beerse, Belgium), 30 mg/kg ketamine (Ketalin 100 mg/ml, Ceva Sante Animale BV Maassluis, the Netherlands) and 1 mg/kg midazolam (Dormicum 5 mg/ml, Roche Nederland BV, Woerden, the Netherlands). After induction, the pigs were placed in supine position on a thermo-controlled operation table to maintain body temperature. Intravenous access was obtained by cannulation of an ear vein; anesthesia was maintained with a combination of intravenous infusion of midazolam (1-2 mg/kg/h) and sufentanil (0.01-0.02 mg/kg/h; Sufenta forte 0.05 mg/ml Janssen-Cilag BV, Tilburg, the Netherlands). Muscle relaxation was obtained with infusion of pancuronium bromide (0.15-0.35 mg/kg/h; pavulon 2 mg/ml, NV Organon, Oss, the Netherlands). Through a midline cervical tracheotomy, an endotracheal tube (9.0 Fr) was placed in the trachea. After tracheotomy the pigs were connected to the EVITA XL ventilator (Dräger Medical, Lubeck, Germany). A catheter was inserted through the right carotid artery for measurement of arterial blood pressure and sampling of blood. A pulmonary artery thermodilution catheter (PAC) (7.5 Fr Edwards Lifesciences, Irvine CA, USA) was inserted through the right jugular vein in the pulmonary artery for the continuous measurement of cardiac output, central venous pressure (CVP), pulmonary artery pressure (PAP), mixed venous hemoglobin oxygen saturation (SvO_2) and central body temperature. The position of the PAC was guided by pressure waveforms, while passing the heart. All catheters for measuring blood pressure were flushed with normal saline containing a low dose of heparin (5 IU/ml; Leo Pharma BV, Breda, the Netherlands) to avoid clotting in the catheters. A catheter was also placed in the urinary bladder to avoid urine retention.

Monitoring equipment

Airway pressure, flow, volume and volume-based capnography were sampled continuously during the experiment (NICO, Novametrix, Wallingford, CT, USA) and dead space was calculated with the Bohr-Enghoff equation. End-expiratory lung volume (EELV) was measured with the LUFU system (Dräger Medical, Lübeck, Germany) connected to the EVITA XL ventilator, which is described in detail elsewhere (26;27). Esophageal pressures were measured with the SmartCath® esophageal catheter connected to the Bicore 2 (Cardinal Health, Palm Springs, CA, USA). The esophageal balloon was inserted to a depth of 50 cm from the incisors and filled with 1 ml of air. Placement was confirmed by the increase of cardiac artefacts as the balloon was withdrawn from the stomach. Electrical impedance measurements were performed at each step in the protocol during 2 min with a silicone belt with 16 integrated electrocardiographic electrodes placed around the thoracic cage at a juxta-diphragmatic level, connected with an EIT device (EIT evaluation kit 2, Dräger, Lübeck, Germany). EIT data were generated by application of a small alternating electrical current of 5 mA at 50 kHz.

EIT analysis

EIT data were stored and analyzed offline using special software (EITdiag, Dräger, Lübeck, Germany). The EIT scans consist of images of impedance with a 32 x 32 color-coded matrix relative to the lowest impedance during the PEEP trial (rel. ΔZ). The difference between rel. ΔZ at the end of inspiration and expiration is defined as tidal impedance variation. This tidal impedance variation is visualized in the functional EIT (fEIT) image, which contains tidal impedance variation per pixel (32 x 32 matrix) averaged over 1 min. For analysis of the regional compliance, the EIT images were subdivided into two symmetrical non-overlapping ventral to dorsal oriented layers defined as regions of interest (ROI). Regional compliance was calculated following equation 1.

The intratidal gas distribution (Fig. 5a + 5B) is calculated according to the study of Löwhagen et al. (14). The inspiratory part of the global tidal impedance variation (TIV) curve was divided in eight equal volume sections. The corresponding time points are translated to the regional TIV curves. In this way the contribution from both lung regions to the inspiration can be calculated.

$$regional\ compliance = \frac{\sum tidal\ impedance\ variation\ (AU)}{driving\ pressure\ (cm\ H_20)}$$

Equation 1

References

1. Ricard JD, Dreyfuss D, Saumon G. Ventilator-induced lung injury. Curr Opin Crit Care 2002; 8: 12-20.
2. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338: 347-54.
3. ARDSnet. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342: 1301-8.

4. Guerin C. The preventive role of higher PEEP in treating severely hypoxemic ARDS. Minerva Anestesiol 2011; 77: 835-45.
5. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010; 303: 865-73.
6. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, et al. Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth Analg 2008; 106: 175-81.
7. Suarez-Sipmann F, Bohm SH, Tusman G, Pesch T, Thamm O, Reissmann H, et al. Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. Crit Care Med 2007; 35: 214-21.
8. Grasso S, Stripoli T, De Michele M, Bruno F, Moschetta M, Angelelli G, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. Am J Respir Crit Care Med 2007; 176: 761-7.
9. Bikker IG, van Bommel J, Dos Reis MD, Bakker J, Gommers D. End-expiratory lung volume during mechanical ventilation: a comparison to reference values and the effect of PEEP in ICU patients with different lung conditions. Crit Care 2008; 12: R145.
10. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? Am J Respir Crit Care Med 2001; 164: 1701-11.
11. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008; 359: 2095-104.
12. Blankman P, Gommers D. Lung monitoring at the bedside in mechanically ventilated patients. Curr Opin Crit Care 2012; 18: 261-6.
13. Frerichs I, Dargaville PA, Dudykevych T, Rimensberger PC. Electrical impedance tomography: a method for monitoring regional lung aeration and tidal volume distribution? Intensive Care Med 2003; 29: 2312-6.
14. Löwhagen K, Lundin S, Stenqvist O. Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol 2010; 76: 1024-35.
15. Bikker IG, Leonhardt S, Reis MD, Bakker J, Gommers D. Bedside measurement of changes in lung impedance to monitor alveolar ventilation in dependent and non-dependent parts by electrical impedance tomography during a positive end-expiratory pressure trial in mechanically ventilated intensive care unit patients. Crit Care 2010; 14: R100.
16. Bikker IG, Preis C, Egal M, Bakker J, Gommers D. Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. Crit Care 2011; 15: R193.
17. Sum-Ping ST, Symreng T, Jebson P, Kamal GD. Stable and reproducible porcine model of acute lung injury induced by oleic acid. Crit Care Med 1991; 19: 405-8.
18. Grotjohan HP, van der Heijde RM, Jansen JR, Wagenvoort CA, Versprille A. A stable model of respiratory distress by small injections of oleic acid in pigs. Intensive Care Med 1996; 22: 336-44.

19. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006; 354: 1775-86.
20. Carvalho AR, Jandre FC, Pino AV, Bozza FA, Salluh J, Rodrigues R, et al. Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. Crit Care 2007; 11: R86.
21. Tusman G, Suarez-Sipmann F, Bohm SH, Pech T, Reissmann H, Meschino G, et al. Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med 2006; 32: 1863-71.
22. Costa EL, Borges JB, Melo A, Suarez-Sipmann F, Toufen C, Jr., Bohm SH, et al. Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. Intensive Care Med 2009; 35: 1132-7.
23. Meier T, Luepschen H, Karsten J, Leibecke T, Grossherr M, Gehring H, et al. Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. Intensive Care Med 2008; 34: 543-50.
24. Kunst PW, de Vries PM, Postmus PE, Bakker J. Evaluation of electrical impedance tomography in the measurement of PEEP-induced changes in lung volume. Chest 1999; 115: 1102-6.
25. Pelosi P, Goldner M, McKibben A, Adams A, Eccher G, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: an experimental study. Am J Respir Crit Care Med 2001; 164: 122-30.
26. Maisch S, Boehm SH, Weismann D, Reissmann H, Beckmann M, Fuellekrug B, Meyer A, Schulte Am EJ. Determination of functional residual capacity by oxygen washin-washout: a validation study. Intensive Care Med. 2007; 33: 912-6.
27. Weismann D, Reissmann H, Maisch S, Fullekrug B, Schulte J. Monitoring of functional residual capacity by an oxygen washin/washout; technical description and evaluation. J Clin. Monit.Comput. 2006; 20: 251-60.

CHAPTER 6

Detection of 'best' positive end-expiratory pressure derived from electrical impedance tomography parameters during a decremental positive end-expiratory pressure trial

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Abstract

Introduction
This study compares different parameters derived from electrical impedance tomography (EIT) data to define 'best' PEEP during a decremental PEEP trial in mechanically-ventilated patients. 'Best' PEEP is regarded as minimal lung collapse and overdistention in order to prevent ventilator-induced lung injury.

Methods
A decremental PEEP trial (from 15 to 0 cm H_2O PEEP in 4 steps) was performed in 12 post-cardiac surgery patients on the ICU. At each PEEP step, EIT measurements were performed and from this data the following were calculated: Tidal Impedance Variation (TIV), regional compliance, ventilation surface area (VSA), center of ventilation (COV), regional ventilation delay (RVD index), global inhomogeneity (GI index), and intratidal gas distribution. From the latter parameter we developed the ITV index as a new homogeneity parameter. The EIT parameters were compared with dynamic compliance and the PaO_2/FiO_2 ratio.

Results
Dynamic compliance and the PaO_2/FiO_2 ratio had the highest value at 10 and 15 cm H_2O PEEP, respectively. TIV, regional compliance and VSA had a maximum value at 5 cm H_2O PEEP for the non-dependent lung region and a maximal value at 15 cm H_2O PEEP for the dependent lung region. GI index showed the lowest value at 10 cm H_2O PEEP, whereas for COV and the RVD index this was at 15 cm H_2O PEEP. The intratidal gas distribution showed an equal contribution of both lung regions at a specific PEEP level in each patient.

Conclusion
In post-cardiac surgery patients, the ITV index was comparable with dynamic compliance to indicate 'best' PEEP. The ITV index can visualize the PEEP level at which ventilation of the non-dependent region is diminished, indicating overdistention. Additional studies should test whether application of this specific PEEP level leads to better outcome and also confirm these results in patients with acute respiratory distress syndrome.

Introduction
Mechanical ventilation acts as a stress raiser to lung tissue adjacent to collapsed tissue in the dependent lung and the risk of alveolar hyperinflation in the non-dependent lung[1]. An alveolar recruitment maneuver and the use of positive end-expiratory pressure (PEEP) are applied to open up and to keep open the atelectatic lung tissue in an attempt to minimize this stress and overdistention.

The original definition of 'best' PEEP as proposed by Suter *et al.* [2] is the PEEP level with the best compromise between lung aeration and circulatory depression; circulatory depression is caused by compression of capillaries due to hyperinflation. Tusman *et al.* [3] performed an incremental and decremental PEEP trial in eight volume-controlled ventilated surfactant-depleted pigs; they showed that calculation of dead space detected early signs of lung collapse, which correlated well with findings on computed tomography (CT). In a second study, these authors reported that continuous compliance monitoring could identify the onset of alveolar collapse as confirmed by CT, as well as changes in partial arterial oxygen pressure (PaO_2) values[4]. Another experimental study, using an oleic acid-induced acute lung injury (ALI) model, showed that minimizing elastance of the respiratory system could be used to titrate PEEP settings[5]. Maisch et al. performed an incremental and decremental PEEP trial in 20 anesthetized patients undergoing elective surgery and confirmed that dynamic compliance and dead space calculations were able to detect alveolar collapse and/or overdistention, whereas functional residual capacity (FRC) and PaO_2 changes were less sensitive[6]. From these studies it has been concluded that dynamic compliance and dead space calculations are the most reliable global parameters to define the best PEEP at the bedside.

CT is regarded as the gold standard to assess the effect of a recruitment maneuver and the applied PEEP on aeration of the lung[7;8]. However, the obvious drawbacks of repeated CT scans (that is transfer of the mechanically-ventilated patient and excessive radiation exposure) reduce the application of CT as a tool for assessment of PEEP settings. On the other hand, electrical impedance tomography (EIT) is a real-time bedside monitoring tool, which has proven to correlate well with CT for assessment of changes in gas volume and tidal volume[9-11].

Several EIT parameters have been developed to collect more data on ventilation distribution in order to optimize ventilator settings[12-15]. The present study examines whether one specific EIT parameter is able to describe the optimal PEEP level at the bedside; for this, we defined the best PEEP as the PEEP level with minimal lung collapse and minimal overdistention.

Materials and Methods
Study population
Included in this study were 12 mechanically-ventilated post-cardiac surgery patients admitted to the cardiothoracic intensive care unit. Data for the present study were used in an earlier study that analyzed the effect of a decremental PEEP trial on ventilation distribution with EIT measured at two different thoracic levels [16]. Informed consent was obtained from the patient or a legal representative. Using data from this latter study, we re-analyzed data of the EIT measurements made just above the diaphragm only, as this part of the lung is at most risk for formation of atelectasis in mechanically-ventilated patients in the supine position. The Medical Ethical Committee Rotterdam approved the entire study protocol.

Study protocol and measurements

A 16-electrode silicon belt (EIT evaluation kit 2, Dräger, Lübeck, Germany) was placed around the patient's thoracic cage between the 6th and 7th intercostal spaces [16]. Patients were ventilated with pressure-controlled ventilation (PCV) (Engström Carestation, GE Healthcare, Madison, WI, USA) and, throughout the entire study period, the inspiratory pressure above PEEP, the inspiration/expiration (I/E) ratio, frequency and inspired oxygen fraction (FiO_2) remained unchanged. In this study we performed a recruitment maneuver in which mechanical ventilation was continued with a pressure amplitude of 20 cm H_2O while PEEP was rapidly increased from 5 to 20 cm H_2O in incremental steps of 5 cm H_2O: thus, a peak pressure of 40 cm H_2O for a 40-s period, as long as blood pressure remained stable. Thereafter, PEEP was decreased to 15 cm H_2O and the pressure amplitude was decreased from 20 to 10 cm H_2O. A PEEP level of 15 cm H_2O was applied for 15 minutes to achieve a steady state. Thereafter, a decremental PEEP trial was performed from 15 to 0 cm H_2O PEEP in steps of 5 cm H_2O. Each PEEP level was applied for 10 to 20 minutes (depending on hemodynamic stability and blood gas analyses). At the end of each PEEP step, EIT, PaO_2/FiO_2 ratio and dynamic compliance (tidal volume divided by pressure above PEEP) were calculated.

EIT data analysis

EIT data were recorded with a sample rate of 20 Hz and were analyzed using dedicated software (EITdiag, Dräger Medical, Lübeck, Germany). For each PEEP step a stable phase with 10 to 20 consecutive breaths was selected. The EIT signals of these breaths are filtered using a low-pass filter set on 40 beats per minute to minimize signals induced by the cardiovascular system. From the filtered signals a ventilation distribution map was created for each PEEP step (Fig. 1). The surface of the distribution maps was standardized using, the largest EIT image acquired during the PEEP trial for each patient. The EIT signals in the distribution maps are used to calculate the tidal impedance variation (TIV), ventilation surface area (VSA), center of gravity (COG), and the global inhomogeneity (GI index). In order to reliably calculate the intratidal gas distribution, all filtered signals were resampled at 40 Hz to divide the inspiratory part of the TIV curve more accurately into 8-iso volume steps. To calculate the different parameters, the defined surface area was divided into two equal regions of interest, that is, the dependent and non-dependent regions (Fig. 1).

Calculated EIT parameters

EIT measures changes in electrical impedance between electrode pairs. After adequate filtering of EIT signals, the measured impedance changes represent the inspiration and expiration by means of TIV (formula 1), which correlates well with tidal volume[9;11;17;18].

$$TIV = Impedance_{max} - Impedance_{max} \quad [1]$$

(TIV = Tidal Impedance Variation)

The second EIT parameter to be calculated is regional compliance[12]. Calculation of regional compliance is similar to that of dynamic compliance; however, for dynamic compliance tidal

volume is divided by pressure amplitude whereas for regional compliance TIV is divided by pressure amplitude. As we did not connect the EIT device to the ventilator, we were unable to calculate regional compliance using EITdiag software. Therefore, we divided the TIV into dependent and non-dependent lung regions by the EITdiag-generated ventilation distribution map, based on the pressure above PEEP (formula 2). A decrease in regional compliance with *increases* in PEEP indicates that the lung is hyperinflated, whereas a decrease in regional compliance with *decreases* in PEEP indicates alveolar collapse.

$$Compliance_{region} = \frac{TIV_{region}}{Pressure\ above\ PEEP} \quad [2]$$

(TIV = Tidal Impedance Variation)

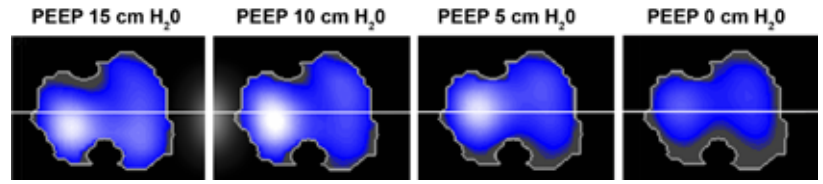


Figure 1: Example of EIT image reconstruction. Distribution of impedance to the dependent and non-dependent lung regions of one representative patient. The lighter the color, the higher the impedance and the more aerated the lung region. The surface area used in all calculations at every PEEP step is equal to the largest surface area (in this case at PEEP 15 cm H_2O). The EIT image is divided into two equal regions of interest represented by the white line; all EIT modalities are calculated using this setup. Decreasing the PEEP value resulted in a decrease in aeration of the lungs, especially in the dependent region.

Using EITdiag software, we calculated the VSA. For this, the number of pixels with an EIT signal in the generated ventilation distribution map was counted for both lung regions. During the recruitment maneuver, the number of ventilated pixels per region is divided by the total number of ventilated pixels in the ventilation distribution map, assuming that all recruitable lung tissue was open at the end of recruitment. In this way, regional ventilation distribution is expressed as a percentage of the maximum ventilated pixels at the end of recruitment. After increasing PEEP levels, higher VSA values indicate alveolar recruitment whereas after decreasing PEEP levels higher VSA values indicate that the lungs were hyperinflated during the previous PEEP level.

In the present study, calculation of the regional ventilation delay (RVD) index describes the percentage of time needed to reach a threshold of 40% of the regional impedance changes, as compared with the total inspiratory time (formula 3)[15;19]. This calculation was not performed using the EITdiag software. Large differences in RVD between both lung regions indicate that the lungs are inhomogeneously ventilated.

$$RVD_i = \frac{\Delta t_i^{40\%}}{t_{max} - t_{max}} \times 100\% \quad [3]$$

(RVD= Regional Ventilation Delay index; i=region; Δ= delta)

The intratidal gas distribution was analyzed according to Löwhagen et al.14 (formula 4), which is integrated in the EITdiag software. To calculate the intratidal gas distribution the inspiratory part of the global TIV curve is divided into eight iso-volume parts. Thereafter, the eight corresponding time points are translated to the regional TIV curves. Using this technique, we calculated the percentile contribution of the dependent and non-dependent regions to the inspiration. Thereafter, we developed the intratidal gas distribution index (ITV index) to evaluate whether the lung is homogeneously ventilated. The ITV index is calculated by dividing the ITV of the non-dependent lung region by the ITV of the dependent region (formula 5). An ITV index of 1 indicates an equal distribution of ventilation to the dependent and non-dependent lung regions.

$$Fractional\ regional\ ITV_{1\text{-}8} = \frac{ITV_{1\text{-}8}TIV_{ROI}}{ITV_{1\text{-}8}TIV_{Global}} \quad [4]$$

$$ITV\text{-}index = \frac{\sum_{t1,8} ITV\ non\text{-}dependent}{\sum_{t1,8} ITV\ dependent} \quad [5]$$

(ITV =Intratidal Gas Distribution; TIV = Tidal Impedance Variation; ROI = Region of Interest; t = iso-volume part)

The COV reflects the distribution of tidal ventilation in the ventral-to-dorsal direction13 (formula 6). Therefore, the TIV of the dependent region is divided by the total TIV of the EIT image. When most of the tidal ventilation distributes to the dependent lung region this will result in a small COV value. We constructed a plot of the centers of ventilation to visualize the shifts in regional lung ventilation in the anterior-to-posterior direction during the PEEP trial.

$$COV = \frac{TIV_{dorsal}}{TIV_{total}} \quad [6]$$

(COV = Center of Ventilation; TIV = Tidal Impedance Variation)

The GI index, developed by Zhao *et al.* [20;21], quantifies ventilation distribution in the lungs. Therefore, the tidal impedance difference per pixel is subtracted by the median tidal impedance difference of the lung. Thereafter, the result of this subtraction is divided by the total impedance changes of all pixels in order to normalize the calculated values (formula 7). Thus, the GI index calculates the variance in impedance per pixel as compared with the total EIT image. The smaller the GI index, the more homogeneous the lung ventilation. This calculation is integrated in the EITdiag software.

$$GI = \frac{\sum_{x,y \in lung} |\ Impedance\ difference_{xy} - Median\ (Impedance\ difference_{lung})|}{\sum_{x,y \in lung} Impedance\ difference_{xy}} \quad [7]$$

GI index formula: (x and y describe the location of the pixel on the x and y axes; ∈ = element of ventilated part of the EIT image)

Statistical analysis

Statistical analyses were performed using SPSS version 21 (IBM, Chicago, IL, USA). Unless specified otherwise, values are presented as means ± SD. Data were tested for normal distribution and homoscedasticity using the Kolmogorov-Smirnov test and the Brown-Forsythe test. If the data had a normal distribution we applied analysis of variance (ANOVA) otherwise the independent samples Kruskal-Wallis test was used. Differences in PaO_2/FiO_2 ratio and dynamic compliance between the PEEP steps were analyzed using mixed linear model analyses. Correlation between the PaO_2/FiO_2 ratio and ITV index was calculated using the two-tailed Spearman rho test. All *p*-values <0.05 are considered to be statistically significant.

Results

Details of patient characteristics are presented in Table 1. During the entire PEEP trial, patients were ventilated with an inspiratory pressure above PEEP of 10 ± 2 cm H_2O. A PaO_2/FiO_2 ratio ≥350 mmHg was defined as an open lung; in two patients we were unable to open up the lung despite the recruitment maneuver and use of a PEEP level of 15 cm H_2O.

Figure 1 shows the distribution of TIV for one representative patient during the decremental PEEP trial. The effects of decremental PEEP on TIV, regional compliance, VSA, COV, RVD and GI index are presented in Figure 2A-F.

Baseline characteristics of the study population.

No. of patients	12
Age (years)	70 ± 9
Male : Female (n)	9 : 3
Weight (kg)	79 ± 12
PBW (kg)	67 ± 9
Height (m)	1.72 ± 0.08
Body mass index	27 ± 4
Respiratory rate (breaths per minute)	15 ± 1
PIP (cm H_2O)	25 ± 2
V_{Te} (mL)	591 ± 120
V_T/PBW (mL/kg)	8.8 ± 1.7

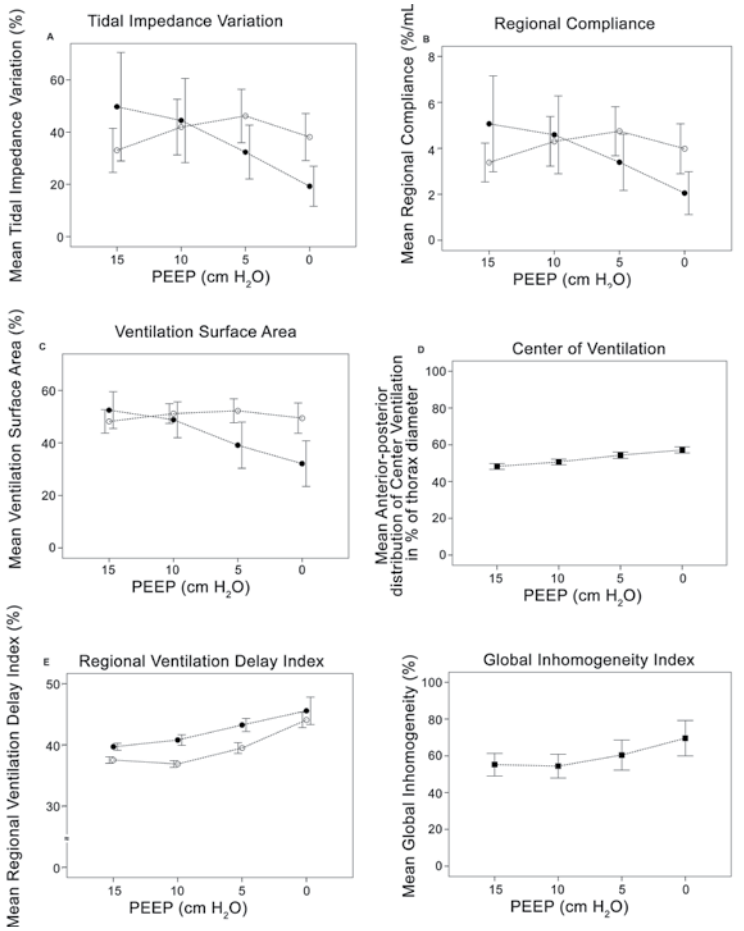
Table 1: Predicted body weight (PBW); Peak Inspiratory Pressure (PIP); Expiratory tidal volume (V_{Te}). Data are presented as means ± SD.

Figure 3 shows the effects of the decremental PEEP trial on the PaO_2/FiO_2 ratio and dynamic compliance for the entire study population. The PaO_2/FiO_2 ratio had the highest value at 15 cm H_2O PEEP but showed a significant decrease after lowering PEEP from 10 to 5 to 0 cm H_2O compared with 15 cm H_2O PEEP (Figure 3A). Dynamic compliance had the highest value at 10 cm H_2O PEEP but showed a significant decrease at a PEEP level of 0 compared with 15 cm H_2O (Figure 3B).

In the non-dependent lung regions, TIV (Figure 2A), regional compliance (Figure 2B) and VSA (Figure 2C) reached the maximum value at 5 cm H_2O PEEP. In contrast, in the dependent region TIV, VSA and regional compliance reached a maximum at the highest PEEP level applied and then decreased during the entire PEEP trial. During the decremental PEEP trial, COV increased steadily towards the anterior part of the thorax cavity, indicating loss of TIV in the dependent region (Figure 2D). During the decremental PEEP trial the RVD index increased in both lung regions and the RVD values of the non-dependent region remained significantly lower than those in the dependent region, except at zero end-expiratory pressure (Figure 2E). The GI index had the lowest values at 15 and 10 cm H_2O PEEP and then increased steadily at lower PEEP levels (Figure 2F), indicating more homogeneous ventilation at higher PEEP levels.

Figure 2: Different electrical impedance tomography (EIT) modalities calculated for the decremental positive end-expiratory pressure (PEEP) trial. Effects of different PEEP levels on regional changes in (A) tidal impedance variation (TIV); (B) regional compliance; (C) ventilation surface area (VSA); (D) center of ventilation (COV); (E) regional ventilation delay (RVD) index; and (F) global inhomogeneity (GI) index. Data are presented as means ± 95% CI. Dashed lines represent the interpolation lines; open circles = non-dependent regions; solid circles = dependent regions; solid squares = entire EIT image.

Figure 3: Changes in partial arterial oxygen pressure (PaO_2)/inspired oxygen fraction (FiO_2) ratio and dynamic compliance during a decremental positive end-expiratory pressure (PEEP) trial. (A) The PaO_2/FiO_2 ratio (mmHg) and (B) dynamic compliance (mL/cm H_2O) are shown for the entire group. The PaO_2/FiO_2 ratio decreased with every PEEP step. The PaO_2/FiO_2 ratio showed a significant decrease at 5 and 0 cm H_2O PEEP compared with 15 cm H_2O PEEP. Dynamic compliance increased after reducing PEEP from 15 to 10 cm H_2O. Thereafter, dynamic compliance decreased with each PEEP step. At 0 cm H_2O PEEP dynamic compliance was significantly reduced compared with 15 cm H_2O PEEP. Solid squares = PaO_2/FiO_2 ratio; solid diamonds = dynamic compliance. *P <0.05.



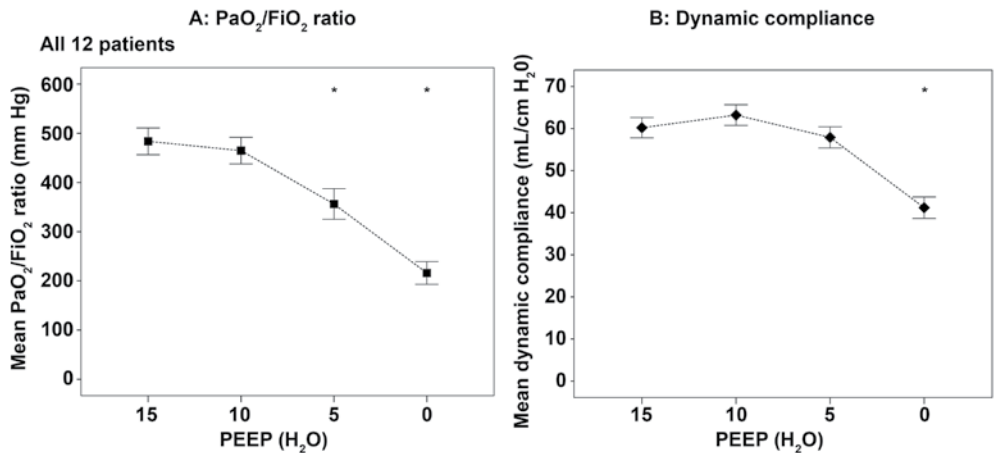


Figure 4 presents the results of intratidal gas distribution. At the highest levels of PEEP, the intratidal gas distribution to the dependent region was higher than that to the non-dependent region. Decreasing the PEEP level resulted in a higher overall gas distribution to the non-dependent region compared with the dependent region. At a PEEP level of 10 cm H_2O, the intratidal gas distribution curves of both regions crossed each other during a breath (Figure 4). Figure 5 shows the calculated ITV index as percentage of 1 for each PEEP level in each individual patient. There was a correlation between the PaO_2/FiO_2 ratio and the ITV index (−0.762; P <0.001).

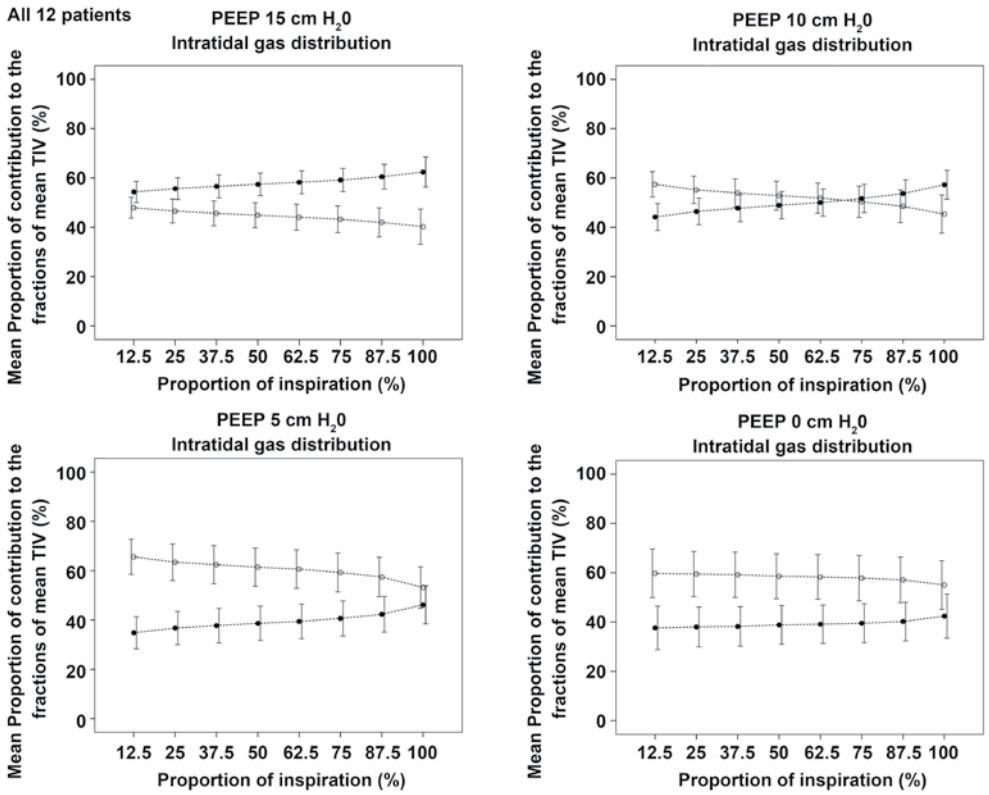


Figure 4: Intratidal gas distribution at varying positive end-expiratory pressure (PEEP) levels. Mean intratidal gas distribution in eight iso-volume steps during four PEEP levels during the decremental PEEP trial. Decreasing the PEEP level resulted in a higher overall gas distribution to the non-dependent region and, subsequently, a lower gas distribution to the dependent region. During the course of inspiration, gas distribution to the non-dependent region decreased whereas it increased to the dependent region. At a PEEP level of 10 cm H_2O, during inspiration the lines representing gas distribution to both regions crossed each other. Dashed lines represent the interpolation lines; open circles = non-dependent region; solid circles = dependent region.

Discussion

This study demonstrates that intratidal gas distribution visualizes the best PEEP as compared with dynamic compliance in post-cardiac surgery patients. In addition, the ITV index is able to determine a specific PEEP level in each individual patient, resulting in an even distribution of tidal volume to the non-dependent and dependent lung regions. Below this specific PEEP level, the intratidal gas distribution is predominantly distributed to the non-dependent region. This indicates that, at these PEEP levels, there is less ventilation in the dependent region due to lung collapse. In contrast, at PEEP levels above this specific level, there is less ventilation in the non-dependent region indicating overdistention.

In an experimental study, Protti *et al.*[22] showed that ventilation with high tidal volumes, resulting in an expiratory volume of 1.5 times FRC (equal to a strain of 1.5), caused severe lung edema; all their study animals died within the observation period of 54 h. In a second study, the authors ventilated all animals with a strain of 2.5 and showed that high tidal volumes with a low level of PEEP damaged the lungs and increased mortality, whereas high PEEP levels together with low tidal volume but with the same strain of 2.5, did not result in edema and all animals in this group survived[23]; it was suggested that application of high PEEP levels might lead to more homogeneous lung ventilation. In 1970, Mead et al. estimated that forces acting on lung tissue increase with a factor 4.5 when lungs are inhomogeneously ventilated[24]. This was recently confirmed by Rausch *et al.*[25] who performed x-ray tomographic microscopy (generating detailed three-dimensional alveolar geometry) in rat lungs and found local strain values of four times the global strain. Therefore, a parameter that describes the ventilation distribution could be of importance in finding the best PEEP in patients with acute respiratory distress syndrome (ARDS).

Intratidal gas distribution was first described by Löwhagen et al. who used this technique in 16 volume-controlled ALI/ARDS patients to describe ventilation distribution to different lung regions within an inspiration[14]; they found that the intratidal gas distribution of the dorsal and mid-dorsal regions increased at higher PEEP levels, indicating redistribution of ventilation to the dependent region[14]. We modified their analysis by combining the ventral and mid-ventral regions into a non-dependent region and their mid-dorsal and dorsal regions into a dependent region[26]. Previously, we used the intratidal gas distribution technique to assess the effect of different assist levels during pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA) on ventilation distribution. We demonstrated that NAVA improved ventilation of the dependent lung region compared with PSV, leading to a more homogeneous ventilation of the lung[26]. In that study using the intratidal gas distribution technique, we demonstrated for the first time, less over-assistance during NAVA whereas there was marked over-assistance at higher pressure support levels[26]. This latter finding indicates that PSV with higher support levels mimics control ventilation with predominantly ventilation of the non-dependent lung. We also used the intratidal gas distribution in an experimental study comparing global and regional parameters to detect best PEEP in healthy and in ARDS lungs[27]. In these animals we found the same trend as in the present study, that is, that the intratidal gas distribution curves of the dependent and non-dependent regions reached each other at a specific PEEP level. Below this specific PEEP level ventilation is mainly distributed to the non-dependent lung and above this level ventilation is mainly distributed to the dependent lung region. Above this specific PEEP level ventilation distribution to the non-dependent lung region diminished at higher

PEEP levels, indicating that this region is overdistended.
In the present study we used a decremental PEEP trial and, as long as the PEEP level is adequate to keep the dependent lung region open, the used pressure amplitude of around 10 cm H_2O was sufficient to ventilate this region; however, after collapse the inspiratory pressures are too low to open up this dependent region. This indicates that ventilation distribution to the dependent lung will be improved if higher inspiratory pressures are used.
To make the intratidal gas distribution an easy-to-use parameter at the bedside, we introduced the ITV index. An ITV index of 1 indicates homogeneous distribution of tidal volume to the non-dependent and dependent lung regions. The intratidal gas distribution shows the behavior of the distribution of tidal volume during one breath. Figure 5 illustrates the ITV index, in which 100% indicates an ITV index of 1, that is, an equal distribution of ventilation to the dependent and non-dependent lung regions.

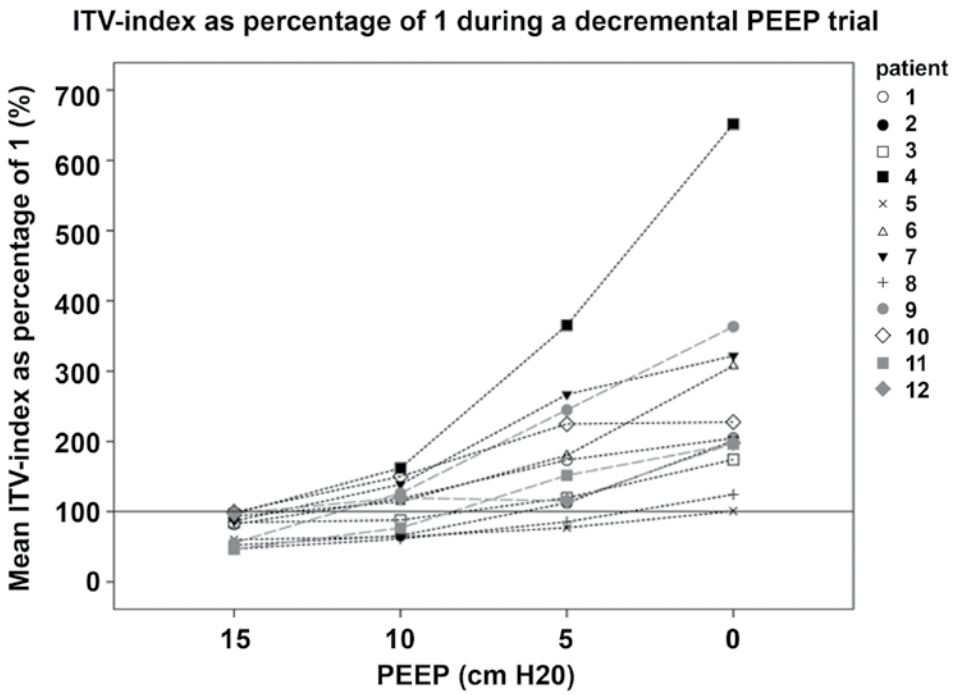


Figure 5: Intratidal gas distribution (ITV) index at varying positive end-expiratory pressure (PEEP) levels for the individual patients. Mean ITV index is shown as a percentage of 1. Here, the value 100% indicates that both lung regions are equally ventilated. Values >100% indicate that ventilation is predominantly distributed to the non-dependent region whereas values <100% indicate that the dependent lung region is predominantly at that PEEP level.

To test whether the intratidal gas distribution reliably defines the optimal PEEP, we compared the optimal PEEP values defined by the intratidal gas distribution, PaO_2/FiO_2 ratio and dynamic compliance. We found a negative correlation between the PaO_2/FiO_2 ratio and the ITV index. A lower ITV index means that more tidal ventilation is distributed to the better perfused dependent lung region, leading to less shunt and improved PaO_2/FiO_2 ratio. In contrast, we found no correlation between ITV and dynamic compliance. Alveoli that open up during inspiration but collapse during expiration give higher compliance values, whereas this cyclic collapse is harmful to the lung. In addition, recruitment of a lung region, but collapse in another lung region at the same time, will not increase dynamic compliance of the entire lung. This latter effect can be visualized by regional or pixel compliance from EIT. Costa et al. introduced the regional or pixel compliance based on EIT measurements during a decremental PEEP trial in two patients with pneumonia[12]. These patients were ventilated with PCV using constant pressure amplitude and the change in impedance represents the change in volume; thus, for each pixel the compliance could be calculated. The highest compliance at a specific PEEP level was indicated as the best PEEP. Above this PEEP value, compliance decreased due to overdistention and below this value compliance decreased due to collapse. The authors showed that the optimal PEEP level was different for the dependent and non-dependent region[12]. Also, in their experimental study, Dargaville et al. demonstrated that ventral, medial and dorsal lung regions have different optimal PEEP levels based on regional compliance values in both normal and surfactant-depleted lungs [28]. This was confirmed by our results, in which the best PEEP level for the non-dependent and dependent regions were 5 and 15 cm H_2O, respectively (Fig. 2B).
In accordance with our previous studies[16;29], we found more ventilation of the dependent region at higher PEEP levels, as described by the parameter COV (Fig. 2D). COV describes the ventilation distribution in the ventral-to-dorsal direction and a value of 50% reflects an even distribution[13]. Thus, COV provides information about the optimal distribution of tidal volume to the non-dependent and dependent regions at a certain PEEP level, but it does not give information about collapse or overdistention during a breath, as is seen with the intratidal gas distribution.
The RVD was developed to assess the homogeneity of aeration of the lung regions[15;19] during a slow inflation maneuver. It has been demonstrated in pigs that ALI lungs are more inhomogeneous compared with healthy lungs[21]; however, application of higher PEEP levels improved the homogeneity of lung ventilation. In addition, the authors showed that the dependent region was slower inflated as compared with the non-dependent region, indicating inhomogeneous ventilation of the dorsal lung parts; however, they used the SDs of the RVD index to create a ventilation homogeneity map[21]. In the present study we calculated the time needed to reach a threshold of 40% of the regional impedance change compared with the total inspiratory time and without the use of a slow flow inflation. We found that RVD values in both lung regions increased at each decremental PEEP step. Therefore, we were unable to detect the best PEEP level by means of RVD, with the used PEEP levels. However, Wrigge et al. described that RVD could only be used during a slow flow inflation maneuver with a tidal volume of 12 mL/kg to describe tidal recruitment [12-15]. Therefore, in the present study the results of the RVD are incorrect. Another index to describe homogeneous ventilation is the GI index, which quantifies the variation in tidal ventilation distribution[20;21] and shows the lowest value in healthy patients and the highest value in patients with ARDS[21]. However, because this index describes homogeneity based on differences in measured impedance, the index value does not take into account the presence of atelectasis or overdistention and, therefore, we believe that this is not an appropriate index. As, within our range of PEEP levels we were unable to detect an optimal PEEP level based on the GI index and RVD index, it is possible that an optimum may have been found if

higher PEEP levels had been applied than used in the present study.

This study has some limitations. First, EIT measures ventilation distribution in a lung slice of approximately 5 to 10 cm[30;31]; therefore, information gathered by EIT has a limited external validity for the remaining lung tissue. However, placing the EIT belt at a higher position is known to reduce the probability to detect inhomogeneity of the lungs at decreasing PEEP levels[16] and, thus, the probability to detect lung areas susceptible to the development of VILI. Therefore, we placed the EIT belt just above the diaphragm to increase the probability of detecting lung collapse.

Second, based on the protocol of our study described previously, EIT measurements were not recorded continuously[16]. However, by treating the EIT data as percentages (instead of absolute values) the baseline shifts are corrected. In addition, the EIT belt was not disconnected from the patient to measure the same lung slice during each measurement. Third, this study was performed with post-cardiac surgery patients who respond well to a recruitment maneuver. However, Reis Miranda *et al.* [32] demonstrated that a PEEP level of 15 cm H_2O was necessary to keep the lung open (PaO_2/FiO_2 >350 mmHg) in cardiac-surgery patients; the authors also showed that if patients are ventilated according to the open lung concept, fewer cytokines are released, FRC recovers faster, less oxygen is required in the normal ward, and that afterload of the right ventricle is lower in these patients [32-35]. Despite the fact that adequate PEEP settings are also important in cardiac-surgery patients, most patients in need of a recruitment maneuver in combination with the best PEEP are ARDS patients. However, ARDS patients show fewer response to a recruitment maneuver compared with cardiac-surgery patients, due to less gravitational dependent infiltrates. Particularly in ARDS patients it is important to achieve homogeneous ventilation to reduce the stress acting on lung tissue. Our earlier experimental study showed the same trend of tidal ventilation distribution during a decremental PEEP trial in both ARDS-induced and healthy lungs[27]. However, additional studies are required to test whether application of this specific PEEP level leads to better outcome and also to confirm the present findings in patients with ARDS.

Conclusion

The ITV index was comparable with dynamic compliance to indicate the best PEEP level in post-cardiac surgery patients. The intratidal gas distribution is able to identify the onset of overdistention in the non-dependent part and recruitment in the dependent part. We believe that the ITV index may be the ideal bedside tool to detect the best PEEP; however, its preventive effect on ventilator-induced lung injury (VILI) and thereby on outcome still needs to be examined in patients with ALI/ARDS.

References

1. Gattinoni L, Carlesso E, Caironi P (2012) Stress and strain within the lung. Curr Opin Crit Care 18: 42-47
2. Suter PM, Fairley B, Isenberg MD (1975) Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292: 284-289
3. Tusman G, Suarez-Sipmann F, Bohm SH, Pech T, Reissmann H, Meschino G et al. (2006) Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med 32: 1863-1871

4. Suarez-Sipmann F, Bohm SH, Tusman G, Pesch T, Thamm O, Reissmann H et al. (2007) Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. Crit Care Med 35: 214-221
5. Carvalho AR, Jandre FC, Pino AV, Bozza FA, Salluh J, Rodrigues R et al. (2007) Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. Crit Care 11: R86
6. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G et al. (2008) Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth Analg 106: 175-81, table
7. Henzler D, Mahnken AH, Wildberger JE, Rossaint R, Gunther RW, Kuhlen R (2006) Multislice spiral computed tomography to determine the effects of a recruitment maneuver in experimental lung injury. Eur Radiol 16: 1351-1359
8. Pelosi P, Rocco PR, de Abreu MG (2011) Use of computed tomography scanning to guide lung recruitment and adjust positive-end expiratory pressure. Curr Opin Crit Care 17: 268-274
9. Frerichs I, Hinz J, Herrmann P, Weisser G, Hahn G, Dudykevych T et al. (2002) Detection of local lung air content by electrical impedance tomography compared with electron beam CT. J Appl Physiol 93: 660-666
10. Meier T, Luepschen H, Karsten J, Leibecke T, Grossherr M, Gehring H et al. (2008) Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. Intensive Care Med 34: 543-550
11. Victorino JA, Borges JB, Okamoto VN, Matos GF, Tucci MR, Caramez MP et al. (2004) Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. Am J Respir Crit Care Med 169: 791-800
12. Costa EL, Borges JB, Melo A, Suarez-Sipmann F, Toufen C, Jr., Bohm SH et al. (2009) Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. Intensive Care Med 35: 1132-1137
13. Frerichs I, Dargaville PA, van GH, Morel DR, Rimensberger PC (2006) Lung volume recruitment after surfactant administration modifies spatial distribution of ventilation. Am J Respir Crit Care Med 174: 772-779
14. Löwhagen K, Lundin S, Stenqvist O (2010) Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol 76: 1024-1035
15. Wrigge H, Zinserling J, Muders T, Varelmann D, Gunther U, von der GC et al. (2008) Electrical impedance tomography compared with thoracic computed tomography during a slow inflation maneuver in experimental models of lung injury. Crit Care Med 36: 903-909
16. Bikker IG, Preis C, Egal M, Bakker J, Gommers D (2011) Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. Crit Care 15: R193
17. Adler A, Amyot R, Guardo R, Bates JH, Berthiaume Y (1997) Monitoring changes in lung air and liquid volumes with electrical impedance tomography. J Appl Physiol 83: 1762-1767

18. Frerichs I, Hahn G, Schiffmann H, Berger C, Hellige G (1999) Monitoring regional lung ventilation by functional electrical impedance tomography during assisted ventilation. Ann N Y Acad Sci 873: 493-505
19. Muders T, Luepschen H, Zinserling J, Greschus S, Fimmers R, Guenther U et al. (2012) Tidal recruitment assessed by electrical impedance tomography and computed tomography in a porcine model of lung injury. Crit Care Med 40: 903-911
20. Zhao Z, Moller K, Steinmann D, Frerichs I, Guttmann J (2009) Evaluation of an electrical impedance tomography-based Global Inhomogeneity Index for pulmonary ventilation distribution. Intensive Care Med 35: 1900-1906
21. Zhao Z, Steinmann D, Frerichs I, Guttmann J, Moller K (2010) PEEP titration guided by ventilation homogeneity: a feasibility study using electrical impedance tomography. Crit Care 14: R8
22. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D et al. (2011) Lung stress and strain during mechanical ventilation: any safe threshold? Am J Respir Crit Care Med 183: 1354-1362
23. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T et al. (2013) Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?. Crit Care Med 41: 1046-1055
24. Mead J, Takishima T, Leith D (1970) Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 28: 596-608
25. Rausch SM, Haberthur D, Stampanoni M, Schittny JC, Wall WA (2011) Local strain distribution in real three-dimensional alveolar geometries. Ann Biomed Eng 39: 2835-2843
26. Blankman P, Hasan D, van Mourik MS, Gommers D (2013) Ventilation distribution measured with EIT at varying levels of pressure support and Neurally Adjusted Ventilatory Assist in patients with ALI. Intensive Care Med 39: 1057-1062
27. Bikker IG, Blankman P, Specht P, Bakker J, Gommers D (2013) Global and regional parameters to visualize the 'best' PEEP during a PEEP trial in a porcine model with and without acute lung injury. Minerva Anestesiol 79: 983-992
28. Dargaville PA, Rimensberger PC, Frerichs I (2010) Regional tidal ventilation and compliance during a stepwise vital capacity manoeuvre. Intensive Care Med 36: 1953-1961
29. Bikker IG, Leonhardt S, Bakker J, Gommers D (2009) Lung volume calculated from electrical impedance tomography in ICU patients at different PEEP levels. Intensive Care Med 35: 1362-1367
30. Erlandsson K, Odenstedt H, Lundin S, Stenqvist O (2006) Positive end-expiratory pressure optimization using electric impedance tomography in morbidly obese patients during laparoscopic gastric bypass surgery. Acta Anaesthesiol Scand 50: 833-839
31. Lindgren S, Odenstedt H, Olegard C, Sondergaard S, Lundin S, Stenqvist O (2007) Regional lung derecruitment after endotracheal suction during volume- or pressure-controlled ventilation: a study using electric impedance tomography. Intensive Care Med 33: 172-180
32. Reis MD, Struijs A, Koetsier P, van Thiel R, Schepp R, Hop W et al. (2005) Open lung ventilation improves functional residual capacity after extubation in cardiac surgery. Crit Care Med 33: 2253-2258
33. Reis MD, Gommers D, Struijs A, Meeder H, Schepp R, Hop W et al. (2004) The open lung concept: effects on right ventricular afterload after cardiac surgery. Br J Anaesth 93: 327-332

34. Reis MD, Gommers D, Struijs A, Dekker R, Mekel J, Feelders R et al. (2005) Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery. Eur J Cardiothorac Surg 28: 889-895
35. Reis MD, Klompe L, Mekel J, Struijs A, van BJ, Lachmann B et al. (2006) Open lung ventilation does not increase right ventricular outflow impedance: An echo-Doppler study. Crit Care Med 34: 2555-2560

CHAPTER 7

Detection of optimal PEEP for equal distribution of tidal volume by volumetric capnography and Electrical Impedance Tomography during decreasing levels of PEEP in post cardiac-surgery patients

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Abstract

Background

Homogeneous ventilation is important for prevention of ventilator-induced lung injury. Electrical impedance tomography (EIT) has been used to identify optimal positive end-expiratory pressure (PEEP) by detection of homogenous ventilation in non-dependent and dependent lung regions. We aim to compare the capability of volumetric capnography (Vcap) with EIT with respect to detect homogenous ventilation between the two lung regions.

Methods

Fifteen mechanically-ventilated post-cardiac surgery patients were studied. Ventilator settings were adjusted to volume-controlled mode with a fixed tidal volume (Vt) of 6-8 ml/kg predicted body weight. Different PEEP levels were applied (14 to 0 cm H_2O, in steps of 2 cm H_2O) and blood gases, Vcap and EIT were measured.

Results

Tidal impedance variation of the non-dependent region was highest at 6 cm H_2O PEEP, and decreased significantly at 14 cm H_2O PEEP indicating decrease in the fraction of Vt in this region. At 12 cm H_2O PEEP, homogenous ventilation was seen between both lung regions. Bohr and Enghoff dead space calculations decreased from a PEEP of 10 cm H_2O. Alveolar dead space divided by alveolar Vt decreased at PEEP levels ≤6 cm H_2O. The normalized slope of phase III significantly changed at PEEP levels ≤ 4 cm H_2O. Airway dead space was higher at higher PEEP levels and decreased at the lower PEEP levels.

Conclusions

In postoperative cardiac patients, dead space calculations according to Bohr and Enghoff agreed well with EIT to detect the optimal PEEP for an equal distribution of inspired volume among the non-dependent and the dependent lung regions. Airway dead space reduces at decreasing PEEP levels.

Introduction

Ventilator-induced lung injury (VILI) is a well-recognized complication of mechanical ventilation, which occurs in both patients with acute respiratory distress syndrome (ARDS)[1] and healthy lungs[2;3]. The deleterious effects of mechanical ventilation are considered to be caused due to large amounts of stress and strain acting on lung tissue due to inhomogeneous ventilation of the lungs[4-6]. Although, protective lung strategies using low tidal volumes have been strongly recommended to prevent the development of VILI, the amount of Positive End-Expiratory Pressure (PEEP) that should be applied is still under debate[7;8]. The positive effect of PEEP depends on the recruitability of lung tissue, which varies between patients[9;10], but also from day to day. Therefore, setting the PEEP level without a reliable tool to estimate the distribution of inspiratory tidal volume (Vt) at the bedside is a challenging activity.

Volumetric capnography (Vcap) is a non-invasive technique that describes the CO_2 exhalation during one breath, and can be used to calculate alveolar and airway dead space[11]. Because elimination of CO_2 depends on alveolar ventilation and pulmonary perfusion, V/Q mismatches in either hyperinflated or collapsed lung areas will affect the amount of exhaled CO_2 and thereby Vcap. Recently, a multi-center observational study showed that an increased dead space fraction in patients with ARDS was associated with an increased mortality[12]. Several studies showed the capability of Vcap in detecting optimal PEEP level during mechanical ventilation in various lung pathological conditions[13-15]. Böhm *et al.*[14] showed in 11 morbidly obese patients undergoing bariatric surgery, Slope III (S_{III}) has a high sensitivity and specificity to detect lung recruitment. They concluded that S_{III} was useful for identifying appropriate levels of PEEP in those patients. In 20 obese patients undergoing laparoscopic bariatric surgery Tusman *et al.*[13] found that both Vcap and pulse-oximetry, as compared to respiratory compliance, are accurate parameters for detection of alveolar collapse. Fengmei *et al.*[15] found that best PEEP based on dead space fraction corresponded well with best PEEP according to highest respiratory compliance, in 23 ARDS patients. Therefore, Vcap is promising technique to detect alveolar collapse and recruitment at the bedside.

Electrical Impedance Tomography (EIT) is a non-invasive, radiation-free, real time imaging modality, which has proven to correlate well with Computed Tomography (CT) according to assessment of changes in gas volume and tidal volume[16-18]. Recently, we showed that the intratidal gas distribution calculated from EIT measurements is able to define a patient specific PEEP level at which the lungs are homogeneously ventilated among dependent and non-dependent lung regions. This parameter was evaluated in both experimental studies and in patients[19-21], but also during pressure support ventilation (PSV), Neurally Assisted Ventilatory Assist (NAVA) and pressure control ventilation (PCV)[22;23]. In addition, EIT has been used to visualize hyperinflation in the non-dependent region at a certain PEEP level when pixel-compliance is decreased[24;25]

Suter *et al.*[26] defined optimal PEEP as the balance of adequate PaO_2 levels, good compliance and elimination of CO_2. However, we believe that stress and strain are important contributors to lung injury as both factors increases with inhomogeneous ventilation[5;6]. Therefore, the main goal of this study was to compare the results of Vcap measurements with that of EIT in finding the optimal PEEP with an equal distribution of the inspiratory volume among the dependent and the non-dependent regions.

Materials and Methods

Study population

In the present prospective pilot-study, 15 mechanically ventilated post-cardiac surgery patients, who underwent coronary-artery bypass grafting and/or cardiac-valve surgery, admitted to the cardiothoracic intensive care unit (ICU) were included. The local medical ethical committee approved the study protocol and written informed consent was obtained from each patient or their relatives. Data was collected between January and July in 2014.

The inclusion criteria were age >18 years, written informed consent, hemodynamically stable. Exclusion criteria were a pacemaker, pneumothorax, thoracic deformations and severe airflow defined as forced expiratory volume in 1 second below 70% of forced vital capacity.

Data on patient demographics and characteristics

Patient characteristics			
No. of patients		15	
Age (year)		70 ± 8	
Male/Female		13/2	
Height (cm)		176 ± 13	
Weight (kg)		86 ± 18	
Predicted body weight (kg)		70 ± 13	
Body mass index		28 ± 4	
CPB time (min)		112 ± 35	
Type of surgery	**CABG**	**Valve replacement**	**CABG + Valve replacement**
	10	3	2

Hemodynamic data at admission on ICU

Mean arterial pressure (mmHg)	70 ± 9
Heart rate (BPM)	77 ± 15

Ventilator settings and respiratory parameters at admission on ICU

Positive end-expiratory pressure (cm H_2O)	8 ± 1
Peak inspiratory pressure (cm H_2O)	22 ± 2
Expiratory tidal volume (ml)	494 ± 74
Expiratory tidal volume /	7.1 ± 0.6
Predicted body weight (ml/kg PBW)	
Respiratory rate (breaths/min)	17 ± 2
PaO_2/FiO_2 (mmHg)	350 ± 101
$PaCO_2$ (mmHg)	42.2 ± 4.5

Table 1: Data are presented as mean ± SD unless otherwise specified. Predicted body weight (PBW), Cardiopulmonary bypass (CPB), Coronary artery by-pass graft (CABG), Arterial partial pressure of O_2 (PaO_2), Fraction of inspired oxygen (FiO_2), Arterial partial pressure of CO_2 ($PaCO_2$)

Study protocol

For Vcap measurements a mainstream CO_2 sensor was placed between the endotracheal tube and ventilator tubing's, and was connected to a NICO-capnograph (Novametrix, Wallinford, Connecticut, USA). Specific software (Analysis plus, Novametrix, Wallinford, Connecticut, USA) was used to record all Vcap data. In order to perform electrical impedance tomography (EIT) measurements, a silicon belt with 16 electrodes was placed around the thoracic cage between the 5th and 6th intercostal space (Pulmovista 500, Dräger, Lübeck, Germany). Ventilator settings were set to volume-controlled mode (Evita-infinity, Dräger, Lübeck, Germany) with a fixed tidal volume of 6-8 ml/kg predicted body weight and inspiration/expiration (I/E) ratio of 1:2. We deliberately choose volume control in order to avoid a change in the minute volume due differences in lung compliance at different levels of PEEP. The initial setting of the respiratory rate and fraction of inspired oxygen was adjusted to maintain an end-tidal carbon dioxide tension and oxygen saturation within a range of 35-45 mmHg and 97-100%, respectively. PEEP was set according to the attending physician. Vt, respiratory rate (RR), I/E ratio remained unchanged throughout the entire study period.

We are reluctant to apply high levels of PEEP (> 15 cm H_2O) in postoperative patients after cardiac surgery who obviously have no ALI or ARDS, as these patients are generally prone to hemodynamic instability. Therefore, the patients were not subjected to recruitment maneuvers. After baseline measurements of Vcap and EIT, the PEEP level was increased to 14 cm H_2O. This PEEP level was maintained for 15-20 minutes in order to reach a steady state situation, as assessed by a stable signal of the volume of exhaled carbon dioxide (VCO_2). Thereafter, the PEEP was decreased from 14 to 0 cm H_2O PEEP in steps of 2 cm H_2O. Each PEEP level was applied for 5 to 10 minutes depending on hemodynamically stability. Blood gas analysis, Vcap and EIT were measured during each PEEP step.

Data analysis

Volumetric capnography; model fitting and parameters

Vcap, which is constructed from expired CO_2 concentration and expired volume, can be represented by a mathematical function, which is previously introduced by Tusman *et al.*[27;28]. This makes the analysis of the Vcap data less susceptible to noise. To obtain this mathematical function from Vcap data, a non-linear least square curve fitting algorithm according to Tusman *et al.*[27] was used in a custom-made Matlab® (The MathWorks, Natick, MA, USA) program. From this model, parameters were derived for further analysis. First, the Vcap curve was divided into three phases (Phase I, II and III) (Fig.1). Phase I indicates the CO_2 volume originated from the airways, whereas phase III is the CO_2 from the alveoli. Phase II therefore is the phase with CO_2 from both the airways and alveoli. The inflection point of Phase II (Point A), which is determined by the maximum of the first derivative of the fitted model, was defined as the mean airway-alveolar interface that separates the airway from the alveolar compartment. Airway dead space (VD_{aw}) is the volume from the beginning of the expiration until point A. Slope II (S_{II}) is the slope of the inflection point of Phase II. Slope III (S_{III}) is the slope of phase III, which is calculated according to Tusman *et al.*[27;28]. Therefore, $phase_{III}$ was divided into three even sized segments.

A line was fitted through the second segment of $phase_{III}$ by the least-square method. The slope of this fitted line was determined as S_{III}. Thereafter slope III was divided by the fraction of end tidal CO_2 ($FECO_2$) in order to normalize the value and make it comparable between patients[28;29].

Normalized Slope III (SnIII) represents the homogeneity of ventilation and pulmonary perfusion, which is considered as a good indicator of the global V/Q matching. SnIII increases in lung conditions associated with a mismatch of ventilation and perfusion like atelectasis or pulmonary artery embolism, whereas low values indicate homogeneous V/Q matching.

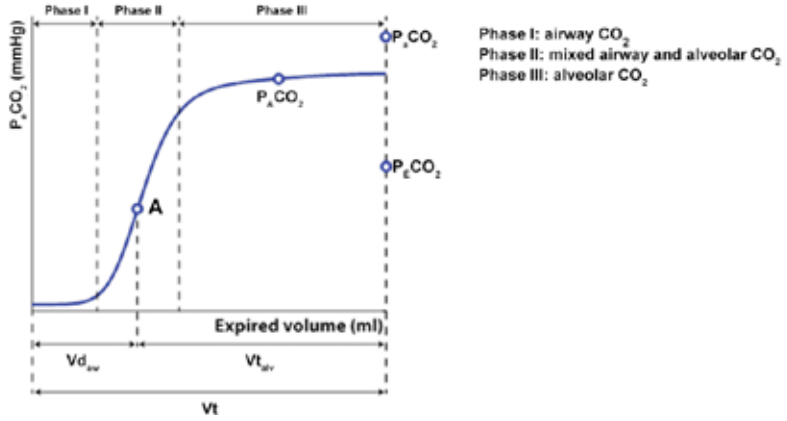


Figure 1: Schematic model of three phases of the expiration. The Vcap curve is divided in three phases. Phase I represents exhaled CO_2 from the airways, whereas phase III represents exhaled CO_2 from the alveoli. Phase II is a mixed phase with CO_2 from both the airways and alveoli. Point A is the inflection point of phase II, which is the theoretical point where the airway compartment is separated from the alveolar compartment. Airway dead space (VDaw); Alveolar tidal volume (Vt_{alv}); Tidal volume (Vt).

Physiological dead space was calculated according to the formula developed by Bohr, and the Enghoff modification of Bohr's formula [30] (formula 1 + formula 2):
(Mean alveolar partial pressure of CO_2 (P_aCO_2); mixed expired partial pressure of CO_2 ($P\bar{E}CO_2$ =))

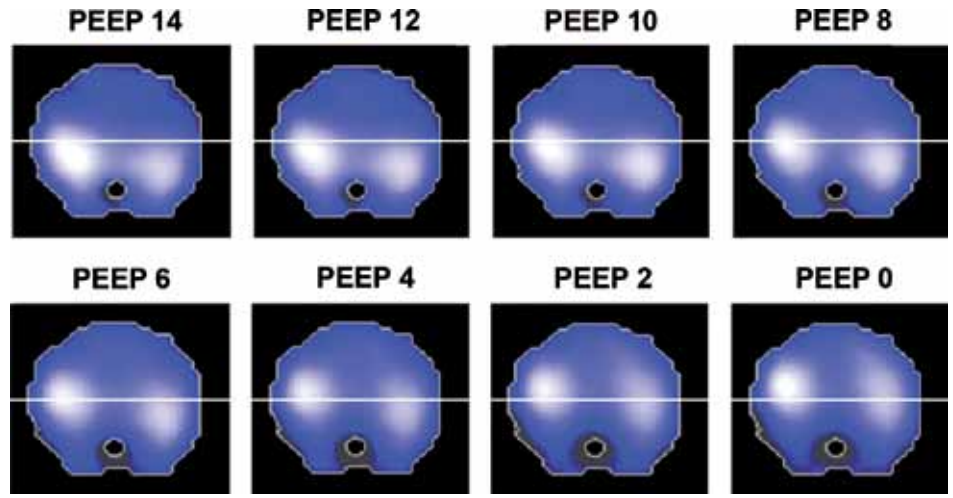
$$VD_{Bohr}/VT = \frac{P_ACO_2 - P\bar{E}CO_2}{P_ACO_2} \quad [1]$$

$$VD_{Enghoff}/VT = \frac{P_aCO_2 - P\bar{E}CO_2}{P_aCO_2} \quad [2]$$

Alveolar dead space (VD_{alv}) was computed by subtracting VD_{aw} from $VD_{Enghoff}$. We chose to subtract VD_{aw} from $VD_{Enghoff}$ as the $VD_{Enghoff}$ contains all causes of V/Q inhomogeneity, whereas the Bohr formula is not supposed to contain shunts and low V/Q regions. The ratio of VD_{alv} to alveolar tidal volume (VT_{alv}) was obtained by dividing VD_{alv} by VT_{alv} (VT_{alv}=VT - VD_{aw}), in which VT_{alv} represents alveolar tidal volume.

EIT parameters

EIT data were recorded with a sample frequency of 20 Hz. Data was reconstructed and analyzed using special software (EITdiag, Dräger, Lübeck, Germany). For each PEEP level, 10 to 20 consecutive breaths at the end of each PEEP step were selected for analysis, with the assumption that the lungs were best adapted to the ventilator settings at that time. EIT data contains signals induced by the respiratory system and the circulatory system. Therefore, to filter out signals related to the circulatory system, EIT data was filtered using a low pass-filter set to 40 beats per minute. The reconstructed image was represented as a ventilation distribution map, which was generated by tidal impedance changes caused, by inspiration and expiration. These impedance changes are presented as tidal impedance variation (TIV) and have been shown to correlate well with gas volume changes as measured by CT-scans [16-18]. The surface area of the distribution map was divided into two equal regions of interest (ROIs), to know the non-dependent and dependent lung regions (online supplement Fig.1). The surface area of the EIT map was kept equal for all PEEP steps.



Online supplement figure 1: Example of reconstructed EIT images during the decremental PEEP trial. The lighter the color, the higher the impedance and the more aerated the lung region is. The surface area used in the EIT parameter calculations at every PEEP step is equal to the largest surface area (in this case at PEEP 12 cm H_2O). The white line divides the EIT image into two equal regions of interest, to be known as the dependent and non-dependent lung region. During the decremental PEEP trial the aeration of the lungs decreased and shifted from the dependent towards the non-dependent lung region.

The intratidal gas distribution (ITV) was developed by Löwhagen *et al.*[21] (formula 3). The ITV describes the amount of the impedance distributed to each region of interest within one inspiration. For this calculation Löwhagen *et al.*[21] divided the inspiratory part of the global impedance curve into eight equal volume sections. In other words each part of the inspiration is 12.5% of the entire inspiration. Thereafter, they transposed the time needed for each section of the inspiration to the regional curves. In this way they were able to calculate the contribution of four

different regions of interest to the inspiration during a single breath. According to our previous publications[19;20;22;31] we calculated the ITV for two instead of four regions of interest. Using the ITV calculation one is able to analyze the ventilation homogeneity during the inspiration. In order to reliably calculate the ITV, the filtered EIT signals were re-sampled with a frame rate of 40 Hz. This step is important in order reliably divide the inspiratory part of the global TIV curve into eight iso-volume sections. (ITV = *Intratidal Gas Distribution*; TIV = *Tidal Impedance Variation*; ROI = *Region of Interest*; t = *iso-volume part*)

$$Fractional\ regional\ ITV_{1\text{-}8} = \frac{ITV_{1\text{-}8}\ TIV_{ROI}}{ITV_{1\text{-}8}\ TIV_{Global}} \qquad [3]\ ^{21}$$

In addition to the capnography and EIT parameters we also calculated the dynamic compliance. Dynamic compliance was calculated by dividing the expiratory tidal volume by Peak Inspiratory Pressure (PIP) minus PEEP.

Statistical Analysis

Statistical analyses were carried out using SPSS 21 (Chicago, IL, USA). Data are stated as mean ± SD unless otherwise specified. Normal distribution of the data was tested using the Kolmogorov-Smirnov test, whereas homoscedasticity was tested using the Brown-Forsythe test. Changes in Vcap and EIT parameters during the entire protocol were tested using mixed linear models. Differences between two sequent PEEP steps are tested using the paired-t test for normal distributed data, and using the Wilcoxon rank sum test for not normal distributed data. For all statistical test $p < 0.05$ was considered statistically significant.

Results

The initial physiological data, measured shortly before 14 cm H_2O was applied, is summarized in Table 1. During the different PEEP levels, blood gases and dynamic compliance remained stable down to a PEEP level of 2 cm H_2O and decreased significantly at 0 PEEP (ZEEP) (Table 2). Figure 2 shows the TIV for the dependent and non-dependent lung region. The 14 cm H_2O PEEP step was chosen as reference, and the TIV of both lung regions together was set to 100% at 14 cm H_2O, Therefore, at lower PEEP levels the sum of TIV of both regions can be more or less than 100%, as compared to PEEP 14 cm H_2O. At 14 cm H_2O of PEEP, most of the ventilation was distributed to the dependent lung region and from PEEP level of 10 cm H_2O and lower, the non-dependent lung region became predominant ventilated (Fig. 2). TIV in the dependent lung region decreased during each PEEP step reduction from a PEEP of 12 cm H_2O, indicating less ventilation at lower PEEP levels due to collapse (Fig. 2). TIV in the non-dependent region had the highest value at 6 cm H_2O of PEEP (Fig. 2). In addition, ventilation was evenly distribution among dependent and non-dependent regions at 12 and 10 cmH_2O PEEP (Fig. 3).

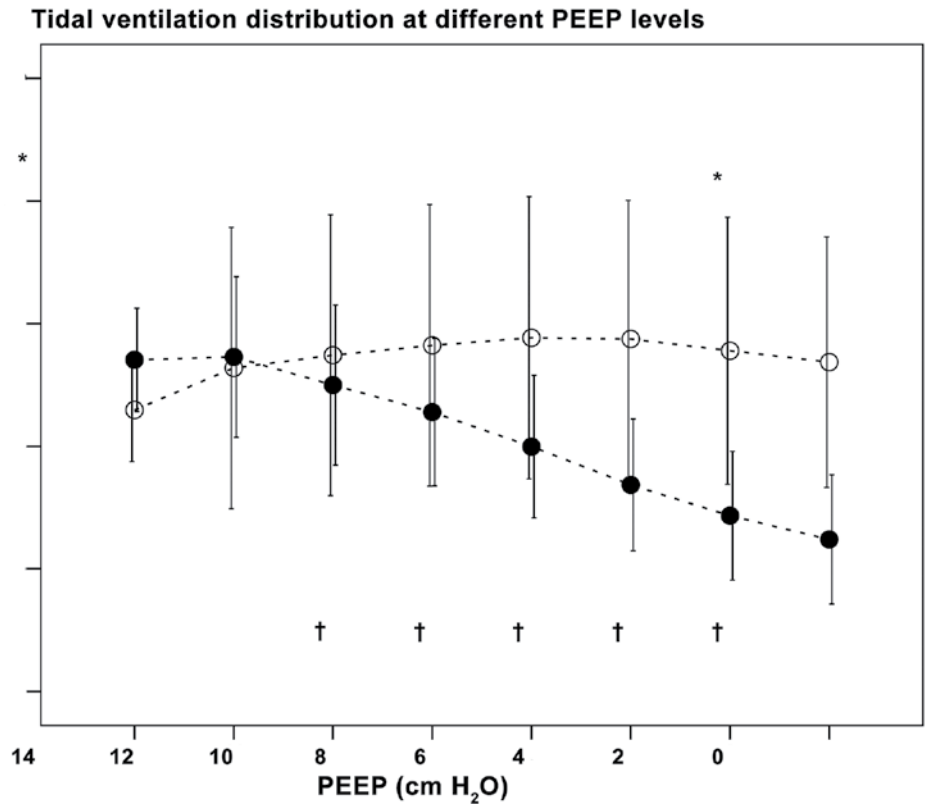


Figure 2: Tidal Impedance Variation at different PEEP levels. Data are shown as mean ± SE. In the dependent lung region the ventilation distribution was decreased when PEEP was lowered, whereas in the non-dependent region received more ventilation as compared to PEEP 14 cm H_2O. * Indicates a significant reduction in TIV of the non-dependent region according to 6 cm H_2O. # Indicates a significant reduction in TIV of the dependent region as compared to 12 cm H_2O. Dashed lines represents the interpolation lines; open circles = non-dependent region; solid circles = dependent region. $p < 0.05$ was considered significant.

Dead space variables, blood gas analysis and compliance during the decremental PEEP trial								
PEEP (cm H_2O)	**14**	**12**	**10**	**8**	**6**	**4**	**2**	**0**
VT (ml)	472 ± 80	476 ± 77	474 ± 80	473 ± 77	472 ± 76	471 ± 78	474 ± 81	473 ± 81
VD_{aw} (ml)	214 ± 40	209 ± 42	204 ± 39	196 ± 40*	188 ± 39	182 ± 36	174 ± 32	167 ± 26
VD_{alv} (ml)	52 ± 37	52 ± 34	47 ± 31	45 ± 33	42 ± 33*	35 ± 32	39 ± 31	35 ± 29
VD_{Bohr}/VT	0.48 ± 0.06	0.47 ± 0.07	0.45 ± 0.07*	0.43 ± 0.07	0.40 ± 0.07	0.38 ± 0.07	0.35 ± 0.07	0.33 ± 0.07
$VD_{Enghoff}$/VT	0.57 ± 0.07	0.55 ± 0.08	0.53 ± 0.08*	0.52 ± 0.08	0.49 ± 0.08	0.47 ± 0.09	0.46 ± 0.08	0.44 ± 0.08
VD_{alv}/VT_{alv}	0.19 ± 0.11	0.18 ± 0.1	0.17 ± 0.09	0.15 ± 0.09	0.14 ± 0.1*	0.12 ± 0.1	0.13 ±0.09	0.11 ± 0.09
Sn_{III} (mmHg/ml)	0.95 ± 1.19	0.73 ±0.64	0.62 ±0.31	0.62 ±0.43	0.58 ±0.33	0.48 ±0.25*	0.47 ±0.26	0.50 ±0.21
$VTCO_{2,br}$ (ml)	12.5 ± 3.3	13.3 ± 3.7*	13.9 ± 3.7	14.3 ± 3.6	14.7 ± 3.7	15.2 ± 3.7	15.7 ± 3.8	16.0 ± 3.9
VIII/VT	0.42 ± 0.14	0.39 ± 0.13	0.41 ± 0.14	0.43 ± 0.13*	0.46 ± 0.13	0.46 ± 0.13	0.48 ± 0.12	0.51 ± 0.11
Pa-$ETCO_2$ (mmHg)	3.6 ± 2.8	3.4 ± 2.5	3.7 ± 2.6	3.2 ±2.5	2.9 ± 2.7	2.7 ± 2.4	3.1 ± 2.4	2.8 ± 2.5*
$PaCO_2$ (mmHg)	43 ± 5	43 ± 5	44 ± 5	43 ± 5	42 ± 5	42 ± 5	42 ± 5	41 ± 5*
PaO_2 (mmHg)	138 ± 35	140 ± 32	145 ± 25	145 ± 24	145 ± 23	139 ± 21	132 ± 24	127 ± 23*
PaO_2/FiO_2 (mmHg)	346 ± 87	349 ± 80	359 ± 71	371 ± 71	372 ± 68	357 ± 65	338 ± 72	324 ± 70*
Dynamic compliance (ml/cm H_2O)	34 ± 6	36 ± 8	35 ± 6	35 ± 7	35 ± 7	34 ± 7	33 ± 7	31 ± 7*

Table 2: Data are presented as mean ± SD. The first statistical change compared with 14 cm H_2O PEEP is indicated by *. p <0.05 was considered significant. Positive End-Expiratory Pressure (PEEP), Tidal volume (VT), Airway dead space (VD_{aw}), Alveolar dead space (VD_{alv}), Alveolar dead space to alveolar tidal volume ratio (VD_{alv}/VT_{alv}), Normalized slope of phase III (Sn_{III}), Amount of expired CO_2 within one breath ($VTCO_{2'br}$), Volume of phase III to tidal volume ratio (VIII/VT), Arterial minus end-tidal partial pressure of CO_2 (Pa-$ETCO_2$), Arterial partial pressure of O_2 (PaO_2), Arterial partial pressure of CO_2 ($PaCO_2$), Fraction of inspired oxygen (FiO_2).

Table 2 shows changes in different Vcap parameters. VD_{Bohr}/VT and $VD_{Enghoff}$/VT significantly decreased from a PEEP of 10 cm H_2O and less as compared to 14 cm H_2O PEEP. The ratio of alveolar dead space to alveolar tidal volume significantly decreased from a PEEP level of 6 cm H_2O and less as compared to 14 cm H_2O PEEP. The normalized slope of phase III significantly changed at a PEEP levels of 4 cm H_2O or less, whereas volume of phase III corrected for tidal volume (V_{III}/VT) increased significantly as compared to 14 cm H_2O PEEP at ≤8 cm H_2O PEEP, indicating more alveolar ventilation at lower
PEEP levels. In addition, VD_{aw} decreased significantly from a PEEP level of 8 cm H_2O or less. Shunt fraction calculated as the difference between arterial CO_2 minus end-tidal CO_2 (Pa-$_{ET}CO_2$) [32] only significantly differed at ZEEP.
Figure 4 shows the effect of PEEP on the Vcap curve. When lower PEEP levels are applied the Vcap curve is shifted to the left, as a consequence of decreased VD_{aw}. VD_{aw}/VT significantly decreased at 10 cm H_2O and lower as compared to 14 cm H_2O PEEP (Table 2).

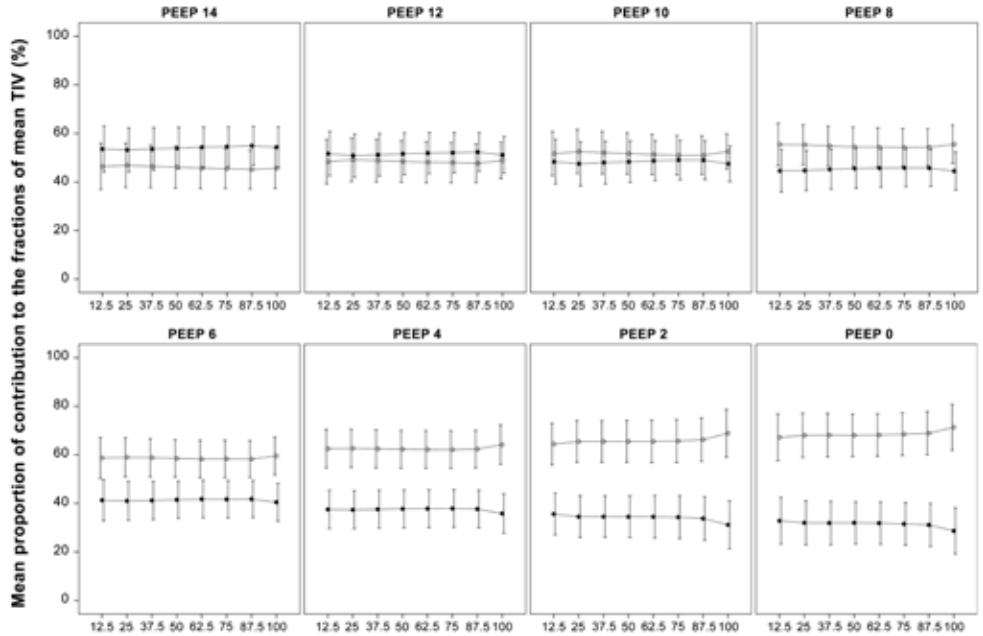


Figure 3: Mean intratidal gas distribution (ITV) curve of all the patients at each PEEP step. Data are shown as mean ± SE. ITV curve represents the mean percentile contribution (%) of ventilation distribution in non-dependent and dependent lung regions during the entire inspiration. At PEEP 12 and 10 cm H_2O, intratidal gas distribution curves stayed close to each other showing equal distribution to both regions. Dashed lines represents the interpolation lines; open circles = non-dependent region; solid circles = dependent region.

Discussion

In the present study we found that dead space calculations according to Bohr and Enghoff agreed well with the PEEP level resulting in homogeneous ventilation as measured by EIT. In contrast, VD_{alv}/VT_{alv} and Sn_{III} were insensitive to detect lung inhomogeneity. In addition, we found that in relatively healthy lungs, without the application of a RM, higher PEEP levels mainly induce airway distention rather than improve alveolar ventilation.

Recently, we demonstrated that homogeneous ventilation by means of ITV agreed well with a PEEP level with the highest dynamic compliance[20]. We compared the whole dependent with the non-dependent lung region and found that the dependent lung region had the highest TIV at 12 cm H_2O PEEP and decreased with each decremental PEEP step indicating collapse in that region. At a PEEP level of 12 cm H_2O the dependent and non-dependent lung regions were in balance. Above this PEEP the dependent region received most of the tidal volume, whereas below this PEEP the non-dependent region was predominantly ventilated. Thus EIT is the first device able to visualize collapse and hyperinflation of lung tissue at the bedside.

In an experimental study by Tusman *et al.*[32] a RM followed by decremental PEEP trial from 24 to 0 cm H_2O in steps of 2 cm H_2O was performed, in 8 lung lavaged pigs. They investigated the ability of Vcap to detect optimal PEEP, as compared to computed tomography scans (CT), and found that dynamic compliance, VD_{alv}/VT_{alv} and $Pa\text{-}_{ET}CO_2$ correlated best with the amount of non-aerated lung tissue as detected by CT-scans. Yang *et al.*[33] performed a decremental PEEP trial on eight lung-lavaged piglets. After a RM they stepwisely reduced the PEEP from 20 cm H_2O to 4 cm H_2O in steps of 4 cm H_2O. At PEEP levels below 16 cm H_2O they found that VD_{alv}/VT_{alv} was well correlated to non-aerated and normally aerated lung tissue as assessed by CT-scans. In addition, they found that the lowest S_{III} value was closely related to best lung function. They concluded that VD_{alv}/VT_{alv} and S_{III} are best predictors for alveolar collapse or hyperinflation. Therefore, from these two studies it can be concluded that Vcap is a reliable tool to detect both collapse and hyperinflation of lung tissue, as confirmed by CT-scans which is the golden standard to assess alveolar collapse or hyperinflation.

Maisch *et al.*[34] performed an incremental and decremental PEEP trial in 20 anesthetized patients with healthy lungs undergoing faciomaxillary surgery. During the PEEP trial, PEEP levels between 0 and 15 cm H_2O were applied in PEEP steps of 5 cm H_2O. They showed that after a RM physiological dead space was the lowest at 10 cm H_2O PEEP, whereas static compliance of the respiratory system was the highest at that PEEP level. In addition, functional residual capacity and PaO_2 were insensitive parameters for detection of alveolar hyperinflation as they decreased with each PEEP step. Therefore, they concluded that physiological dead space and static compliance of the respiratory system are suitable parameters for PEEP titration. Interestingly, we found that the PEEP level at which VD_{Bohr}/VT and $VD_{Enghoff}/VT$ significantly decreased (Table 2), suggesting a reduction in V/Q mismatch, agreed well with the PEEP level at which the inspired air was homogeneously distributed to the dependent and non-dependent lung regions, as measured by EIT (Fig. 2 and Fig. 3). However, at lower PEEP levels VD_{Bohr}/VT and $VD_{Enghoff}/VT$ keeps decreasing indicating that this parameter adds no additional information about ventilation homogeneity at lower PEEP. In addition, the exhaled CO_2 per breath ($VCO_{2,br}$) and the Sn_{III} both showed that elimination of CO_2 improved at lower PEEP levels (table 2), but no optimum could be found. Therefore, in the present study design and study population, Vcap is not able to detect homogeneous ventilation.

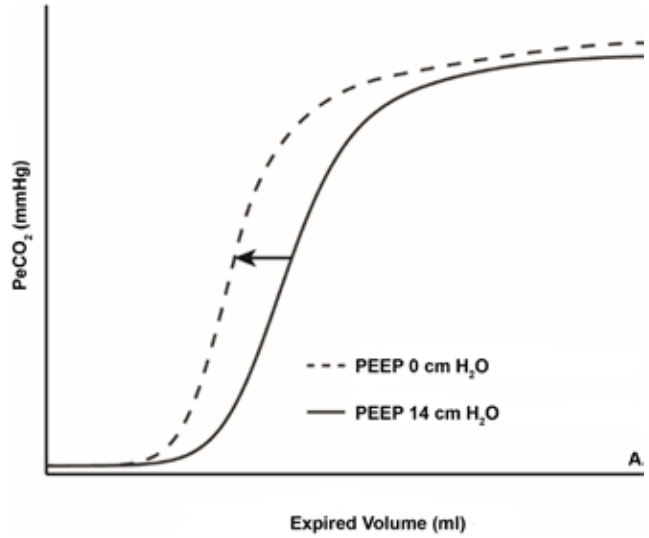


Figure 4. Effect of increased PEEP on the Vcap curve. Figure 4 demonstrates the effect of two PEEP levels on the Vcap curve. Due to the PEEP application the Vcap curve shifts to the right, indicating an increase in airway dead space.

Our finding in Vcap that PEEP mainly increases the airway-volume rather than improves alveolar ventilation is apparently in contradiction with the results of other studies published earlier[14;32;33]. Lower PEEP levels cause a shift of the Vcap curve to the left (fig. 4a), indicating increased airway dead space at higher PEEP levels. These opposing results could be explained by the fact that post-cardiac surgery patients have relatively healthy lungs. Although the patients in our study may have atelectasis, there is no question of surfactant depletion and we assume that the atelectasis is recruited without the need of high PEEP levels. In contrast, the previous studies used the lung-lavaged models with large amount of shunt area, which are recruitable at high PEEP levels. However, Nieman *et al.*[35-41] found during *in vivo* microscopy in normal and surfactant deactivated pigs during ventilation with tidal volumes of 6, 12 and 15 ml/kg that in normal lungs the alveolar area at end-inspiration and end-expiration ($I\text{-}E_{\Delta}$) did not differ between the three different tidal volumes, whereas in the surfactant deactivated lungs $I\text{-}E_{\Delta}$ increased significantly at higher tidal volumes. In a next study[35] they used different tidal volumes (6, 12, 15 ml/kg) and PEEP levels (5, 10, 20 cm H_2O) and found that $I\text{-}E_{\Delta}$ did not change in normal lungs, whereas in surfactant deactivated lungs the alveolar size significantly increased as compared to normal lungs with equal settings. From these studies it can be concluded that in normal lungs with stable alveoli, PEEP volume results in airway distention, whereas in ALI/ARDS lungs PEEP keeps the alveoli open and stabilized. In addition, airway distention due to high PEEP might also explain why physiological dead space calculated according to Enghoff increases at higher PEEP levels whereas $PaCO_2$ did not significantly differ during the different PEEP levels except at ZEEP. This explains the absence of a change in SIII and the left shift of SII in the Vcap curves at decreasing PEEP levels in our patients.

There are limitations to this study. Firstly, we did not apply a RM before the PEEP reduction in order to avoid serious deterioration of hemodynamics in the direct post-operative period. It

has been shown that Vcap parameters after a RM are more sensitive to detect changes in CO_2 elimination as compared to PEEP trials without a RM[42;43]. Secondly, EIT describes the ventilation distribution in a lung slice of approximately 5-10 cm thick[42;44]. Therefore, the image obtained from the single cross-section does not represent the entire lung. In addition, PEEP increases results in changed chest size and intrathoracic blood volume. However, by using two large regions of interest the corresponding lung tissue to the individual pixel is limited. The effect of changed intrathoracic blood volume is limited as EIT is hundred times more sensitive to impedance changes caused by aeration as compared to impedance changes caused by the cardiac system[45-47]. Thirdly, the time intervals of 5-10 minutes at each PEEP level might be too short to achieve a steady state for obtaining reliable data. However, a recent study showed that elimination of CO_2 reached a new stable period within 5 minutes of a PEEP change[48]. It is known that Vcap is influenced by both the cardiac system and the pulmonary system. In this study we did not perform cardiac output measurements, which limit us to assess Vcap changes induced by deteriorated cardiac output at higher PEEP levels. However, we did not find significant differences in blood pressure and heart rate between PEEP 14 and ZEEP. Therefore, we assume that the influence of the change in cardiac output with different PEEP levels on dead space was not profound.

Conclusion

In post-operative cardiac patients with low shunt fractions, dead space calculations according to Bohr and Enghoff agreed well with EIT. EIT is able to detect the optimal PEEP level for equal distribution of inspired air among the non-dependent and the dependent regions of the lungs. In contrast, VD_{alv}/VT_{alv} and Sn_{III} were unable to detect this distribution. In addition, we found that in relatively healthy lungs applying higher PEEP levels mainly induced airway distention rather than improvement of alveolar ventilation.

References

1. Plotz FB, Slutsky AS, van Vught AJ, Heijnen CJ: Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. Intensive Care Med 2004; 30: 1865-72
2. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De JA, Bazin JE, Pereira B, Jaber S: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369: 428-37
3. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? Anesthesiology 2007; 106: 1226-31
4. Mead J, Takishima T, Leith D: Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 1970; 28: 596-608
5. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: any safe threshold? Am J Respir Crit Care Med 2011; 183: 1354-62

6. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L: Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?. Crit Care Med 2013; 41: 1046-55
7. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010; 303: 865-73
8. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P: Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann. Intern.Med. 2009; 151: 566-76
9. Cressoni M, Cadringher P, Chiurazzi C, Amini M, Gallazzi E, Marino A, Brioni M, Carlesso E, Chiumello D, Quintel M, Bugedo G, Gattinoni L: Lung inhomogeneity in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2014; 189: 149-58
10. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G: Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006; 354: 1775-86
11. Suarez-Sipmann F, Bohm SH, Tusman G: Volumetric capnography: the time has come. Curr Opin Crit Care 2014; 20: 333-9
12. Kallet RH, Zhuo H, Liu KD, Calfee CS, Matthay MA: The Association Between Physiologic Dead-Space Fraction and Mortality in Subjects With ARDS Enrolled in a Prospective Multicenter Clinical Trial. Respir Care 2014; 59: 1611-8
13. Tusman G, Groisman I, Fiolo FE, Scandurra A, Arca JM, Krumrick G, Bohm SH, Sipmann FS: Noninvasive monitoring of lung recruitment maneuvers in morbidly obese patients: the role of pulse oximetry and volumetric capnography. Anesth Analg 2014; 118: 137-44
14. Bohm SH, Maisch S, von SA, Thamm O, Passoni I, Martinez AJ, Tusman G: The effects of lung recruitment on the Phase III slope of volumetric capnography in morbidly obese patients. Anesth Analg 2009; 109: 151-9
15. Fengmei G, Jin C, Songqiao L, Congshan Y, Yi Y: Dead space fraction changes during PEEP titration following lung recruitment in patients with ARDS. Respir Care 2012; 57: 1578-85
16. Frerichs I, Hinz J, Herrmann P, Weisser G, Hahn G, Dudykevych T, Quintel M, Hellige G: Detection of local lung air content by electrical impedance tomography compared with electron beam CT. J Appl Physiol 2002; 93: 660-6
17. Meier T, Luepschen H, Karsten J, Leibecke T, Grossherr M, Gehring H, Leonhardt S: Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. Intensive Care Med 2008; 34: 543-50
18. Victorino JA, Borges JB, Okamoto VN, Matos GF, Tucci MR, Caramez MP, Tanaka H, Sipmann FS, Santos DC, Barbas CS, Carvalho CR, Amato MB: Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. Am J Respir Crit Care Med. 2004; 169: 791-800
19. Bikker IG, Blankman P, Specht P, Bakker J, Gommers D: Global and regional parameters to visualize the 'best' PEEP during a PEEP trial in a porcine model with and without acute lung injury. Minerva Anestesiol 2013; 79: 983-92

20. Blankman P, Hasan D, Groot JE, Gommers D: Detection of 'best' positive end-expiratory pressure derived from electrical impedance tomography parameters during a decremental positive end-expiratory pressure trial. Crit Care 2014; 18: R95
21. Löwhagen K, Lundin S, Stenqvist O: Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol 2010; 76: 1024-35
22. Blankman P, Hasan D, van Mourik MS, Gommers D: Ventilation distribution measured with EIT at varying levels of pressure support and Neurally Adjusted Ventilatory Assist in patients with ALI. Intensive Care Med 2013; 39: 1057-62
23. Blankman P, van der Kreeft SM, Gommers D: Tidal ventilation distribution during pressure-controlled ventilation and pressure support ventilation in post-cardiac surgery patients. Acta Anaesthesiol Scand 2014; 18: 997-1006
24. Bikker IG, Leonhardt S, Reis MD, Bakker J, Gommers D: Bedside measurement of changes in lung impedance to monitor alveolar ventilation in dependent and non-dependent parts by electrical impedance tomography during a positive end-expiratory pressure trial in mechanically ventilated intensive care unit patients. Crit Care 2010; 14: R100
25. Costa EL, Borges JB, Melo A, Suarez-Sipmann F, Toufen C, Jr., Bohm SH, Amato MB: Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. Intensive Care Med 2009; 35: 1132-7
26. Suter PM, Fairley B, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 1975; 292: 284-9
27. Tusman G, Scandurra A, Bohm SH, Suarez-Sipmann F, Clara F: Model fitting of volumetric capnograms improves calculations of airway dead space and slope of phase III. J Clin Monit Comput 2009; 23: 197-206
28. Tusman G, Gogniat E, Bohm SH, Scandurra A, Suarez-Sipmann F, Torroba A, Casella F, Giannasi S, Roman ES: Reference values for volumetric capnography-derived non-invasive parameters in healthy individuals. J Clin Monit Comput 2013; 27: 281-8
29. Ream RS, Schreiner MS, Neff JD, McRae KM, Jawad AF, Scherer PW, Neufeld GR: Volumetric capnography in children. Influence of growth on the alveolar plateau slope. Anesthesiology 1995; 82: 64-73
30. Fletcher R, Jonson B, Cumming G, Brew J: The concept of deadspace with special reference to the single breath test for carbon dioxide. Br J Anaesth 1981; 53: 77-88
31. Blankman P, van der Kreeft SM, Gommers D: Tidal ventilation distribution during pressure-controlled ventilation and pressure support ventilation in post-cardiac surgery patients. Acta Anaesthesiol Scand 2014; 58: 997-1006
32. Tusman G, Suarez-Sipmann F, Bohm SH, Pech T, Reissmann H, Meschino G, Scandurra A, Hedenstierna G: Monitoring dead space during recruitment and PEEP titration in an experimental model. Intensive Care Med 2006; 32: 1863-71
33. Yang Y, Huang Y, Tang R, Chen Q, Hui X, Li Y, Yu Q, Zhao H, Qiu H: Optimization of positive end-expiratory pressure by volumetric capnography variables in lavage-induced acute lung injury. Respiration 2014; 87: 75-83
34. Maisch S, Reissmann H, Fuellekrug B, Weismann D, Rutkowski T, Tusman G, Bohm SH: Compliance and dead space fraction indicate an optimal level of positive end-expiratory pressure after recruitment in anesthetized patients. Anesth Analg 2008; 106: 175-81, table

35. Halter JM, Steinberg JM, Gatto LA, DiRocco JD, Pavone LA, Schiller HJ, Albert S, Lee HM, Carney D, Nieman GF: Effect of positive end-expiratory pressure and tidal volume on lung injury induced by alveolar instability. Crit Care 2007; 11: R20
36. Nieman GF, Bredenberg CE, Clark WR, West NR: Alveolar function following surfactant deactivation. J Appl Physiol Respir Environ Exerc Physiol 1981; 51: 895-904
37. Schiller HJ, McCann UG, Carney DE, Gatto LA, Steinberg JM, Nieman GF: Altered alveolar mechanics in the acutely injured lung. Crit Care Med 2001; 29: 1049-55
38. Halter JM, Steinberg JM, Schiller HJ, DaSilva M, Gatto LA, Landas S, Nieman GF: Positive end-expiratory pressure after a recruitment maneuver prevents both alveolar collapse and recruitment/derecruitment. Am J Respir Crit Care Med 2003; 167: 1620-6
39. Schiller HJ, Steinberg J, Halter J, McCann U, DaSilva M, Gatto LA, Carney D, Nieman G: Alveolar inflation during generation of a quasi-static pressure/volume curve in the acutely injured lung. Crit Care Med 2003; 31: 1126-33
40. Steinberg JM, Schiller HJ, Halter JM, Gatto LA, Lee HM, Pavone LA, Nieman GF: Alveolar instability causes early ventilator-induced lung injury independent of neutrophils. Am J Respir Crit Care Med 2004; 169: 57-63
41. Steinberg J, Schiller HJ, Halter JM, Gatto LA, DaSilva M, Amato M, McCann UG, Nieman GF: Tidal volume increases do not affect alveolar mechanics in normal lung but cause alveolar overdistension and exacerbate alveolar instability after surfactant deactivation. Crit Care Med 2002; 30: 2675-83
42. Erlandsson K, Odenstedt H, Lundin S, Stenqvist O: Positive end-expiratory pressure optimization using electric impedance tomography in morbidly obese patients during laparoscopic gastric bypass surgery. Acta Anaesthesiol Scand 2006; 50: 833-9
43. Tusman G, Bohm SH, Suarez-Sipmann F, Turchetto E: Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. Can J Anaesth 2004; 51: 723-7
44. Lindgren S, Odenstedt H, Olegard C, Sondergaard S, Lundin S, Stenqvist O: Regional lung derecruitment after endotracheal suction during volume- or pressure-controlled ventilation: a study using electric impedance tomography. Intensive Care Med 2007; 33: 172-80
45. Barber DC: A review of image reconstruction techniques for electrical impedance tomography. Med Phys 1989; 16: 162-9
46. Brenner D, Elliston C, Hall E, Berdon W: Estimated risks of radiation-induced fatal cancer from pediatric CT. Am J Roentgenol 2001; 176: 289-96
47. Visser KR: Electric properties of flowing blood and impedance cardiography. Ann Biomed Eng 1989; 17: 463-73
48. Tusman G, Bohm SH, Suarez-Sipmann F, Scandurra A, Hedenstierna G: Lung recruitment and positive end-expiratory pressure have different effects on CO_2 elimination in healthy and sick lungs. Anesth Analg 2010; 111: 968-77

CHAPTER 8

Tidal ventilation distribution during pressure-controlled ventilation and pressure support ventilation in post-cardiac surgery patients

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Abstract

Background
Inhomogeneous ventilation is an important contributor to ventilator-induced lung injury. Therefore, this study examines homogeneity of lung ventilation by means of electrical impedance tomography (EIT) measurements during pressure-controlled ventilation (PCV) and pressure support ventilation (PSV) using the same ventilation pressures.

Methods
Twenty mechanically ventilated patients were studied after cardiac surgery. On arrival at the intensive care unit, ventilation distribution was measured with EIT just above the diaphragm for 15 min. After awakening, PCV was switched to PSV and EIT measurements were again recorded.

Results
Tidal impedance variation, a measure of tidal volume, increased during PSV compared with PCV, despite using the same ventilation pressures ($P = 0.045$). The distribution of tidal ventilation to the dependent lung region was more pronounced during PSV compared with PCV, especially during the first half of the inspiration. An even distribution of tidal ventilation between the dependent and non-dependent lung regions was seen during PCV at lower tidal volumes (< 8 ml/kg) and PSV at higher tidal volumes (≥ 8 ml/kg). In addition, the distribution of tidal ventilation was predominantly distributed to the dependent lung during PSV at low tidal volumes.

Conclusion
In post-cardiac surgery patients, PSV showed improved ventilation of the dependent lung region due to the contribution of the diaphragm activity, which is even more pronounced during lower assist levels.

Introduction
In many types of patients, mechanical ventilation is a prerequisite during general anaesthesia and also in the treatment of patients with respiratory failure in the intensive care unit (ICU). It is established that conventional mechanical ventilation itself can cause damage to the lung in critically ill patients, also known as ventilator-induced lung injury (VILI)[1]. In addition, conventional mechanical ventilation during surgery, such as cardio-surgery with cardio-pulmonary bypass or esophagectomy with gastric tube reconstruction, produces inflammatory cytokines and mediators, thereby initiating an inflammatory process[2-7]. Although the transduction of the mechanical stimulus to a biological reaction remains unclear, it is generally considered that the origin of this biotrauma is mechanical stress at the lung parenchyma.
Initially in patients with acute respiratory distress syndrome (ARDS)[8;9], but later also in patients undergoing surgery[3;6;7;10], inflammatory response was attenuated by a ventilation strategy avoiding atelectasis by applying adequate levels of PEEP and minimizing overdistention by use of low tidal volumes. Although high PEEP levels are often required to avoid collapse after recruitment, the application of higher PEEP levels may increase the risk of hyperinflation. Therefore, a compromise must be found between PEEP-induced alveolar recruitment and prevention of hyperinflation.
In 1970, Mead *et al.*[11] estimated that forces acting on lung tissue may be as much as 4.5 times higher when lungs are inhomogeneously ventilated. This was confirmed in experimental work using tomographic microscopy, which generates detailed three-dimensional alveolar geometries[12]. This inhomogeneity raises stress on the border of open and collapsed alveoli and increases the risk to develop VILI[13]. Recently, in 10 mechanically-ventilated patients, we compared three different assist levels during pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA)[14]. It was shown that, if the PSV level is set to high most air distributes to the non-dependent lung region whereas lower assist levels lead to more homogeneous ventilation of the lung. In addition, during NAVA it was shown that, due to respiratory auto-regulation by the patient, the patient is able to evenly distribute the inspired air to the dependent and non-dependent lung region at different gain levels[14].
Therefore, in the present study EIT was used as a tool to analyse ventilation distribution during mechanical ventilation in a non-invasive manner at the bedside, in order to apply homogenous ventilation to each patient. Our hypothesis is that homogenous ventilation, as measured by EIT, is dependent on the tidal volume and the presence of respiratory drive of the patient.

Materials and Methods

Study population

The present study has a prospective observational crossover design, in which 20 post-cardiac surgery patients admitted to the thoracic ICU were studied during mechanical ventilation (Evita Infinity V500, Dräger Medical, Lübeck, Germany).

The local Medical Ethics committee (Medical Ethical Committee Rotterdam: Dr. Molewaterplein 50, 3015 GE Rotterdam, The Netherlands.) approved the study protocol (19 December 2011; permit nr. MEC-2011-301) and informed consent was obtained from the patient or a legal representative. Data was collected between January 2012 and April 2013.

The inclusion criteria were: aged >18 years, written informed consent, hemodynamically stable, and ventilated with PCV. Exclusion criteria were: a pacemaker, pneumothorax and severe airflow obstruction due to chronic obstructive pulmonary disease (COPD). COPD was defined as forced expiratory volume in one second or vital capacity below predicted value minus two standard deviations.

Study protocol and measurements

All patients admitted to the ICU were in sitting position (20-30 degrees) and ventilated with PCV because of the deep sedation level (i.e. Ramsey sedation scale of 5-6) in the immediate postoperative period. At 30 min after ICU admission, a 16-electrode silicon belt was placed around the patient's thoracic cage between the 6th and 7th intercostal spaces. EIT measurements (Pulmovista 500, Dräger Medical, Lübeck, Germany) were performed for 15 min. After the sedation was stopped and the patient was successfully ventilated with PSV for 15 min, we performed a second EIT measurement for 15 min. Between the two measurements the EIT device remained connected to the patient to maintain an equal baseline value and to ensure that the same lung slice was measured again. The inspiratory pressure settings during PCV and PSV were identical. The Inspiration/Expiration (I/E) ratio was 1:1 or 1:2 depending on the $PaCO_2$ during PCV, and the inspiratory flow cut-off was set at 25% during PSV. The fraction of inspired oxygen (FiO_2) was set to achieve a PaO_2 of 10 kPa, whereas positive end-expiratory pressure (PEEP) was set according to the standard FiO_2 PEEP table[8]. During PCV the pressure above PEEP was set to reach tidal volumes of 8 ml/kg predicted body weight (PBW) or a minimum of 7 cm H_2O without automatic tube compensation. The respiratory frequency was set to maintain a $PaCO_2$ of 5-6 kPa.

Data analysis

EIT data were analysed using special software (EITdiag, Dräger Medical, Lübeck, Germany). EIT data consist of signals from both the cardiovascular and respiratory system. Therefore, all data were filtered using a low-pass filter of 40 beats per min (BPM) to exclude all signals related to the cardiovascular system but leaving the signals related to ventilation. Thereafter, the data were resampled with 40 Hz in order to reliably divide the inspiratory part of the global tidal impedance variation (TIV) curve into 8 equal volume sections for the intratidal gas distribution (ITV) analyses. For the two ventilator modes the reconstructed EIT images had an equal surface area, which was divided into two equal regions of interest (ROI). The ROIs were set as non-dependent and dependent lung regions. The PCV measurement was used as reference to compare the changes in ventilation distribution during PSV. Retrospectively, patients were

divided into a high tidal volume group (≥8 ml/kg) and a low tidal volume group (<8 ml/kg). A cut-off value of 8 ml/kg was chosen as this is the upper limit for tidal volumes according to the ARDS network trial [8].

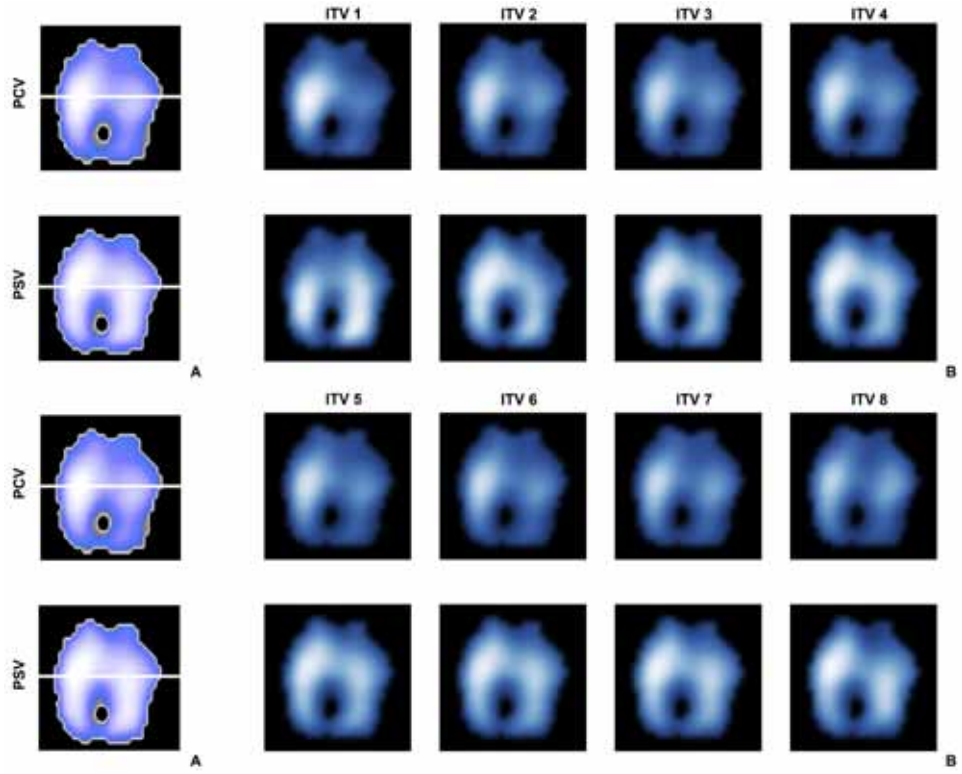

Figure 1: Reconstructed electrical impedance tomography (EIT) images during pressure-controlled ventilation (PCV) and pressure support ventilation (PSV). (A) shows EIT images of one patient ventilated with PCV and PSV during the same ventilator airway pressures. The ventilation surface area of the PSV image is the largest and therefore used for all calculations. The images are divided into two regions of interest (non-dependent and dependent region) by the white line. Impedance changes are shown by a color map from blue (normal impedance) to white (high impedance), whereas the black area is not ventilated. (B) shows the tidal impedance distribution of the same patient during one inspiration. The inspiration is cut into eight iso-volume (ITV) parts. Each ITV step represents 12.5% of a breath. During PCV, most ventilation (white area) started in the right middle lung, whereas during PSV the ventilation started more in the dependent lung region of both the right and left lung.

Ventilation distribution in a lung slice is measured by means of TIV and displayed in a coloured EIT map (Fig. 1A). TIV correlates well with gas volume changes measured with computed tomography (CT)[15-17]. The global TIV curve consists of an inspiratory part and an expiratory part. Löwhagen et al. developed a method to analyse ventilation distribution during the inspiration, which they called the regional ITV[18]. This ITV is calculated by dividing the inspiratory part of

the global TIV curve into 8 iso-volume steps (formula 1). By translating the corresponding time points of the 8 steps from the global to the regional TIV curves the percentile contribution of the dependent and non-dependent regions can be calculated[18].

ITV formula: (ITV = intratidal gas distribution part;
TIV = tidal impedance variation; ROI = region of interest)

$$TIV = Impedance_{max} - Impedance_{min}$$

$$Fractional\ regional\ ITV_{1\text{-}8} = \frac{ITV_{1\text{-}8}TIV_{ROI}}{ITV_{1\text{-}8}TIV_{Global}} \quad [1]$$

Another EIT parameter that was calculated is the intratidal gas distribution (ITV) index; this index was developed by our group and describes the homogeneity of ventilation distribution during the inspiration, which is based on ITV calculations using the method of Löwhagen *et al.*[18]. Therefore, we divided the ITV of the non-dependent region by the ITV of the dependent region. If the ITV index is 1 this indicates that ventilation is homogeneously distributed to the dependent and non-dependent regions, whereas values higher and lower than 1 indicate that more ventilation is distributed to the non-dependent or dependent region, respectively. In addition to the ITV index we calculated another homogeneity index, the global inhomogeneity (GI) index[19;20]. The GI index is calculated by subtracting the median impedance variation of the whole EIT image from the impedance variation per pixel. The result of this subtraction is divided by the sum of impedance difference of all pixels in order to normalize the calculated values. Based on this calculation the ventilation distribution in the lungs can be quantified for each pixel (formula 2). In other words, the GI index calculates the variance in impedance per pixel as compared with the whole EIT image. If there is a small variance in impedance (i.e. the GI index) this indicates that the lung is more homogeneously ventilated.
GI index formula: (x and y describe the location of the pixel on the x and y axes; means element)

$$GI = \frac{\sum_{x,y \in lung} \left| Impedance\ difference_{xy} - Median\ (Impedance\ difference_{lung}) \right|}{\sum_{x,y \in lung} Impedance\ difference_{xy}} \quad [2]$$

Statistical Analysis

Data were tested for normal distribution using the Kolmogorov-Smirnov test and the Brown-Forsythe test was used to test the homoscedasticity. The Mann-Whitney U test was used to analyse TIV, ITV, and the ITV index and GI index. Normally distributed data were analysed with an unpaired Student's t-test.
Statistical analysis was performed using SPSS 21 (IBM, Chicago, IL, USA). For all comparisons $p < 0.05$ was considered statistically significant. Values are presented as mean ± SD unless otherwise specified.

Results

Table 1 presents information on patient demographics and Table 2 presents the respiratory parameters during PCV and PSV. In both ventilator modes peak inspiratory pressure (PIP) and PEEP values were the same and only the respiratory rate, expiratory tidal volume and expiratory time showed significant differences between the two modes (Table 2).

Data on patient demographics and characteristics

No. of patients	20			
Gender (male/female)	12/8			
Age (years)	61 [35-77]			
Height (m)	1.74±0.12			
Weight (kg)	80±18			
Predicted body weight (kg)	67±12			
Body mass index	26±5			
Mean arterial pressure (mmHg)	79±12			
Heart rate (BPM)	85±16			
Respiratory rate (BPM)	15±4			
Positive end-expiratory pressure (cm H_2O)	8±2			
Peak pressure (cm H_2O)	19±4			
Expiratory tidal volume (ml)	481±124			
Expiratory tidal volume/predicted body weight (ml/kg)	7±2			
PaO_2/FiO_2 (kPa)	45.9±16.5			
CPB time (min)	79±49			
Diagnoses	CABG	CABG+VR	VR	Other
	6	1	9	4
ARDS score*	No	Mild	Moderate	Severe
	12	7	1	0

Table 1: Data are presented as mean ± SD unless otherwise specified. Age is presented as mean + range. Cardiopulmonary Bypass (CPB); Coronary Artery Bypass Graft (CABG); Valve Replacement. *ARDS score according to the new Berlin criteria: mild ARDS = PaO_2/FiO_2 26-40 kPa; moderate ARDS = PaO_2/FiO_2 13-26 kPa; severe ARDS = PaO_2/FiO_2 <13 kPa.

Tidal impedance variations per individual ITV step for one patient are shown in figure 1B. During PCV, most ventilation (white area) started in the right middle lung, whereas during PSV the ventilation started more in the dependent lung region of both the right and left lung. The total TIV of the entire image was significantly higher during PSV as compared with PCV ($p=0.045$). This increased TIV is explained by the higher tidal volumes during PSV compared with PCV (Table 2). Despite use of the same ventilatory pressures, the increased tidal volume during PSV is a result of the respiratory drive, i.e. diaphragm activity. During PCV, no spontaneous breaths were detected (Table 2). The TIV was significantly higher for the non-dependent lung region during PCV, whereas during PSV the TIV was similar in both the dependent and non-dependent lung regions (Fig. 2).

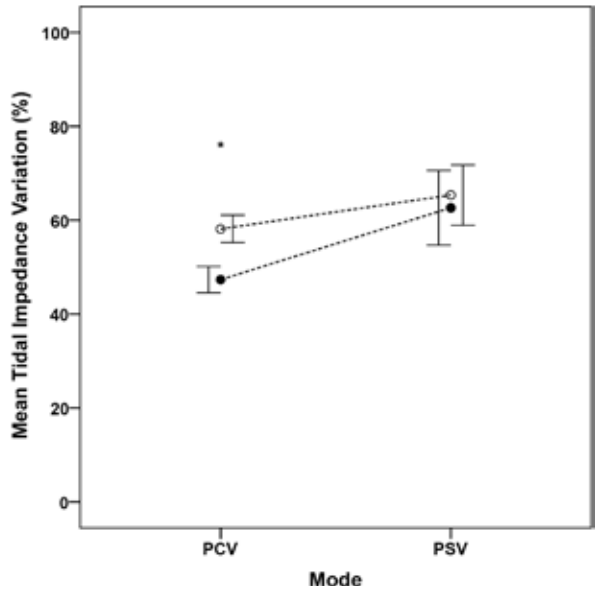

Figure 2: Variation in tidal impedance (TIV) during pressure-controlled ventilation (PCV) and pressure support ventilation (PSV). Data are presented as mean ± SE. During PCV, the nondependent lung region received significantly better ventilation compared with the dependent region, whereas during PSV, no difference in TIV was found between the two lung regions. Open circles = nondependent region; solid circles = dependent region. *Significant difference in TIV between the dependent and non-dependent lung regions. Differences are considered significant when P is < 0.05.

Respiratory parameters during pressure controlled ventilation (PCV) and pressure support ventilation (PSV)

	PaO_2 (kPa)	$PaCO_2$ (kPa)	PaO_2/FiO_2 (kPa)	PEEP (cm H_2O)	Pressure above PEEP (cm H_2O)	Ppeak (cm H_2O)	Tve (ml)
PCV	17.4±4.8	5.2±1.2	45.9±16.5	8±2	11±3	19±4	481±124
PSV	17.0±3.2	5.7±1.3	46±9.3	8±2	11±3	19±4	602±232*

	Tve/PBW (ml/kg)	Mve (l/min)	RR (breaths per min)	Inspiratory time (s)	Expiratory time (s)	Tve/PBW (ml/kg)
PCV	7.2±1.9	8.3±2.4	17±2 (0%)	1.5±0.4	2.0±0.4	7.2±1.9
PSV	9.1±3.5*	7.4±2.3	13±4* (100%)	1.9±0.9	3.1±1.3*	9.1±3.5*

Table 2: Data are presented as mean ± SD. After the switch from PCV to PSV the respiratory rate (RR), expiratory tidal volume (Tve) and the expiratory time showed a significant change between PCV and PSV. The percentages presented behind the respiratory rates are the percentage of spontaneous breaths during use of each ventilatory mode. Peak pressure (Ppeak); Expiratory tidal volume per kilogram predicted body weight (Tve/PBW); Expiratory minute volume (Mve). *p <0.05.

The distribution of tidal ventilation during inspiration, expressed as ITV, was predominantly to the non-dependent lung region during PCV, indicating that most of the tidal volume during a breath was distributed to the non-dependent region of the lung (Fig. 3). In contrast, ITV was more in balance during PSV; however, at the end of inspiration more tidal distribution was distributed to the non-dependent lung region during PSV (Fig. 3). The contribution of the dependent lung region of an inspiration was significantly higher during PSV compared with PCV (p=0.008) (Fig. 3). From figure 3 we also calculated the ITV as volumes instead of percentages. During PSV significantly more air is distributed towards the dependent and non-dependent lung regions per ITV step as compared to PCV (Table 3). In addition, we found that during the first half of the inspiration (ITV steps 1-4) significantly more air distributed towards the dependent lung region during PSV as compared to PCV (Table 3), whereas for the non-dependent lung region no difference was found.

Tidal volume distribution during the inspiration

Intratidal gas distribution step	Region	PCV	PSV	*p-value*
ITV 1 (ml)	Non-dependent	32±13	34±17	0.892
	Dependent	28±8	41±17	0.001*
ITV 2 (ml)	Non-dependent	33±13	37±17	0.626
	Dependent	27±8	38±16	0.002*
ITV 3 (ml)	Non-dependent	34±13	38±16	0.499
	Dependent	26±8	38±17	0.003*
ITV 4 (ml)	Non-dependent	34±13	38±16	0.417
	Dependent	26±8	37±17	0.010*
ITV 5 (ml)	Non-dependent	34±13	39±16	0.330
	Dependent	26±8	36±18	0.023*
ITV 6 (ml)	Non-dependent	34±13	40±16	0.204
	Dependent	26±9	36±18	0.079
ITV 7 (ml)	Non-dependent	34±12	41±17	0.137
	Dependent	27±9	34±17	0.304
ITV 8 (ml)	Non-dependent	34±13	50±21	0.017*
	Dependent	26±11	25±14	0.808

Table 3: Data are presented as mean ± SD. Each intratidal gas distribution (ITV) step represents 12.5% of the inspiration. During the first part of the inspiration (ITV-step 1-5) significantly more tidal volume distributed towards the dependent lung region during Pressure Support Ventilation (PSV) as compared to Pressure Controlled Ventilation (PCV). * p < 0.05 between PCV and PSV.

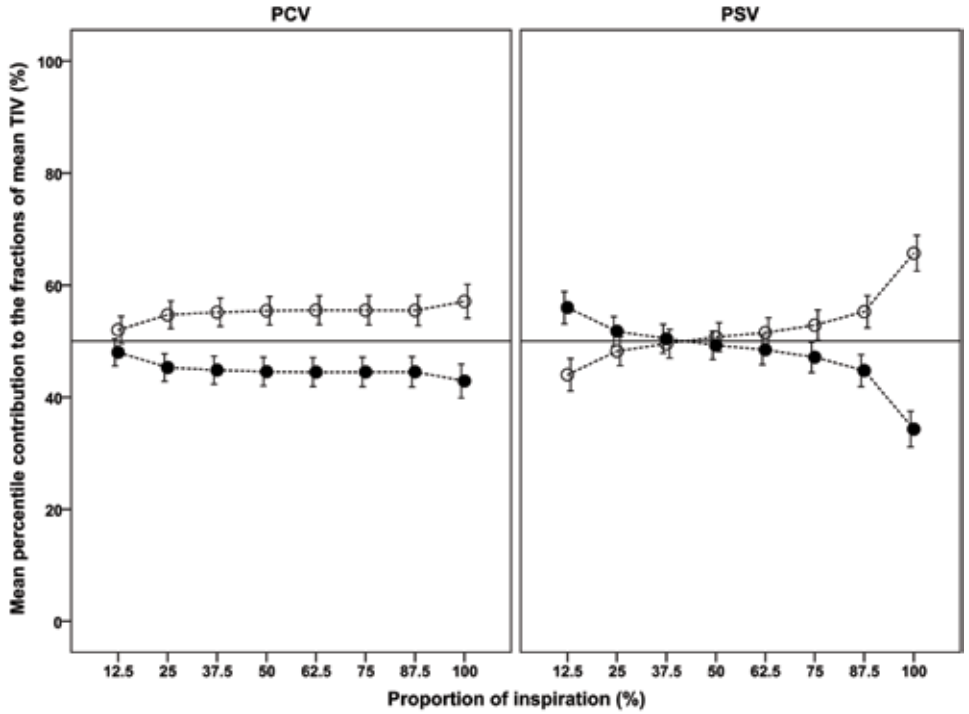

Figure 3: Intratidal gas distribution during pressure-controlled ventilation (PCV) and pressure support ventilation (PSV). Data are presented as mean ± SE. Tidal ventilation distributed to the non-dependent lung region within the inspiration during PCV. The dependent lung region was predominant during the first part of the inspiration with PSV. Open circles = non-dependent region; solid circles = dependent region.

Except for ITV, no significant difference was found between PCV and PSV for any of the EIT parameters. Therefore, we retrospectively divided the patients into a high tidal volume (≥8 ml/kg) and a low tidal volume (<8 ml/kg) group for both ventilator modes. During PCV 14 patients received tidal volumes of <8 ml/kg and 6 patients received tidal volumes >8 ml/kg, whereas during PSV this was 5 and 15 patients, respectively. The mean tidal volume during PCV was 6±1 vs. 9±1 mL/kg PBW (p<0.001) in the lower and higher tidal volume groups, respectively, whereas during PSV this was 5±1 vs. 10±3 mL/kg PBW (p<0.001). Tidal volume distribution was clearly in the dependent lung region during PSV at low tidal volume (Fig. 4) whereas ventilation was more evenly distributed during ventilation with high tidal volumes; however, at the end of the inspiration tidal volume distribution shifted to the non-dependent lung region (Fig. 4). Tidal volume was evenly distributed between both lung regions during PCV at low tidal volume (Fig. 4). During PCV at high tidal volume, tidal volume distribution was predominantly in the non-dependent lung region (Fig. 4).
Table 4 presents the indices of homogeneity: the GI index and the ITV index. There were no significant differences in the GI index between the groups (Table 4). The ITV index showed improved ventilation of the dependent region during PSV (Table 4).

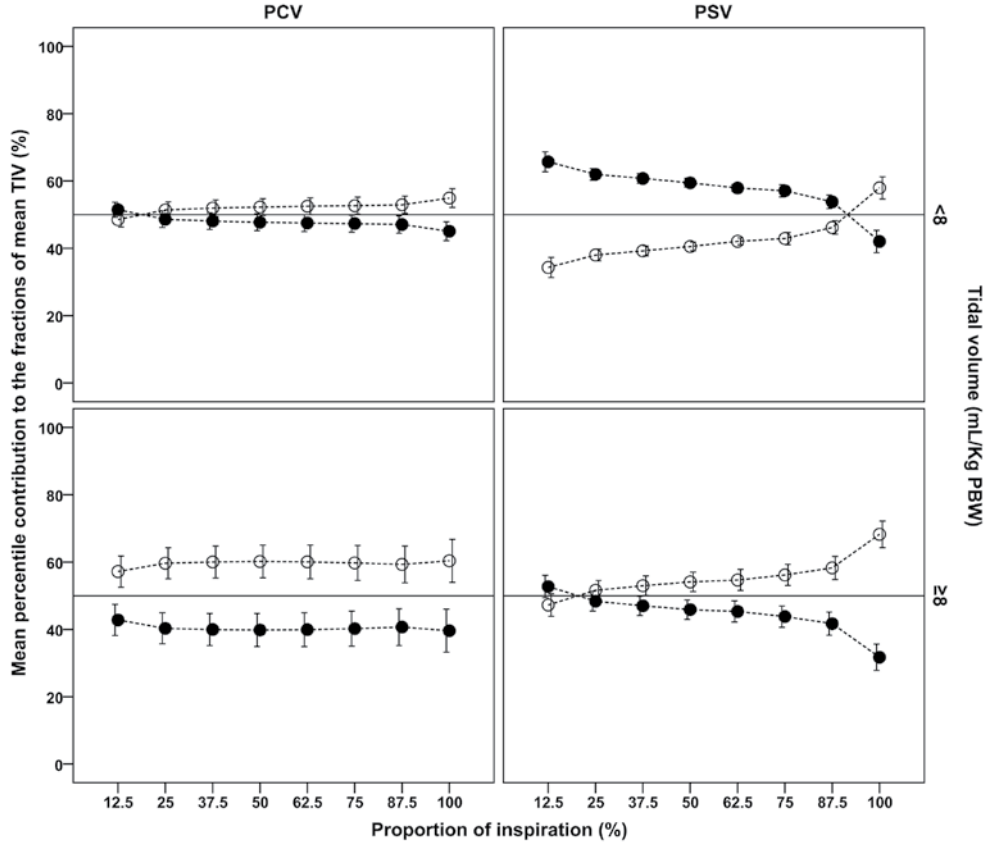

Figure 4: Intratidal gas distribution calculated for different tidal volumes during pressure-controlled ventilation (PCV) and pressure support ventilation (PSV). Data are presented as mean ± SE. The contribution of the dependent lung region to the inspiration was significantly higher in the group ventilated with tidal volumes of < 8 ml/kg predicted body weight, during both ventilator modes as compared with tidal volumes ≥ 8 ml/kg. Open circles = non-dependent region; solid circles = dependent region.

Discussion

In the present study, PSV improved ventilation of the dependent lung region due to contribution of the diaphragm, which is more pronounced during lower tidal volume in post-cardiac surgery patients. Also, homogeneous ventilation (as measured by EIT) can be achieved during PCV when lower tidal volumes (<8 ml/kg PBW) are used. In this study, although the same airway pressures were used with both ventilation modes, tidal volume was significantly higher during PSV due to diaphragm activity of the patient as compared with PCV. In this latter mode no spontaneous breaths were detected due to the deep level of sedation.
Although both PCV and PSV are well-accepted modes of mechanical ventilation, there is some debate as to which ventilator mode is preferable. In a model of acute lung injury (ALI), Spieth et al. showed that PSV improved gas exchange and reduced pulmonary inflammatory response compared with PCV[21]. Yoshida *et al.*[22] compared PSV with Airway Pressure Release Ventilation

in 18 ALI/ARDS patients using CT scans and found an improved gas exchange during PSV. However, these authors showed no significant reduction in hyperinflated or non-aerated lung tissue during PSV. Dellinger et al. used vibration response imaging (VRI) during PCV, PSV and volume-controlled ventilation with equal tidal volumes and found that PSV led to more ventilation of the lower lung regions compared with volume-controlled ventilation; however, the authors found no difference between PCV and PSV[23]. During VRI measurements it is possible to differentiate between cranial and caudal lung regions, but not between dependent and non-dependent lung regions as seen with EIT. An EIT study by Radke *et al.*[24] compared spontaneous breathing, and PCV and PSV, in patients undergoing elective surgery and showed that ventilation is mainly distributed to the non-dependent lung regions during both PCV and PSV compared with spontaneous breathing; however, no difference was found in ventilation distribution between PCV and PSV. In contrast, Mauri *et al.*[25] and Blankman *et al.*[14] found improved ventilation of the dependent lung region with EIT at lower PSV assist levels in patients recovering from ARDS. Andersson *et al.*[26] found comparable findings in a study comparing three different types of continuous positive airway pressure (CPAP) PAP (High Flow-CPAP; Ejector drive-CPAP (E-CPAP); Ventilator-CPAP) in 14 healthy volunteers, using mask ventilation. They showed that E-CPAP, provided the least assist, resulted in more ventilation distribution towards the dependent lung region, as assessed with ITV calculations of EIT data. It was concluded that due to the lower assist, the respiratory demands of the patients are probably not fulfilled, leading to a higher activity of the diaphragm and thus more ventilation distribution towards the dependent region. Already in 1974, Froese and Bryan[27] showed that during spontaneous breathing there is a contraction of the diaphragm, with more displacement of the posterior part, resulting in more homogeneous ventilation distribution and a better ventilation/perfusion ratio in three adult volunteers, both awake and anesthetized. Wrigge et al. [28] showed in an experimental study that Airway Pressure Release Ventilation (APRV) with spontaneous breathing improved dependent ventilation compared to APRV without spontaneous breathing. Thus active contribution of the diaphragm will increase the ventilation distribution towards the dependent lung region from the beginning of a breath.

The ITV developed by Löwhagen *et al.*[18] is an ideal tool to assess ventilation distribution within an inspiration. In a PEEP trial, these authors showed that the contribution of the dependent region improved when higher PEEP levels are used[18]. This was confirmed by our group in an experimental model in which different global and EIT parameters were studied in normal and ARDS lungs to find 'best PEEP' [29]. In the latter study, in contrast to Löwhagen *et al.*[18], we calculated the ITV for two lung regions. We found that in both healthy and ARDS lungs the ITV is able to detect a specific PEEP level during which the dependent and non-dependent regions are equally ventilated. PEEP levels above this specific level resulted in ventilation distribution mainly to the dependent regions, whereas at lower PEEP levels the non-dependent region was predominant. In another recent study, our group confirmed these latter results in post-cardiac surgery patients on the ICU[30].

The intratidal gas distribution is able to detect the point where overdistention of the non-dependent region and recruitment in the dependent region starts. In addition, we were able to find such a cross-section in each individual patient. If the dependent lung region is kept open during expiration by applying an adequate level of PEEP, the tidal volume will distribute more easily to that lung region. This could be the reason why Radke *et al.*[24] found no significant

difference between PSV and PCV. In their study they did not apply any PEEP, whereas we used a PEEP level of 8±2 cm H_2O (Table 1). In the present study, the tidal ventilation was evenly distributed to both the dependent and non-dependent lung regions during PSV compared with PCV (Fig. 3). Furthermore, the ITV in patients ventilated with low tidal volumes (<8 ml/kg PBW), despite the same airway pressures, showed that lower tidal volumes improved the contribution of the dependent region irrespective of the type of ventilation (Fig. 4). During PSV the tidal volume is dependent on both the set amount of pressure assist and the amount of patient effort. The contribution of diaphragm activity during PSV increases transpulmonary pressure leading to extra delivery of tidal volume, especially at the dependent region. This is confirmed by our findings of ITV calculations in volumes instead of percentages (Table 3). As a result of increased tidal volumes, during PSV the respiratory rate is decreased according to the patient's respiratory drive (Table 2). Ventilation distribution was clearly in the dependent lung region during PSV with lower tidal volumes (<8 ml/kg) and this was shifted to the non-dependent lung region at high tidal volume (>8 ml/kg) despite using the same airway pressures; this indicates that also low tidal volume should be used during PSV to prevent hyperinflation of the non-dependent lung due to over-assistance. Low tidal volume is always used during volume or pressure controlled modes and is never tested during support ventilation strategies.

Homogeneity indices calculated from electrical impedance tomography data

Parameter	Tidal volume/PBW	Region	PCV	PSV	*p-value*
GI index (%)	<8 ml/kg	Non-dependent	21.7±1.6	19.6±2.7	0.574
		Dependent	21.4±1.3	25.2±1.5	0.328
	≥8 ml/kg	Non-dependent	27.5±2.6	25.7±1.8	0.681
		Dependent	19.5±1.7	21.3±1.6	0.428
ITV index	<8 ml/kg	-	1.1±0	0.7±0.1	<0.001
	≥8 ml/kg	-	1.3±0.2	1.1±0.3	0.028

Table 4: Data are presented as median ± SE. 14 patients were ventilated with tidal volumes <8 ml/kg predicted body weight (PBW) during pressure controlled ventilation (PCV) and 6 patients with tidal volumes of ≥8 ml/kg. During pressure support ventilation (PSV), 5 and 15 patients were ventilated with tidal volumes <8 and ≥8 ml/kg PBW, respectively. The global inhomogeneity (GI) index shows no significant difference between the groups. The intratidal gas distribution (ITV) index shows improved ventilation of the dependent region during PSV.

The present study has some limitations. First, EIT measures ventilation distribution in a lung slice of approximately 5-10 cm implying that information obtained by EIT measurements has a limited external validity for the remaining lung tissue. However, it is known that placing the EIT belt at a higher position reduces the probability to detect ventilation inhomogeneity of the lungs[31]. Therefore, we chose to place the belt just above the diaphragm, which is where atelectasis is most likely to occur in mechanically ventilated patients in supine position. Second, because changes in impedance are measured compared with a reference electrode, electrode dislocation can cause differences in measured impedance changes; for this reason, we did not disconnect the EIT belt between the two measurements. Third, in this study we did not use a second technique to measure ventilation homogeneity. However, two recent experimental

studies assessed ventilation homogeneity using EIT as compared with CT or magnetic resonance imaging (MRI). Dunster et al. compared ventilation homogeneity in 7 rats using hyperpolarised helium MRI (He3 MRI) and EIT; they found comparable values for the GI index for both imaging methods, during different body positions [32]. Elke et al. [33] found high correlations in ventilation homogeneity calculated from EIT and Xenon CT (XeCT) of 9 mechanically ventilated pigs. This indicates that our results are reliable and EIT can be used for assessment of ventilation homogeneity at the bedside. Fourth, absolute exclusion of spontaneous breathing activity during PCV only can be assessed with techniques like esophageal pressure measurements. However, in the present study we did not perform such measurements but we detected no spontaneous breaths by analyzing the flow and pressure curves and/or detection by the ventilator (total respiratory rate vs. installed frequency). Due to the deep sedation of the patients (Ramsay score 5-6) we are convinced that deep spontaneous breaths are excluded. Fifth, we have chosen to use pressure controlled instead of volume controlled ventilation in order to apply the same airway pressures to the entire lung to study the ventilation distribution. Despite adapting the pressure levels to achieve target tidal volume, six patients were ventilated with tidal volumes >8ml/kg during the PCV mode due to better compliance. Finally, the present study included post-cardiac surgery patients with relatively healthy lungs; although the short monitoring period is acceptable to describe a physiological phenomenon, it is too short to describe potential effects on patient outcome. Additional studies are needed to compare the effect of PCV and PSV on ventilation distribution and patient outcome in ALI/ARDS patients.

Conclusion

In conclusion, in this study PSV improved ventilation of the dependent lung region due to contribution of the diaphragm, which is more pronounced during lower tidal volume in post-cardiac surgery patients. Also, homogeneous ventilation (as measured by EIT) can be achieved during PCV when lower tidal volumes (<8 ml/kg PBW) are used. Finally, EIT can be used to optimize ventilator settings to achieve homogeneous lung ventilation in the individual patient at the bedside when using either a PSV or PCV ventilator mode.

References

1. Ricard JD, Dreyfuss D, Saumon G (2002) Ventilator-induced lung injury. Curr Opin Crit Care 8:12-20
2. Loer SA, Kalweit G, Tarnow J (2000) Effects of ventilation and nonventilation on pulmonary venous blood gases and markers of lung hypoxia in humans undergoing total cardiopulmonary bypass. Crit Care Med 28:1336-1340
3. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L et al. (2006) Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study. Anesthesiology 105:911-919
4. Reis MD, Gommers D, Struijs A, Dekker R, Mekel J, Feelders R et al. (2005) Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery. Eur J Cardiothorac Surg 28:889-895
5. Rothenburger M, Soeparwata R, Deng MC, Schmid C, Berendes E, Tjan TD et al. (2001) Prediction of clinical outcome after cardiac surgery: the role of cytokines, endotoxin, and anti-endotoxin core antibodies. Shock 16 Suppl 1:44-50

6. Wrigge H, Uhlig U, Baumgarten G, Menzenbach J, Zinserling J, Ernst M et al. (2005) Mechanical ventilation strategies and inflammatory responses to cardiac surgery: a prospective randomized clinical trial. Intensive Care Med 31:1379-1387
7. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S et al. (2005) Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: a randomized clinical trial. J Thorac Cardiovasc Surg 130:378-383
8. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network (2000) N Engl J Med 342:1301-1308
9. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M et al. (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327-336
10. Reis MD, Struijs A, Koetsier P, van Thiel R, Schepp R, Hop W et al. (2005) Open lung ventilation improves functional residual capacity after extubation in cardiac surgery. Crit Care Med 33:2253-2258
11. Mead J, Takishima T, Leith D (1970) Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 28:596-608
12. Rausch SM, Haberthur D, Stampanoni M, Schittny JC, Wall WA (2011) Local strain distribution in real three-dimensional alveolar geometries. Ann Biomed Eng 39:2835-2843
13. Gattinoni L, Carlesso E, Caironi P (2012) Stress and strain within the lung. Curr Opin Crit Care 18:42-47
14. Blankman P, Hasan D, van Mourik MS, Gommers D (2013) Ventilation distribution measured with EIT at varying levels of pressure support and Neurally Adjusted Ventilatory Assist in patients with ALI. Intensive Care Med 39:1057-1062
15. Frerichs I, Hinz J, Herrmann P, Weisser G, Hahn G, Dudykevych T et al. (2002) Detection of local lung air content by electrical impedance tomography compared with electron beam CT. J Appl Physiol 93:660-666
16. Meier T, Luepschen H, Karsten J, Leibecke T, Grossherr M, Gehring H et al. (2008) Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. Intensive Care Med 34:543-550
17. Victorino JA, Borges JB, Okamoto VN, Matos GF, Tucci MR, Caramez MP et al. (2004) Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. Am J Respir Crit Care Med 169:791-800
18. Löwhagen K, Lundin S, Stenqvist O (2010) Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol 76:1024-1035
19. Zhao Z, Moller K, Steinmann D, Frerichs I, Guttmann J (2009) Evaluation of an electrical impedance tomography-based Global Inhomogeneity Index for pulmonary ventilation distribution. Intensive Care Med 35:1900-1906
20. Zhao Z, Steinmann D, Frerichs I, Guttmann J, Moller K (2010) PEEP titration guided by ventilation homogeneity: a feasibility study using electrical impedance tomography. Crit Care 14:R8

21. Spieth PM, Carvalho AR, Guldner A, Kasper M, Schubert R, Carvalho NC et al. (2011) Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. Crit Care Med 39:746-755
22. Yoshida T, Rinka H, Kaji A, Yoshimoto A, Arimoto H, Miyaichi T et al. (2009) The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: airway pressure release ventilation versus pressure support ventilation. Anesth Analg 109:1892-1900
23. Dellinger RP, Jean S, Cinel I, Tay C, Rajanala S, Glickman YA et al. (2007) Regional distribution of acoustic-based lung vibration as a function of mechanical ventilation mode. Crit Care 11:R26
24. Radke OC, Schneider T, Heller AR, Koch T (2012) Spontaneous breathing during general anesthesia prevents the ventral redistribution of ventilation as detected by electrical impedance tomography: a randomized trial. Anesthesiology 116:1227-1234
25. Mauri T, Bellani G, Confalonieri A, Tagliabue P, Turella M, Coppadoro A et al. (2013) Topographic distribution of tidal ventilation in acute respiratory distress syndrome: effects of positive end-expiratory pressure and pressure support. Crit Care Med 41:1664-1673
26. Andersson B, Lundin S, Lindgren S, Stenqvist O, Odenstedt HH (2011) End-expiratory lung volume and ventilation distribution with different continuous positive airway pressure systems in volunteers. Acta Anaesthesiol Scand 55:157-164
27. Froese AB, Bryan AC (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242-255
28. Wrigge H, Zinserling J, Neumann P, Muders T, Magnusson A, Putensen C et al. (2005) Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: a randomized controlled computed tomography trial. Crit Care 9:R780-R789
29. Bikker IG, Blankman P, Specht P, Bakker J, Gommers D (2013) Global and regional parameters to visualize the 'best' PEEP during a PEEP trial in a porcine model with and without acute lung injury. Minerva Anestesiol 79:983-992
30. Blankman P, Hasan D, Groot JE, Gommers D (2014) Detection of 'best' positive end-expiratory pressure derived from electrical impedance tomography parameters during a decremental positive end-expiratory pressure trial. Crit Care 18:R95
31. Bikker IG, Preis C, Egal M, Bakker J, Gommers D (2011) Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. Crit Care 15:R193
32. Dunster KR, Friese ME, Fraser JF, Galloway GJ, Cowin GJ, Schibler A (2012) Ventilation distribution in rats: Part 2--A comparison of electrical impedance tomography and hyperpolarised helium magnetic resonance imaging. Biomed Eng Online 11:68
33. Elke G, Fuld MK, Halaweish AF, Grychtol B, Weiler N, Hoffman EA et al. (2013) Quantification of ventilation distribution in regional lung injury by electrical impedance tomography and xenon computed tomography. Physiol Meas 34:1303-1318

CHAPTER 9

Ventilation distribution measured with EIT at varying levels of pressure support and Neurally Adjusted Ventilatory Assist in patient with ALI

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Abstract

Purpose
The purpose of this study was to compare the effect of varying levels of assist during pressure support and neurally adjusted ventilator assist (NAVA) on the aeration of the dependent and non-dependent lung regions by means of electrical impedance tomography (EIT).

Methods
We studied 10 mechanically ventilated patients with acute lung injury (ALI). Positive end-expiratory pressure (PEEP) and PSV level were both 10 cm H_2O during the initial PSV step. Thereafter, we changed the inspiratory pressure to 15 and 5 cm H_2O during PSV. The electrical activity of the diaphragm (EAdi) during pressure support 10 was used to define the initial NAVA gain (100%). Thereafter, we changed NAVA gain to 150% and 50%, respectively. After each step the assist level was switched back to PSV 10 cm H_2O or NAVA 100% to get a new baseline. EIT registration was performed continuously.

Results
Tidal impedance variation significantly decreased during descending PSV levels within patients, whereas not during NAVA. The dorsal-to-ventral impedance distribution, expressed according to the center of gravity index, was lower during PSV compared to NAVA. Ventilation contribution of the dependent lung region was equally in balance with the non-dependent lung region during PSV 5 cm H_2O, NAVA 50% and 100%.

Conclusion
NAVA ventilation had a beneficial effect on the ventilation of the dependent lung region and showed less over-assistance compared to PSV in patients with ALI.

Introduction
One of the main reasons for admission to the intensive care unit (ICU) is requirement for mechanical ventilation[1]. During mechanical ventilation the dependent lung region is of special interest, due to the high risk for development of atelectasis. During controlled mechanical ventilation, air is pushed into the lungs and the diaphragm is passively moved to the abdomen with as result that tidal volume is mostly distributed to the non-dependent lung region due to better compliance of this area[2]. In contrast during spontaneous breathing, there is a contraction of the diaphragm, with more displacement of the posterior part, leading to more homogenous ventilation distribution[3]. Spontaneous breathing has been shown to lead to better ventilation/perfusion ratio[3;4] and less atelectasis[5].
Pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA) are commonly used partial ventilatory assist modes. PSV uses flow- or pressure triggering in the ventilator circuit and a pre-set, constant, amount of pressure assistance is delivered with a decelerating flow pattern. NAVA uses a special feeding tube in order to measure the diaphragm electrical activity (EAdi), and the amount of pressure assistance is proportional in relation with the measured EAdi. This enables the patient to control their tidal volume by regulation of their EAdi signal. Several studies[6-13] have shown that NAVA improves patient-ventilator synchrony compared to PSV. In addition, it has been found that NAVA reduces the risk of over-assistance due to down regulation of the EAdi signal[7;9;12,14-18].
Electrical impedance tomography (EIT) is a non-invasive, bedside, radiation-free monitoring technique. Small currents are passed through the skin by using 16-32 electrodes on the thoracic cage skin surface[19;20]. We have shown that EIT is a reliable tool to discriminate aeration between the dependent and non-dependent lung region[19;21]. During a decremental positive-end expiratory pressure (PEEP) trial, we have shown that ventilation was lost in the dependent lung region in both healthy and diseased lungs at lower PEEP levels[19].
The purpose of this study was to visualize the effect of varying levels of pressure support and NAVA gain on the aeration of the dependent lung region by means of electrical impedance tomography (EIT) at the bedside. Our hypothesis was that NAVA leads to more ventilation of the dependent lung region compared to PSV.

Materials and Methods
Study population.
In the present study, 10 patients admitted to the ICU were studied during mechanical ventilation. The protocol was approved by the local institutional human investigations committee. The inclusion criteria were: > 18 years of age, pressure support ventilation, weaning phase of mechanical ventilation, respiratory failure according to the New Berlin ARDS criteria (mild ARDS: PaO_2/FiO_2 200-300 mmHg; moderate ARDS: PaO_2/FiO_2 100-200 mmHg; severe ARDS: PaO_2/FiO_2 <100 mmHg).

Study protocol and measurements.
EIT measurements were performed with a 16-electrode silicon belt placed around the patient's thoracic cage, just below the nipples between the 6th and 7th intercostal spaces[21] (Pulmovista 500, Dräger Medical, Lübeck, Germany). Data were gathered with a sample frequency of 20 Hz. At the time of enrollment all patients were pressure support ventilated (PSV), using the Servo-

I (Maquet, Solna, Sweden), according to our local ventilation protocol. All included patients had already a NAVA catheter for clinical reasons. Each patient received three different assist levels during pressure support and NAVA. During each assist level EIT measurements were performed. For more detail see electronic supplement.

Statistical analysis.

All statistical analyses were carried out using SPSS 20 (Chicago, IL). The values are stated as mean ± SD unless specified otherwise. We assessed the distribution of our data using the Kolmogorov Smirnov one sample test for goodness of fit, and the homogeneity of variance between two distributions by means of the Brown-Forsythe test. The primary endpoint of the study was to investigate changes in ventilation distribution in the dependent lung region between NAVA and PSV. We performed a mixed linear model for repeated measures (assist levels as independent factor) to analyze changes in the average of center of gravity (COG) index and tidal impedance variation (TIV) (dependent variables). Our secondary endpoint was to assess over-assistance of the non-dependent region during one breath, between the different assist levels during both NAVA and PSV. Therefore, we analyzed the intratidal gas distribution. Since the intratidal gas distribution data did not meet the assumption of normality, we analyzed the difference of the intratidal gas distribution between dependent and non-dependent lung regions by means of non-parametric statistical tests.

In addition we analyzed the differences in EAdi, peak pressure, respiratory rate, mean inspiratory pressure, expiratory tidal volume (Tve) and Tve/kg predicted body weight values between PSV and NAVA by means of mixed linear models. For both PSV 10 cm H_2O and NAVA 100% there were no significant differences between the three baseline periods. Therefore, the data of the three baseline periods for both PSV 10 cm H_2O and NAVA 100% are averaged for the statistical analysis. Differences are considered to be significant when $p < 0.05$.

Results

Entry characteristics of the study population are presented in Table 1 (electronic supplement). The ventilatory data including the amount of pressure support given and the resulting EAdi values during each PSV and NAVA step are shown in Table 1. At the lowest assist level the peak pressure was significantly lower during PSV compared to NAVA (Table 1). Increasing the level of assist, tidal volume ($p < 0.0003$) and mean inspiratory pressure ($p < 0.027$) increased significantly, whereas respiratory rate decreased significantly ($p < 0.008$) during PSV whereas not during NAVA (Table 1).

Respiratory parameters varying Pressure Support and NAVA assist levels

Ventilator mode	50%	100%	150%	
PSV	Assist pressure (cm H_2O)	6±1*	10±1	16±1
	Ppeak (cm H_2O)	16±0	21±0	26±0
	Mean inspiratory pressure (cm H_2O)	11.5±0.3	13.2±0.2$^{\$}$	14.3±0.6**
	EAdi (μV)	17±13	14±12	12±9
	Respiratory Rate (ventilatory) (BPM)	22±8	21±7	18±7**
	Tve (mL)	508±160	581±188$^{\$}$	681±210**
	Tve (mL/PBW)	7.5±2.5	8.6±2.9$^{\$}$	10.1±3.0**
NAVA	Gain (cm H_2O/μV)	0.6±0.7	1.3±1.4	2.0±2.1
	Assist pressure (cm H_2O)	10±5	9±3	19±6
	Ppeak (cm H_2O)	19±1	22±2	28±2
	Mean inspiratory pressure (cm H_2O)	11.2±0.3	12.3±0.2	12.6±0.3
	EAdi (μV)	16±10	14±12	13±9
	Respiratory Rate (ventilatory) (BPM)	23±8	21±7	21±7
	Tve (mL)	532±152	539±165	557±166
	Tve (mL/PBW)	7.9±2.3	8±2.6	8.3±2.6

Table 1: Expiratory tidal volume (Tve); Peak pressure (Ppeak); Electrical activity of the diaphragm (EAdi); Predicted body weight (PBW); Breaths per minute (BPM); * = Significant different vs. NAVA 50%; $^{\$}$ = significant different vs. NAVA 100%; ** = significant different vs. NAVA 150%.

During NAVA, respiratory rate and tidal volume were comparable despite the different levels of assist (Table 1). At the highest applied ventilatory assist, tidal volume was significantly higher with PSV compared to NAVA (Table 1).

The dorsal-to-ventral impedance distribution, expressed as center of gravity index, was higher during NAVA compared to PSV which means that more tidal impedance variation was located in the dependent lung region (Fig. 1). Higher levels of assist resulted in more tidal impedance variation in the non-dependent lung region (Fig. 1).

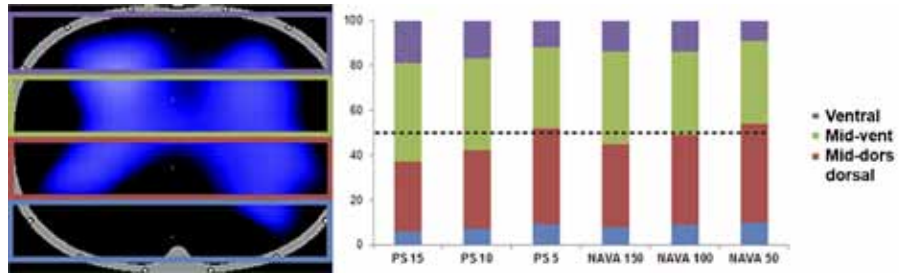

Figure 1: Impedance distribution. The EIT image is divided in four regions of interest (purple= ventral; green= mid-ventral; red= mid-dorsal; blue= dorsal). The bars on the right side represent the percentage of the total tidal impedance variation located in each region, for each assist level. The dashed-line represents the 50% border.

Figure 2 shows the results of the intratidal gas distribution between the dependent and non-dependent regions for both NAVA and PSV. During NAVA 150%, PSV 10 and 15 cm H_2O the non-dependent lung region was responsible for the greatest part of the tidal ventilation and this contribution further increased during the time period of a breath for both PSV 10 and 15 but not during NAVA 150% (Fig. 2). On the other hand during NAVA 100%, 50% and PSV 5 cm H_2O the dependent and non-dependent lung region had an equal contribution to the tidal ventilation (Fig. 2).

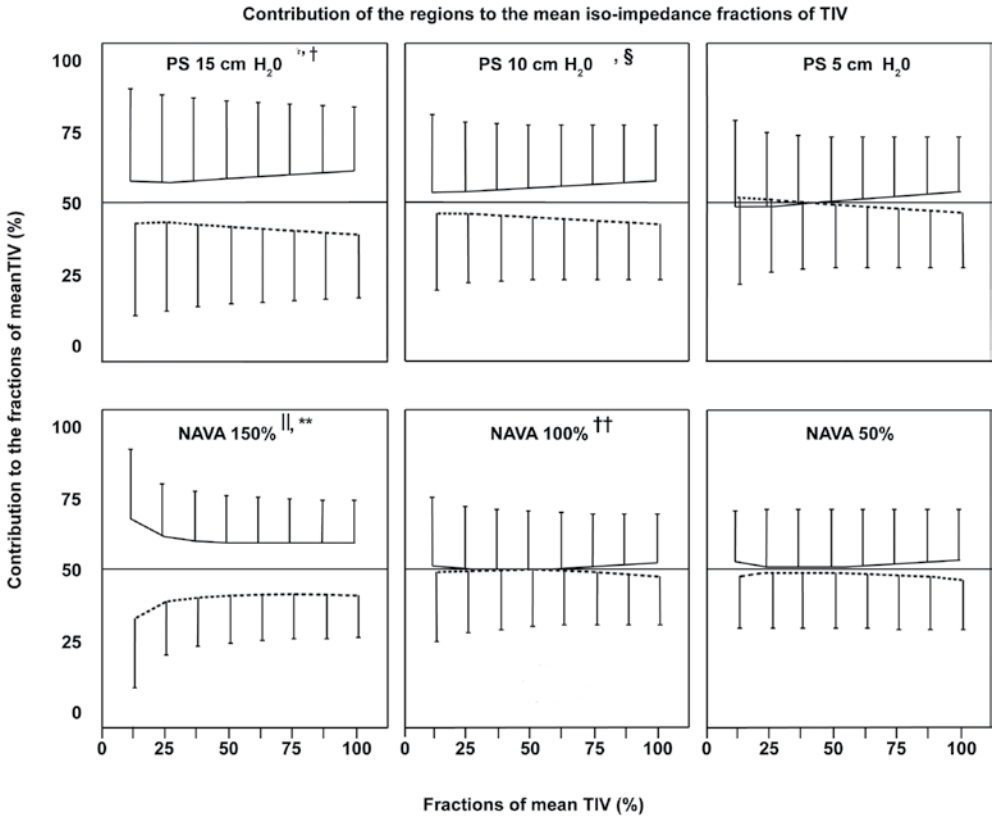

Figure 2: Mean Intratidal gas distribution in eight iso-volume steps during inspiration at the varying levels of pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA). The intratidal gas distribution is calculated from one breath. The total contribution of the non-dependent and the dependent lung regions to each iso-volume step is 100%. Significant difference in distribution by Mann-Whitney U test: * $p = .002$ between PSV 15 and PS 10 cm H_2O, † $p = .001$ between PSV 15 and PS 5 cm H_2O, ‡ $p = .001$ between PSV 10 and PS 5 cm H_2O, § $p = .001$ between PSV 10 and NAVA 100%, ll $p = .001$ between NAVA 150% and NAVA 100%, ** $p = .001$ between NAVA 150% and NAVA 50%, †† $p = .027$ between NAVA 100% and NAVA 50%. Solid line = non-dependent lung region; dashed line = dependent lung region.

Discussion

In the present study, NAVA 100% ventilation showed an improved ventilation of the dependent lung region compared to PSV 10 cm H_2O at the same pressures. Reduction of ventilatory assist during PSV led to less ventilation of the lung whereas not during NAVA. The contribution of the dependent lung region was in-balance with non-dependent lung region during PSV 5 cm H_2O and NAVA 50 and 100% (Fig. 2), indicating more homogenous ventilation. During PSV 10 and 15 cm H_2O, the contribution of the non-dependent lung region increased during the time period of a breath, indicating over-assistance.

Löwhagen and colleagues[22] introduced the intratidal gas distribution based on EIT measurements during a PEEP trial in 16 volume-controlled ventilated patients. They used the intratidal gas distribution to analyze how the tidal volume was distributed within the lung during inspiration and found that the gas distribution in the dependent lung region improved when PEEP was increased. In the present study, we performed the intratidal gas distribution analyses and found a homogenous gas distribution at the lowest ventilatory assist for both NAVA and PSV (Fig. 2). Tidal ventilation was also homogenously distributed with NAVA 100% (Fig. 2) and had more ventilation in the dependent region (Fig. 1) compared to PSV 10 cm H_2O, despite that these two ventilator settings had comparable inspiratory peak pressure and EAdi values (Table 2). At the highest applied ventilator assists for both NAVA and PSV, the gas distribution in the dependent lung region was less compared to the contribution of the non-dependent lung region, and this was also seen at PSV 10 cm H_2O. In addition, the gas contribution of the non-dependent lung region increased even during inspiratory phase during both PSV 10 and 15 cm H_2O whereas not during NAVA 150%. During NAVA, tidal volume was comparable despite the different levels of assist, whereas tidal volume increased during increasing levels of pressure support (Table 2). This can be explained by down-regulation of the EAdi signal at higher assist levels. Like previous articles[9;16-18] we found a suppression of the EAdi signal when the assist levels are increased during both NAVA and PSV. Because NAVA uses the EAdi signal to define the assist level, the amount of increase in pressure was less due to down-regulation of the EAdi signal. In contrast during PSV the patient will receive a constant, pre-chosen amount of pressure assist that is independently of the activity of the diaphragm. Therefore, tidal volumes will increase at higher support levels. The upslope of the non-dependent intratidal gas distribution curves during PSV 10 and 15 means that the increased tidal volume during support ventilation may lead to ventilation of the more compliant part of the lung, i.e. the non-dependent lung region, with risk of over-inflation of this lung region. This indicates that during pressure support there is more risk for over-assistance whereas this is less with NAVA.

Several[6;9-11;13] studies have shown that NAVA has a beneficial effect on patient-ventilator synchrony. Colombo *et al.*[9] compared the effect of different ventilatory assists during NAVA versus PSV on blood gases and respiratory parameters, and showed that NAVA has the advantage to reduce both patient-ventilator asynchrony and over assistance compared to PSV. This was also seen in the present study in which NAVA resulted in more homogenous ventilation compared to PSV and with less over-assistance of the non-dependent lung region (Fig. 3). Also TIV at the different used ventilatory assists during NAVA was more comparable for both dependent and non-dependent lung regions compared to PSV (Fig. 2 supplement).

There are also limitations in this study. EIT measurement covered a cross-sectional slice of 5-10 cm of the lung depending on the placement level of the electrodes[21]. We have chosen to place

the electrodes just above the diaphragm, because this is the predominant site of atelectasis in the ventilated patient in supine position. Data obtained by EIT measurement depend on many factors (patients' posture, impedance of the electrode-patient contacts, etc.) and therefore the absolute TIV values cannot be used to compare differences between patients directly but only the absolute changes of the effect of the different ventilatory support within a patient can be used (Fig. 2 supplement). Therefore, avoiding electrode dislocation during EIT registration is important and in this study the belt with the electrodes was not disconnected during the entire measurement period of around 1.5 hour.

Conclusion

NAVA ventilation has a beneficial effect on the ventilation of the dependent lung region compared to PSV at the same pressure in patients with ALI. Reduction of ventilatory assist during PSV led to less ventilation of the lung but the ventilation distribution improved in the dependent region. This indicates that levels of assist should be titrated in the individual patient in order to avoid over-assistance as seen at the highest used assist levels. During NAVA, we found less over-assistance compared to PSV and with less variation in tidal volume and tidal impedance variation despite the different used ventilator assists, indicating that the patient chooses his own optimal tidal ventilation and adjusts to the imposed ventilatory assist. Despite ventilation of the dependent lung region is more pronounced with NAVA, it is unclear whether this may lead to shorter length of stay on the ventilator. Therefore, outcome studies are needed.

References

1. Tobin MJ (2001) Advances in mechanical ventilation. N Engl J Med 344:1986-1996
2. Reber A, Nylund U, Hedenstierna G (1998) Position and shape of the diaphragm: implications for atelectasis formation. Anaesthesia 53:1054-1061
3. Froese AB, Bryan AC (1974) Effects of anesthesia and paralysis on diaphragmatic mechanics in man. Anesthesiology 41:242-255
4. Putensen C, Mutz NJ, Putensen-Himmer G, Zinserling J (1999) Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 159:1241-1248
5. Hedenstierna G, Tokics L, Lundquist H, Andersson T, Strandberg A, Brismar B (1994) Phrenic nerve stimulation during halothane anesthesia. Effects of atelectasis. Anesthesiology 80:751-760
6. Antonelli M, Bonten M, Cecconi M, Chastre J, Citerio G, Conti G et al. (2013) Year in review in Intensive Care Medicine 2012: III. Noninvasive ventilation, monitoring and patient-ventilator interactions, acute respiratory distress syndrome, sedation, paediatrics and miscellanea. Intensive Care Med
7. Beck J, Campoccia F, Allo JC, Brander L, Brunet F, Slutsky AS et al. (2007) Improved synchrony and respiratory unloading by neurally adjusted ventilatory assist (NAVA) in lung-injured rabbits. Pediatr Res 61:289-294
8. Clement KC, Thurman TL, Holt SJ, Heulitt MJ (2011) Neurally triggered breaths reduce trigger delay and improve ventilator response times in ventilated infants with bronchiolitis. Intensive Care Med 37:1826-1832

9. Colombo D, Cammarota G, Bergamaschi V, De LM, Corte FD, Navalesi P (2008) Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 34:2010-2018
10. de la Oliva P, Schuffelmann C, Gomez-Zamora A, Villar J, Kacmarek RM (2012) Asynchrony, neural drive, ventilatory variability and COMFORT: NAVA versus pressure support in pediatric patients. A non-randomized cross-over trial. Intensive Care Med 38:838-846
11. Piquilloud L, Vignaux L, Bialais E, Roeseler J, Sottiaux T, Laterre PF et al. (2011) Neurally adjusted ventilatory assist improves patient-ventilator interaction. Intensive Care Med 37:263-271
12. Sinderby C, Beck J, Spahija J, de MM, Lacroix J, Navalesi P et al. (2007) Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest 131:711-717
13. Spahija J, de MM, Albert M, Bellemare P, Delisle S, Beck J et al. (2010) Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 38:518-526
14. Allo JC, Beck JC, Brander L, Brunet F, Slutsky AS, Sinderby CA (2006) Influence of neurally adjusted ventilatory assist and positive end-expiratory pressure on breathing pattern in rabbits with acute lung injury. Crit Care Med 34:2997-3004
15. Brander L, Leong-Poi H, Beck J, Brunet F, Hutchison SJ, Slutsky AS et al. (2009) Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest 135:695-703
16. Lecomte F, Brander L, Jalde F, Beck J, Qui H, Elie C et al. (2009) Physiological response to increasing levels of neurally adjusted ventilatory assist (NAVA). Respir Physiol Neurobiol 166:117-124
17. Patroniti N, Bellani G, Saccavino E, Zanella A, Grasselli G, Isgro S et al. (2012) Respiratory pattern during neurally adjusted ventilatory assist in acute respiratory failure patients. Intensive Care Med 38:230-239
18. Terzi N, Pelieu I, Guittet L, Ramakers M, Seguin A, Daubin C et al. (2010) Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. Crit Care Med 38:1830-1837
19. Bikker IG, Leonhardt S, Reis MD, Bakker J, Gommers D (2010) Bedside measurement of changes in lung impedance to monitor alveolar ventilation in dependent and non-dependent parts by electrical impedance tomography during a positive end-expiratory pressure trial in mechanically ventilated intensive care unit patients. Crit Care 14:R100
20. Costa EL, Borges JB, Melo A, Suarez-Sipmann F, Toufen C, Jr., Bohm SH et al. (2009) Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography. Intensive Care Med 35:1132-1137
21. Bikker IG, Preis C, Egal M, Bakker J, Gommers D (2011) Electrical impedance tomography measured at two thoracic levels can visualize the ventilation distribution changes at the bedside during a decremental positive end-expiratory lung pressure trial. Crit Care 15:R193
22. Löwhagen K, Lundin S, Stenqvist O (2010) Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol 76:1024-1035

Supplement

Methods

The measurements were performed at least one hour after placement of the NAVA catheter. During the entire study, the pressure limit was 30 cm H_2O. During PSV the flow trigger was -5 L/min and a cycling-off of 30%. The backup modes for NAVA ventilation were first PSV and secondly pressure control ventilation (PCV). For both ventilation modes a PEEP of 10 cm H_2O PEEP and pressure support or pressure above PEEP level of 10 cm H_2O. For PCV a frequency of 15 breaths per minute was chosen.

Only patients were included when a PEEP of 10 cm H_2O was used at that time. This PEEP level was not changed during the entire study period. In all patients we first started with a pressure support level of 10 cm H_2O (PSV 10) for 10 min. Thereafter, pressure support level was increased to 15 (PSV 15) for 10 min. In order to get a new baseline, pressure support of 10 cm H_2O was applied for 5-10 min. Subsequently, pressure support level was reduced to 5 cm H_2O (PSV 5) for 10 min. Thereafter the ventilation mode was switched to NAVA. During PSV 10, EAdi values were measured and the average peak value of the last 5 minutes was calculated, from the trend menu of the ventilator, and stored for each patient. During NAVA 100%, the NAVA gain was titrated in order to reach the same peak EAdi values as seen during PSV10. After 10 min, the NAVA gain was changed into 150% and 50%, respectively, both for 10 min. According to PSV, between each NAVA gain step the NAVA gain was turned back to NAVA 100% to obtain a new baseline. At the end of each ventilation period, EIT measurements were performed.

With a special program (Servotracker, Maquet, Solna, Sweden) all ventilatory parameters during the trial were collected. Data were processed offline, using the EIT viewer 6.1 and EITdiag (Dräger Medical, Lübeck, Germany) and Matlab R2012A (MathWorks, Natick, MA). EIT images consist of a 32 × 32 pixel matrix. The difference in impedance between the end of inspiration and expiration is defined as tidal impedance variation (TIV). In the EIT viewer raw datasets were exported into several ASCII files per patient. In order to filter out hemodynamic signals a Butterworth filter was applied.

Intratidal gas distribution calculation

Analysis of the intratidal gas distribution was based on research by Löwhagen et al.[1]. This study focused on recruitment and different levels of PEEP, but the analysis method can be adapted to our purpose. The tidal impedance variation represents the inspiration and expiration. All inspirations used to construct the previously described minute-image were used for the intratidal gas distribution. The inspiratory part of the global tidal impedance variation curve is divided in eight iso-impedance parts (each step is 12.5% of the inspiration). The corresponding time points of the iso-impedance parts were transferred to the regional tidal impedance variation curves. In this way, the relative contribution of the dependent and non-dependent regions to the global tidal impedance variation curve could be calculated. In other words the area under the curve of the dependent and non-dependent TIV curves is calculated as percentage of the area under the curve of the global tidal impedance variation curve.

Center of Gravity

COG index describes the dorsal-to-ventral impedance distribution [2]. EIT images are divided in four equal lung regions (ventral, mid-ventral, mid-dorsal and dorsal regions) (Fig.1). The COG index was calculated by dividing the dorsal tidal impedance variation (sum of mid-dorsal and dorsal) by the total tidal impedance variation of the four regions. The COG index [%] describes the percentage tidal impedance variation located in the dependent lung region.

Results

Figure 2 shows the effect of the three different assist levels on tidal impedance variation during PSV and NAVA for the non-dependent and dependent regions. During PSV, tidal impedance variation decreased significantly after lowering the ventilator assist in the non-dependent region, and in the dependent region this was only significant different between PSV 15 and 5 cm H_2O (Figs. 2a and b). During NAVA, tidal impedance variation decreased significantly between 150 and 50% in the non-dependent lung region but not in the dependent region (Figs. 2a and b).

Entry characteristics of the patient population

Entry characteristic	Mean ± SD		
Age (years)	62±10		
Male/Female	6/4		
Heart rate (BPM)	88±14		
Mean Arterial Pressure (mmHg)	82±13		
Weight (kg)	91.2±19.1		
BMI	30±7		
PBW (kg)	68.0±8.4		
Height (m)	1.70±0.18		
PaO_2/FiO_2 (mmHg)	267.8±54.2		
PEEP (cm H_2O)	10±1		
Ppeak (cm H_2O)	17±5		
Mean inspiratory pressure (cm H_2O)	14.5±0.6		
Tve (mL)	576.6±153.1		
Tve PBW (mL/kg)	8.5±2.4		
ARDS category	Mild	Moderate	Severe
(Number of patients)	9	1	0

Table 1: Body Mass Index (BMI); Predicted body weight (PBW); Peak pressure (Ppeak); Expiratory tidal volume (Tve). Acute Respiratory Distress Syndrome (ARDS); Mild= PaO_2/FiO_2: 200-300 mmHg; Moderate= PaO_2/FiO_2: 100-200 mmHg; Severe= PaO_2/FiO_2: <100 mmHg.

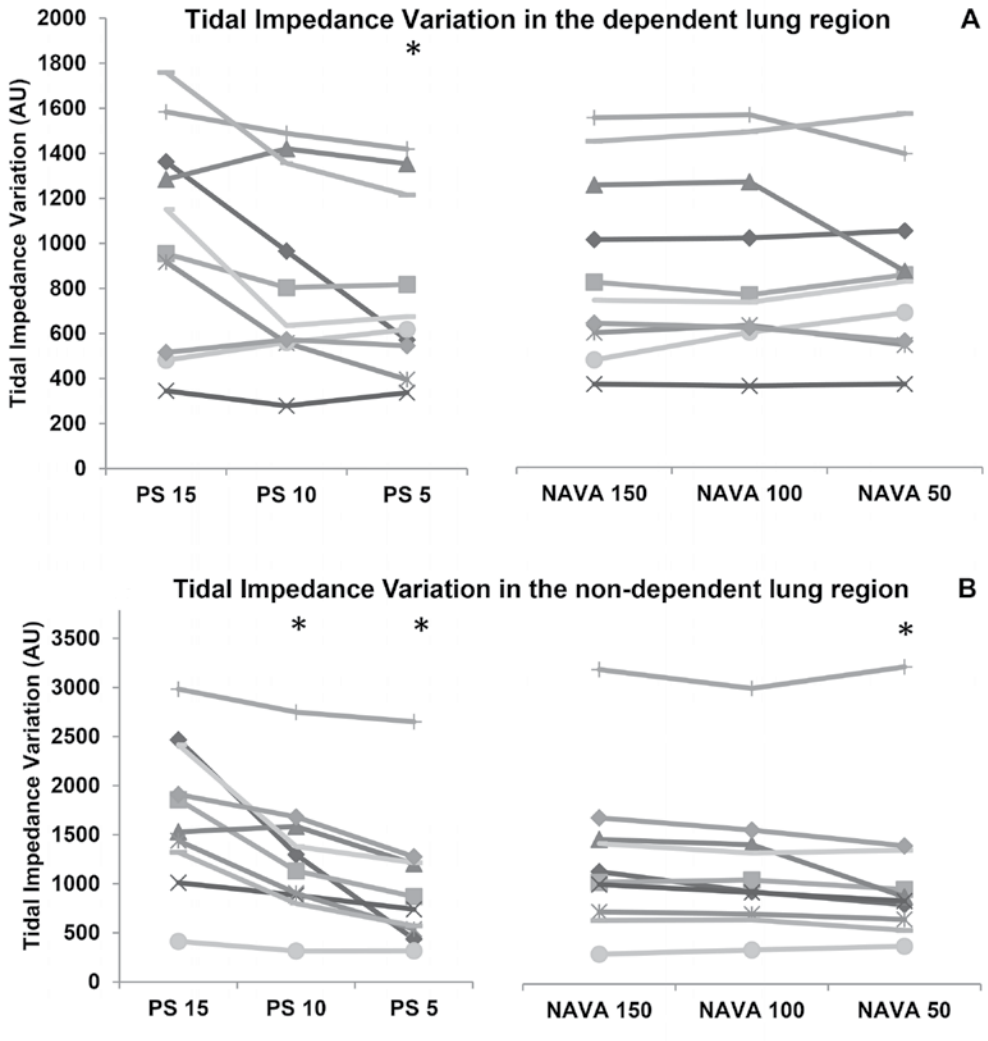

Figure 2: Tidal Impedance Variation (TIV) during varying levels of pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA) for the dependent (Fig.2A) and the non-dependent (Fig.2B) lung region. In both lung regions, the amount of TIV keeps more stable between varying NAVA gain levels compared to PSV. Especially in the non-dependent lung region the TIV decreased significantly when decreasing the PSV level. *p <.05 compared to the highest ventilatory assist in each ventilation mode.

Discussion

The flow- and pressure-curves between PSV and NAVA are different. During PSV a decelerating flow pattern is applied whereas during NAVA an accelerating flow curve occurs. This is due to the differences in pressure curves between both ventilation types: PSV has a square wave form, whereas the NAVA pressure curve follows the EAdi curve and is an accelerating curve

(Fig. 4). The consequence is that the peak pressure during NAVA reached its maximum at the end of inspiration, resulting in a lower mean inspiratory pressure compared to PSV (Table 2). The question arises if the slower increase in pressure- and flow during NAVA is responsible for the even dorsal-to-ventral impedance distribution.

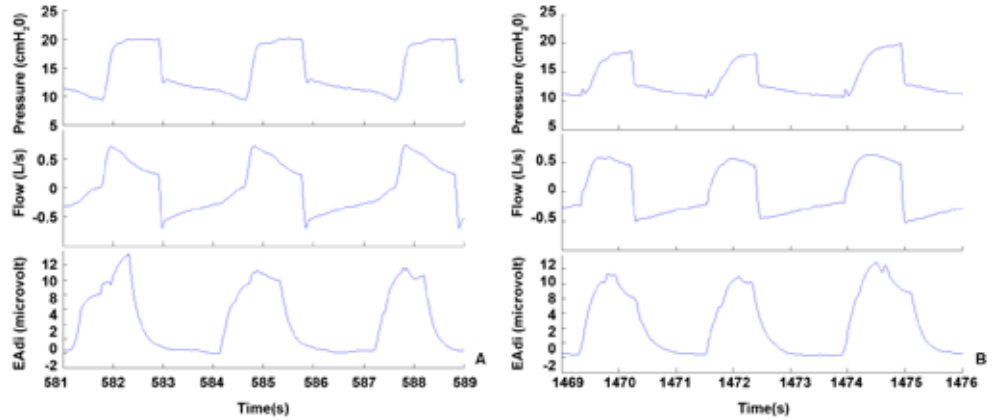

Figure 4: Fig 4A represents the flow, pressure and EAdi curve during PSV 10. Fig 4B shows the same curves during NAVA 100%. It can be seen that during NAVA the pressure curves varies according to the EAdi signal, whereas during PSV the pressure is equal for each breath despite variation in the EAdi signals. During PSV, the pressure curve shows a square shape, whereas the NAVA pressure curve follows the EAdi signal. PSV has a decelerating flow-curve and NAVA has an accelerating flow-curve. EAdi and peak pressures where equal during PSV 10 and NAVA 100.

References

1. Löwhagen K, Lundin S, Stenqvist O (2010) Regional intratidal gas distribution in acute lung injury and acute respiratory distress syndrome--assessed by electric impedance tomography. Minerva Anestesiol 76:1024-1035
2. Luepschen H, Meier T, Grossherr M, Leibecke T, Karsten J, Leonhardt S (2007) Protective ventilation using electrical impedance tomography. Physiol Meas 28:S247-S260

CHAPTER 10

General discussion and future perspectives

General discussion and future perspectives

In the field of intensive care medicine, ventilator-induced lung injury (VILI) remains an important issue. VILI is lung damage induced or aggravated by mechanical ventilation. Although there is no explicit description of what VILI actually is, it is most often described as being a combination of lung edema, capillary damage and inflammation[1-3]. The hallmark paper of the ARDSnetwork trial published in 2000, demonstrates that ventilation with small tidal volumes (6 ml/kg) improves survival in patients with acute respiratory distress syndrome (ARDS). In this scenario, however, the precise role of positive end-expiratory pressure (PEEP) is also unclear. Although multiple studies have reported an improvement in secondary endpoints with higher PEEP levels, they were unable to show a significant reduction in mortality[4-7]. However, two meta-analyses[8;9] have shown that high PEEP levels improved survival in patients with severe ARDS, whereas patients with mild ARDS are best treated with lower PEEP levels. The beneficial effect of high PEEP levels in severe ARDS patients was attributed to the recruitment of atelectatic tissue and a reduction of life-threatening hypoxemia[9]. In the mild ARDS group, high PEEP levels may induce hyperinflation of already open alveoli, mostly located in the non-dependent (ventral) part of the lung, thereby inducing additional lung damage.

Hyperinflation increases forces acting on the alveolar wall and can be described by the terms 'stress' and 'strain'. These two terms were introduced in the 1960s by pulmonary physiologists to describe respiratory mechanics[10]. Stress is defined as the internal distribution of forces per unit of area of a specific material by an external force. The resulting change in the shape of the material is called strain. Hence, lung stress describes the distribution of forces due to PEEP and tidal volume, whereas strain describes the resulting change in lung volume. In 1970 Mead *et al.*[11] constructed a lung model composed of multiple balloons. These balloons were positioned in a honeycomb shape, similar to real alveoli. Using this model the authors were able to calculate the effect of inhomogeneous ventilation due to atelectasis and hyperinflation on the forces on the walls of their model. They calculated that lung stress is increased with a factor 4.5 during inhomogeneous lung insufflation. Protti *et al.*[12] showed that pigs which were mechanically ventilated to an inspiration volume more than twice their functional residual capacity (strain > 2), developed lung edema and died. In a second study[13] the authors demonstrated that pigs ventilated with a strain of 2.5 (mainly consisting of tidal volume), developed lung edema and died. However, when the strain was mainly due to PEEP in combination with low tidal volume, the lungs did not develop lung edema and all animals survived the 3-day observation period. The authors concluded that tidal volume is harmful to the lungs, whereas application of PEEP could protect the lungs. Therefore, PEEP and tidal volume should be balanced in order to avoid hyperinflation resulting in lung injury.

Fernandez-Perez *et al.*[14] performed a prospective case control study to investigate intraoperative ventilation settings and lung injury after elective surgery. In their cohort of 4000 patients, the incidence of lung injury was 3%. No correlation was found between lung injury and the applied amounts of tidal volume, PEEP or fraction of inspired oxygen. Lung injury mainly developed in patients with a history of chronic obstructive pulmonary disease or smoking. Futier *et al.*[15] studied 400 patients randomized to a non-protective ventilation protocol (tidal volumes 10-12 ml/kg and no PEEP) or a lung protective ventilation protocol (tidal volumes 6-8 ml/kg and 6-8 cm H_2O PEEP). The authors showed that the lung protective

ventilation protocol resulted in a significant decrease in pulmonary and extrapulmonary complications (10.5% vs. 27.5%) within the first 7 postoperative days. In addition, the lung protective strategy resulted in a 69% reduction of patients requiring ventilatory support in the first 7 days postoperatively. The authors concluded that PEEP reduced the risk of cyclic atelectasis, whereas low tidal volumes reduced hyperinflation. However, important limitations of that study are the differences between the two protocols in both the applied PEEP level and the amount of tidal volume; this implies that no clear conclusions about the effect of PEEP can be drawn. Later, the PROVEnetwork investigated 900 patients undergoing open abdominal surgery[16]. These patients were randomized to an intraoperative ventilation protocol using 12 cm H_2O PEEP and recruitment maneuvers (high PEEP group), or a ventilation protocol using <2 cm H_2O PEEP without recruitment maneuvers (low PEEP group). All patients were ventilated with a tidal volume of 8 ml/kg. This study found no difference in postoperative pulmonary complications between the two groups; the authors concluded that the patients undergoing open abdominal surgery should be ventilated according to the low PEEP protocol.

From these results we conclude that an inhomogeneous pattern of ventilation could be the key factor in the development of VILI. In healthy lungs alveoli are a network filling the thoracic cavity. During ventilation, the tidal volume is evenly distributed over the entire lung. However, when the lung becomes injured some areas of the lung may collapse. Due to the collapse, the open alveoli will have more space in the thoracic cavity and can then become hyperinflated due to high tidal volume ventilation. This is in accordance with the work of Nieman *et al.*[17-23]. Using an experimental model this group showed that, in healthy lungs, the ratio of alveolar surface area at end-inspiration and end-expiration did not differ between three different tidal volumes (6, 12 and 15 ml/kg). In surfactant-depleted lungs, the alveolar surface area increased significantly as compared to healthy lungs with similar settings. When PEEP was applied, this ratio of alveolar surface area at end-inspiration and end-expiration decreased. The authors concluded that application of PEEP is more effective in stabilizing alveoli than in reducing tidal volume. In addition, they concluded that the mechanism of lung injury is mechanical rather than inflammatory. From these studies it can be concluded that PEEP opens atelectatic tissue and keeps it open, whereas in healthy lungs PEEP may cause airway distention.

The intratidal gas distribution (ITV) derived from electrical impedance tomography (EIT) measurements is able to monitor ventilation homogeneity at the bedside. During partially assisted ventilation, such as pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA), the diaphragm contracts during inspiration with the largest displacement at the dorsal part. We found that tidal volume was mainly distributed to the dependent lung during low tidal volume ventilation (< 8 ml/kg; Chapter 8), whereas ventilation distribution was homogeneous at high tidal volumes (> 8 ml/kg) during PSV. In addition, NAVA resulted in more homogeneous ventilation compared to PSV at different levels of assist (Chapter 9). This is the result of the ventilator being guided by the neural activity (EAdi) of the diaphragm at the moment of triggering, but also during inspiration. With this mechanism the patient is able to influence the amount of tidal volume during mechanical ventilation. If the assist is relatively large the lungs may become hyperinflated and the stretch receptors will inhibit the respiratory drive, leading to lower tidal volumes during subsequent inspirations. We have shown that, during NAVA ventilation, patients aimed to achieve a tidal volume of around 8 ml/kg, irrespective of the respiratory settings.

Yoshida *et al*.[24] performed EIT and computed tomography (CT) scans in pigs with lung injury. Lung injury was induced by surfactant depletion due to repeated lung lavage and, thereafter, ventilation with large tidal volumes. The authors found that spontaneous breathing at a low PEEP level resulted in tidal recruitment associated with pendelluft. Pendelluft is a redistribution of air from the ventral regions towards the dorsal regions at initiation of the inspiration. Pendelluft causes tidal recruitment in the dorsal regions thereby improving oxygenation, but also lung injury due to cyclic atelectasis with increased lung strain. During spontaneous ventilation with optimal PEEP minor tidal recruitment or pendelluft was seen, whereas during controlled ventilation the dorsal regions were less ventilated as compared to spontaneous breathing. The authors concluded that pendelluft during spontaneous breathing with low PEEP levels resulted in regional volu-trauma in the dorsal lung regions comparable with the effect of ventilation with tidal volumes up to 15 ml/kg with muscle paralysis during controlled mechanical ventilation.

Thus, homogeneous ventilation during spontaneous breathing is also of importance. In Chapters 8 and 9 we demonstrated that although both NAVA and PSV are able to ventilate the lungs homogeneously, it is necessary to titrate the ventilator settings. During PSV, a decelerating flow pattern is used with a peak flow immediately after initiation of inspiration. This could be an advantage for patients with 'air hunger', such as ARDS patients in the acute phase. However, in patients without lung pathology, Manning *et al*.[25] found that both a high and a low flow pattern increased the sensation of dyspnea. At low flow, patients sensed a shortage of air, whereas a sensation of hyperinflation was felt at high flow. We found that discomfort can be avoided by the use of NAVA ventilation in patients in the weaning phase. NAVA has an accelerating flow curve and the highest inspiratory pressures are found at the end of inspiration.

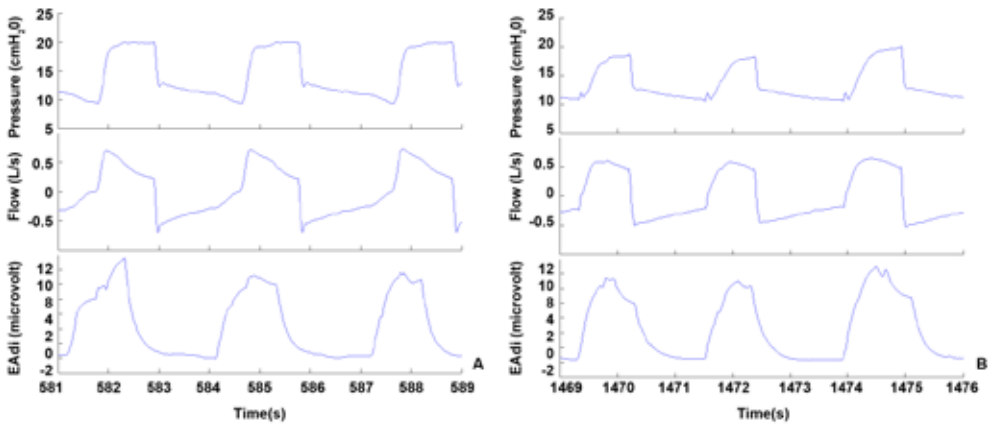

Fig. 1: A: shows the pressure, flow and the neural activity of the diaphragm (EAdi) curve during pressure support ventilation (PSV). B: shows the same curves but during neurally adjusted ventilatory assist (NAVA). During PSV the flow curve has a decelerating pattern with a peak flow immediately after initiation of the inspiration. NAVA shows an accelerating flow curve. The accelerating flow curve during NAVA results in a peak pressure at the end of inspiration, whereas during PSV a more squared pressure curve is seen.

Recently, an old technique was re-introduced in order to optimize ventilatory settings. The esophageal pressure is used as a surrogate for pleural pressure and is used to calculate transpulmonary pressures (airway pressure minus pleural pressure). Talmor *et al*.[7] investigated the ability of esophageal pressure measurements to optimize PEEP settings. A PEEP level was chosen in each patient leading to a positive end-expiratory transpulmonary pressure. The authors found that, in the esophageal pressure-guided PEEP group, a significantly higher PEEP level was used compared to the control group in which PEEP was chosen based on the FiO_2-PEEP table. In addition, it has been suggested that this transpulmonary pressure at the end of inspiration is responsible for the development of VILI[26]. Transpulmonary pressure is low during spontaneous breathing but also during controlled mechanical ventilation with high inspiratory pressures (≥ 30 cm H_2O) in patients with low compliance of the thoracic cage (Fig 2A and 2B). However, transpulmonary pressure can be high during PSV with low airway pressure but with very low pleural pressures due to active contraction of the diaphragm (Fig. 2C).

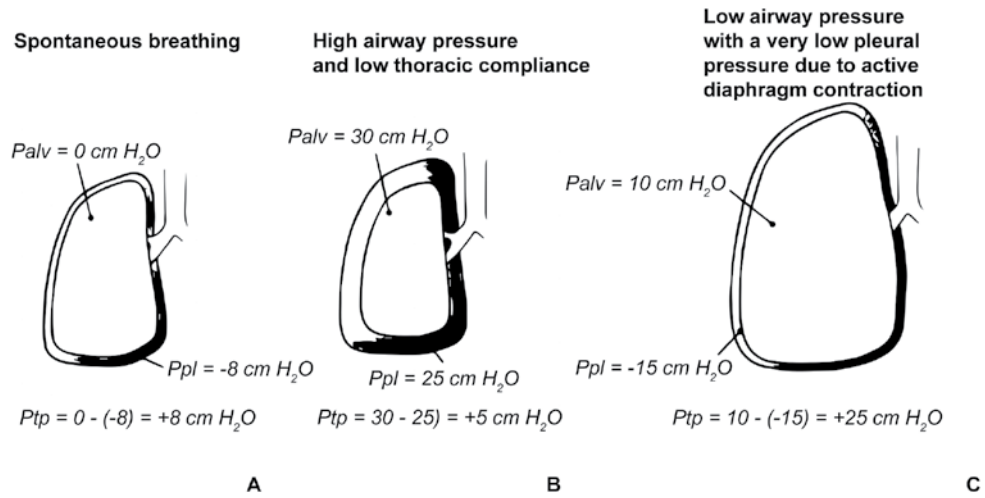

Fig. 2: Figure A represents the alveolar pressure (Palv), pleural pressure (Ppl) and the transpulmonary pressure (Ptp) during spontaneous breathing. Figures B and C represent the alveolar, pleural and transpulmonary pressures during different pulmonary status. During spontaneous breathing transpulmonary pressure is low (A), but also during ventilation with high airway pressures and high pleural pressures (B). However, during active diaphragm

Moreover, esophageal pressure measurements are challenging. The position, as well as the filling of the esophageal pressure balloon is a delicate process. An over-filled or under-filled balloon measures a too high or too low esophageal pressure, respectively[27]. In addition, the pleural pressure based on the esophageal pressure is under-estimated in the dorsal regions and over-estimated in the ventral lung regions. Therefore, esophageal pressure measurements are also not the definitive answer in the aim to optimize ventilator settings. We believe that non-invasive ITV measurements could be an effective alternative to identify the 'best' PEEP and tidal volume at the bedside. Therefore, a multicenter clinical study should be performed to investigate optimal ventilator settings based on ventilation homogeneity, rather than measurements of transpulmonary pressures, to test the effect on outcome in patients with ARDS.

References

1. Kuiper JW, Plotz FB, Groeneveld AJ, Haitsma JJ, Jothy S, Vaschetto R, Zhang H, Slutsky AS: High tidal volume mechanical ventilation-induced lung injury in rats is greater after acid instillation than after sepsis-induced acute lung injury, but does not increase systemic inflammation: an experimental study. BMC.Anesthesiol. 2011; 11: 26
2. D'angelo E, Pecchiari M, Baraggia P, Saetta M, Balestro E, Milic-Emili J: Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. J.Appl.Physiol (1985.) 2002; 92: 949-56
3. Fu Z, Costello ML, Tsukimoto K, Prediletto R, Elliott AR, Mathieu-Costello O, West JB: High lung volume increases stress failure in pulmonary capillaries. J.Appl.Physiol (1985.) 1992; 73: 123-33
4. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N.Engl.J.Med. 2004; 351: 327-36
5. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 637-45
6. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl JL, Lefrant JY, Prat G, Richecoeur J, Nieszkowska A, Gervais C, Baudot J, Bouadma L, Brochard L: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2008; 299: 646-55
7. Talmor D, Sarge T, Malhotra A, O'Donnell CR, Ritz R, Lisbon A, Novack V, Loring SH: Mechanical ventilation guided by esophageal pressure in acute lung injury. N.Engl.J.Med. 2008; 359: 2095-104
8. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G: Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 2010; 303: 865-73
9. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P: Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann. Intern.Med. 2009; 151: 566-76
10. Wilson TA: Solid mechanics. American Physiological Society., Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts. Baltimore, MD Waverly, 1986, pp 35-9
11. Mead J, Takishima T, Leith D: Stress distribution in lungs: a model of pulmonary elasticity. J.Appl.Physiol 1970; 28: 596-608
12. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: any safe threshold? Am.J.Respir.Crit Care Med. 2011; 183: 1354-62

13. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L: Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics? Crit Care Med. 2013; 41: 1046-55
14. Fernandez-Perez ER, Sprung J, Afessa B, Warner DO, Vachon CM, Schroeder DR, Brown DR, Hubmayr RD, Gajic O: Intraoperative ventilator settings and acute lung injury after elective surgery: a nested case control study. Thorax 2009; 64: 121-7
15. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De JA, Bazin JE, Pereira B, Jaber S: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N.Engl.J.Med. 2013; 369: 428-37
16. Hemmes SN, Gama de AM, Pelosi P, Schultz MJ: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014; 384: 495-503
17. Halter JM, Steinberg JM, Schiller HJ, DaSilva M, Gatto LA, Landas S, Nieman GF: Positive end-expiratory pressure after a recruitment maneuver prevents both alveolar collapse and recruitment/derecruitment. Am.J.Respir.Crit Care Med. 2003; 167: 1620-6
18. Halter JM, Steinberg JM, Gatto LA, DiRocco JD, Pavone LA, Schiller HJ, Albert S, Lee HM, Carney D, Nieman GF: Effect of positive end-expiratory pressure and tidal volume on lung injury induced by alveolar instability. Crit Care 2007; 11: R20
19. Nieman GF, Bredenberg CE, Clark WR, West NR: Alveolar function following surfactant deactivation. J.Appl.Physiol Respir.Environ.Exerc.Physiol 1981; 51: 895-904
20. Schiller HJ, McCann UG, Carney DE, Gatto LA, Steinberg JM, Nieman GF: Altered alveolar mechanics in the acutely injured lung. Crit Care Med. 2001; 29: 1049-55
21. Schiller HJ, Steinberg J, Halter J, McCann U, DaSilva M, Gatto LA, Carney D, Nieman G: Alveolar inflation during generation of a quasi-static pressure/volume curve in the acutely injured lung. Crit Care Med. 2003; 31: 1126-33
22. Steinberg J, Schiller HJ, Halter JM, Gatto LA, DaSilva M, Amato M, McCann UG, Nieman GF: Tidal volume increases do not affect alveolar mechanics in normal lung but cause alveolar overdistension and exacerbate alveolar instability after surfactant deactivation. Crit Care Med. 2002; 30: 2675-83
23. Steinberg JM, Schiller HJ, Halter JM, Gatto LA, Lee HM, Pavone LA, Nieman GF: Alveolar instability causes early ventilator-induced lung injury independent of neutrophils. Am.J.Respir. Crit Care Med. 2004; 169: 57-63
24. Yoshida T, Roldan R, Beraldo MA, Torsani V, Gomes S, De Santis RR, Costa EL, Tucci MR, Lima RG, Kavanagh BP, Amato MB: Spontaneous Effort During Mechanical Ventilation: Maximal Injury With Less Positive End-Expiratory Pressure. Crit Care Med. 2016;
25. Manning HL, Molinary EJ, Leiter JC: Effect of inspiratory flow rate on respiratory sensation and pattern of breathing. Am.J.Respir.Crit Care Med. 1995; 151: 751-7
26. Slutsky AS, Ranieri VM: Ventilator-induced lung injury. N.Engl.J.Med. 2013; 369: 2126-36
27. Talmor DS, Fessler HE: Are esophageal pressure measurements important in clinical decision-making in mechanically ventilated patients? Respir.Care 2010; 55: 162-72

CHAPTER 11

Summary
Nederlandse samenvatting

Summary

Mechanical ventilation is a cornerstone in the treatment of patients with Acute Respiratory Distress Syndrome (ARDS). However, mechanical ventilation itself can cause additional lung injury or aggravate already existing lung damage. In **Chapter 1** an introduction is given about the different aims of research considering optimizing ventilatory settings in order to avoid Ventilator Induced Lung Injury (VILI). The hallmark study of the ARDSnetwork group revealed that protective mechanical ventilation with small tidal volume improved survival of ARDS patients. Studies thereafter in which higher amount of Positive End-Expiratory Pressure (PEEP) were used did not affect mortality rate. In Rotterdam, we are believers of the Open Lung Concept (OLC) in which relative high PEEP level is used in combination with small tidal volume in order to keep the dependent lung open and to avoid overdistention of the non-dependent lung. In this thesis we studied the use of bedside monitoring systems in order to apply the best PEEP and/or inspiratory assist levels in the individual patient. We used Electrical Impedance Tomography (EIT), End-Expiratory Lung Volume (EELV) measurements and volumetric capnography.
Chapter 2 is a review in which lung monitoring techniques are described, including the two systems as used in this thesis, which are EIT and EELV. It is important to realize that EIT is technique that measures regional ventilation distribution, whereas EELV is a global measurement of lung volume. Both techniques are easy to use and are able to provide valuable and reliable information at the bedside. These techniques can describe the changes of the pulmonary status especially during a recruitment maneuver or PEEP change.
In the search to a personalized PEEP strategy, we performed a randomized study in **Chapter 3** in 37 patients with mild to moderate ARDS. In the intervention group, PEEP was set according the patients predicted EELV and in controls based on PEEP-FiO_2 table, as used in the ARDSnetwork trial. In the intervention group, the PEEP had to be increased significantly and arterial oxygenation improved whereas PEEP was decreased in the control group during the two days observation period and EELV increased spontaneously. Therefore we concluded that the EELV-guided PEEP strategy in patients with mild to moderate ARDS was not beneficial.
In **Chapter 4** we calculated stress, specific elastance and strain based on the EELV measurements, without the use of additional esophageal pressure measurements, during a decremental PEEP trial in three category ICU patients. Stress increased linearly with the PEEP and the highest values were around 20-25 cmH_2O in the present study. Strain has low values in low collapse-prone lungs, whereas high values in high collapse-prone lungs after increasing PEEP. This indicates that recruitability of lung tissue influences strain more compared to collapse of lung tissue.
In **Chapter 5** we compared seven different EIT parameters in 12 post cardiac-surgery patients, to investigate which parameter should be preferred for PEEP titration. It was shown that the intratidal gas distribution agreed well with dynamic compliance to indicate best PEEP in post cardiac-surgery patients. In addition, the intratidal gas distribution was able to detect the PEEP level at which the tidal volume is even distributed over the dependent and non-dependent lung region. Furthermore, each patient had his own optimal PEEP level to reach this homogenous distribution of tidal volume.
Different global and regional parameters were compared in **Chapter 6** to detect best PEEP in a porcine model with and without lung injury. Best PEEP was comparable between regional compliance of the dependent lung region by EIT and the global indicators: dynamic compliance, arterial oxygenation, alveolar dead space and venous admixture. The EIT derived parameter, intratidal gas distribution, was able to indicate at which PEEP level overdistention of the non-dependent lung started Best PEEP should prevent lung collapse and also overdistention; therefore, a combination of parameters should resemble both of these physiological principles.
Volumetric capnography is a widely investigated tool to optimize ventilatory settings at the bedside. In **Chapter 7** we compared volumetric capnography and the EIT derived parameter intratidal gas distribution.in 15 post cardiac-surgery patients. The specific PEEP level based on EIT was comparable with best PEEP level according to dead space calculations using the Bohr and Enghoff formulas, which are the most simplistic presentation of dead space. In addition, this study showed that higher PEEP levels mainly induced airway distention rather than alveolar distention in patients without lung disorders.
In 2008, it has been shown that controlled mechanical ventilation for only 1 to 3 days resulted already in atrophy of the diaphragm muscles. Therefore, Pressure Support Ventilation (PSV) is the preferable mode of ventilation in our hospital. In **Chapter 8** we compared Pressure Control Ventilation (PCV) and PSV in 20 post cardiac-surgery patients using equal pressure settings and studied the effect on ventilation distribution. PSV improved ventilation of the dependent lung region due to contribution of the diaphragm, which is more pronounced during lower tidal volume. Homogeneous ventilation can also be achieved during PCV when lower tidal volumes (<8 ml/kg PBW) are used.
In **Chapter 9** PSV was compared to Neurally Adjusted Ventilatory Assist (NAVA), which is also a partially assist ventilatory mode and the amount of pressure assist is dependent on the electrical activity of the diaphragm. During NAVA, tidal volume was comparable despite the different levels of assist, whereas tidal volume increased during increasing levels of pressure support. This can be explained by the lowered measured electrical activity of the diaphragm at higher assist levels. Reduction of ventilatory assist during PSV led to less ventilation of the lung but the ventilation distribution improved in the dependent region. This indicates that levels of assist should be titrated in the individual patient in order to avoid over-assistance as seen at the highest used assist levels. NAVA ventilation had a beneficial effect on the ventilation of the dependent lung region and showed less over-assistance compared to PSV.

Samenvatting

Mechanische beademing is een hoeksteen in de behandeling van patiënten met Acute Respiratory Distress Syndroom (ARDS). Echter, mechanische beademing kan zelf ook leiden tot het longschade of reeds bestaande longschade verergeren. In **Hoofdstuk 1** wordt een korte introductie gegeven over de verschillende doelen van het onderzoek naar de optimalisatie van mechanische beademing om Ventilator geïnduceerde longschade (VILI) te voorkomen. Een van de belangrijkste studies van de ARDSnetwork group toont aan dat protectieve mechanische beademing met kleine teugvolumina leidt tot een betere overleving van ARDS patiënten. Studies die daarop volgden, waarin een hogere positief eind-expiratoire druk (PEEP) werd gebruikt, toonden geen effect op de mortaliteit. In Rotterdam wordt geloofd in het zogenaamde open long concept (OLC), waarbij een relatief hoge PEEP in combinatie met kleine teugvolumina wordt toegepast om de dorsale longregio open te houden en om overrekking van de ventrale longregio te voorkomen. In dit proefschrift hebben we het gebruik van monitorsystemen aan het bed getest om de optimale PEEP en/of inspiratoire druk ondersteuning voor de individuele patiënt in te stellen. Hiervoor is gebruikt gemaakt van electrische impedantie tomografie (EIT), eind-expiratoire longvolume (EELV) en volumetrische capnografie.

Hoofdstuk 2 toont een overzicht van de verschillende long monitoring systemen, waaronder de twee systemen die voor dit proefschrift gebruikt zijn: EIT en EELV. Het is belangrijk om te realiseren dat EIT een techniek is waarbij de verdeling van de regionale ventilatie wordt gemeten, terwijl EELV een globale meting van het longvolume is. Beide technieken zijn eenvoudig te gebruiken en verschaffen waardevolle en betrouwbare informatie aan het bed van de patiënt. Deze technieken kunnen de veranderingen van de long toestand beschrijven, voornamelijk tijdens een recruitment manoeuvre of verandering in PEEP.

Om een patiënt specifieke PEEP strategie te definiëren hebben we in **Hoofdstuk 3** een gerandomiseerde studie verricht in 37 patiënten met milde tot matige ARDS. In de interventiegroep werd de PEEP ingesteld volgens de voorspelde EELV voor de patiënt. In de controlegroep werd de PEEP gebaseerd om de PEEP-FiO_2 tabel, zoals gebruikt wordt in de ARDSnetwork studie. De PEEP werd significant verhoogd in de interventiegroep en de arteriële oxygenatie verbeterde terwijl in de controlegroep de PEEP tijdens de tweedaagse observatie periode werd verlaagd en EELV spontaan verhoogde. Derhalve concludeerden wij dat de EELV-geleide PEEP strategie in patiënten met milde tot matige ARDS niet voordeliger is.

In **Hoofdstuk 4** berekenen we stress, specifieke elasticiteit en strain met behulp van de EELV metingen, zonder gebruik van additionele oesophageale drukmetingen, tijdens afbouwende PEEP stappen in drie typen IC patiënten. Stress nam lineair toe moet de PEEP en de hoogste waardes waren ongeveer 20-25 cmH_2O in deze studie. Strain heeft lage waardes in de longen die niet neigen tot samenvallen, terwijl in de longen die wel neigen samen te vallen hoge waarden gemeten werden na verhoging van de PEEP. Dit betekent dat de recruteerbaarheid van het longweefsel meer invloed heeft op strain dan de neiging tot samenvallen van het longweefsel.

In **Hoofdstuk 5** vergelijken wij zeven verschillende EIT parameters in 12 patiënten na cardiothoracale chirurgie, om te onderzoeken welke parameter de voorkeur heeft om PEEP te titreren. Er werd aangetoond dat de distributie van het teugvolume (ITV) goed overeenkomt met de dynamische compliantie om de beste PEEP te identificeren in deze patiënten na cardiale

chirurgie. Hiernaast kon met de ITV het PEEP niveau waarop het teugvolume gelijkmatig wordt verdeeld over de dorsale en ventrale longregionen worden gedetecteerd. Tevens had elke patiënt zijn eigen optimale PEEP niveau om deze homogene verdeling van het teugvolume te bereiken.

Verschillende globale en regionale parameters zijn in **Hoofdstuk 6** gebruikt om de optimale PEEP te bepalen in varkens met en zonder longschade. De beste PEEP was vergelijkbaar tussen regionale compliantie van de dorsale longregio zoals bepaald met EIT en globale indicatoren: dynamische compliantie, arteriële oxygenatie, alveolaire dode ruimte en veneuze vermenging. Met de ITV verkregen met EIT, kon worden bepaald bij welk PEEP niveau de overrekking van de ventrale longregio startte. De optimale PEEP zou samenvallen van de long en ook overrekking moeten voorkomen; daarom moet een combinatie van parameters deze beide fysiologische principes omvatten.

Volumetrische capnografie is een alom onderzocht hulpmiddel om de beademingsinstellingen aan het bed te optimaliseren. In **Hoofdstuk 7** vergelijken we volumetrische capnografie en de via EIT verkregen parameter ITV in 15 patiënten na cardiale chirurgie. Het specifieke PEEP niveau gebaseerd op EIT was vergelijkbaar met het beste PEEP niveau volgens de dode ruimte berekening met de Bohr en Enghoff formules, welke de meest simplistische weergave van de dode ruimte zijn. Deze studie toont tevens dat, in patiënten zonder longziekten, hogere PEEP niveaus voornamelijk leiden tot verwijding van de luchtweg in plaats van verwijding van de alveoli.

In 2008 is aangetoond dat gecontroleerde mechanische beademing gedurende slechts 1 tot 3 dagen al leidt tot atrofie van de spieren van het diafragma. Daarom is druk ondersteunende beademing (PSV) de voorkeursbenadering in ons ziekenhuis. In **Hoofdstuk 8** vergelijken we de drukgecontroleerde beademing (PCV) en PSV in 20 patiënten na cardiale chirurgie met gelijke druk instellingen en bestudeerden we het effect op de ventilatie distributie. PSV verbeterde de ventilatie van de dorsale longregio door een bijdrage van het diafragma, welke meer uitgesproken is tijdens lagere teugvolumina. Homogene ventilatie kan ook bereikt worden tijdens PCV mits er lagere teugvolumina (<8 ml/kg PBW) worden gebruikt.

In **Hoofdstuk 9** vergelijken we PSV met Neurally Adjusted Ventilatory Assist (NAVA); een partieel ondersteunende beademingstechniek waarbij de hoeveelheid ondersteuning afhangt van de elektrische activiteit van het diafragma. Teugvolumina waren vergelijkbaar tijdens NAVA ondanks de verschillende niveaus van ondersteuning, terwijl het teugvolume toenam tijdens verhoogde levels van druk ondersteuning. Dit kan worden uitgelegd door een verlaagde hoeveelheid gemeten elektrische activiteit van het diafragma tijdens hogere niveaus van ondersteuning. Afname van de beademingsondersteuning tijdens PSV leidde tot minder ventilatie van de long, maar een verbeterde distributie van de ventilatie in de dorsale longregio. Dit geeft aan dat het niveau van ondersteuning per individuele patiënt getitreerd dient te worden, om teveel ondersteuning zoals gezien bij de hoogst toegepaste niveaus van ondersteuning te voorkomen. NAVA beademing had een positief effect op de ventilatie van de dorsale longregio en toonde minder overmatige ondersteuning dan tijdens PSV.

Dankwoord

Professor Gommers, beste Diederik, onze samenwerking is begonnen nadat ik in het 2e jaar van mijn opleiding geneeskunde onderwijs kreeg over beademing in het kader van het keuzeonderwijs anesthesiologie en Intensive Care geneeskunde. Aangestoken door jouw enthousiasme, ben ik als student begonnen met onderzoek naar de mogelijkheden om met EIT aan het bed een pneumonie te diagnosticeren. Uiteindelijk is onze samenwerking via mijn keuzeonderzoek uitgemond in dit promotietraject. Door de vele kansen die je me geboden hebt in de afgelopen jaren, heb ik veel verschillende ervaringen op kunnen doen zowel op het gebied van research als nu ook klinisch. Dit heeft zeker een belangrijke bijgedrage gehad aan het in opleiding komen bij de anesthesiologie. Bedankt voor de vele kansen die ik gekregen heb en je begeleiding in de afgelopen jaren. Hopelijk kan onze samenwerking ook na deze promotie blijven voortduren!

Beste Djo, de eerste keer dat ik jou ontmoette op de IC van het Ruwaard van Putten ziekenhuis was in het kader van een interview over beademing. Uiteindelijk hebben we die dag geen interview afgenomen, maar heb je mij meerdere colleges over beademing gegeven. Later ben ik bij je terug gekomen om met behulp van EIT metingen meer inzicht in NAVA beademing te krijgen. Hier is uiteindelijk een succesvolle samenwerking uit voortgekomen met jou als copromotor. Je enthousiasme, wanneer je weer iets ontdekt hebt, werkt zeer motiverend om zelf ook weer in een onderwerp te duiken. Als ik weer eens vastliep kon ik altijd bij je terecht, of dat nou in Rotterdam, België of zelfs in Portugal was, maakte dan niets uit. Ik heb ongelofelijk veel van je geleerd de afgelopen jaren, zowel op research gebied als daar buiten! Dank voor je fijne begeleiding!

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van een onvervalste hoe-sessie, een KK-tje of een BB-tje. Bedankt voor al je steun de afgelopen jaren en bedankt dat je mijn paranimf wilt zijn!

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Beste Els, ondanks je verwoede pogingen om de agenda van Diederik enigszins werkbaar te houden, wist je toch altijd wel weer een gaatje te toveren voor mij. Ook stond je deur altijd open voor een praatje. Bedankt!

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Lieve Eva, de afgelopen jaren heb ik je niet altijd de tijd en aandacht gegeven die je verdient. Je bent me altijd blijven steunen en zonder jouw hulp had ik deze promotie niet zo kunnen doorlopen. Nu mijn promotie er op zit, is het tijd voor die van jou. Ik ben ongelooflijk trots op je.

Curriculum vitae

Paul Blankman werd geboren op 18 oktober 1987 in Heerhugowaard. In 2005 behaalde hij zijn HAVO diploma aan het Minkema College te Woerden. Vervolgens heeft hij in 2006 zijn VWO diploma behaald aan het Luzac College te Utrecht. Na een jaar Beleid Management Gezondheidzorg (iBMG) aan de Erasmus Universiteit Rotterdam gestudeerd te hebben is hij in 2007 begonnen aan de opleiding geneeskunde, eveneens aan de Erasmus Universiteit. In maart 2011 behaalde hij zijn doctoraal voor de opleiding geneeskunde. Tijdens de opleiding geneeskunde is hij begonnen als student onderzoeker waarna hij van maart 2011 tot april 2016 promotie onderzoek verrichtte op de afdeling Intensive Care voor volwassenen. Vanaf maart 2014 liep hij zijn co-schappen welke hij in april 2016 afsloot met het artsexamen. Per 1 mei 2016 is hij gaan werken als ANIOS op de Intensive Care voor volwassenen. Vanaf 1 mei 2017 zal hij zijn vervolgopleiding tot Anesthesioloog volgen in het Universitair Medisch Centrum Utrecht, met als opleider Dr. R.G. Hoff.

Publications

Publications related to this thesis

1. Blankman P, Gommers D: Lung monitoring at the bedside in mechanically ventilated patients. *Curr Opin Crit Care* 2012; 18:261-266
2. Blankman P, Hasan D, van Mourik MS, et al: Ventilation distribution measured with EIT at varying levels of pressure support and Neurally Adjusted Ventilatory Assist in patients with ALI. *Intensive Care Med* 2013; 39:1057-1062
3. Bikker IG, Blankman P, Specht P, et al: Global and regional parameters to visualize the 'best' PEEP during a PEEP trial in a porcine model with and without acute lung injury. *Minerva Anesthesiol* 2013; 79:983-992
4. Blankman P, Hasan D, Groot JE, et al: Detection of 'best' positive end-expiratory pressure derived from electrical impedance tomography parameters during a decremental positive end-expiratory pressure trial. *Crit Care* 2014; 18:R95
5. Blankman P, van der Kreeft SM, Gommers D: Tidal ventilation distribution during pressure-controlled ventilation and pressure support ventilation in post-cardiac surgery patients. *Acta Anaesthesiol Scand* 2014; 58:997-1006
6. Blankman P, Hasan D, Bikker IG, Gommers D: Lung stress and strain calculations in mechanically ventilated patients in the intensive care unit.: *Acta Anaesthesiol Scand 2016; 60(1):69-78*
7. Blankman P, Shono A, Hermans BJM, Wesselius T, Hasan D, Gommers D: Detection of optimal PEEP for equal distribution of tidal volume by volumetric capnography and Electrical Impedance Tomography during decreasing levels of PEEP in post cardiac-surgery patients.: *Br J Anaest 2016; 116(6):862-9*
8. Blankman P, Bikker IG, Hasan D, Gommers D: End-expiratory lung volume-guided positive end-expiratory pressure setting in moderate acute respiratory distress syndrome: a randomized controlled trial.: *Submitted to Minerva Anesthesiol*

Publications not related to this thesis

1. Blankman P, Gommers D: Protectieve beademing perioperatief. *A&I* 2011; 3:41-47.
2. Blankman P, Gommers D. Optimaliseren van beademingsinstelling aan het bed met behulp van Electrical Impedance Tomography. *Venticare* 2014
3. Blankman P, Gommers D: Electrical Impedance Tomography parameters to optimize mechanical ventilation in ICU patients. *Journal für Anästhesie und Intensivbehandlung* 2013; 1:5-9
4. Blankman P, Gommers D, Bikker IG: Elektrische impedantietomografie perioperatief en op de IC-unit. *A&I* 2015; 4:36-40

Abstracts

1. Blankman P, Groot Jebbink E, Preis C, Bikker I, Gommers D. Ventilation area measured with EIT in order to optimize PEEP settings in mechanically ventilated patients. *ESICM 2012*
2. Blankman P, Hasan D, Gommers D. Ventilation distribution during different pressure support and NAVA levels. *ESICM 2012*
3. Mourik MS, Blankman P, Hasan D, Gommers D, Ventilation distribution measured with EIT at different assistant levels during pressure support vs. NAVA in ICU patients. *ISICEM 2013*
4. Blankman P, Hasan D, Gommers D. Intratidal gas distribution is able to point out the best PEEP in mechanically ventilated patients. *ESICM 2013*
5. Blankman P, Hasan D, Woude van der D, Gommers D. Impact of tube size and ventilator setting on tube impedance. *ESICM 2013*
6. Somhorst P, Mourik MS, Vries R, Blankman P, Gommers D. Flow characteristics and tidal volume distribution. *ESICM 2014*
7. Shono A, Blankman P, Somhorst P, Gommers D, Sito Y. The detection of optimal PEEP based on ventilation distribution measured by Electrical Impedance Tomography (EIT). *The 62nd Annual Meeting of the Japanese Society of Anesthesiologists*
8. Shono A, Blankman P, Somhorst P, Gommers D, Sito Y. The effect of muscle relaxant on ventilation distribution based on Electrical Impedance Tomography (EIT) in patients with severe ARDS. *The 62nd Annual Meeting of the Japanese Society of Anesthesiologists*

PhD Portfolio

Name PhD student: Blankman P Erasmus MC Department: Intensive Care Research school Coeur	
	Year
General academic skills	
Biomedical English writing	2012
Reviewer for British Journal of Anesthesia (5x)	2013-2015
Research skills	
BROK course	2013
In-depth courses	
Intensive Care research	2012
Presentations	
"The role of recruitment maneuvers during mechanical ventilation", research seminar, Intensive Care, Rotterdam	2012
"Mechanische beademing", onderwijs IC-verpleegkundigen Rotterdam	2013
"NAVA the workshop", Apeldoorn	2013
"Electrical Impedance Tomography", onderwijs nurse practitioners, Rotterdam	2013
"Neurally Adjusted Ventilatory Assist: How it works", onderwijs nurse practitioners, Rotterdam	2013
"How to set PEEP", onderwijs intensivisten, Rotterdam	2013
"How to set Pressure Support", onderwijs intensivisten, Rotterdam	2014
"How to set mechanical ventilation", Utrecht	
International conferences ESICM, Milan 2016	
Erasmus Critical Care Days, Rotterdam	2011
Winter workshop Intensive Care, Alpbach	2012
ISICEM, Brussels	2012
Symposium ARDS, Rotterdam	2012
ESICM, Lisbon	2012
Tweede ECMO dag EMC, Rotterdam	2012
Symposium "een dag om nooit meer te vergeten, Apeldoorn	2013
Symposium Eurregio, Maastricht	2013
Intensivemedizin und Intensivpflegen, Bremen	2013
Erasmus Critical Care Days 2, Rotterdam	2013
ESICM, Paris	2013
Venticare, Utrecht	2014
Seminars and workshops	2012
Heart valve implantation	2012
Focus on aging	2012
Dutch pharmacology	2012
Refereer avond: Mechanische beademing	2012
Refereer avond: Colloids: friend or foe	2013
Supervising students	
8x: Technical medicine student (11 weeks)	2011-2014
Master thesis: G.J. Baakman, M.S. van Mourik	2013-2014