Recruitment of small size lungs – experimental studies

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Till mamma och pappa
Solveig och Rolf

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ABSTRACT

Background: Patients - both children and adults - undergoing anesthesia and mechanical ventilation rapidly develop atelectasis. Even more severe problems occur in patients with acute lung injury/acute respiratory distress syndrome. To prevent the lung from further injury use of lung protective ventilation including a recruitment maneuver (RM) and a positive end-expiratory pressure (PEEP) titration are parts of the treatment. Children differ from adults not only in size but also in physiology. Studies in pediatric size animals should precede clinical studies.

Methods: 52 pediatric size piglets, weighing about 10 kg were surfactant depleted using a lung injury model with saline lavage. In the first two of four studies tidal elimination of CO_2 (V_TCO_2) was evaluated as a marker of optimal recruitment and dynamic compliance (Cdyn) was evaluated as a marker of incipient collapse during a RM and downward PEEP titration respectively. In all four studies the titrated PEEP was used during different follow-up-ventilation periods.

Aeration, airway pressures including driving pressure (DP), Cdyn and oxygenation were recorded. Iterated CT scans were taken at every change of ventilation for measurement of aeration during the first two studies and during the follow-up-ventilation in three studies.

The effect of a RM and PEEP titration for a prolonged (3 h) follow-up-ventilation was compared with a group with elevated PEEP (PEEP10-group) but without a foregoing RM. Ventilation after a RM was also compared with a control group ventilated with standard ventilation without a prior RM.

In a final study continuous cardiac output (CO) was measured during the RM and PEEP titration for detailed information of central hemodynamics in eight piglets.

Results: During the different follow-up-ventilation periods; 5, 15, 60 and 180 min, ventilation performed with the titrated PEEP resulted in improved aeration as assessed by repetitive CT scans, higher Cdyn, lower DP and better oxygenation compared with ventilation before the RM.

V_TCO_2 peaked or levelled off during the recruitment and corresponding CT scans showed a recruited lung. In addition minimally improved aeration was found when airway pressure was increased above the V_TCO_2 peak/plateau. The first decline of Cdyn during PEEP titration corresponded to an increasing amount of lung collapse according to CT scans.

CO and blood pressure decreased at the highest airway pressure during the RM. CO remained at a lower level but blood pressure recovered entirely. PEEP elevation in the PEEP10-group resulted in improved aeration, higher Cdyn and oxygenation and lower DP but not as much as in the RM-group. The control group did not improve in aeration, Cdyn or oxygenation but was stable.

Conclusion: Ventilation after a RM and PEEP titration results in improved aeration, improved lung mechanics and lower airway pressures compared with baseline and compared with control groups ventilated without a foregoing lung recruitment. V_TCO_2 peak/plateau indicates a recruited lung and Cdyn is a good indicator of increasing derecruitment during the PEEP titration. CO was persistingly and blood pressure temporarily decreased during the RM.

Key Words: lung recruitment, PEEP titration, V_TCO_2, Cdyn, computed tomography, cardiac output, atelectasis, lung aeration, driving pressure

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Contents

Abbreviations

ALI	acute lung injury
ANOVA	analysis of variance
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
Cdyn	dynamic compliance
CO	cardiac output
CO_2	carbon dioxide
CPAP	continuous positive airway pressure
CT	computed tomography
CVP	central venous pressure
DP	driving pressure, in this thesis synonymous with ventilatory amplitude (VA)
EELV	end-expiratory lung volume
EIP	end-inspiratory pressure
EIT	electric impedance tomography
$ETCO_2$	end tidal carbon dioxide
FiO_2	inspired fraction of oxygen
FRC	functional residual capacity
HU	Hounsfield unit
ICU	intensive care unit
I:E	inspiratory to expiratory ratio
MAP	mean arterial pressure
MawP	mean airway pressure
MPAP	mean pulmonary artery pressure
OI	oxygenation index
$PaCO_2$	partial pressure of carbon dioxide in arterial blood
$PACO_2$	partial pressure of carbon dioxide in alveolar gas
$P(A\text{-}a)CO_2$	alveolar-arterial pCO_2 difference
PaO_2	partial pressure of oxygen in arterial blood
PaO_2/FiO_2	fraction of arterial oxygen to inspired oxygen
Paw	airway pressure
PEEP	positive end-expiratory pressure
PV	pressure volume
RDS	respiratory distress syndrome
ROI	region of interest
RM	recruitment maneuver
RMp	recruitment maneuver to V_TCO_2 peak/plateau
RMp+	recruitment maneuver above V_TCO_2 peak/plateau
VA	ventilatory (pressure) amplitude, in this thesis synonymous with driving pressure (DP)

Vd	dead space
VILI	ventilator induced lung injury
V_T	tidal volume
V_{Tinsp}	inspiratory tidal volume
V_TCO_2	tidal elimination of carbon dioxide
ZEEP	zero end-expiratory pressure

List of publications

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

I. **V_TCO_2 and dynamic compliance-guided lung recruitment in surfactant-depleted piglets: A computed tomography study.** Hanson A, Göthberg S, Nilsson K, Larsson LE, Hedenstierna G. *Pediatr Crit Care Med 2009; 10: 687-692*

II. **Lung aeration during ventilation after recruitment guided by tidal elimination of carbon dioxide and dynamic compliance was better than after end-tidal carbon dioxide targeted ventilation: A computed tomography study in surfactant-depleted piglets.** Hanson A, Göthberg S, Nilsson K, Hedenstierna G. *Pediatr Crit Care Med 2011; 13; e362-368*

III. **Recruitment and PEEP level influences long-time aeration in saline-lavaged piglets: an experimental model.** Hanson A, Göthberg S, Nilsson K, Hedenstierna G. *Pediatr Anesth 2012; Febr 20 [Epub ahead of print]*

IV. **Hemodynamic effects during lung recruitment: an experimental study in pediatric size piglets.** Hanson A, Göthberg S, Nilsson K, Hedenstierna G. *Manuscript*

Introduction

"Children are not small adults and neonates are certainly not small children". Children differ not only in size from adults; also physiology is different, especially in neonates. Experiences and results from adult studies and practice cannot directly be transferred to and used in small children.

Lung development

The lungs of the foetus develop during the entire pregnancy with growth of the bronchial tree and increasing number of airway generations. Alveoli are present from week 28-32 [1]. Surfactant is first detectable week 20-24 and the concentration increases rapidly after the 30th week [2].
In the newborn the lungs are not fully developed; the number of alveoli is 20-50 millions compared to the 300 millions in the adult lung. The newborn lung is not a small copy of the adult lung. A newborn has a lower lung volume in relation to body surface area than older infants meaning that they have less reserve for gas exchange in relation to the high oxygen consumption. The infantile rib cage is cartilaginous, the intercostal muscles are not fully developed and the chest wall compliance is high.
The amount of alveoli increases during the first few years of life [3, 4]. Further lung growth depends primarily on an increase of the size of the alveoli [5]. The increase in lung volume is proportional to body length and continues until the thorax has reached adult dimensions.
During the first two years of life the respiratory muscles develop and mineralization of the rib cage cartilage occurs. The chest wall becomes stiffer, the chest wall compliance decreases approaching lung compliance as in adults [2].

Surfactant

Surfactant containing 90% phospholipids and 10% lipoproteins is produced by the type II alveolar epithelial cells (pneumocytes) during the last half of pregnancy [5].
Alveolar surfaces are lined with surfactant that reduces surface tension in the alveoli stabilizing the alveoli and lung.

According to the Laplace equation (P=2T/r), constant surface tension (T) will result in higher pressure (P) in small alveoli with small radius (r) with impaired expansion of small lung units. In the human lung the surface tension decreases as the radius decreases and increases when the size of an alveoli increases; the stability in small and large alveoli is maintained [5].
Surfactant deficiency, seen in premature neonates with RDS (respiratory distress syndrome), after meconium aspiration or lung bleeding increases surface tension and decreases compliance and makes the lung prone to collapse [2].

Differences between children and adults

Due to the smaller size, children have smaller dimensions of airways than adults. A minimal reduction of the radius can dramatically increase airway resistance (Figure 1).

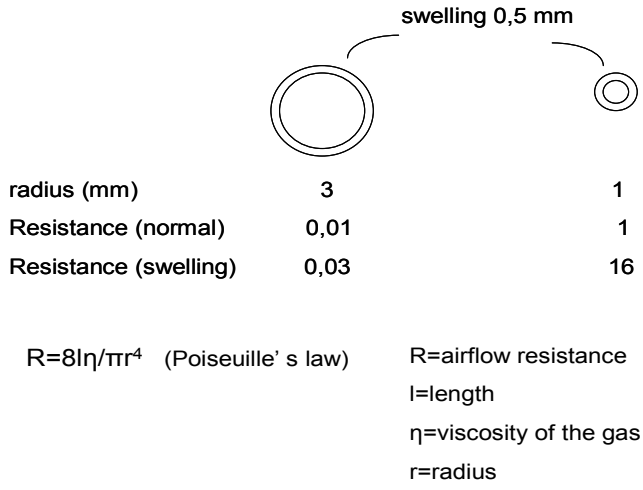

Figure 1. Effect of swelling on resistance in small and larger airways.

For breathing the infant uses the intercostal muscles and the diaphragm, both not fully developed. The relatively large abdomen and a high respiratory frequency make the infant susceptible to fatigue.
Compliance of the respiratory system is a combination of lung and chest wall components. During mechanical ventilation in adults and older children about one half of the inspiratory pressure is required to expand the lungs and one half to expand the chest wall [5]. The more compliant chest wall in infants requires almost

no force for expansion. Lower airway pressure during mechanical ventilation will result in lung expansion.
In healthy humans the relation between tidal volume (V_T) and dead space during breathing remains almost constant through life. The smaller V_T in infants and children makes an increase of dead space more critical [5].
Functional residual capacity (FRC) serves as an oxygen reservoir and is important in infants with a high oxygen consumption of about 6-8 ml/kg/min compared with 3 ml/kg/min in adults. FRC is about 25 ml/kg in small children and increases to 40 ml/kg in adults. In anesthetized small infants FRC is even lower; 20 ml/kg [6] (Table 1).
Closing volume is the lung volume where small, dependent airways begin to close and ventilation cease during maximal expiration. Infants have a proportionally higher closing volume than adults because the elastic supporting structure of the lung is not completely developed. Thus, the sensitivity for small airway diseases as bronchiolitis is higher.

Table 1. Normal values for lung functions (modification from Motoyama)
¤ according to Thorsteinsson, [a] nose breathing, *100 ml/cmH_2O for the whole respiratory system according to Tobin

	newborn	1 year	8 year	adult (male)
weight (kg)	3,3	10	26	73
FRC/weight (ml/kg)	20¤	25	46	42
V_T (ml)	20	78	180	500
breaths/min	30-40	24	18	12
Vd (ml)	7,5	21	75	150
resistance (cmH_2O/l/sec)	29[a]	13	6	2
compliance (lungs) (ml/cmH_2O)	5	16	71	163*
Cdyn (ml/kg/cmH2O)	1-2			2

Respiratory failure

Patients undergoing anaesthesia or mechanical ventilation rapidly develop atelectasis independent of age and anesthetics used [7-9]. Formation of atelectasis is associated with reduction of compliance, increase of resistance and impaired oxygenation in both adults and children [7, 10-12]. Atelectasis is present in more than 90% of anesthetized patients [13, 14] and use of high FiO_2 during anesthesia promote further development [15].
Atelectasis can persist for more than two days after major surgery [16]. The incidence of pulmonary complications is 2.5% after non-cardiac surgery [17], 5% if cardiac surgery is included [18] and even more than 5%, in high-risk patients [19].

Accordingly, avoidance and reversal of per- and postoperative atelectasis are important.

Acute respiratory failure (ARF) is defined as an acute need for mechanical ventilation for more than 24 hours and can develop into acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). ARDS was first described in 1967 and the authors stated that the pathophysiology closely resembled that of the infantile respiratory distress [20]. ARDS is a serious complication with about 40% mortality. The total mortality has not decreased from 1994 to 2006 [21]. In the USA the incidence of ALI is about 80/100.000 and person-years [22].

ARDS is caused by different primary disorders. Pneumonia and aspiration are common causes of pulmonary ARDS while sepsis is common in extra-pulmonary ARDS.

ALI and ARDS were defined in 1994 by the American-European Consensus Conference on ARDS [23] and are characterized by an acute onset. The definition consists of a) a PaO_2/FiO_2 ratio of less than 300 mmHg (40 kPa) for ALI and less than 200 mmHg (27 kPa) for ARDS, b) bilateral infiltrates on chest radiographs and c) pulmonary artery wedge pressure less than 18 mmHg. If a pulmonary artery catheter is not available the absence of clinical signs of pulmonary hypertension is a surrogate criterion.

The above definition has been debated [24] as it takes no attention to the positive end-expiratory pressure (PEEP) level used or FiO_2 given and a new classification was presented at the European Society of Intensive Care Medicine in Berlin 2011 (Pelosi, personal communication) and will be further validated in 5000 patients before set as presented at International Symposium if Intensive Care and Emergency Medicine in Brussels 2012 (Ranieri, personal communication).

Respiratory failure in children

Studies in adults with respiratory failure far outnumber studies performed in children. Results from adult studies cannot in general be adopted and used in the pediatric age group.

The definitions for ALI/ARDS in children are the same as for adults [23]. The incidence of ALI/ARDS in children is lower than the incidences in adults. A study from Australia and New Zealand reported an incidence of ALI of 2.95/100.000 <16 years [25]. A large variation of mortality has been reported; for ARDS 31-38% [25-27] and for ALI or ALI/ARDS 22-35% [25, 27, 28]. Underlying diseases in children with ALI are primary pulmonary disorders such as respiratory syncytial virus infection or bacterial pneumonia (30%), septic shock (30%), near-drowning (9%) and cardiac and oncologic disorders [27, 28]. The highest mortality rate is with near-drowning (54%) and the lowest with pneumonia (11%) [28].

Ventilator induced lung injury (VILI)

Mechanical ventilation is life saving and a prerequisite for advanced extensive surgery. In experimental studies ventilation with high peak airway pressures and large tidal volumes resulted in a lung damage similar to ARDS [29, 30]. Healthy children anesthetized and mechanically ventilated for cardiac catheterization showed an altered immune profile after two hours [31]. In contrast, a study performed in healthy adults ventilated with high or low V_T in combination with PEEP or zero end-expiratory pressure (ZEEP) reported no release of cytokines into the systemic circulation irrespective of the ventilatory strategy [32]. The incidence of VILI in mechanically ventilated adult patients without initial ALI is reported to be 24%. The main risk factors for the development were high tidal volumes and transfusion of blood products [33].

In patients with ALI or ARDS, inappropriate ventilation worsens the lung injury. Use of high tidal volumes (V_T) causes volutrauma and high airway pressures cause barotrauma [30, 34]. Repetitive opening and closing of unstable alveoli and small airways during ventilation (atelectrauma) [35] can lead to VILI [36, 37]. Injurious ventilatory strategies can cause release of inflammatory cytokines and cells into the lung and circulation, measured in bronchoalveolar fluid and blood samples (biotrauma) [38, 39]. Local and systemic activation of the inflammatory response can culminate in multiple organ dysfunction syndrome [39, 40].

Lung protective ventilation

Following reports that ventilation per se could induce and worsen lung injury new ventilatory strategies arose. More emphasis was put on lung protection than, as before, on gas exchange. Better outcome than expected was reported in patients with ARDS after a reduction of V_T and inspiratory pressure and use of permissive hypercapnia [41]. A reduction of 28 days mortality from 71% to 38% was reported when reducing V_T from 12 ml/kg to 6 ml/kg, increasing PEEP, limiting driving pressure (DP) and using recruitment maneuvers and permissive hypercapnia [42]. These results were confirmed in the ARDSnet study where lower V_T and plateau pressure resulted in a reduction of mortality from 40 to 31% before the study was interrupted [43].

The use of a V_T of 6 ml/kg is widely accepted but the adequate PEEP levels for lung protection are not yet defined. The recommendations from ARDSnet are limitations of V_T (6 ml/kg) and a plateau pressure-limit of 30 cmH_2O. PEEP settings according to FiO_2 are also included in the protocol [44] but are debated [45]. Recruitment maneuvers followed by a decremental PEEP titration is proposed for an individual PEEP level to keep the lung open [46-48].

Lung recruitment

Several methods for recruitment using different airway pressures, duration and ventilatory modes have been proposed [48-53].
The benefit of applying PEEP to prevent atelectasis is well established but the need for an individual downward PEEP titration has only recently been evaluated in adult pigs using dynamic compliance (Cdyn) or dead space estimations [48, 54].
A recruitment maneuver (RM) followed by application of PEEP for maintaining the lung volume has been shown to reduce the amount of atelectasis in adults and children [12, 37, 55] and increase dynamic compliance, end-expiratory lung volume (EELV) and oxygenation [56].
The concept "Open up the lung and keep the lung open" [37] was presented in 1992. The basic principles are to open up the lung by high inspiratory pressure above the opening pressure for a sufficiently long period and keep the lung open by a PEEP above closing pressure. The pressure amplitude should also be minimized to reduce shear stress [57]. These principles are still fundamental in lung recruitment and lung protective ventilation.

Sustained inflation/Vital capacity maneuver

Application of a high constant airway pressure and maintaining it for a defined but varying period of time is probably the most studied recruitment maneuver. Different pressures and times for the maneuver are suggested, 40 cmH_2O for 15 s reduced atelectasis in healthy anesthetized adults [50], 40 cmH_2O for 40 s improved oxygenation in patients with early ARDS [58] but 60 cmH_2O for 30 s did not improve oxygenation in patients with cerebral injury and ALI [59].

Prone position

Prone position in combination with a RM (extended sigh) improved oxygenation in patients with early ARDS [60]. Persisting improvement of gas exchange and compliance in patients with ALI were reported when turning from prone back to supine position [61]. Although prone position often improves oxygenation and lung mechanics in patients with ALI/ARDS the complete mechanism of the effects is not fully understood and it does not seem to improve survival [62].

Sighs

Intermittent deep breaths – sighs – are part of the normal spontaneous breathing in both adults and children [63, 64]. In patients with ARDS a sigh administered once per min with at least 35 cmH_2O using continuous positive airway pressure (CPAP) improved oxygenation, EELV and compliance momentarily but the improved

parameters returned to baseline when going back to initial settings [65]. Similar results were found when three consecutive sighs/min with 45 cmH_2O plateau pressure, were used [66].

Application of PEEP

During ongoing and constant tidal volume ventilation application of higher PEEP increases the inspiratory pressure. PEEP itself does not recruit collapsed alveoli because recruitment is an inspiratory phenomenon [67]. If the PEEP level is above closing pressure end-expiratory collapse is prevented and the lung will be kept open [57].

Recruitment maneuvers during ongoing ventilation

Recruitment maneuvers in adults have been performed in pressure control mode using different inspiratory pressure and PEEP levels. Some of the procedures include a PEEP titration for the following ventilation. Use of stepwise increased peak inspiratory pressure with an upper limit of 40 to 60 cmH_2O [46, 55, 68, 69] and PEEP levels of 10 to 45 cmH_2O have been reported. A constant driving pressure was used in some studies [46, 69, 70].

Lung recruitment in children

In contrast to adult experience, few pediatric studies are reported. Five studies are performed in healthy children during general anesthesia [9, 11, 12, 71, 72], one after cardiac surgery [56], three in children with ALI [73-75] and two in children ventilated in the pediatric intensive care unit [76, 77]. The RM used included sustained inflation at 30-40 cmH_2O for 5 to 30 s [11, 72, 76, 77], application of PEEP 5-8 cmH_2O [9, 12, 56], combination of ventilation with high inspiratory pressure for some breaths and application of PEEP [12, 56]. RM where the opening and closing pressure were assessed and a PEEP titration was performed was reported in three studies, all in children with ALI [73-75]. Effects of RM in children have been assessed by computed tomography (CT) or magnetic resonance imaging [9, 12, 71, 73], oxygenation [56, 74, 76, 77] and/or compliance [56, 73, 74, 77]. Most studies reported improvement of parameters monitored after the intervention but in a study with a RM performed after endotracheal suctioning no improvement was found compared to before [77].

Respiratory monitoring

A method indicating optimally recruited lungs would greatly enhance a recruitment maneuver and the evaluation of possible benefits. Presently recruitment can be assessed by computed tomography, which cannot easily be used bedside and electric impedance tomography (EIT), a new promising non-invasive and radiation-free technique which can be used bedside.

Computed tomography

CT has been used for assessment of lung aeration in both experimental and clinical settings. In the intensive care the use is restricted by difficulties with transportation of very sick patients and the radiation load. Conventional chest X-ray exams do not detect early stages of atelectasis [7, 16] and the differences between dense and normal aeration are less apparent than using CT [78]. In addition, with CT the total lung volume as well as the subdivided content of aerated parenchyma can be calculated according to attenuation intervals [79].
Standard definitions of lung aeration according to the attenuation values based on Hounsfield units (HU) [80-82]; [–1000 to –900 overaeration, –900 to –500 normal aeration, –500 to –100 poor aeration, –100 to +100 atelectasis (collapsed lung tissue) and -1000 to 100 total lung] [81] are often used.

Electric impedance tomography (EIT)

EIT is a technique that allows imaging of changes of lung volume and perfusion. Electrodes are placed on the skin surface circumferentially around the chest wall and small alternating currents are induced between pairs of electrodes. Changes of impedance are recorded in a rotating process and represents a cross-sectional plane of the thorax [83]. An image represents real-time conditions and can be obtained 10-50 times per second [84, 85]. The technique has been used for evaluating lung recruitment in adult ICU patients [86, 87].

Carbon dioxide/Tidal elimination of carbon dioxide (CO_2/V_TCO_2)

Carbon dioxide is produced in the mitochondria and transported to the capillaries via the cytoplasm. CO_2 diffuses from the pulmonary capillaries into the alveoli due to the alveolar/arterial pCO_2 difference ($P(A\text{-}a)CO_2$). Blood leaving the alveoli is considered to have the same pCO_2 as alveolar gas meaning that arterial pCO_2 ($PaCO_2$) is usually very close to alveolar pCO_2 ($PACO_2$). In healthy people end tidal CO_2 ($ETCO_2$) is almost identical to $PACO_2$ if ventilation and perfusion are well matched. $ETCO_2$ represents the $PACO_2$ from all ventilated alveoli and $PaCO_2$ represents all perfused alveoli. An $ETCO_2$ lower than $PaCO_2$ indicates

underperfused alveoli. Under normal conditions the difference is less than 0.5 kPa [2].
Hyperventilation causes a sudden decline of $ETCO_2$ because it is governed primarily by ventilation and the capacity of the CO_2 stores. Hypoventilation causes a gradual incline of $ETCO_2$ dependent only of the CO_2 production and the level of hypoventilation [2].
The content of CO_2 and bicarbonate ion in the body is large; in adults about 120 l stored in kidneys, skeletal muscles, bones, fat and other organs. The content of O_2 is approximately 1% of the CO_2 stores [2]. In a situation with a constant CO_2 production a change in ventilation changes the $PaCO_2$ levels slowly whereas changes in O_2 levels are rapid.
The CO_2 production is about 200 ml/min in an adult at resting conditions.

V_TCO_2 is the tidal elimination of CO_2 and measured in ml breath-by-breath. In our studies V_TCO_2 is calculated by the Servo-i by integrating the product of flow and CO_2 concentration (area under the CO_2 curve) during expiratory flow (Methods).
V_TCO_2 in response to a lung recruitment is the result of a complex interaction of several factors in which cardiac output (CO), pulmonary blood flow, dead space and alveolar ventilation are of importance.
Lung recruitment with elevated airway pressures will temporarily increase the CO_2 elimination by increasing the gas-exchanging alveolar surface area until optimal recruitment has been reached. At higher end-inspiratory pressure (EIP) no further increase in gas-exchanging area occurs, rather overdistension of aerated alveoli and compression of alveolar walls. The pulmonary vascular resistance increases and lung capillary perfusion is impaired causing less CO_2 elimination and theoretically a peak or plateau of the V_TCO_2.
The finding that an increase of PEEP decreased the elimination of CO_2 in healthy lungs has been reported in earlier experimental and clinical studies [88, 89].
V_TCO_2, CO and pulmonary CO have been measured in a study in healthy and surfactant depleted pigs during a procedure including increased PEEP levels, a RM and decreased PEEP levels [90]. The main findings were that lung recruitment and PEEP changes have different effects on CO_2 elimination in healthy and surfactant depleted lungs and that the elimination depends on a complex interaction between lung perfusion, alveolar ventilation and to a lesser extent diffusion through the alveolar-capillary membrane. The efficacy of CO_2 elimination in injured lungs was directly related to recruitment/derecruitment.

Compliance

Compliance is defined as the lung volume change achieved per unit of airway pressure change. The compliance of the respiratory system in the adults consists of equal parts of lung and chest wall compliance. Children have proportionally higher

chest wall compliance than adults thus lung compliance contributes to larger part of the total compliance. Airway pressures during mechanical ventilation must consequently be considered and often reduced compared to adult settings. Lung compliance is related to lung volume and adults have higher compliance than children. A period of hypoventilation results in decreased compliance especially in sick lungs but can be restored by some deep breaths. Spread atelectasis as in ALI/ARDS cause a reduction in lung volume and thus a lower compliance. If a recruitment is able to open up the lung compliance will increase.

Static compliance is calculated during stable airway conditions where there is no air flow, ventilation is interrupted with an inspiratory and expiratory hold and time is given for the lung to stabilize during the procedure. Dynamic compliance (Cdyn) is measured during ongoing ventilation without time for the lung to stabilize. In volume controlled mode of the ventilator there is a short end-inspiratory pause that offers time for stabilization. Static compliance is greater than Cdyn by an amount determined by the degree of time dependency of the elastic behaviour of the lung. Cdyn is also dependent of respiratory frequency and more influenced by pulmonary disease than static compliance.
In this presentation dynamic compliance of the respiratory system is monitored and referred to as Cdyn. Cdyn was automatically calculated by the Servo-i ventilator by dividing the inspiratory V_T by the end-inspiratory pressure minus the end-expiratory pressure of the preceding breath [V_{Tinsp}/(EIP-PEEP)].
Compliance is reported to correlate with improved aeration after a lung recruitment [91]. During a decremental PEEP trial dynamic compliance identified the beginning of lung collapse in a pig model [48].
In our first two studies Cdyn was evaluated as a marker of incipient collapse during a downward PEEP titration based on the rationale that when the lung collapses less lung tissue is participating in the ventilation for a given airway pressure which leads to decreased compliance.

Pressure volume curves (PV curves)

PV curves are used for evaluation of lung mechanics. Observing the shape of the curve on the ventilator during ongoing ventilation gives some information of the current lung status but the interpretation is difficult. Methods for setting PEEP by using the lower inflection point of the inflation limb have been proposed [92] and later challenged [93]. The statement that recruitment is an ongoing process of alveolar units along the inflation limb of the PV curve [94] are accepted as well as that derecruitment occurs on the deflation limb [95].

Hemodynamic monitoring and cardiac output

Respiratory failure irrespective of ethiology is often combined with circulatory failure. Therefore ventilator treatment and intensive care often involve close hemodynamic monitoring including invasive blood pressure, central venous pressure (CVP) and sometimes CO measurement. The benefit of the pulmonary artery catheter is debated [96] although information given can be of great value.
Lung recruitment with application of high airway pressures including high PEEP has hemodynamic consequences. Elevated intrathoracic pressure reduces the venous return, CO and blood pressure [53, 97]. The negative effects on circulation can partly be reduced by adjusting fluid balance [51, 56].
Several methods for recruitment resulting in varying hemodynamic responses have been reported using different airway pressures, duration and ventilatory modes [48-53]. In experimental situations hemodynamic reactions can be quite different according to the actual lung injury model and protocol for recruitment [53].
Monitoring of CO during a recruitment has been performed in experimental and clinical studies using thermodilution [49, 51, 53], Doppler techniques [98], pulse contour analysis [99, 100] or transthoracic bioreactance [100].
Marked decrease of CO and mean arterial pressure (MAP) during the RM have been reported both in experimental and clinical studies [49, 51, 53, 98, 100] whereas other clinical studies have shown minor CO effects of the RM [52, 68, 101].
Few studies on hemodynamic consequences of a RM in children or in pediatric size experimental studies have been published [74, 76, 102] as extensive invasive monitoring is not feasible in small infants and there are limitations of available equipment.
CO can be evaluated with intermittent monitoring techniques when procedures with slow changes of airway pressure are used. During rapid changes continuous measurement of CO is required for detailed evaluation of the hemodynamic effects caused by the lung recruitment. Different techniques for measuring CO, invasive or less invasive, are available.

Pulmonary artery bolus thermodilution

Pulmonary artery catheterization is invasive and associated with risks such as arrhythmias, valvular lesions, pulmonary infarction and infection. Pulmonary artery bolus thermodilution technique is regarded as the golden standard for CO measurements and most new techniques are evaluated against this method. The principle of measurement is based on an injection of defined amount of liquid with known temperature and the mixing of this liquid with blood. The difference in temperature over time is measured downstream by a thermistor at the tip of the catheter. Calculation of CO is based on the Stewart-Hamilton equation

$$CO = \frac{VI * (TB - TI) * K1 * K2}{\int \Delta TB(t) dt}$$

where *CO* is cardiac output, *VI* is injectate volume, *TB* is blood temperature, *TI* is injectate temperature, *K1* is a density factor, *K2* is a computation constant and the denominator is the integral of blood temperature change over time [103].
The presence of intracardiac shunts or tricuspid regurgitation affects the result.

Continuous pulmonary thermodilution

This continuous technique uses the thermodilution principles. Instead of using a cold indicator the blood is warmed. A thermal filament heats the blood intermittently and the thermal signal is measured by a thermistor downstream the catheter. This technique offers continuous measurement with updated values every 30 seconds and a calculated value that reflects CO during the last three to six minutes. With a special mode (stat CO) the average of the last three measurements can be displayed [104].

Transpulmonary bolus thermodilution

Transpulmonary thermodilution uses arterial thermodilution for calculation of CO. An ice-cold indicator is injected intermittently in a central line and the temperature is registered by a thermistor-tipped arterial line. CO calculations are based on the Stewart-Hamilton equation. The reliability is comparable to pulmonary artery thermodilution [105].

Doppler technique

Using ultrasound and the Doppler technique blood flow velocity can be measured and CO calculated. Oesophageal Doppler measures flow velocity in the descending aorta and transtracheal Doppler in the ascending aorta. Aortic blood flow is calculated by multiplying the flow velocity with the defined aortic area taken from a nomogram or measured.
Descending aortic blood flow represents about 70% of total CO [106].

Pulse contour analysis

Analysis of the arterial pulse contour offers a continuous CO monitoring. Calculation of CO is based on the principle that stroke volume is proportional to the

systolic area under the arterial pressure waveform divided by the vascular impedance as in the Wesseling formula

$$Vs = \frac{As}{Z}$$

where *Vs* is the stroke volume, *As* is the systolic portion of the area of the arterial pressure waveform and *Z* is the impedance of the system. This technique needs calibration using another method of cardiac output determination [107]. The disadvantage of techniques based on pulse contour analysis is the possible changes in calibration factors with alterations in vascular tone and that recalibration can be necessary.
LiDCO, FloTrac and PiCCO are three systems based on pulse contour analysis.

LiDCO

This technique uses calibration by injection of a small amount of lithium in a central or peripheral vein. The indicator is detected by a lithium-sensitive electrode attached to an arterial line [108]. Concurrent use of muscle relaxants can interfere with the lithium sensor and affect calibration.

FloTrac

A special blood flow sensor (FloTrac) is connected to the arterial line and no external calibration is necessary. Aortic impedance is estimated from characteristics of the arterial pressure waveform and from demographic data from the patient e.g. age, weight and body surface area [109]. The device calculates stroke volume by using arterial pulsatility. CO is calculated every 20 seconds by multiplying stroke volume by heart rate [110]. Rapid changes in vascular tone can impair the accuracy of the system as no external calibration technique is incorporated in the system [104].

PiCCO

The PiCCO system uses a specially designed arterial catheter with a thermistor tip. The system is calibrated by transpulmonary thermodilution. Ice-cold liquid is injected in a central vein and detected downstream by the arterial catheter and CO is calculated. Stroke volume is calculated from the area under the systolic portion of the arterial pulse curve divided by the aortic impedance derived from transpulmonary thermodilution and based on MAP and CVP.
The pulse contour analysis enables continuous monitoring, where beat-to-beat changes are interesting for evaluating the circulatory influences inflicted by rapid or short lived interventions. Pulse contour CO analysis has been compared to pulmonary artery or transpulmonary thermodilution with good correlation during stable conditions [111, 112] but also during hemodynamic instability [113, 114].

Other reports found disagreement between pulse contour CO and thermodilution CO [115-118].
The PiCCO system has been validated in pediatric size animals and children [119, 120].

Aims of this thesis

Children and adults are different in size and physiology. To be able to perform clinical trials in children experimental studies in "pediatric models" must precede.
The overall aim of this work was to study lung recruitment and decremental PEEP titration guided by V_TCO_2 and dynamic compliance respectively and the effect of the recruitment maneuver on aeration in an experimental set up with small size lungs assessed by repetitive CT scans.
Specific aims were:

- To evaluate ventilation and aeration after a RM during different periods of follow-up-ventilation
- To evaluate V_TCO_2 as a marker of optimal recruitment during the increase of airway pressure
- To evaluate dynamic compliance as a marker of incipient collapse during a downward/decremental PEEP titration
- To compare ventilation and aeration after a RM with a control group ventilated at an elevated PEEP without a prior RM
- To evaluate ventilation and aeration after a RM compared to a control group ventilated with a standard ventilation ($ETCO_2$ targeted)
- To evaluate hemodynamic consequences of a RM

Material and Methods

Animals

Fifty two (52) piglets of mixed breed (Yorkshire and Swedish country breed) and of both sexes were included in the four studies (6 in Study I, 17 in Study II, 21 in Study III and 8 in Study IV). The piglets were 5-9 weeks old and weighing 8-13 kg. All procedures and protocols were reviewed and approved by the local Animal Research Ethics Committee of Uppsala University and the study was performed according to the National Research Council guide for "Principles of laboratory animal care".

Anesthesia

Anesthesia was induced with Sevoflurane in all piglets. A single dose of propofol i.v. was given prior to intubation using a cuffed endotracheal tube. Anesthesia was maintained with a continuous infusion of ketamine, fentanyl, midazolam and pancuronium in buffered glucose, 25 mg/ml. In addition physiologic saline was infused to maintain normovolemia. No other hemodynamic management was routinely administered unless a persisting MAP beneath 50 mmHg was measured.

Experimental lung injury model

Lung injury was caused by surfactant depletion induced by bronchoalveolar lavage as earlier described [121]. The lungs were lavaged with the piglets in supine position with aliquots (30 ml/kg) of saline at body temperature aiming at an oxygenation index (OI) [MawP (cmH_2O) x FiO_2 x 100/ PaO_2 (kPa) x 7.5] of 10 - 20. Lavage was interrupted if a high and persisting mean pulmonary artery pressure (MPAP) developed.

Monitoring

Hemodynamic monitoring

Systemic and pulmonary artery pressures, central venous pressure, pulse rate and core temperature (rectal) were continuously measured. In Study III CO was measured by pulmonary artery thermodilution every 30 minutes. In Study IV CO was continuously measured and analysed using pulse contour analysis by the PiCCO system with a PiCCO catheter placed in the femoral artery. The PiCCO system was calibrated immediately before the start of the study protocol by transpulmonary thermodilution using three injections of ice-cold saline.

Ventilatory monitoring

Ventilatory pressures, respiratory rate, volume and flow were continuously measured by the built-in system of the Servo-i. Cdyn was measured during uninterrupted mechanical ventilation and calculated as the inspiratory tidal lung volume divided by the ventilatory pressure amplitude [V_{Tinsp} / (EIP-PEEP)]. V_TCO_2 was calculated by the Servo-i, by integrating the product of flow and CO_2 concentration (area under the CO_2 curve) measured by a mainstream infrared sensor during expiratory flow

$$raw\,VTCO_2 = \int_{One\ breath} flow(t-\Delta t)\cdot CO_2(t)\cdot dt$$

$$VTCO_2 = raw\,VTCO_2\,\frac{273\cdot P_{baro}}{294\cdot P_{standard}}$$

where raw V_TCO_2 is calculated from ambient pressure at 21 degrees Celsius and standard temperature is 273 Kelvin, 21 degrees Celsius is 294 Kelvin, $P_{standard}$ is standard pressure, P_{baro} is ambient pressure and t is time.

Gas exchange

Continuous blood gas measurements (Study I, II and IV) were monitored by a Paratrend sensor (Paratrend, Diametrics Medical Ltd, Buckinghamshire, England) inserted through a carotid artery line. After insertion the sensor was calibrated and adjusted against an arterial blood gas. In Study III blood gases were manually collected and analyzed every 30 min.

Computed tomography (Study I, II and III)

CT scans were performed during Study I, II and IV for assessment of aeration. In Study I and II a CT scan was taken at every change of ventilation according to the protocols. The images were performed as single slices with inspiratory breath holding during recruitment and reopening and with expiratory breath holding at all other ventilatory settings. In Study II three helical scans were added; two at the beginning of the protocol and one at the end of the study.

Before the study protocols were initiated the piglets were positioned in the CT scanner (Somatom Sensation 16, Siemens Medical Systems, Erlangen, Germany) and remained there for the entire study. An initial topogram was used to position a slice, chosen to be 1 cm above the diaphragm dome.

In Study III only helical scans were performed every 30 minutes. The image corresponding to a level 1 cm above the diaphragm dome was selected for analysis of aeration. Helical scans were performed with expiratory breath holding. Total lung gas volume was calculated from the helical scans.

Lung aeration was analyzed using the CT image analysis software Maluna (Modular Lung Analyzing Software by Dr Peter Herrmann, version 2.041, University Hospital, Göttingen, Germany). A specially trained person blinded to the actual ventilatory settings manually delineated the region of interest (ROI), and performed the calculations. The inner rib cage and the mediastinal structures were taken as the lung boundaries. We used standard definitions of lung aeration according to the attenuation values based on Hounsfield units (HU) [80-82]; overaeration, normal aeration, poor aeration and atelectasis (collapsed lung tissue).

Ventilatory settings

During the study periods all piglets were ventilated in pressure control mode using a Servo-i with 15 mm tubing, adult mode with circuit compliance compensation. The respiratory rate was set at 24 breaths per minute with an inspiratory:expiratory (I:E) ratio of 1:1. FiO_2 was kept at 1.0 in Study I, II and IV but was reduced to 0.5 after the recruitment maneuver in Study III. During preparation and stabilization time PEEP was set to 5-6 cmH_2O and EIP to generate a target V_T of 10 ml/kg. $ETCO_2$ was kept between 4 and 6 kPa by adjusting EIP.

Basic experimental protocol

All studies were performed with a similar recruitment protocol (Figure 2). The basic principles are described here and detailed for each study below.

The protocols started with initial baseline ventilation performed at PEEP 5 cmH_2O and EIP for a target V_T of 10 ml/kg and $ETCO_2$ 4-6 kPa for 30 min. Ventilation without PEEP (ZEEP) for 5 min followed. The RM started with a stepwise increase of PEEP (0-5-10-12-15) with 3 breaths at each step up to 15 cmH_2O. EIP was then increased in steps of 3-5 cmH_2O until the peak/plateau value of V_TCO_2 was reached. At this EIP we assumed that the lungs were optimally recruited and that additional increase of EIP would not add any significant amount of normally aerated lung as assessed by CT images. EIP was then decreased to target V_T and PEEP stepwise decreased by 1 cmH_2O down to PEEP 4. The PEEP level when Cdyn started to decline was assumed to indicate the beginning of lung collapse, derecruitment, also defined as closing pressure.
After the downward PEEP titration the lungs were partly collapsed and a reopening was performed for 1 min at PEEP 15 cmH_2O and EIP corresponding to the V_TCO_2 peak/plateau during the foregoing recruitment. During recruitment and PEEP titration a 20 seconds equilibration period was allowed at each step before the CT scan was performed.
After the reopening, ventilation with the titrated PEEP and the target V_T of 10 ml/kg was performed. The duration of the follow-up-ventilation differed between the studies.

Details for each study

Study I

The experimental protocol for this initial study included two complete RMs performed one after the other. The first starting with ventilation without PEEP for 5 min followed by a 10-minutes period of baseline ventilation; PEEP 6 cmH_2O and EIP 25 cmH_2O or a level to achieve a target V_T (10 ml/kg). PEEP was then increased to 12 or 15 cmH_2O depending on ventilatory settings during baseline ventilation. From this level EIP was increased in 3-4 steps of 5 cmH_2O. EIP was deliberately increased above the point of V_TCO_2 peak/plateau to identify the amount of overdistension/overaeration.
Each RM was completed by a 5-minutes period of follow-up-ventilation. The second RM was performed in the same way but started directly after the 5-min ventilation without PEEP.

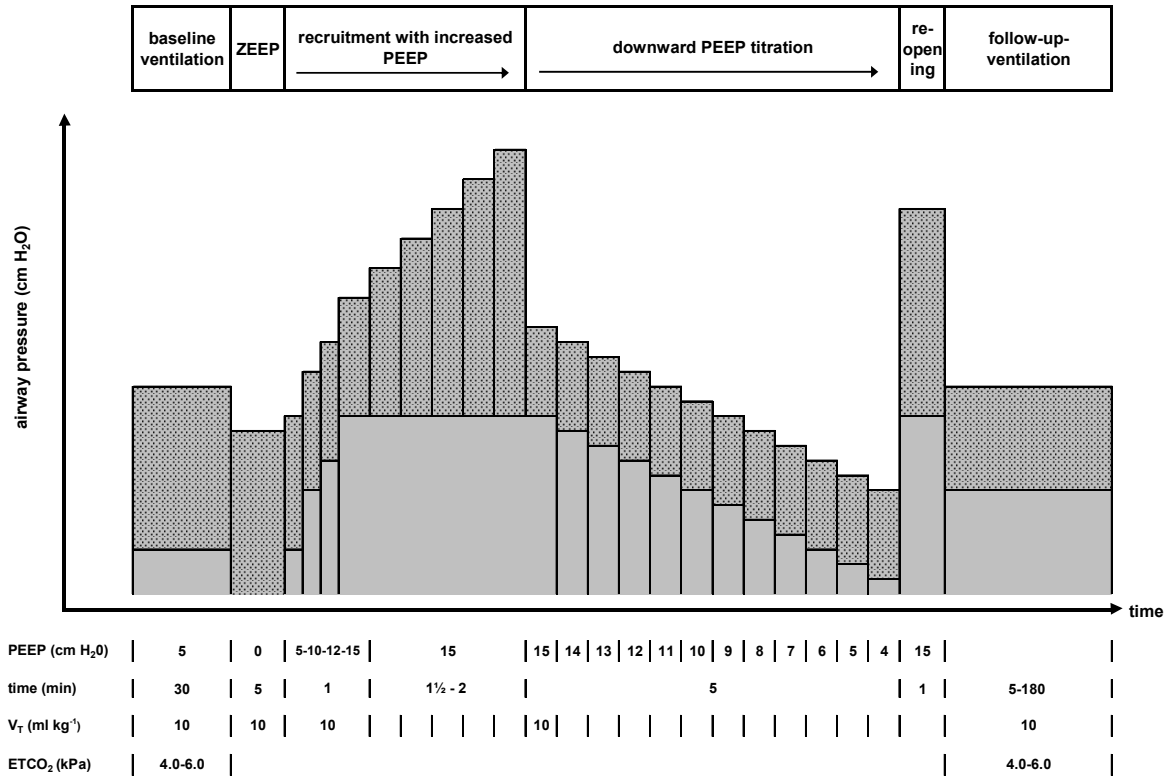

Figure 2. Schematic illustration of the basic experimental protocol. Modifications are detailed below.

Study II

Three experimental protocols were used in this study. Two different RM groups (RMp and RMp+) with six piglets in each group and a control group with seven piglets were included. All piglets were initially ventilated with baseline ventilation and a 5-minutes period of ZEEP ventilation to promote lung collapse. In the control group, after the ZEEP ventilation, ventilator settings were adjusted back to baseline ventilation for the remaining study period (53-163 min) without any other adjustment than EIP - if necessary - for the target V_T and $ETCO_2$.

In the RM groups the RM was performed as described above (Figure 2). In the RMp group no further increase of EIP was undertaken after the V_TCO_2 peak/plateau was identified. In the RMp+ group EIP was increased in two more steps of 3 cmH_2O beyond the peak/plateau of V_TCO_2. The two extra increases of EIP above V_TCO_2 peak/plateau were performed for assessing if a higher EIP would result in a more recruited lung according to CT scans.

The follow-up-ventilation for the RM groups was set to 15 minutes.

Helical CT scans were performed after baseline ventilation, after ventilation with ZEEP and at the end of the study for all piglets.

Study III

21 piglets, 8 piglets in the RM-group and 13 piglets in the PEEP10-group were ventilated with baseline ventilation followed by ventilation at ZEEP to induce lung collapse.

In the RM-group a RM and a downward PEEP titration according to the protocol was followed by a 3-hour follow-up-ventilation.

In the PEEP10-group, after the ZEEP ventilation PEEP was increased to 10 cmH_2O (without a foregoing RM). The PEEP level was based on previous results to be an optimal level (Study I and II). EIP was adjusted to achieve the target V_T as in the RM-group. This ventilation also persisted for 3 hours.

In both groups $ETCO_2$ was kept at 4-6 kPa. FiO_2 was reduced to 0.5 during the 3-hour follow-up-ventilation. If the target V_T increased or decreased by more than 10% despite $ETCO_2$ within the postulated limits, EIP was adjusted ±1 cmH_2O.

CO was measured using pulmonary thermodilution, blood gases analyzed and a helical CT scan was taken every 30 min, starting at the end of baseline.

Study IV

In eight piglets a RM and PEEP titration was conducted as above (Figure 2). The final protocol step was a 60-minutes follow-up-ventilation. The study was performed without CT scans.

CO was continuously measured during the entire study using pulse contour analysis. A PiCCO catheter was inserted in the femoral artery for CO analysis and blood pressure monitoring. The PiCCO system was calibrated by transpulmonary thermodilution just before the initiation of the protocol. CO was recorded at each step of the recruitment protocol.

Statistics

Study I

Results from individual animals are presented as median and range unless otherwise stated. Sign Rank Test and Student's t-test was used for analysis of CT measures of different lung volumes, Cdyn and airway pressures.

Study II-IV

Data are presented as mean and standard deviation, (mean±SD).

Study II

Student's t-test was used for comparing lung aeration, ventilatory and circulatory parameters in the two merged recruitment groups with the control group and for comparing baseline ventilation with follow-up-ventilation in the RM groups/control group respectively. ANOVA with Bonferroni correction was used for comparing separated recruitment groups with the control group.

Study III

Aeration, Cdyn, airway pressures and circulatory parameters including CO within and between the two study groups were evaluated using Student's t-test.
Mixed model ANOVA SAS statistical package was used for extended evaluation of the adequacy of the t-test and influence of multiple analyses (SAS 9.2 Institute Inc., Cary, NC, USA).

Study IV

CO, blood pressure and ventilatory parameters were analyzed using Student's t-test.

$P<0.05$ was considered statistically significant in all studies.
Statistical analysis were performed by Statistica 7, StatSoft, Tulsa, OK, USA (sign rank test and t-test), SPSS 16.0, SPSS Inc, Chicago, IL, USA (ANOVA with Bonferroni correction) and SAS 9.2 Institute Inc., Cary, NC, USA (mixed model ANOVA).

Results

Piglets in all studies were lavaged with 2-14 aliquots of saline to establish the injury model of surfactant depletion. This resulted in an oxygenation index of 3-28.5 after lavage.

Study I

In this initial study a RM and decremental PEEP titration was performed twice in each piglet including a 5 min follow-up-ventilation ("open lung ventilation"). Aeration was assessed by CT.
The amount of normally aerated lung during baseline ventilation was doubled from 27 to 57% during "open lung ventilation" after the RM ($p<0.01$). The amount of atelectasis decreased from 48% during ventilation with ZEEP to 23% during baseline ventilation ($p<0.05$) and was almost eliminated, 3%, during "open lung ventilation" ($p<0.01$ vs. baseline). Minimal overaeration was seen during recruitment (0.5%) and during "open lung ventilation" (<0.4%) and there were no radiological or clinical signs of pneumothorax (Table 2). There were no significant differences between the two recruitments performed in each piglet.

The 5 min "open lung ventilation" was performed at PEEP 11 cmH_2O, guided by the foregoing PEEP titration. EIP was higher during baseline than during "open lung ventilation" (25 vs. 20.5 cmH_2O) ($p<0.05$). For a V_T of 10 ml/kg the ventilatory pressure amplitude (EIP-PEEP) during baseline ventilation was 19 and could be lowered to 11 cmH_2O during "open lung ventilation". Cdyn improved from baseline ventilation and was significantly higher during "open lung ventilation", 5.5 vs. 10 ml/cmH_2O respectively ($p<0.01$). PaO_2 also improved from baseline 24 kPa to 89 kPa during "open lung ventilation" ($p<0.05$).

Table 2. Aeration and respiratory parameters. V_TCO_2=tidal elimination of CO_2, Cdyn=dynamic compliance, EIP=end-inspiratory pressure, PEEP=positive end-expiratory pressure, V_T=tidal volume.
† p<0.05 between ventilation with no PEEP and baseline ventilation, * p<0.05 between baseline ventilation and open lung ventilation, ** p<0.01 between baseline ventilation and open lung ventilation. Values presented as median and range.

	Ventilation with no PEEP		Baseline ventilation		Ventilation at V_TCO_2 max/plateau		Ventilation at Cdyn max		Open lung ventilation	
Content of lung tissue (%)										
collapse	48	(38-70)	23	(8-34)†	2	(2-8)	3	(2-8)	3	(2-12)**
poorly aerated	35	(23-51)	45	(36-64)	13	(8-25)	42	(21-60)	40	(17-58)
normally aerated	11	(7-18)	27	(13-57)†	85	(68-90)	54	(38-77)	57	(39-81)**
overaeration	0	(0)	0.02	(0-0.13)	0.46	(0.10-1.20)	0.11	(0.01-0.59)	0.16	(0-0.32)
Airway pressures (cmH_2O)										
EIP	24	(14-33)	25	(25-35)	47	(35-60)	22	(15-36)	20.5	(17-31)*
PEEP	0	(0)	6	(6-8)	12	(12-15)	10	(8-13)	11	(9-13)**
Ventilatory Pressure amplitude	24	(14-33)	19	(19-27)	35	(23-45)	12	(6-24)	11	(6-18)**
V_T (ml)	108	(86-129)	120	(75-210)	200	(178-258)	127	(112-157)	107	(81-127)
Dynamic compliance (ml/cmH_2O)	4.2	(3.2-6.8)	5.5	(3.8-11.3)	6.1	(4.4-10.2)	9.9	(5.6-20.4)	10	(5.7-18.1)**
PaO_2 (kPa)	9.4	(7.3-13)	24.2	(9.5-102)†	68	(9.9-106)	93.6	(12.3-106)	88.9	(35.5-106)*

In all piglets V_TCO_2 peaked or leveled off during the recruitment if the PEEP chosen for the RM was above closing pressure; 12 cmH_2O was sufficient in three piglets and 15 cmH_2O was required in the other three piglets. After V_TCO_2 had peaked or leveled off a further increase in EIP caused an increase in overaerated lung of 0.2%, minor or no increase in normally aerated lung (0.7%) or decrease of poorly aerated lung (0.8%). Atelectasis was hardly affected (<0.2%). During the downward PEEP titration Cdyn decreased before the CT scans showed any sign of increased lung collapse (Figure 3).
During the recruitment and PEEP titration PaO_2 did not increase or decrease in a predictable way. The amount of collapse was already 8.0% during PEEP titration when PaO_2 fell by 10% or more compared with the highest PaO_2 directly after recruitment.

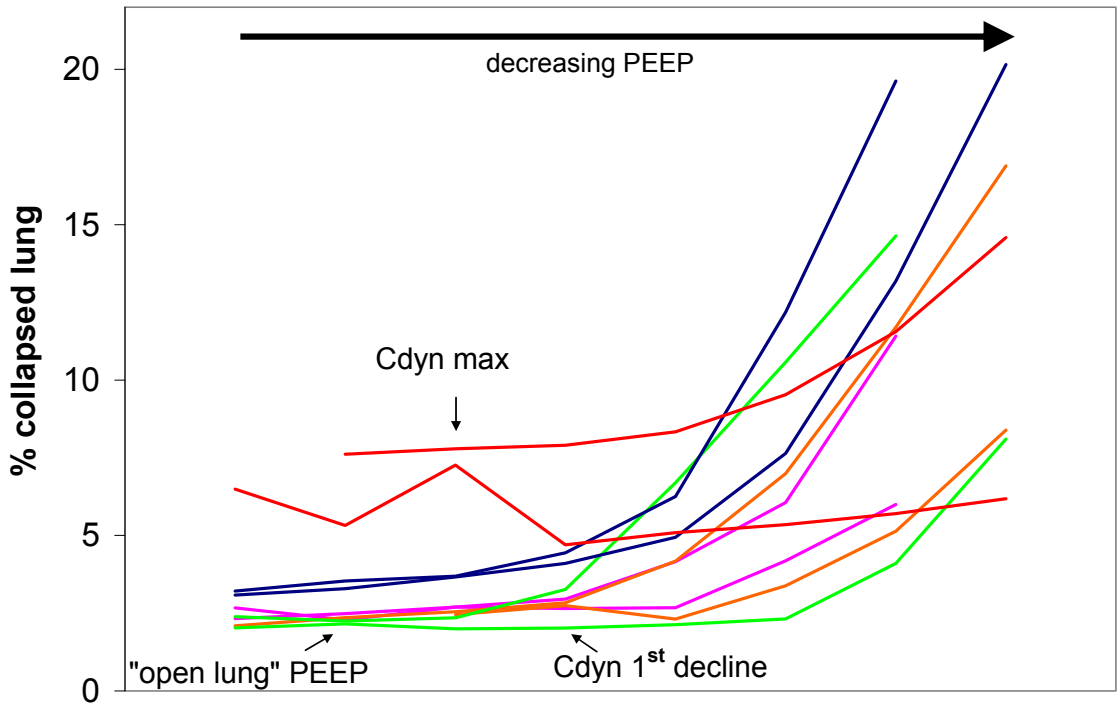

Figure 3. Amount of collapse % during the downward PEEP titration. Not all PEEP levels are presented. Two procedures in each piglet with identical colors.

Study II

Two recruitment groups were compared with a control group without any intervention. Aeration differed between the merged RM groups after the 15 min "open lung ventilation" and the control group at the end of the study. Atelectasis was 4±3% in the RM groups and 14±9% in the control group ($p<0.01$) and normally aerated lung 65±13 and 46±11% respectively ($p<0.01$). The amount of poorly aerated and overaerated lung was not significantly different between the RM groups and the control group.

The RM and PEEP titration resulted in improved aeration. CT scans from the merged RM groups revealed that the proportion of normal lung increased from 42±11% during baseline ventilation to 65±13% during the "open lung ventilation" period ($p<0.001$), atelectasis decreased from 15±7% to 4±3% ($p<0.001$) and the amount of poorly aerated lung from 43±8% to 32±12% for the corresponding periods. The gas volume doubled from 17 ml/kg to 34 ml/kg ($p<0.001$) (Figure 4). Cdyn increased by 68% between baseline and the end of the "open lung ventilation" period ($p<0.001$). PaO_2 in the RM groups was 57% higher during the final "open lung ventilation" period compared to baseline ventilation ($p<0.01$).

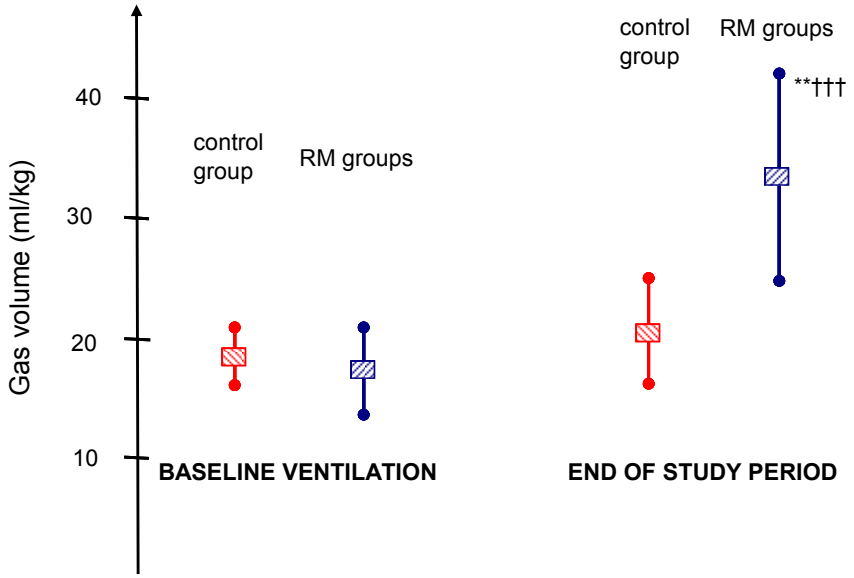

Figure 4. Gas volume per kg for control group and recruitment groups. Values are presented as mean±SD.
** p<0.01 RM groups vs. control group at the end of the study, ††† p<0.001 baseline ventilation vs. at the end of the study in the RM groups.

PEEP titration in the RM groups resulted in PEEP 10 cmH_2O for the "open lung ventilation". For a target V_T of 10 ml/kg the ventilatory pressure amplitude (EIP-PEEP) during baseline ventilation was 16 compared to 8 cmH_2O during final ventilation ($p<0.001$).
In the control groups there was no significant change of aeration, oxygenation or Cdyn during the study period.
Only 1% of normally aerated lung was added by increasing EIP above the V_TCO_2 peak/plateau in the RMp+ group. All piglets were recruited with minimal overaeration, 0.8 ±0.7% at the highest individual EIP.
During PEEP titration the first decline of Cdyn corresponded to 4 ±1% of atelectatic lung. At the first step of the downward PEEP titration the normally aerated lung was 84 ±5%, gradually decreasing to 65±14% at the first decline of Cdyn. This significant decrease corresponded to an almost identical increase of poorly aerated lung with no increase in atelectasis (Figure 5).

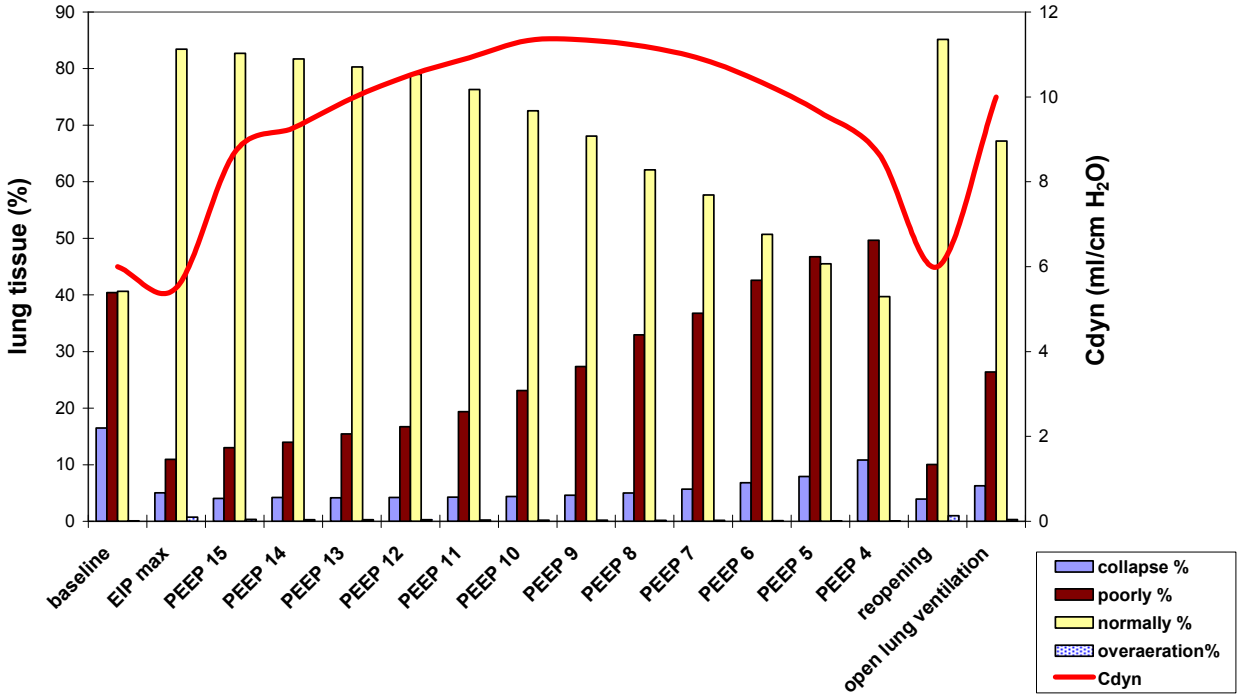

Figure 5. Lung aeration and dynamic compliance during the recruitment maneuver (selected time points). Values are presented as mean.

Study III

Ventilation after a RM and PEEP titration was compared with ventilation after a PEEP elevation without a foregoing recruitment. The final assessment was performed after a 3-hour follow-up-ventilation in both groups.

After the recruitment and PEEP titration the RM-group was ventilated with PEEP 10±0.6 cmH_2O, which did not differ from the predefined level for the PEEP10-group.

After the 3-hour follow-up-ventilation, EIP and DP were lower in the RM-group; 20±1 and 10±1 cmH_2O respectively, compared to 22±2 and 12±2 cmH_2O in the PEEP10-group ($p<0.01$). EIP was also lower compared to baseline in the RM-group ($p<0.05$) but not in the PEEP10-group.

After 3-hour ventilation DP was lower than baseline in both groups; 10±1 vs. 15±3 cmH_2O in the RM-group 12±2 vs. 17± 4 cmH_2O in the PEEP10-group ($p<0.001$) (Figure 6).

The CT scans showed increased aeration in both groups compared to baseline and the total gas volume/kg more than doubled at the end of the study.

Cdyn after recruitment/PEEP titration or PEEP elevation increased compared to baseline in both groups. Cdyn was higher at the end of the study in the RM-

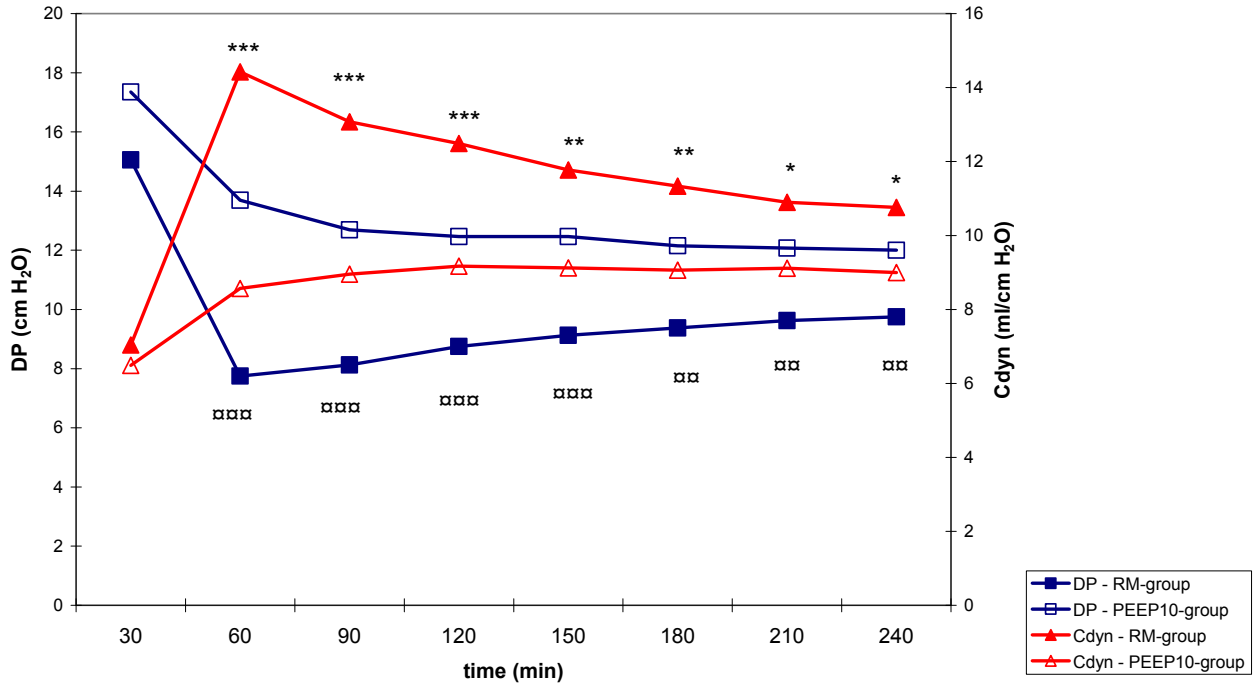

Figure 6. Dynamic compliance and driving pressure during the entire study. Values are presented as mean.
* p<0.05 Cdyn in the RM-group vs. PEEP10-group, ** p<0.01 Cdyn in the RM-group vs. PEEP10-group, *** p<0.001 Cdyn in the RM-group vs. PEEP10-group, ¤¤ p<0.01 DP in the RM-group vs. PEEP10-group, ¤¤¤ p<0.001 DP in the RM-group vs. PEEP10-group.

group than in the PEEP10-group; 10.8±1.3 vs. 9.0±1.9 ml/cmH_2O (p<0.05) (Figure 6).
In the RM-group, EIP and consequently the DP were increased by 2 cmH_2O from immediately after the RM/PEEP titration and to the end of the study to fulfill the $ETCO_2$ target. In the PEEP10-group EIP and DP were decreased by 2 cmH_2O from immediately after the PEEP elevation during the same time (Figure 6).
In the RM-group Cdyn was at its highest level immediately after the recruitment, reaching 14.4 ml/cmH_2O. It then fell slowly over the 3-hour ventilation to 10.8 ml/cmH_2O, but was still higher than in the PEEP10-group (p<0.05). The latter showed a slow mean increase over the 3-hour period (Figure 6).

Study IV

For an extended evaluation of hemodynamics CO was continuously measured during the RM, PEEP titration and a 60-min follow-up-ventilation.
The increase of PEEP to 15 cmH_2O at the start of the RM resulted in a significant decrease of CO by 15±7% ($p<0.01$). At the highest EIP during the RM CO decreased by 22±9% compared to baseline ($p<0.01$) (Figure 7 and 8). Thus 2/3 of the total decrease of CO occurred during the initial increase of PEEP. CO increased in all individual piglets during the following downward PEEP titration however group means did not differ significantly. During the 1 min reopening CO was not further affected and remained 18±11% lower than baseline ($p<0.01$). CO increased during the 1-hour-long ventilation after the RM but was still 14±9% lower than during baseline at the end of the study ($p<0.01$) (Figure 7). Like CO, MAP decreased at the initial PEEP increase to 15 cmH_2O and was 26±12% lower than baseline at the highest EIP ($p<0.001$) (Figure 7 and 8).
MAP recovered during the downward PEEP titration but temporarily decreased during the 1 min reopening and was 31±12% lower than baseline ($p<0.001$).

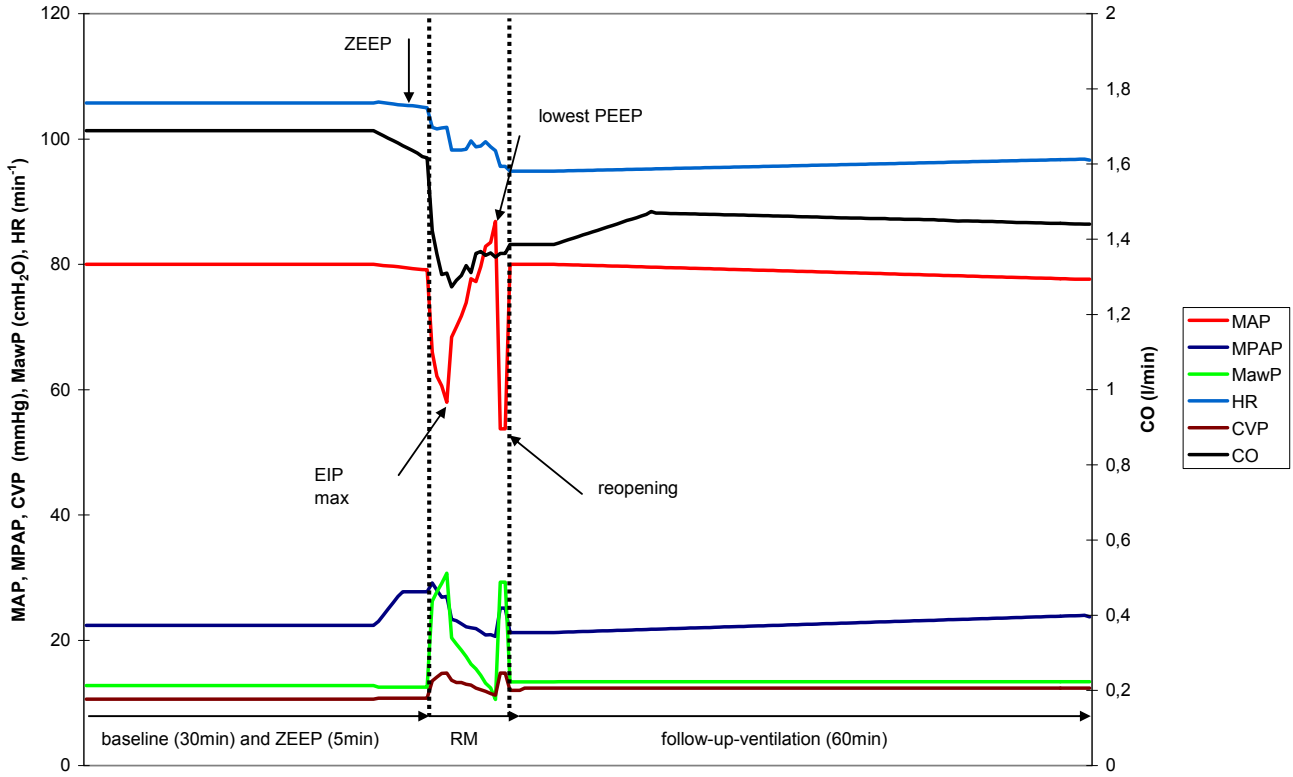

Figure 7. Hemodynamic parameters and mean airway pressure during the entire protocol. RM is limited by the dotted lines.

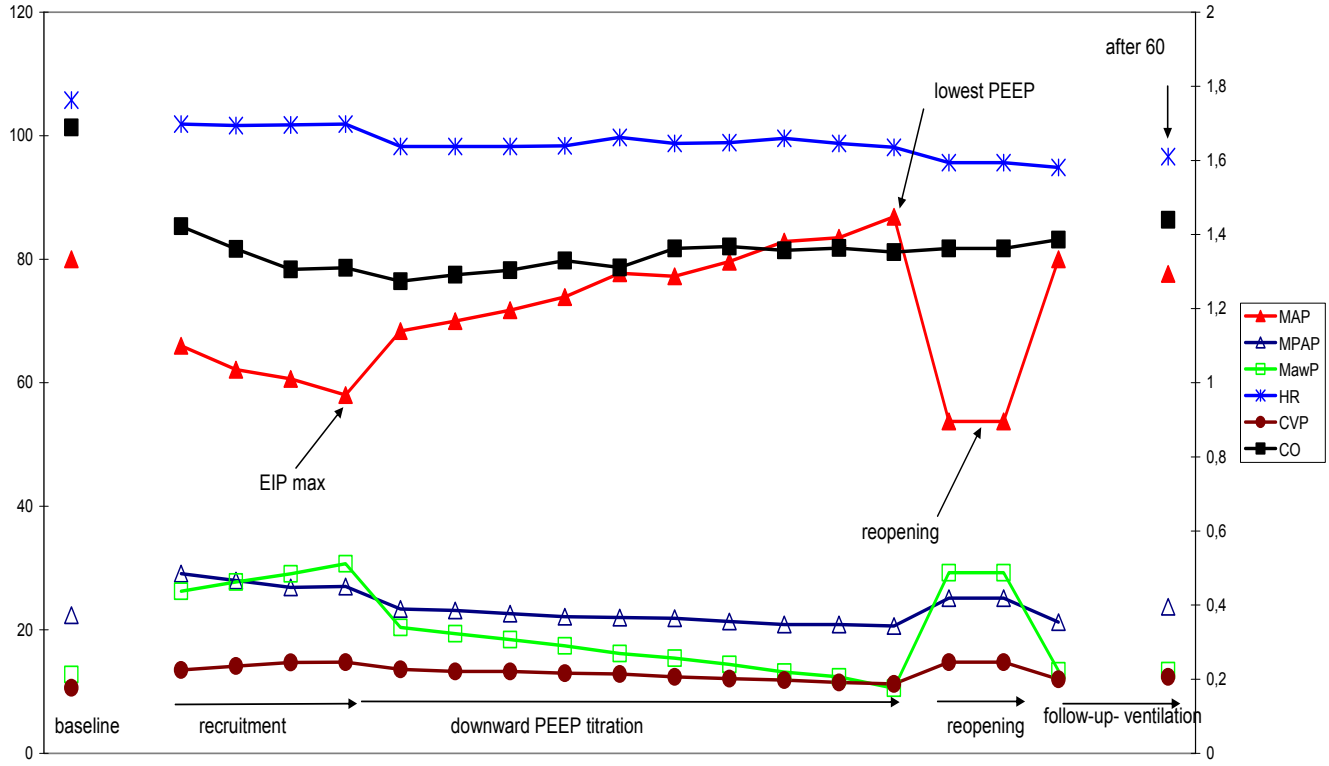

Figure 8. The recruitment maneuver (RM). 30 sec between every point except for baseline values to the left and follow-up-ventilation after 60 min to the right.

MAP did not differ from baseline during the 60-min follow-up-ventilation (Figure 7).
Heart rate at maximal EIP during the RM was not different from baseline. During the PEEP titration and reopening heart rates were significantly lower than baseline. A lower heart rate was also recorded at the end of the follow-up-ventilation, 97±16, compared to baseline, 106±12 ($p<0.05$) (Figure 7 and 8).
The DP was lower during the follow-up-ventilation than baseline; 8±1.1 cmH_2O compared to 16±2.4 ($p<0.001$). The EIP for the target V_T was 18±2 cmH_2O vs. 21±2 cmH_2O ($p<0.01$) and Cdyn >50% ($p<0.001$) higher compared to baseline.

Discussion

Main findings

The main findings of the experimental studies are:

- A recruitment maneuver was effective and resulted in increased aeration during the follow-up-ventilation with less atelectasis and more normally aerated lung as assessed by repetitive CT scans

- Ventilation after a recruitment maneuver and downward PEEP titration was performed with lower end-inspiratory pressure and driving pressure and higher dynamic compliance compared with the ventilation before the recruitment maneuver

- Improvements of aeration, driving pressure and dynamic compliance during the ventilation after the recruitment maneuver and PEEP titration were stable during a three hour follow-up-ventilation

- V_TCO_2 indicates an optimal recruited lung during the opening phase of a lung recruitment and an elevation of opening pressure above V_TCO_2 peak/plateau did not result in further recruitment

- Dynamic compliance indicates incipient collapse during a downward PEEP titration and a decline coincided with increasing collapse

- A recruitment maneuver and PEEP titration resulted in higher dynamic compliance and lower driving pressure during the follow-up-ventilation compared with ventilation after PEEP elevation without a foregoing recruitment

- Ventilation after a recruitment maneuver and PEEP titration resulted in better aeration, lower airway pressures and higher dynamic compliance compared with a control group ventilated without a lung recruitment

- A recruitment maneuver and PEEP titration resulted in significant hemodynamic effects with a transient decrease of blood pressure and a persistent decrease of continuously measured cardiac output but no vasoactive support was necessary

The overall aim of this thesis was to evaluate if V_TCO_2 and Cdyn could guide a lung recruitment and downward PEEP titration in small size lungs. For evaluation of the procedure and lung aeration repeated CT scans were performed for every change of ventilatory parameters during the two first studies. RM and PEEP titration are parts of lung protective ventilation and strategies for limiting airway pressures and optimizing lung mechanics are continuously evaluated.
Pediatric studies are sparse and studies from adults can not be extrapolated into pediatric practice. Experimental studies with pediatric dimensions must precede clinical studies.

"Open lung ventilation"

Lung protective ventilation is one of the challenges in modern intensive care. Different ventilatory strategies for preventing baro-, volu-, atelect- and biotrauma have been proposed. A protective ventilation strategy with low V_T (6 ml/kg), higher PEEP, limited driving pressure, use of recruitment maneuvers and permissive hypercapnia reduced mortality in ARDS patients [42]. The study from the ARDSnet comparing the use of low (6 ml/kg) vs. high (12 ml/kg) V_T and plateau pressures ($\leq$30 cmH_2O vs. $\leq$50 cmH_2O) also reported decreased mortality [43].
Reduction of V_T and plateau pressure reduces lung injury caused by overdistension but not the shear stress that arise from repetitive opening and closing of alveoli and small airways [122]. It is therefore suggested that a PEEP that prevents end-expiratory collapse and a driving pressure that avoids overdistension are used for ventilation [37], in this presentation called "open lung ventilation". This term is our modification based on the expression "open lung PEEP" [48]. In this presentation it means ventilation after a RM and decremental PEEP titration.
Information on the history of lung aeration and mechanics from ventilation after RMs during a prolonged follow-up time is sparse both from experimental and clinical studies [46, 123]. We describe different periods of "open lung ventilation". We started with five min in Study I increasing to 15 min, 60 min and 180 min in Study II, IV and III respectively.

Aeration. CT scans during "the open lung ventilation" were performed at the end of Study I-III and in Study III every 30 min. Aeration improved in all studies with a reduction of the amount of atelectasis and an increase of normally aerated lung compared to ventilation before the RM (Figure 5 and 9). Despite a higher PEEP the amount of overaeration was not affected. In Study II "open lung ventilation" compared with standard ventilation (the same ventilation as during baseline) without a RM in a control group showed better aeration. Aeration was

recovered in the control group after the ZEEP ventilation but no further improvement was seen. In two studies in healthy children and adults during anesthesia the mere application of PEEP 5 cmH_2O did not reduce atelectasis but in one of the studies oxygenation increased [12, 55].
In Study III both the RM-group and the PEEP10-group was followed for 3 hours after the RM and the PEEP elevation. After this follow-up-ventilation both groups showed better aeration with less atelectasis, less poorly and more normally aerated lung compared to baseline ventilation. No intergroup differences were seen at the end of the study.

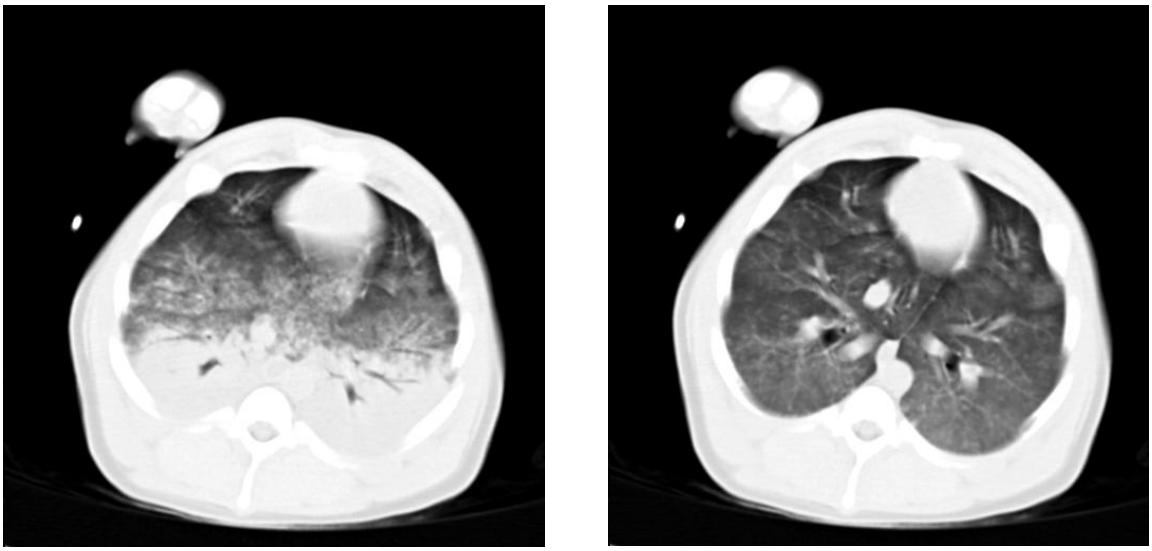

Figure 9. CT images during baseline ventilation with PEEP 5 cmH_2O (to the left) and during "open lung ventilation" with PEEP 10 cmH_2O (to the right)

Cdyn. After a lung recruitment maneuver an increase of compliance is expected due to the increase in lung volume for the same airway pressure. In all our present studies Cdyn was higher after the RM and at the end of the study. In a study in ARDS patients increased compliance was reported after daily RM [124]. During anesthesia in adults improvement was reported after a RM and two hours of follow-up [55].
In Study II no improvement of Cdyn occurred in the not recruited control group. In Study III the PEEP10-group had a higher Cdyn after the PEEP elevation than during baseline and at the end of the study indicating that recruitment and increase of lung volume occurred. In the RM-group Cdyn was higher at the end of the study than in the PEEP10-group which supports the use of a RM foregoing a PEEP titration [47].
During the follow-up period Cdyn slowly increased in the PEEP10-group and slowly decreased in the RM-group. At the same time normally aerated lung slowly increased in the PEEP10-group but was stable in the RM-group. The increase in Cdyn could be explained by an increase of lung volume. The

decrease in Cdyn was not accompanied by any change of aeration during the same period.

Airway pressures. Limitation of DP with less alveolar stretch and a plateau pressure <30 cmH_2O contributes to lung protective ventilation [42, 43, 122]. In adults lower plateau pressure (< 28 cmH_2O) are suggested due to the finding of tidal hyperinflation in normally aerated lung despite a plateau pressure below 30 cmH_2O and that the lower limit is more lung protective [125]. In all our studies a RM and PEEP titration resulted in a lower EIP and DP for the "open lung ventilation". In Study III DP was still 33% lower after 3 hour follow-up than during baseline ventilation. The PEEP titration resulted in a higher PEEP but as EIP was lower the reduction in DP is a "true" reduction and not only an effect of a higher PEEP level. This suggests that in combination with the marked reduction of poorly aerated lung and minimal overaeration the "open lung ventilation" is performed with less tidal opening and closing and is more lung protective.
In Study III in the PEEP10-group a similar decrease of DP was found as PEEP was increased.

Oxygenation. Improvements in oxygenation after a RM have been demonstrated in several studies [58, 66, 123, 126]. A rapid decline in oxygenation after the initial increase is reported [66, 123]. The duration of such improvement is probably influenced by the PEEP level used after the RM [46, 127]. The lack of sustained improvement of oxygenation can probably be related to inadequate PEEP.
High FiO_2 are associated with formation of atelectasis especially during anesthesia as shown in many studies and thus excessive administration should be avoided [128, 129].
We used FiO2 1.0 during all RM and PEEP titrations. In Study I, II and IV the same FiO_2 was used during the "open lung ventilation". Oxygenation (PaO_2) improved after the RM and remained high throughout the procedures.
In Study III FiO_2 was reduced to 0.5 for the "open lung ventilation" and the follow-up-ventilation in the PEEP10-group. After 3 hour ventilation oxygenation was the same as during baseline in both groups in spite of the reduced FiO_2. PaO_2 was still at supranormal values suggesting that FiO_2 could have been further reduced.

Comparison between RM and PEEP elevation. RM and PEEP titration resulted in lower EIP and DP and higher Cdyn than a PEEP elevation measured directly after the intervention. After 3 hour ventilation there was still a difference between the groups. This suggests a more protective ventilation after a RM and PEEP titration compared with a PEEP elevation despite the same PEEP level.

Lung recruitment and V_TCO_2

Sustained inflation or a vital capacity maneuver with application of constant high airway pressure for a defined time is the most studied recruitment strategy. A RM during ongoing ventilation can be performed with predefined or incremental airway pressures. In adults PaO_2/FiO_2>50 kPa (375 mmHg), $PaO_2+PaCO_2 \geq 400$ mmHg or Cdyn have been used as indications of a recruited lung [46, 68, 74].

We have used a standardised RM during ongoing pressure controlled ventilation exploring the hypothesis that V_TCO_2 peak/plateau is an indicator of optimally recruited lung. The rationale is that increasing inspiratory pressure during a stepwise recruitment of an atelectatic lung will increase V_T and result in a temporary increase of V_TCO_2. When the lung is maximally recruited no further increase in gas exchange will occur and thus V_TCO_2 will level off and/or decrease. This can be explained by two simultaneous mechanisms 1) increased dead space ventilation and 2) decreased lung blood flow due to beginning of overdistension with concomitant compression of small vessels and thus less CO_2 delivery to the alveoli.

Aeration was assessed by iterated CT scans for each change of ventilatory parameters. In Study I and II we found a peak/plateau of V_TCO_2 in all piglets if the set PEEP level for the RM was above closing pressure. The opening pressure was increased above V_TCO_2 peak/plateau to evaluate if this would lead to even more recruitment or just overaeration increasing the risk of pneumothorax. Analysis of CT images revealed that the lungs had been recruited and atelectatic areas markedly reduced at V_TCO_2 peak/plateau. Increase of airway pressures above V_TCO_2 peak/plateau only recruited a minimal amount of lung with minimal effects on the amount of atelectasis. Despite the use of high airway pressures minute overaeration and no pneumothorax was seen. This is in agreement with a clinical study in ARDS patients where no immediate barotrauma was seen despite the use of airway pressure of 60 cmH_2O [46]. We found no covariation between the recruitment and oxygenation reported by others [46, 48]. Even if oxygenation has been used as the principal clinical variable for assessing recruitment, there is no convincing relation between oxygenation and recruited lung as evaluated in adults with ALI/ARDS [130].

In Study III and IV V_TCO_2 peak/plateau was used as a marker of an optimal recruited lung. When using "optimally" recruited lung "optimal" only relate to that special lung and at that occasion.

PEEP titration and Cdyn

The open lung strategy for ventilation was described in 1992 in an editorial "Open up the lung and keep the lung open" [37] and proposals for lung protective ventilation were later presented [42]. The level of best individual PEEP and how to define it is still a matter of discussion. For titration of an optimal PEEP that keeps the lung open preventing repetitive opening and closing of lung units, the lung has to be optimally recruited and the effect of the hysteresis used [131]. Otherwise there is a risk for underestimating collapse during the PEEP titration and thus the PEEP level [47]. During decremental PEEP titrations a decrease of oxygenation and dynamic compliance and dead space data have been shown to be useful markers of incipient collapse as verified by CT scans [48, 54]. The sigmoid shape of the oxygen saturation curve makes it insensitive to lung collapse as large amounts of lung might already have collapsed before any change in saturation occurs, especially at high FiO_2 [86].

We have evaluated Cdyn as marker of collapse during the downward PEEP titration. PEEP titration was performed after a RM and we supposed the lung to be optimally recruited before the titration. In Study I and II lung aeration and collapse were evaluated with CT scans during the entire PEEP titration. The first decline of Cdyn during the PEEP titration was a good indicator of incipient collapse. At the same time point a decrease of normally aerated lung corresponding to an almost similar increase of poorly aerated lung was seen on CT. Poorly aerated lung may be the most instable part of the lung with cyclic recruitment-derecruitment present and thus probably the most prone for VILI [132, 133].

The finding that Cdyn is a good marker of collapse during PEEP titration is coherent with studies in larger pigs even with the lower PEEP level in our studies [48, 54].

We also compared CT scans with PaO_2 measurements to see if a drop of PaO_2 coincided with onset of lung collapse as reported [48, 54]. PaO_2 did not decrease as predicted according to the CT scans. The amount of collapse was already 8.0% during PEEP titration when PaO_2 fell by 10% or more compared with the highest PaO_2 directly after recruitment.

It is impossible to determine or monitor exactly when the collapse occurs during PEEP titration. The first decline value of dynamic compliance is probably the best indication of collapse or closing pressure. In order not to underestimate the optimal PEEP level the PEEP for the follow-up-ventilation was set 2 cmH_2O above this PEEP as in other studies [48, 54].

Hemodynamic effects of a recruitment maneuver

Application of high airway pressures as during a RM has negative hemodynamic consequences. Although there are studies reporting circulatory effects of lung recruitment few have measured during the RM and the actual time when the highest airway pressures are used [53, 87, 98]. Continuous methods are necessary to capture rapid changes of circulatory parameters.

We observed a marked decrease (mean 30%) of MAP at the V_TCO_2 peak/plateau and during the reopening. The decrease was transient and only four of thirty-four piglets received a single rescue dose of phenylephrine. CO was 22% lower than baseline at the highest EIP (Study IV) and during the reopening CO was still lower than during baseline but no further drop was measured.

A marked decrease of cardiac output and blood pressure measured during a RM has been reported in post-cardiac surgical patients [51, 100] and in porcine experiments [49, 53, 87, 98]. Other studies have shown only minor changes of CO but report effects on blood pressure during the RM [52, 68, 101]. Diverging results are obviously related to the actual recruitment procedure and the time-points at which recordings are collected. The use of intermittent CO techniques precludes other measurements than before and after the RM.

Sustained inflation/vital capacity maneuver seems to give more pronounced consequences compared to a RM performed during ongoing pressure control ventilation [49, 52]. With a sustained inflation a prolonged high intrathoracic pressure are applied without the cyclic pressure release during continuous ventilation.

We assessed the piglets in our studies to be normovolemic due to laboratory principles of fluid administration. No extra volume loading was given in any protocol. Experimental [49, 98] and clinical studies [68] have reported use of prophylactic volume expansion to attenuate the negative circulatory consequences of recruitment maneuvers.

MAP regularly recovered quickly when airway pressure was reduced and CO slowly increased but was still lower compared with baseline values. We assume that the use of higher PEEP during the "open lung ventilation" in Study IV compared to baseline may explain the lower CO [53]. We also speculate that the initial CO during baseline is representing a hyperdynamic circulation due to massive lung collapse. In Study III we measured CO every 30 min. After the RM and PEEP titration CO had decreased. After 60 min of "open lung ventilation" we observed a similar reduction of CO as measured at the end of Study IV compared to baseline values.

Methodological considerations

CT. CT scans were used to assess the effect of the recruitment and PEEP titration. CT is an exceptional tool for assessing aeration and morphology in experimental and clinical studies [134]. It has added much to the understanding of the pathophysiology of ALI/ARDS. The disadvantages with CT are the difficulties with transport of patients to the radiologic department. The amount of radiation from frequent investigations can also be of importance. The method for calculating aeration is reliable if the region of interest (ROI) is correctly delineated. The intraobserver variability of this technique has been evaluated and found to be 1.7% of mean area of a single ROI [135]. In Study I and II a single level of the initial topogram was selected and exposed for every change of ventilation that was performed and the amount of normally, poorly and overaerated lung was calculated as well as the amount of collapsed lung. Our recruitment protocol included rapid changes of ventilatory settings and these single exposures made it possible to assess the entire procedure. When aeration is changed during the protocol the selected lung level of the CT scan may vary in position and not represent the initial level [134].

CO. The pulse contour cardiac output analysis enables continuous monitoring, beat-to-beat, essential for the repeated measures during the RM. The CO value is updated every 12 s using a floating average. The best alternative would be the oesophageal Doppler technique that offers a continuous monitoring of aortic blood flow but is not validated for pigs. In our study (IV) recalibration was not possible during the RM although frequent recalibration has been recommended in some studies during profound hemodynamic instability or conditions with possible changes in vascular tone [111, 136]. In Study IV a transient sudden drop in MAP during reopening occurred and without a corresponding drop in CO. We cannot exclude that a fall of stroke volume passed undetected.

Experimental model. We used the same lung lavage model in all animals. This model of surfactant depletion makes the piglets very prone to develop atelectasis and is thus suitable for these kinds of experimental studies [49, 121]. The model does not have all the systemic features as a model of ARDS. Results from studies using different lung injury models are not exactly comparable. Consequently, commonly used animal models mimic known etiologies of ARDS but may respond differently to ventilatory maneuvers [49, 127].
In our set-up the number of lavage ranged between 2 and 14 resulting in an OI of 3-28.5. The large range in OI is a weakness but in some piglets we were not able to achieve the target OI because of a persisting high MPAP that prevented further lavage. The overall impression was that there was no clinical noticeable association between OI and the degree of lung injury. However, we observed in

one piglet with the highest OI; 28.5, that recruitment was more difficult to achieve than in the other piglets.

Clinical and future perspectives

The focus of this thesis has been to evaluate a method of lung recruitment in small size lungs. All studies are performed in piglets weighing about 10 kg. Several experimental studies with animals of adult dimensions are published. Few clinical studies on lung recruitment in children are reported [9, 11, 12, 73, 74].

The benefit of applying PEEP to reduce atelectasis during anesthesia is well known [7, 8]. In post-op cardiac children a RM has been studied with positive effect on lung aeration. Children with respiratory failure are a heterogeneous group and there treatment needs to be individualized. Some children may benefit from lung recruitment adjusted for size and maturity.

A RM guided by V_TCO_2 to avoid unnecessary high opening pressure reduces the risk for gross barotrauma and negative hemodynamic effects.

All patients with respiratory failure may benefit from an individually set PEEP after a RM to minimize shear stress and reduce driving pressure. Downward PEEP titration guided by Cdyn offers a simple and reliable method.

Our studies add information for future controlled clinical application of recruitment and selection of PEEP levels in small children. This would assist in designing a strategy for a lung protective ventilation resulting in less lung injury in infants and children.

Conclusions

- Ventilation after a RM and PEEP titration resulted in improved aeration according to CT scans and lung mechanics (lower end-inspiratory pressure and driving pressure and higher dynamic compliance) after the different follow-up-ventilation periods (5, 15, 60 and 180 min) compared to baseline ventilation

- V_TCO_2 was a marker of optimally recruited lung during the opening phase of the recruitment and an increase of airway pressure above the V_TCO_2 peak/plateau did not improve aeration

- Dynamic compliance indicated incipient collapse during the decremental PEEP titration

- Ventilation after a RM and PEEP titration resulted in improved lung mechanics compared with the PEEP elevation group not exposed to a RM after a 3 hours follow-up-ventilation. The final aeration did not differ between the groups

- Ventilation after a RM showed improved aeration, lower end-inspiratory and driving pressure and higher dynamic compliance compared with a control group ventilated with a standard ventilation

- A RM resulted in a significant reduction of cardiac output and blood pressure. The decrease of cardiac output persisted whereas blood pressure reduction was transient

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Populärvetenskaplig sammanfattning

Respiratorbehandling är vid många sjukdomstillstånd livräddande och en förutsättning för att stor kirurgi ska kunna genomföras. Under narkos faller delar av lungan samman och s.k. atelektaser bildas. Detta drabbar alla, barn som vuxna oavsett ålder. Så mycket som 10-15% av lungan kan vara sammanfallen utan att det syns på en vanlig röntgenbild. Med hjälp av datortomografi (skiktröntgen) kan mycket små atelektaser ses. Hos en för övrigt frisk patient som bara behöver en kort tids respiratorvård spelar uppkomst av atelektaser sannolikt en mindre roll.

Akut lungsvikt som kräver respiratorbehandling kan orsakas av sjukdomar i lungan men även av andra allvarliga sjukdomar. Lungsvikt hos barn är i högre grad än hos vuxna orsakad av lungsjukdomar och har bättre prognos. Det första tecknet på lungsvikt kan vara att kroppen får för lite syre. Tidigare har behandlingen styrts för att säkerställa syrgasbehovet och uppnå normal syrgashalt i kroppen. Respiratorbehandling är nödvändig men kan också leda till ytterligare lungskada. Rekommendationer för lungskyddande respiratorbehandling baserade på studier i vuxenvärlden används till både vuxna och barn i frånvaro av barnstudier. En teknik med små andetagsvolymer jämfört med stora och en begränsning av inandningstrycket till 30 cmH_2O har visats skydda lungan och ge en bättre överlevnad hos vuxna. Liknande studier på barn saknas.

Respiratorbehandling som sker utan lungskyddande strategi kan orsaka sjukdom och livshotande svikt också i andra organ än lungan. Man har också sett att lungan avger ämnen som ger en allvarlig inflammation i hela kroppen och ytterligare försämrar tillståndet.

Sammanfallen lungvävnad – atelektaser - uppkommer vid akut lungsvikt och spelar då en betydligt större roll än under narkos. Atelektaser innebär att lungvävnad som ska hjälpa till att syrsätta blodet och vädra ut koldioxid som bildats i kroppen inte luftfylls och således inte fungerar. Försök att öppna upp atelektaser s.k. lungrekrytering och att efter det hålla lungan öppen ingår i lungskyddande respiratorbehandling. Rekrytering sker genom att man under en kort tid ökar inandningstrycket så att lungan öppnas upp. Efter en rekrytering (öppning) av lungan hålls den öppen genom att total luft-tömning förhindras vid utandning genom ett mottryck i respiratorn. Detta kallas positivt end-expiratoriskt tryck (PEEP) och bör bestämmas individuellt genom en s.k. PEEP-titrering.

Lungvävnad/lungblåsor som är delvis sammanfallna öppnas och stängs vid varje andetag. De utsätts för dragkrafter under in- och utandning vilket också skadar lungan. Lungblåsorna kan stabiliseras med en avpassad PEEP-nivå.
När man gör en rekrytering av lungan behöver olika lungor olika högt inandningstyck i respiratorn för att öppna sig. Ofta används ett förutbestämt inandningstryck som i studier visat sig tillräckligt. För att bestämma PEEP-nivå kan man välja en teoretiskt lämplig nivå eller söka en individuellt avpassad nivå genom PEEP-titrering.
Avhandlingen sammanfattar fyra olika studier gjorda på smågrisar dvs. lungor i barnstorlek. Den syftar till att hitta en "barnanpassad" metod att öppna upp lungan och hålla den öppen under så lång tid som möjligt.
Under höjning av inandningstrycket under rekryteringsproceduren följde vi hur mycket koldioxid som andades ut under varje andetag (V_TCO_2) och som ökade när lungan öppnades. När lungan inte kunde öppnas mer minskade koldioxidutsköljningen. För att få fram den individuellt bästa PEEP-nivån som håller lungan öppen dvs. förhindrar lungan från att falla samman vid utandning, mätte vi lungans eftergivlighet - dynamisk compliance - som sjönk när lungan under utandning började falla samman.
För att mäta och säkerställa att våra hypoteser om att V_TCO_2 och dynamisk compliance indikerade lämpligt respiratortryck för rekryteringen respektive när lungan började falla samman vid PEEP-titreringen, tog vi datortomografiska bilder av lungan för varje ändring av trycken i respiratorn. Vid analys av bilderna visade det sig att lungan var optimalt öppnad när V_TCO_2 var vid sitt högsta värde och att en ytterligare höjning av inandningstrycket inte öppnade lungan mer. Bilderna under PEEP-titreringen visade att dynamisk compliance var en god markör för att lungan började falla samman under utandning. På så sätt kunde det individuellt bästa PEEP-värdet bestämmas.
Efter att lungan rekryterats och PEEP-nivå bestämts kunde individuellt anpassade tryck ställas in på respiratorn för att skydda lungan. Under en uppföljningstid på maximalt tre timmar kunde vi med datortomografi följa lungans lufthalt och att den hölls öppen.

Sammanfattningsvis visar avhandlingen på en metod att öppna upp en sammanfallen lunga och att hålla den öppen. Studierna är gjorda med en djurmodell av barnstorlek och utgör en bas för fortsatta studier på barn. Vi hoppas att detta ska leda till en förbättrad respiratorvård som resulterar i mindre lungskada för våra små patienter.

Original studies (I-IV)